Unique Approaches Towards the Synthesis of Polycyclic Sesquiterpene Targets

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

By

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Declaration of Copyright

Acknowlegements

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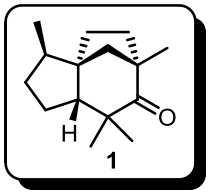
Abstract

A programme of work towards the total synthesis of the natural product sesquithuriferone has been performed, with significant advances towards the realisation of this overall goal achieved.



sesquithuriferone

From this perspective, two main synthetic strategies have been investigated towards the synthesis of a common early-stage intermediate, critical to the construction of the core tricyclic scaffold. In this regard, both of these preparative pathways were explored simultaneously, with the aim of developing a robust and versatile route through to the natural product target.

The first of these approaches involved the development of a novel [3+3]-sigmatropic rearrangement, to provide access to range of substituted cyclopentanones. Towards this aim, significant progress has been achieved, with late stage compounds having been prepared. Initial studies concentrated specifically on the synthesis of a novel ε-lactone key to the synthesis of sesquithuriferone. Additionally, a novel strategy to access a range of substituted systems of structural similarity has been developed and, within the body of this research, a number of preparative pathways designed to access these systems have been explored. As each of the individual routes have been investigated, short optimisation studies have been pursued.

The second route towards the synthesis of the common intermediate involved an umpolung conjugate addition strategy. Towards this aim, a robust and versatile set of protocols have been developed to provide access to both the racemic and asymmetric variants of this compound.

Towards the construction of the key tricyclic core of sesquithuriferone, a Pauson-Khand approach was pursued. In this regard, a wide range of structural derivatives were synthesised and examined, under a spectrum of standard protocols, to identify an optimal structure to facilitate this key organometallic annulation. Upon completion of this optimisation

programme, a range of synthetic strategies were explored towards the completion of the desired natural target. Significant progress towards this goal has been achieved, with the preparation of several late stage compounds completed. In addition, through the development of this route towards sesquithuriferone, several points of diversity have been identified and investigated with the aim of assessing if the identified synthetic strategy under investigation could be applicable to the synthesis of other members of the same family of natural compounds.

Abbreviations

Ac	Acetyl
atm	Atmospheres
ADMET	Acyclic diene metathesis
ATPH	Aluminum tris(2,6-diphenylphenoxide)
Aux	Auxilliary
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BNO	Brucine *N*-oxide
^{n}BuSMe	^{n}Butyl methyl sulfide
Cat.	Catalyst
CNC	Colloidal cobalt nanoparticles on charcoal support
CDP	Cyclodepolymerisation
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMAP	4-*N*,*N*-Dimethylaminopyridine
DME	Dimethoxyethane
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DodSMe	Dodecyl methyl sulfide
d.r.	Diastereomeric ratio

e.e.	Enantiomeric excess
Eq.	Equivalents
e.r.	Enatiomeric ratio
Et	Ethyl
Et_3N	Triethylamine
Ether	Diethyl ether
EWG	Electron-withdrawing group
g	Grammes
Grubbs I	Grubbs 1st generation catalyst
Grubbs II	Grubbs 2nd generation catalyst
h	Hours
HPLC	High-performance liquid chromatography
Hz	Hertz
ICP-EAS	Inductively coupled plasma atomic emission spectroscopy
IR	Infrared
^{i}Pr	Isopropyl
LDA	Lithium diisopropylamide
M	Molar
Me	Methyl
MeLi	Methyllithium
MeCN	Acetonitrile
mg	Milligrammes

MHz	Megahertz
min	Minutes
ml	Millilitres
mmol	Millimoles
mol	Moles
MVK	Methyl vinyl ketone
NHC	*N*-Heterocycle carbene
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance spectroscopy;
	s - singlet
	d - doublet
	dd - doublet doublet
	t - triplet
	tq - triplet of quartets
	q - quartet
	m - multiplet
OPP	Pyrophosphate
Petrol	Petroleum ether b.pt. 40-60 ^{o}C
Ph	Phenyl
P-K	Pauson-Khand
ppm	Parts per million
RCM	Ring closing metathesis

r.t.	Room temperature
s	Seconds
SBA	Mesoporous silica nanoparticles (Santa Barbara Amorphous)
TBAF	*tert*-Butylammonium flouride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDMSOTf	*tert*-Butyldimethylsilyl triflate
TDSOTf	Dimethylthexylsilyl trifluoromethanesulfonate
Temp.	Temperature
TESOTf	Triethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofuran
TMANO	Trimethylamine *N*-oxide
TMSCl	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl triflate
TMS	Trimethylsilyl
TMTU	Tetramethylthiourea
p-TSA	*para*-Toluenesulfonic acid

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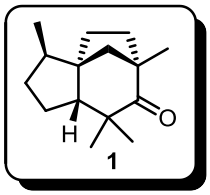
1 Research Aims

Over recent years, studies within our laboratory have focused on the development of new organometallic techniques and their direct application in organic synthesis. Indeed, at present, projects involving organochromium, cobalt, iridium, magnesium, and palladium processes are being explored within both synthetic methodology and total synthesis contexts. Towards this aim, the basis of this PhD programme was the total synthesis of sesquithuriferone **1**, a key member of the cedrene family of natural products.



sesquithuriferone

Critical to the success of this project was the Pauson-Khand reaction and its ability to generate high levels of structural complexity from relatively simple and accessible starting materials. Using the vast array of knowledge in the development and understanding of the Pauson-Khand reaction, we hoped to not only complete the synthesis of sesquithuriferone **1**, but also identify a generalised synthetic strategy to allow access to the various core structures present in this wider family of natural compounds.

The following section will begin by providing key background information on the specific molecule of interest, before outlining the previous attempts to synthesise sesquithuriferone **1** within the literature. Following this, a detailed account of previous work within the group will be reviewed, to demonstrate how these investigations have influenced the synthetic approach adopted. Finally, before entering into discussions surrounding the strategies attempted towards the synthesis of sesquithuriferone **1** as part of this body of work, a review of the Pauson-Khand reaction itself is presented, to provide a clear understanding of the fundamental principles surrounding the scope and applicability of this reaction and to relate why we feel this process has considerable potential as a synthetic tool in modern natural product synthesis.

2 Introduction

2.1 Sesquiterpenes and the Cedrene Family of Natural Products

Sesquiterpenes are a class of compound consisting of three isoprene units, fifteen carbons in size. Derived from farnesyl pyrophosphate, cyclisation of this core structure has been shown to generate more than 300 skeletal structures, and accounts for more than 10,000 individual compounds.[1] Isolated from various higher order organisms including fungi, marine animals, and flowering plants, sesquiterpenes have revealed their participation in a vast array of biological functions such as acting as insect attractants, phytoalexins, pheromones, juvenile hormones, and as components of essential oils.[2,3] It is this variety in structural arrangement and function which makes them particularly interesting as lead compounds in the medicinal and agrochemical industries. Indeed, polygodial **2** and parthenolide **3**, amongst others, have been investigated and proved active as potential fungicides and cancer treatments (**Figure 1**).[4–9]

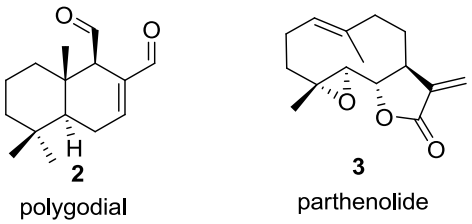


Figure 1. Absolute configuration of polygoial and parthenolide

In relation to this general field, the cedrene family of sesquiterpenes has been identified as one of the major components in the essential oils of cedar wood. Found in many varieties of the *Juniperius* species, cedrene was originally isolated by Walter in 1841 as a mixture of α-cedrene **4** and β-cedrene **5** (**Figure 2**).[10]

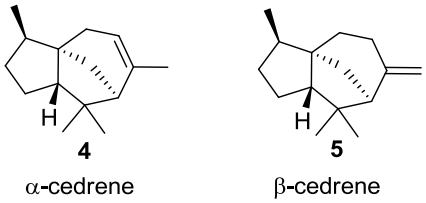


Figure 2. Absolute configuration of α-cedrene and β-cedrene

Since the initial discovery of cedrene however, improved analytical and spectroscopic techniques have allowed the identification of many closely related compounds, significantly expanding the known structural array of molecules within this natural product family. In

2000, Barrero and co-workers conclusively elucidated the structure of several new members of the cedrene family (**Figure 3**).[11] The key structural arrangement, common to all the products is a fused tricyclic core, containing ring sizes ranging from five to seven carbon units. Indeed, it was this common structural arrangement that was of particular interest to our research group. From a synthetic perspective, no direct methods are currently available to generate such complex fused scaffolds in a concise manner.

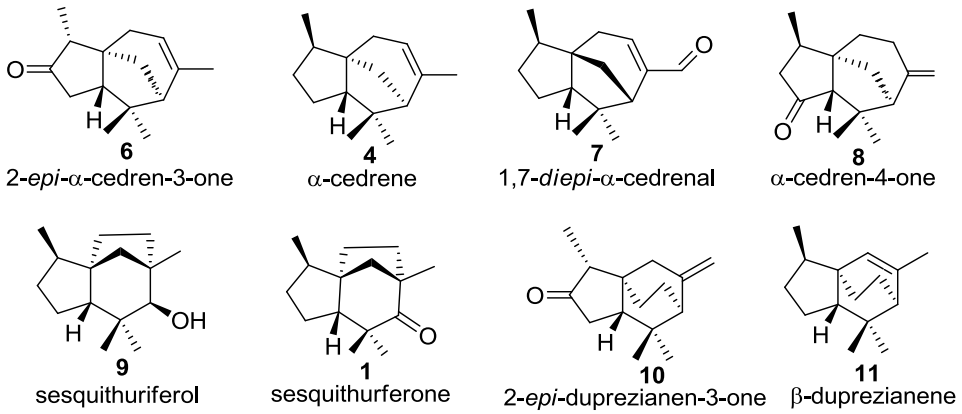


Figure 3. Various structural derivatives within the cedrene family of natural compounds

It was from this perspective that we hoped to demonstrate that by implementing a Pauson-Khand strategy towards the synthesis of these molecules, significant improvements in preparative efficiency could be achieved. Indeed, to date, the syntheses of α-cedrene **4** and 2-*epi*-α-cedren-3-one **6** have been completed using this type of approach (*vide infra*).[12–14] In an effort to further exemplify the advantages of applying this strategy and expand the potential substrate scope, the synthesis of sesquithuriferone **1** was targeted.

Importantly, sesquithuriferone **1** has a subtle change in structural arrangement comparative to the previous targets, containing a [5,6,5]-fused ring system, as opposed to the previous [5,5,6]-systems of α-cedrene **4** and 2-epi-α-cedren-3-one **6** (**Figure 4**). It was immediately recognised that if this methodology could be employed to synthesise these various fused ring systems, the strategy could prove applicable to access a wide range of compounds within this family of natural products.

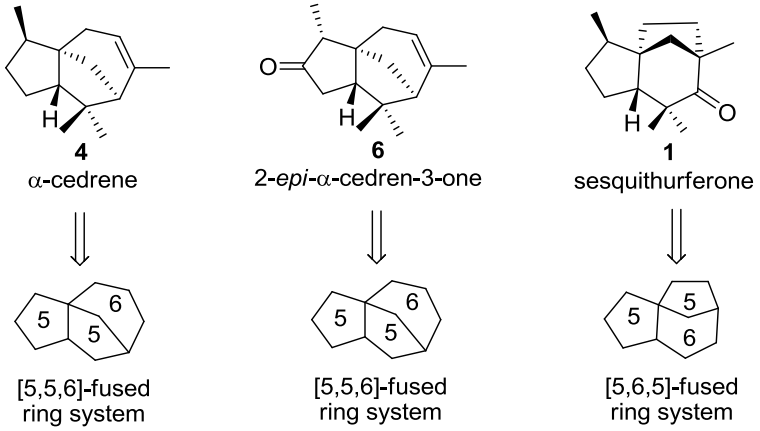


Figure 4. Notation used to describe the fused ring systems

2.2 Sesquithuriferone

Following the structural elucidation by Ralph and co-workers in 1976, sesquithuriferone **1** and the closely related sesquithuriferol **9** (**Figure 5**), have been discovered in a wide variety of plant species, as a common component of essential plant oils.[15] At present, little is known of the biological role of sesquithuriferone within the plant, though recent biological screening has identified cytotoxicity and antimicrobial activity.[7]

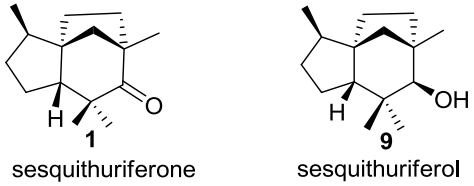
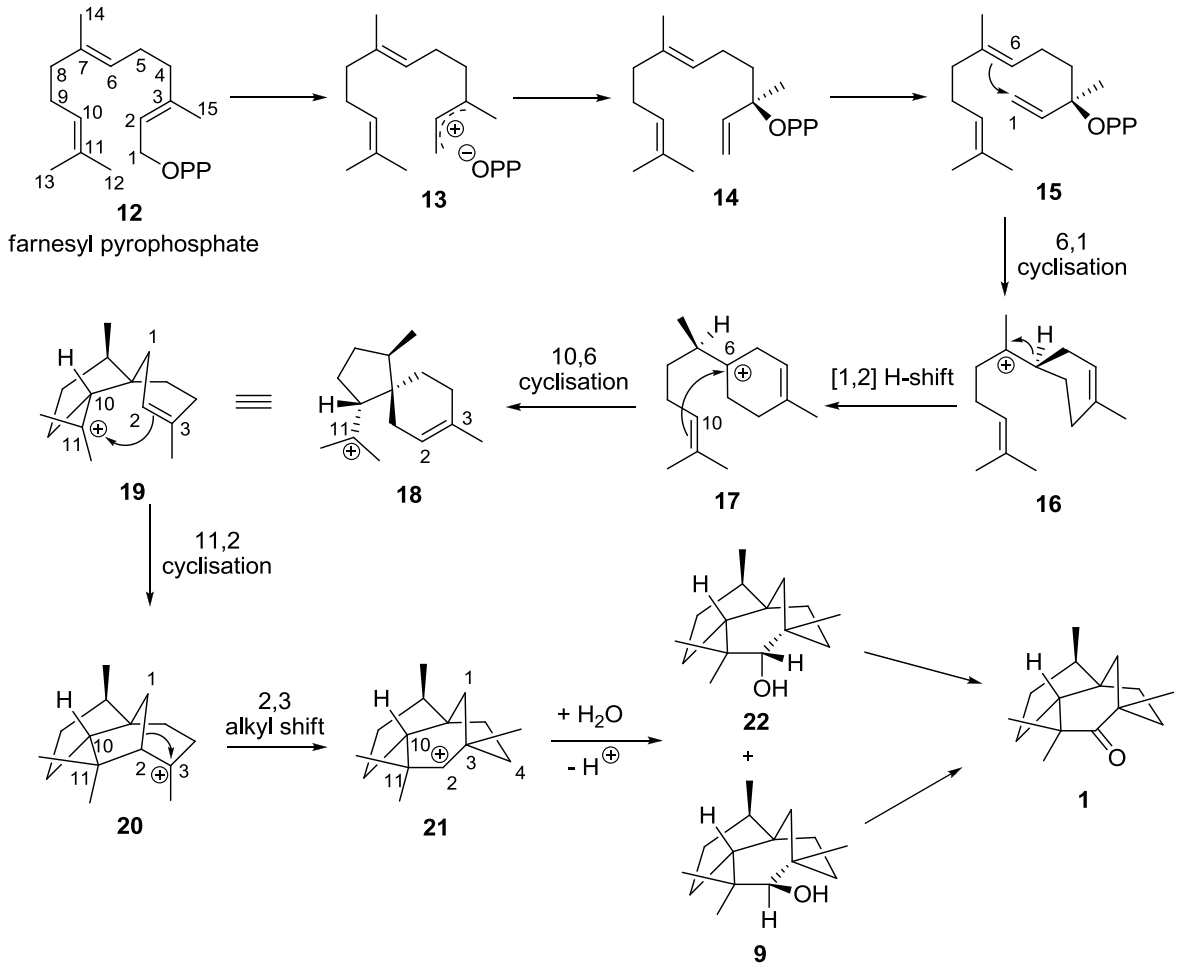


Figure 5. Absolute configuration of sesquithuriferone and sesquithuriferol

Taking a closer look at the structure of sesquithuriferone **1** reveals that it contains four stereogenic centres, three of which are contiguous. It is also composed of a fused [5,6,5]-ring system, containing only one major functional group: a ketone present in the six-membered ring. It was this level of both complexity and simplicity that makes sesquithuriferone **1** such a challenging substrate to synthesise in a concise manner.

2.3 Biosynthetic Pathway and Stereochemical Elucidation

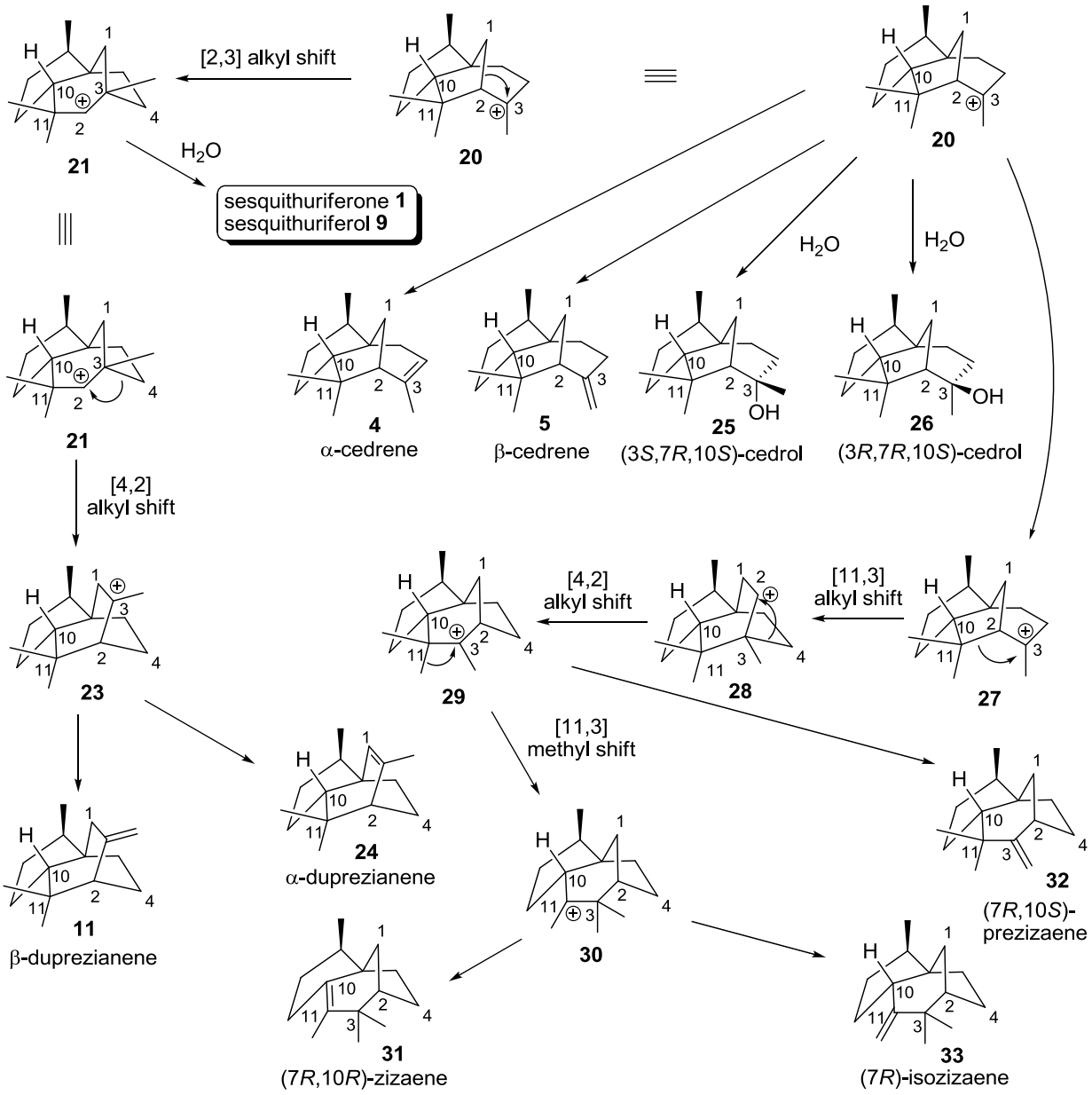
In 2009 Hong and co-workers formally resolved the biosynthetic pathway responsible for the formation of various sesquiterpenes, including that of sesquithuriferone **1** and sesquithuriferol **9**, from farnesyl pyrophosphate **12** (**Scheme 1**).[16]



Scheme 1. Biosynthetic synthesis of sesquithuriferone 1

Starting from farnesyl pyrophosphate **12**, it was believed that an initial 1,3-diphosphate rearrangement was key to the initiation of the overall cyclisation sequence. This process occurred primarily to facilitate the initial olefinic migration to **14** and secondly, to allow the key rotation to **15**, which promotes the subsequent cyclisation cascade that follows. Closure of the first six-membered ring in **16** effectively sets up the first cationic intermediate required to promote two further consecutive cyclisations to form the fused [5,5,6]-ring system in **20**. Following a 1,2-alkyl shift of the bridging methylene in **20**, the required [5,6,5]-ring system was established in **21**, which promotes the addition of water to form sesquthuriferol as a mixture of two stereoisomers **9** and **22**. Completion of the biosynthetic pathway was achieved through a final oxidation to provide sesquithuriferone **1** (**Scheme 1**).

Further information obtained from the biosynthetic pathway demonstrates just how closely linked each of the individual compounds within the family of natural products are. It is from the same common starting intermediate **20**, that cedrene **4**-**5**, cedrol **25**-**26**, duprezianene **11** and **24**, and zizaene **31**-**33** are all readily accessible, through subtle changes in the direction of the alkyl shifts and the points at which the intermediates are quenched (**Scheme 2**).

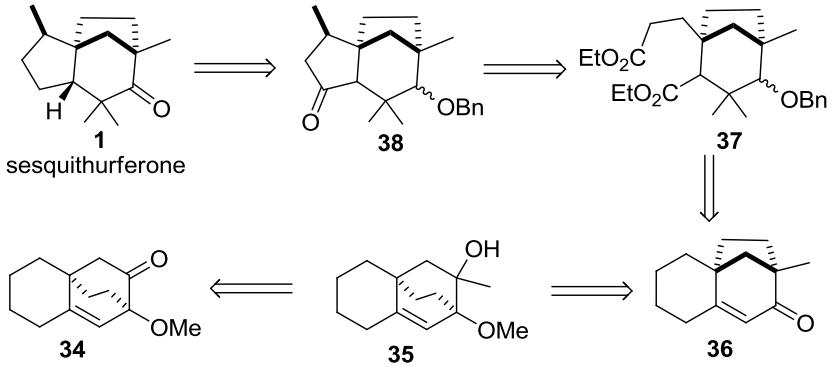


Scheme 2. Biosynthetic link between the various members of the cedrene family of natural products

With such a close biosynthetic link, it was hoped that the synthetic strategy used to access α-cedrene **4**, could be applicable to the synthesis of sesquithuriferone **1** and other members of the same family.

2.4 Previous Syntheses of Sesquithuriferone

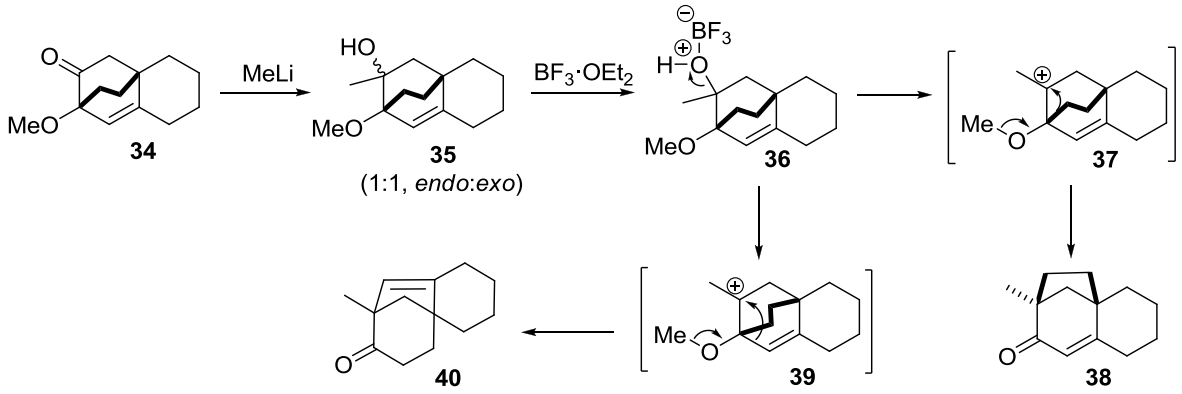
To date there have been two successful syntheses of sesquithuriferone **1**; the first completed in 1994 by Selvakumar and co-workers (**Scheme 3**).[17]



Scheme 3. Retrosynthetic strategy towards the synthesis of sesquithuriferone

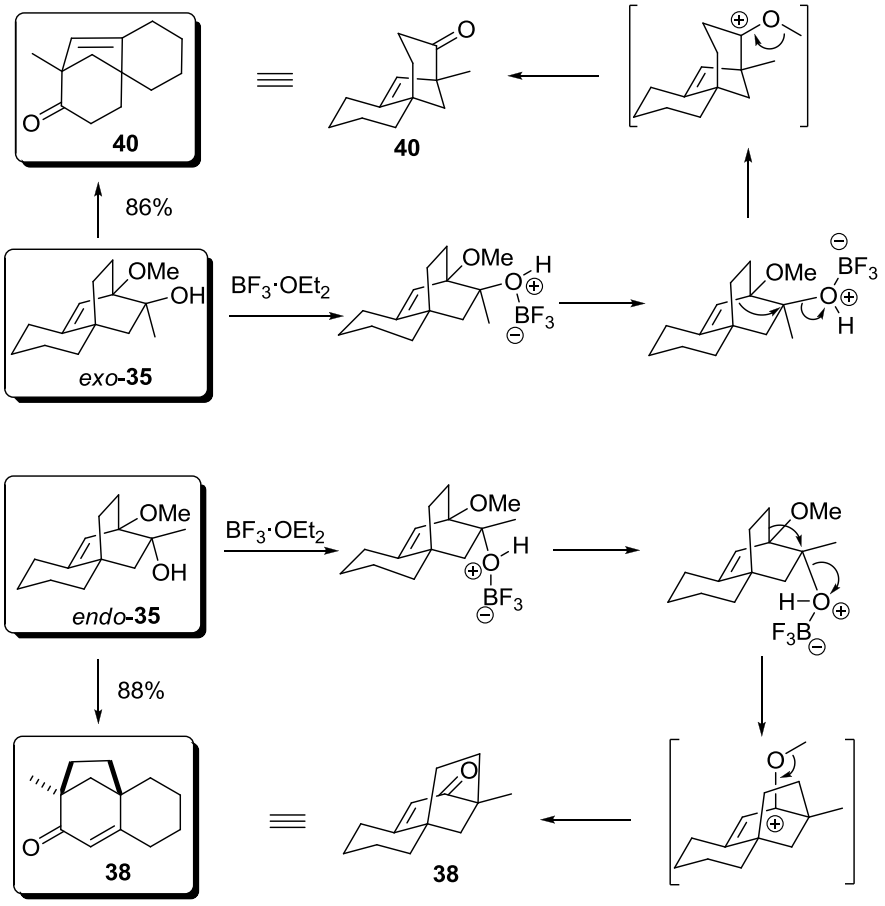
From the outset, the Selvakumar group had envisioned the construction of the tricyclic core in **36**, from known ketone **34**.[18] Key to this process was a Lewis acid-promoted rearrangement of alcohol **35**, to provide **36**. Although this process should result in the desired formation of a bicyclo[3.2.1]octane portion in **36**, the molecule would still contain a six-membered ring adjacent to this structure, instead of the desired five-memebered ring in **1**. To circumvent this issue and install the desired methyl, the Selvakumar group proposed that through a series of simple transformations, the six-membered ring could be first fragmented to form **37** and then cyclised, to provide **38**. From this point, sesquithuriferone **1** could be accessed through sequential removal of the ketone, benzyl deprotection, and a final oxidation (**Scheme 3**).

Upon implementation of the proposed route, the Selvakumar group immediately recognised that stereocontrol played a significant role in determining product formation. The first step in the synthetic sequence involved the formation of alcohol **35** (**Scheme 4**). This was achieved through the addition of MeLi to ketone **34**, resulting in a 1:1 (*endo*:*exo*) mixture of alcohols **35**. The absence of facial selectivity in the first step was not initially deemed problematic, since the proposed Lewis acid-promoted rearrangement of **35** should involve the formation of a tertiary carbocation at this position (**36**→**37**). However, treatment of the mixture of diastereomers with $BF_3{\cdot}OEt_2$ was found to promote, not just the expected migration of the bridging ethylene section, to form the desired product **38**, but also a novel transformation to isolate **40** *via* a migration of the vinyl group (**Scheme 4**).



Scheme 4. Synthesis of 38 and 40 through Lewis acid-promoted rearrangement of alcohol 35

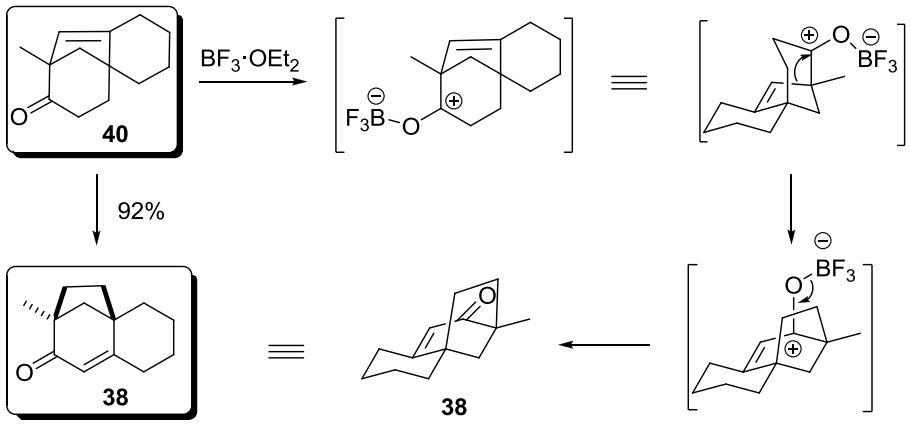
Following separation of the two diastereomers of **35**, it was revealed that treatment of the *exo*-alcohol **35** with $BF_3{\cdot}OEt_2$ predominantly formed compound **40**, whilst rearrangement of the *endo*-alcohol **35** preferentially provided **38** (**Scheme 5**).[19]



Scheme 5. Products of the Lewis acid-promoted rearrangement of *exo*-35 and *endo*-35

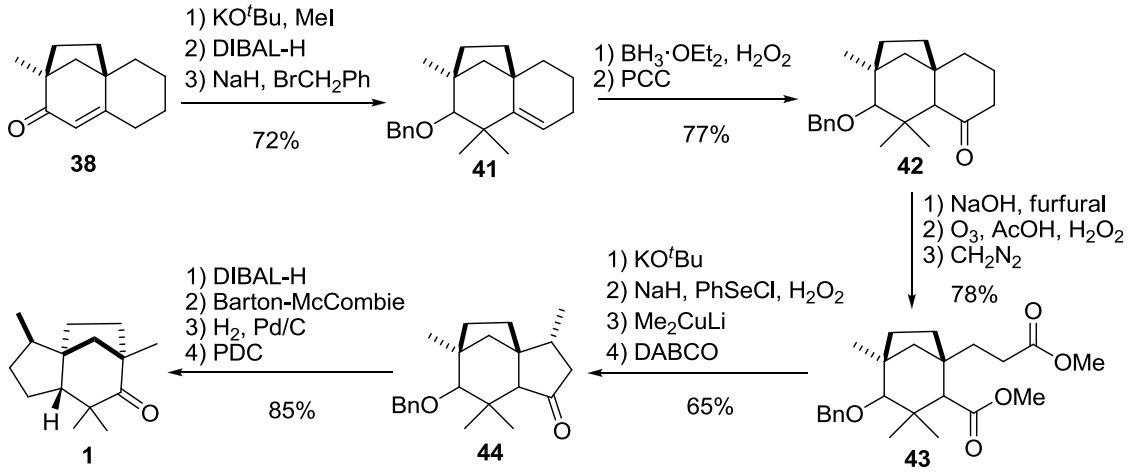
This result indicated that the rearrangement appeared to be more concerted in action than previously envisioned, with the migration of the alkyl portion largely dictated by the relative orientation (*endo* or *exo*) of the starting hydroxyl in **35**. Crucially, a comprehensive screening

of reaction conditions revealed that by refluxing **40** in the presence of $BF_3{\cdot}OEt_2$, a second Lewis acid-promoted rearrangement could be achieved, to provide **38** almost exclusively (**Scheme 6**). Whilst the divergence of product formation in the early stages of the proposed sequence was not ideal, the adaption of this additional protocol did solve the key selectivity issues surrounding the addition of MeLi prior to the formation of **38**.



Scheme 6. Lewis acid-promoted rearrangement of 40 to provide 38

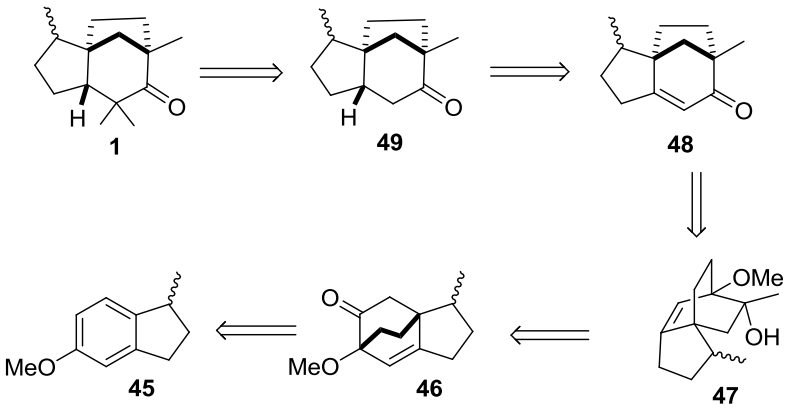
It was from **38**, following a series of ring openings and functional group changes that sesquithuriferone **1** was isolated (**Scheme 7**). This process was initiated by sequential α-alkylation of the enone moiety, followed by reduction of the ketone and protection of the free alcohol as the benzyl derivative **41**. By following this sequence of steps, the preferential migration of the alkene moiety into the unwanted six-membered ring could be achieved, ultimately allowing the formation of ketone **42** through hydroboration and oxidation.



Scheme 7. Synthesis of sesquithuriferone 1 from 38

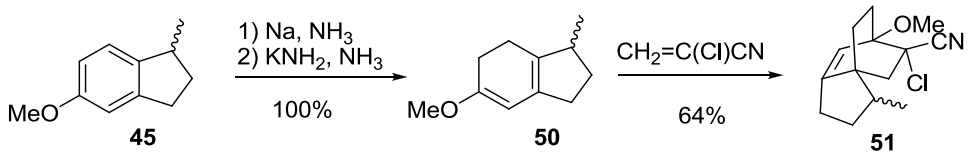
To achieve the desired ring fragmentation, an initial condensation of **42** with furfural, followed by ozonolysis and esterification was pursued to isolate **43**. This provided an ideal substrate to allow Dieckmann condensation to provide the required five-membered ring. However, the newly instated ring system still lacked the methyl required to complete the synthesis of sesquithuriferone **1**. Fortunately, enone formation using selenium methodologies provided an excellent opportunity to add this substituent in the desired position. Following this, addition of the methyl substituent using the corresponding methyllithium-derived cuprate, not only proved successful, but also selective. Subsequently, a final decarboxylation provided **44**. To complete the synthesis of sesquithuriferone **1**, deoxygenation of ketone **44** was required. This was achieved following a sequential reduction/Barton-McCombie protocol, to deliver the corresponding fused cyclopentane, with deprotection and oxidation providing sesquithuriferone **1**.

In 1995 Selvakumar and co-workers revised the synthesis of sesquithuriferone **1**, this time from a much simpler and inexpensive starting material **45** (**Scheme 8**).[20] In this approach, the authors proposed that if the corresponding Lewis acid-promoted rearrangement proved successful with the five-membered ring already in place, a significant simplification of the synthetic route could be achieved. Crucially, instead of requiring a laborious ring fragmentation/cyclisation protocol, sesquithuriferone **1** could instead be accessed *via* hydrogenation and sequential alkylation of **48**. Whilst it was recognised that the synthetic route under investigation would afford target molecule **1** as a mixture of epimers, the described strategy should also provide a concise route through to sesquithuriferone **1** upon accessing an enantioenriched form of **45**.



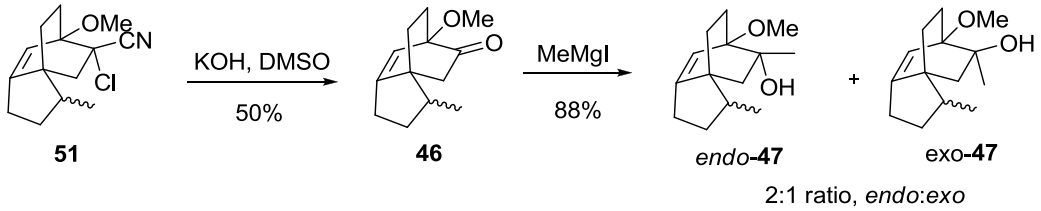
Scheme 8. Retrosynthetic strategy towards the synthesis of sesquithuriferone 1

Accordingly, **45** was subjected to Birch reduction conditions to facilitate the initial partial reduction (**Scheme 9**). Subsequent exposure of the resultant product to KNH_2 in NH_3 provided **50**. Whilst the Diels-Alder reaction that followed showed high levels of regioselectivity, product **51** was once again obtained as a mixture of diastereomers.



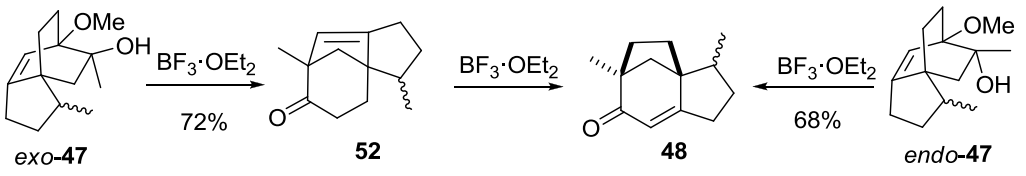
Scheme 9. Synthesis of 51 *via* a Diels-Alder strategy

The conversion of **51** to the ketone **46** proved relatively facile, through hydrolysis in the presence of KOH in DMSO, furnishing the desired product in a yield of 50% (**Scheme 10**). In a change from addition protocols previously examined, the installation of the desired tertiary alcohol was achieved through the use of MeMgI instead of MeLi. Importantly, this subtle change in reagent increased the levels of facial selectivity, with a 2:1 mixture of *endo*:*exo* tertiary alcohols **47** isolated from the reaction mixture.



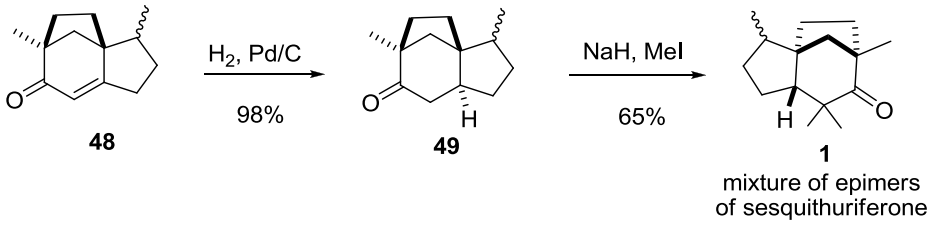
Scheme 10. Synthesis of key tertiary alcohols *endo*-47 and *exo*-47

Following separation of the tertiary alcohols **47** by column chromatography, each of the separate compounds were subjected to $BF_3{\cdot}OEt_2$, under standard conditions (**Scheme 11**). Crucially, a similar and predictable reactivity pattern was observed with *endo*-**47** leading to **48**, whilst *exo*-**47** afforded predominantly **52**. Subsequent treatment of **52** with $BF_3{\cdot}OEt_2$ also proved successful, allowing the majority of the material to be converted to desired compound **48**.



Scheme 11. Lewis acid-promoted rearrangement of tertiary alcohols 47

It is from this point that the synthesis becomes much more concise, when compared to previous attempts (**Scheme 12**). Importantly, catalytic hydrogenation in the presence of Pd/C proved selective, with the hydrogen added exclusively across the α-face, providing **49** in the correct orientation to that required in sesquithuriferone. It was proposed that approach from the β-face of the molecule was unfavoured due to the presence of the ethylene bridging unit. Finally, double alkylation to insert the required *gem*-dimethyl was completed by stirring **49** in a suspension of NaH and MeI to provide sesquithuriferone as a mixture of epimers. Despite the obvious simplification of the synthetic route to sesquithuriferone using this approach, no attempts have been made to date to repeat the described protocols using an enantioenriched form of **45**.



Scheme 12. Completion of the synthesis of sesquithuriferone 1 as a mixture of epimers

2.4.1 Synthesis of 5-epi-Sesquithuriferone

To date, Selvakumar and co-workers are the only research group to have completed a selective synthesises of sesquithuriferone **1**. However, in 2004 Goeke *et al*. reported the successful synthesis of the closely related 5-*epi*-sesquithuriferone **53** (**Figure 6**).[21]

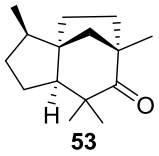
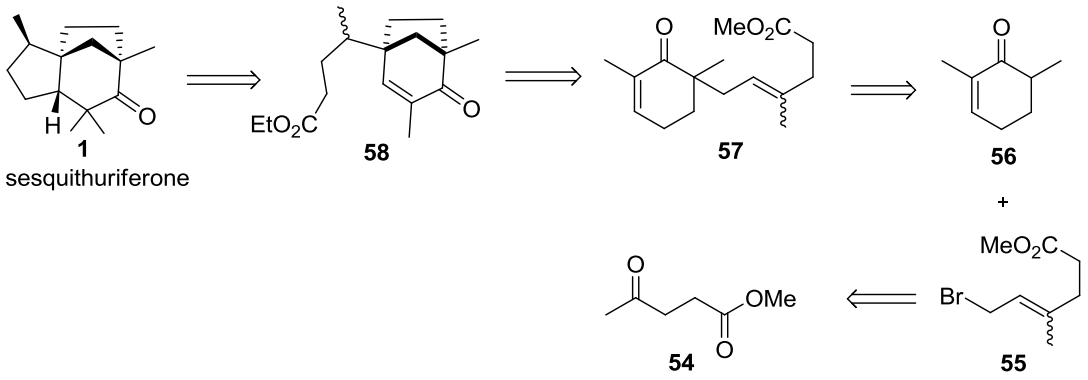


Figure 6. Absolute configuration of 5-*epi*-sesquithuriferone

It should be noted that the synthetic approach followed by Goeke and co-workers was designed towards the total synthesis of sesquithuriferone **1**. Unfortunately, as the synthetic sequence progressed, it became clear that control of the selectivities at certain key points could not be achieved, resulting in 5-*epi*-sesquithuriferone **53** as the major product.

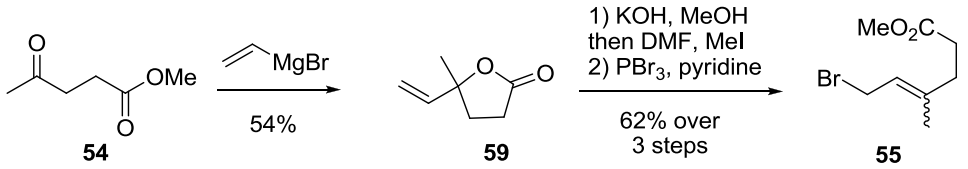
More specifically, the synthetic strategy involved access to the tricyclic core in sesquithuriferone *via* an intramolecular cyclisation from **58**, which in turn could be formed by

an aluminium-mediated rearrangement of **57** (**Scheme 13**). Access to **57** was envisioned through alkylation between **56** and **55**, ultimately synthesised from compound **54**.



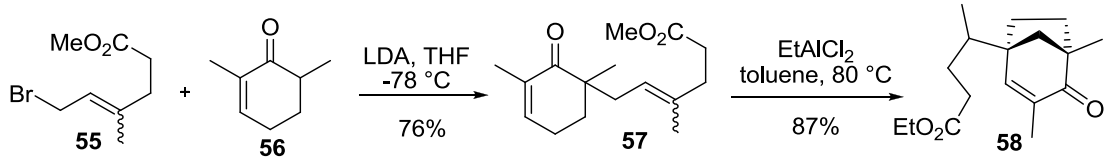
Scheme 13. Synthetic strategy towards the synthesis of sesquithuriferone 1

Synthesis of side-chain **55** involved a three step protocol from commercially available ketoester **54** (**Scheme 14**). The first of these steps involved nucleophilic attack of **54** with vinyl Grignard to form an initial tertiary alcohol, which cyclised *in situ* to provide **59**. Following sequential reaction with KOH and MeI, the corresponding open chain ester was formed, which upon exposure to PBr_3 provided **55**.



Scheme 14. Synthesis of side chain 55

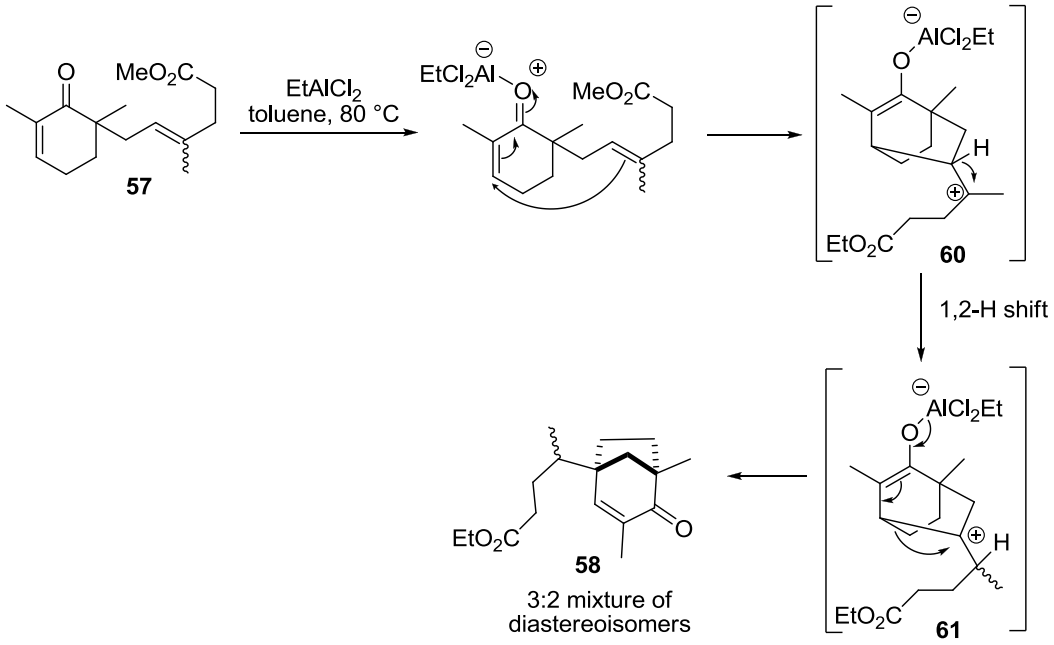
Following the successful formation of the side-chain **55**, subsequent alkylation was achieved through base mediated deprotonation of **56**, followed by addition of **55**, to isolate **57** in a 76% yield. From this point, the proposed cyclisation to form the bicyclo[3.2.1]octane portion of sesquithuriferone in **58** could be pursued. Subsequent exposure of **57** to $EtAlCl_2$ in toluene at 80 °C facilitated the formation of **58** in an 87% yield after purification.



Scheme 15. Synthesis of 58 through sequential alkylation and aluminium-mediated cyclisation

Analysing this key step in more detail reveals that following the co-ordination of the Lewis acidic $EtAlCl_2$ to the enone moiety, the electrophilicity of this functional group is increased

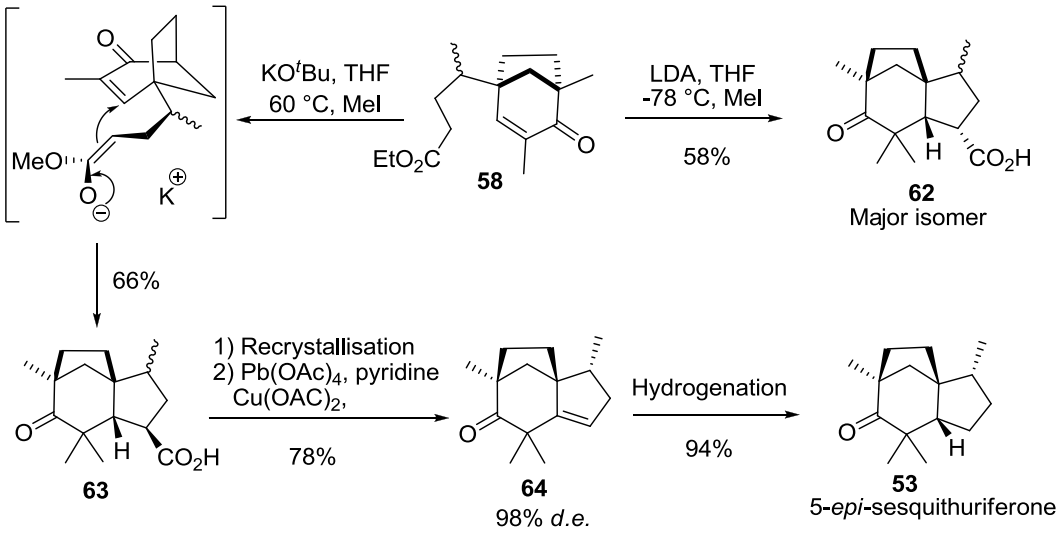
sufficiently to promote the desired 1,4-addition and cyclisation, through a cationic intermediate **60** (**Scheme 16**). Subsequent to the initial cyclisation and prior to the enone moiety reforming, a 1,2-hydride shift occurs to establish the more stabilised carbocation **61**.[22] However, due to this 1,2-hydride shift, the cyclisation is no longer reversible and instead results in the transfer of the alkyl group previously part of the initial six-membered ring, to form a second, kinetically favoured five-membered ring **58**. As expected, little or no selectivity was observed with regard to the methyl on the alkyl portion of the side-chain, with a 3:2 mixture of diastereomers being isolated after purification.



Scheme 16. Proposed mechanism of the aluminium-mediated cyclisation to form 58

Towards the synthesis of **63**, initial attempts to facilitate the base-mediated cyclisation proved somewhat problematic (**Scheme 17**). When the reaction was carried out using LDA, a complex mixture of diastereoisomers was isolated, of which **62** was the major component, containing a *trans* relationship between the ester and the bridgehead hydrogen. However, by switching the base to KO^{t}Bu, a higher level of control could be achieved, with a preferential *syn* relationship obtained as the major component **63**. In an effort to resolve the complex mixture of diastereomers in **63**, a range of crystallisation methods were employed. Towards this aim, the highest levels of enrichment were obtained following fractional crystallisation of the free acid, providing a purity of 98% *d.e.* to be taken forward to for future steps. Subsequent radical decarboxylation of **63** allowed the formation of **64** in a yield of 78%. Surprisingly, however, all attempts to hydrogenate the olefin in **64** resulted in the addition of the hydrogen preferentially onto, what would appear to be, the most hindered face of the

molecule. Despite a wide range of conditions screened, none installed the desired configuration at the bridgehead hydrogen; hence 5-*epi*-sesquithuriferone **53** was isolated as the major product.

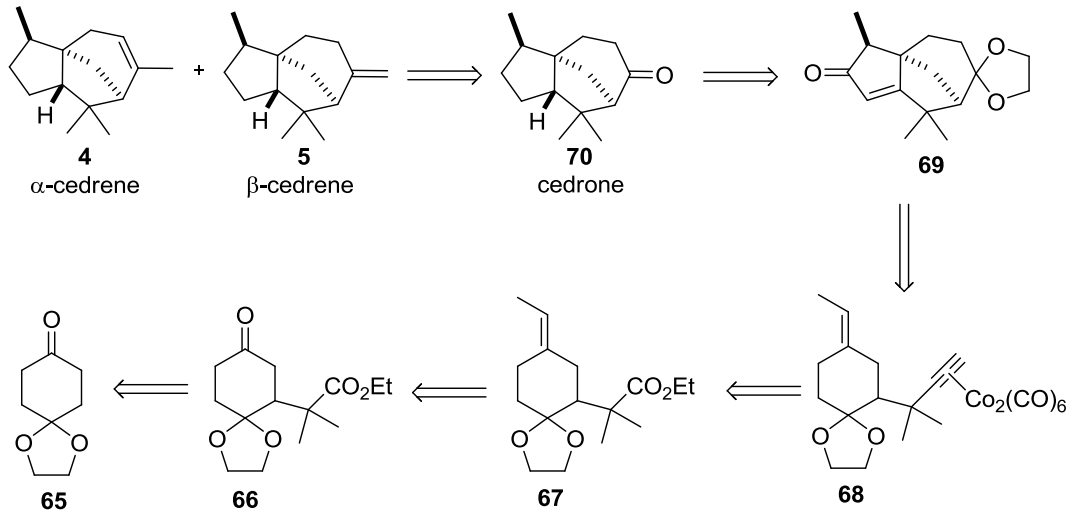


Scheme 17. Synthesis of 5-*epi*-sesquithuriferone 53

To date, no other attempts have been made to synthesise sesquithuriferone within the literature. However, the examples presented highlight just what a challenge it is to achieve the selective synthesis of small, complex natural products. With the aim of adding a novel approach to the published methodologies and improving selectivities at specific points in the syntheses, a Pauson-Khand strategy appeared ideal. Although the proposed approach had as yet not been attempted towards the synthesis of sesquithuriferone **1**, a significant amount of precedent had been established within the Kerr group towards the syntheses of closely related fused ring systems α-cedrene **4** and 2-*epi*-α-cedren-3-one **6**.

2.5 Previous Syntheses of α-Cedrene and 2-epi-α-Cedren-3-one

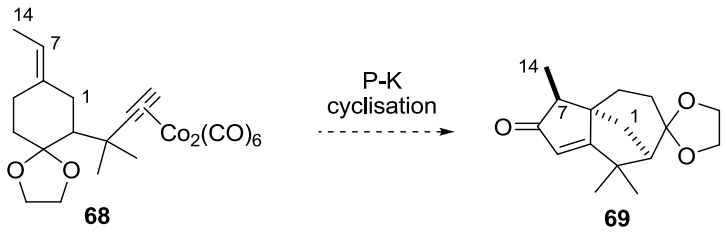
To date there have been several formal syntheses of α-cedrene **4** since the 1950's,[23–25] including one from our own research group.[12,13] The complex fused tricyclic core has proven to be a significant challenge for the development of synthetic methodology, with a variety approaches attempted, including various cycloadditions[26–28] and radical methods.[29] Surprisingly, it was not until 2001 when Kerr and co-workers first demonstrated that the Pauson-Khand (P-K) reaction could be used as an efficient and desirable synthetic strategy towards the synthesis of α-cedrene **4** (**Scheme 18**).[12,13]



Scheme 18. Retrosynthetic strategy towards the synthesis of α-cedrene 4 and β-cedrene 5

Analysing the strategy taken by Kerr and co-workers, it immediately becomes clear that α-cedrene **4**, β-cedrene **5**, and cedrone **70** are all readily accessible from common intermediate **69**, formed by the P-K ring closure of **68**. Importantly, by incorporating the intramolecular P-K reaction at an advanced stage in the reaction sequence, high levels of complexity can be avoided in the early stages of the synthesis, allowing a rapid build up of the basic structural scaffold from a simple and readily accessible starting material **65**.[12,13]

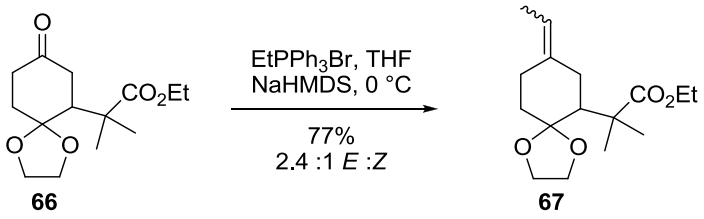
From a synthetic point of view, two key areas were identified as critical to the overall success of this strategy. Firstly, obtaining the desired configuration with respect to the methyl at the C7-position in **69** and secondly, the P-K cyclisation itself, to rapidly build up complexity within the molecule (**Scheme 19**). In the original synthetic sequence devised by Kerr and co-workers, it was proposed that by embedding the desired *E*-geometry in **68** (C14→C1), the *trans*-relationship with respect to the C14 and C1-positions could be maintained in the product, to provide the correct relative orientation of the methyl at the C7-position in **69**.



Scheme 19. Synthesis of 69 by P-K cyclisation

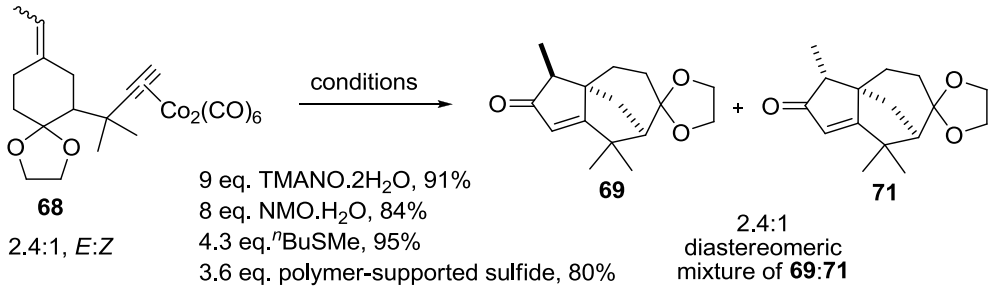
However, before attempting the proposed olefination, it was recognised that controlling selectivity of the olefin presented a major challenge. Looking more closely at ketone **66**, it immediately becomes clear that there was an inherent lack of steric discrimination to develop

selectivity in one direction or the other. Despite this, the authors developed a moderately *E*-selective protocol, providing an inseparable mixture of geometric isomers of **67**, in an *E*:*Z* ratio of 2.4:1 (**Scheme 20**).



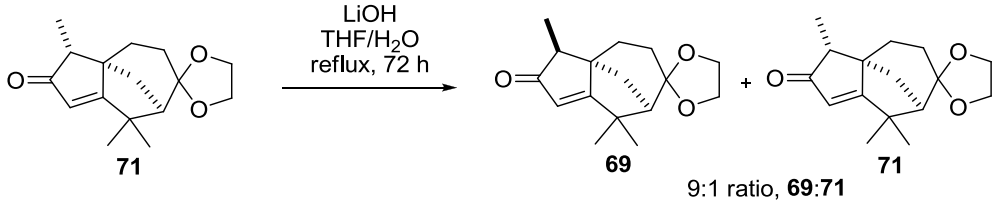
Scheme 20. Synthesis of 67 by Wittig olefination

With the olefin in place, the P-K reaction could be attempted. Following a systematic screening of promoters, optimised conditions were identified, involving the use of sulfide additives (4.3 eq. ^{n}BuSMe), to provide a 2.4:1 diastereomeric mixture of **69** and **71** in an impressive 95% yield (**Scheme 21**).



Scheme 21. Synthesis of 69 and 71 by P-K reaction

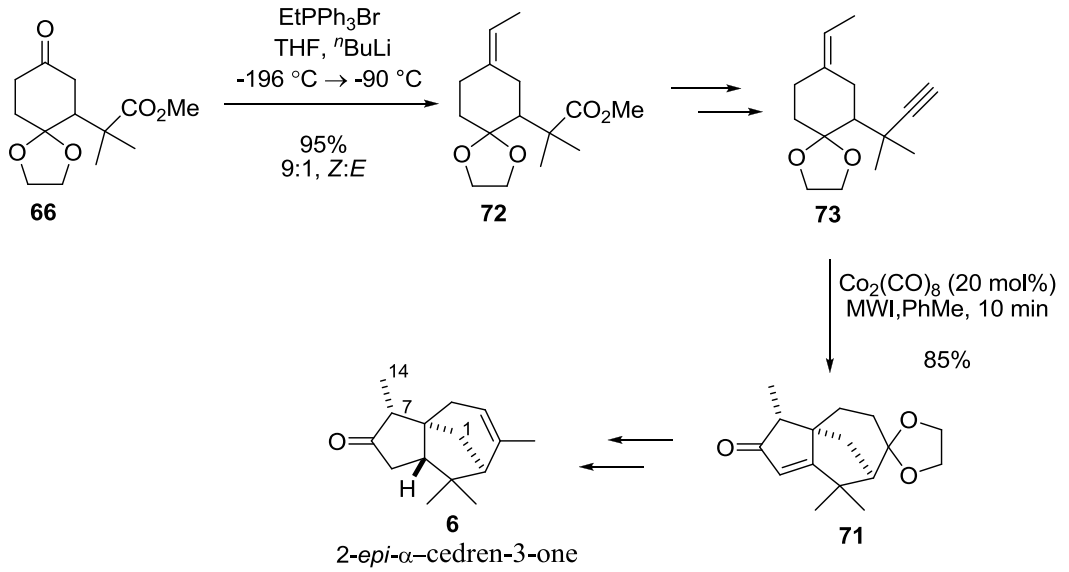
Fortunately, from the stand point of atom economy, Kerr and co-workers were able to develop conditions to allow the effective epimerisation of **71**, to the desired target **69**, ultimately compensating for any loss in olefinic selectivity in the formation of **67** (**Scheme 22**).



Scheme 22. Effective epimerisation of 71 to provide 69

In 2001 Kerr and co-workers successfully completed the synthesis of α-cedrene **4** in an impressive 14 steps, with an overall yield of 11%, clearly demonstrating the significant benefits of the P-K approach towards the synthesis of this complex class of compounds.

Following the successful synthesis of α-cedrene **4**, Kerr *et al*. looked to expand the P-K synthetic strategy to other members of the family of natural products. Towards this aim, the synthesis of 2-*epi*-α-cedren-3-one **6** was completed in 2006 (**Scheme 23**).[14]



Scheme 23. Synthetic strategy towards the synthesis of 2-*epi*-α-cedren-3-one 6

The critical difference between the synthesis of α-cedrene **4** and 2-*epi*-α-cedren-3-one **6** was the reversal of the stereochemistry at the C7-position (**6**, **Scheme 23**). From the outset it was recognised that to provide the opposite orientation, a *Z*-selective olefination of **66** was required to afford **72**. Crucially, despite the lack of steric discrimination adjacent to ketone in **66**, a subsequent temperature study revealed that the *Z*-olefin could be effectively promoted at low temperature, without eroding product conversions (**Table 1**).

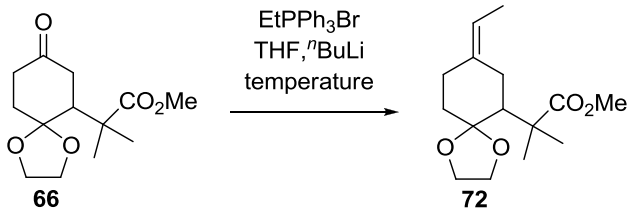
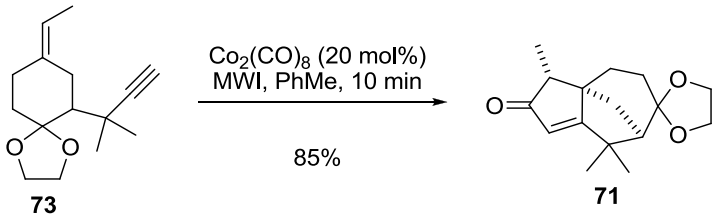


Table 1. Synthesis of *Z*-selective olefin 72 through a low temperature Wittig olefination

Entry	Temperature (°C)	Yield (%)	Selectivity (*Z*:*E*)
1	r.t.	92	2:1
2	-78	99	4:1
3	-196 → -90	95	9:1

As can be seen from **Table 1**, a decrease from room temperature to -78 °C promoted a appreciable increase in the *Z*:*E* ratio from 2:1 to 4:1 (Entries 1 and 2). However, the highest *Z*:*E* selectivities were observed when the reaction was initiated at -196 °C, rising to -90 °C, with a 9:1 ratio being achieved, in an impressive 95% yield.

Crucially, the authors also demonstrated that additional improvements to efficiency of the P-K reaction were possible through the use of microwave promotion (**Scheme 24**). Optimised conditions highlighted that metal loadings as low as 20 mol% could be employed, whilst maintaining a comparable yield of 85%.

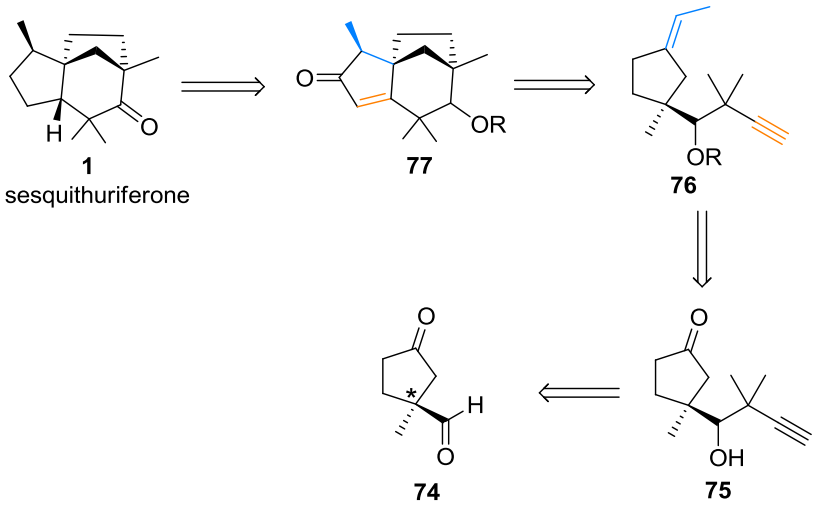


Scheme 24. Catalytic P-K synthesis of 71

It was due to the success of employing a Pauson-Khand strategy towards the synthesis of α-cedrene **4** and-2-*epi*-α-cedren-3-one **6** that we hoped to further expand the number of natural products that this synthetic approach could be used to access. Towards this aim, sesquithuriferone **1** was identified as an ideal synthetic target, containing a [5,6,5]-fused ring system, as opposed to the [5,5,6]-scaffolds previously synthesised.

2.6 Proposed Synthetic Strategy to Access Sesquithuriferone

Following the synthetic strategy previously identified towards the synthesis of α-cedrene **4** and 2-*epi*-α-cedren-3-one **6**, it was envisioned that, once again, complexity could be introduced at a advanced stage in the synthetic sequence using an intramolecular P-K reaction (**Scheme 25**).

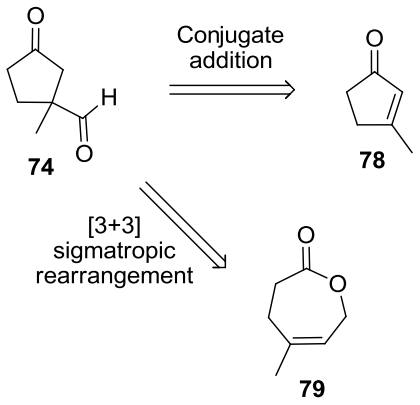


Scheme 25. Synthetic strategy towards the synthesis of sesquithuriferone 1

Accordingly, it was envisioned that sesquithuriferone **1** could be constructed from the enone motif present in **77**, which in turn would be accessible *via* a P-K reaction from **76**. Preparation of **76** was proposed through a *Z*-selective olefination of ketone **75**, ultimately synthesised from the chemoselective addition of the alkynyl side-chain to **74**.

Critical to the success of this proposed strategy were two key areas: firstly, embedding a *Z*-selective olefin in **76** and secondly, from an asymmetric point of view, embedding the correct chiral configuration in **74**, to promote a diastreoeselective P-K reaction. With respect to the *Z*-selective olefination, it was proposed that following the successful implementation of a low temperature protocol in the synthesis of 2-*epi*-α-cedren-3-one **6** (**Table 1**), a similar approach could be pursued to embed the correct geometric isomer in **76**.

Towards the synthesis of compound **74**, both as the racemic and enantioenriched form, two main synthetic approaches were envisioned (**Scheme 26**). The first of these involved the conjugate addition of a masked aldehyde to 3-methylcyclopentenone **78**. This synthetic strategy was expected to be the more concise and selective route, providing the best opportunity of embedding high levels of enantioenrichment in **74**. However, a second and much more elaborate route to **74** was also proposed, involving the transformation of **79** in a three step protocol to form **74**. Key to the success of this approach was a novel [3+3]-sigmatropic rearrangement, as will be discussed in due course. Whilst this route was much more speculative, it would also provide the opportunity to develop methodologies towards the synthesis of novel lactone **79** and keto-aldehyde **74**.

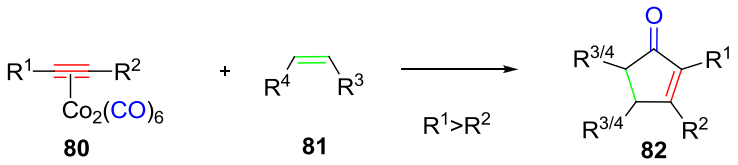


Scheme 26. Proposed strategies to access 74

Having stated the above, and before discussing the specific reaction sequences attempted towards the synthesis of sesquithuriferone **1**, a comprehensive review of the Pauson-Khand reaction was undertaken. With regards to the content of the review, a clear emphasis was placed on the cobalt-mediated P-K reaction. Whilst other metal systems are known within the literature to promote the transformation, our research group have been primarily interested in the development and promotion of the P-K reaction using the $Co_2(CO)_8$ complex.

2.7 The Pauson-Khand Reaction

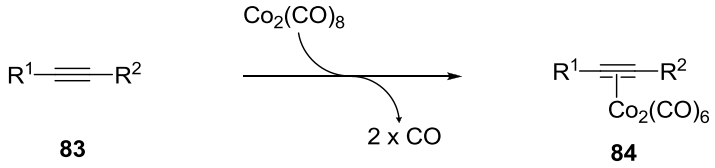
In 1971 Ihsan U. Khand and Peter L. Pauson first reported the synthesis of cyclopentenones *via* a cobalt mediated annulation.[30,31] Formally a [2+2+1] cycloaddition, the Pauson-Khand (P-K) reaction involves the coupling of an alkyne, alkene, and carbon monoxide to furnish cyclopentenones in a single transformation.[32–40] Although initial investigations concentrated primarily upon the usage of stoichiometric amounts of cobalt, as illustrated in **Scheme 27**, subsequent developments have allowed catalytic protocols to be achieved (*vide infra*).[41,42]



Scheme 27. Dicobalt octacarbonyl mediated Pauson-Khand reaction

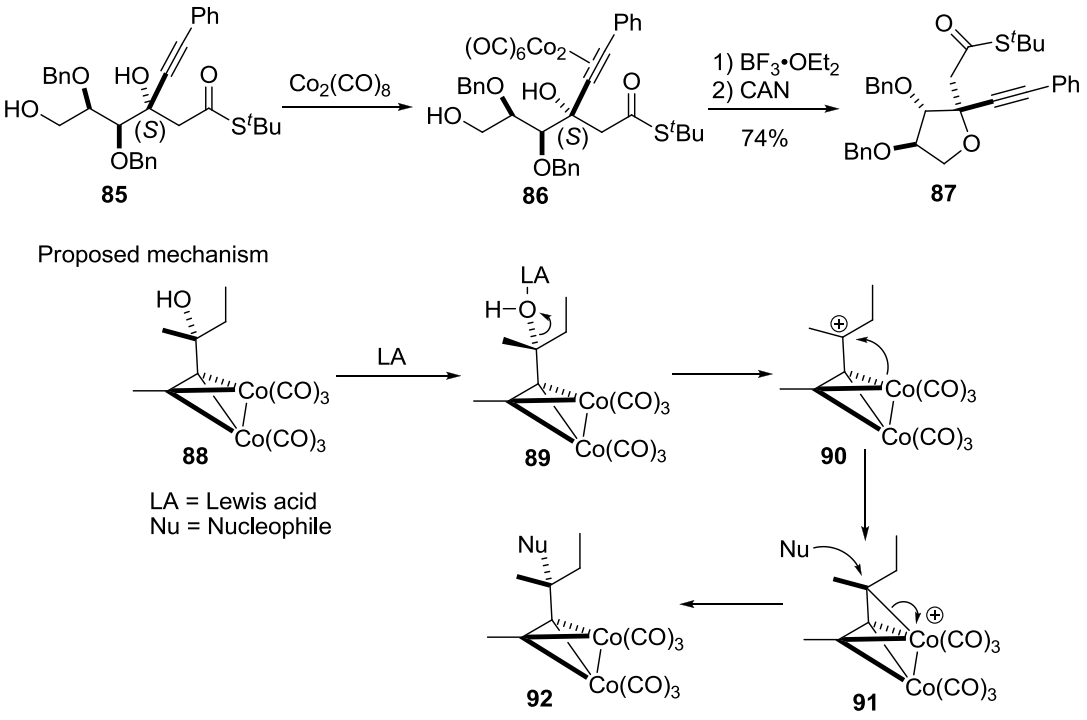
2.8 Alkyne-Cobalt Complexes

Preparation of cobalt complexes such as **84**, can be reliably obtained by stirring alkyne **83** with the octacarbonyldicobalt complex ($Co_2(CO)_8$), generally in an inert solvent, such as petrol or chlorinated media (**Scheme 28**). As the cobalt complex co-ordinates to the alkyne, two bridging carbon monoxide ligands are displaced, forming typically deep red/brown solids or oils.[43]



Scheme 28. Alkyne-dicobalt complex formation

Once formed from this simple procedure, alkyne-cobalt complexes such as **84** have shown remarkable stability; surviving chromatographic purification, indefinite storage under a N_2 atmosphere at -20 ^oC, and short to medium term exposure to air. The stability of the complexes are further exemplified in the Nicholas reaction (**Scheme 29**).[44–46] Crucially, as the reaction progresses, cobalt complex **86** not only survives functional group exchanges, but is also proposed to stabilise cationic intermediates (**90**→**91**) involved in the transformation, without significant degradation.[47]



Scheme 29. Nicholas reaction stabilised by alkyne-dicobalt complexes

In relation to the structure, X-ray crystal analysis of complexes such as **93** has identified two η^2 bridging bonds between the cobalt atoms and the carbons of the alkyne (**Figure 7**). Within the complex, the carbon atoms of the alkyne are observed to have a distorted tetrahedral geometry, whilst each of the individual cobalt atoms assumes a distorted octahedral geometry. As a consequence, the resultant C_2Co_2 arrangement forms a *pseudo*-tetrahedral geometry; with the alkyne carbons arranged perpendicular to the Co-Co bond. Crucially, this means that if the complexed alkyne is unsymmetrical, the two cobalt atoms become enantiotopic and the overall complex becomes prochiral.[48]

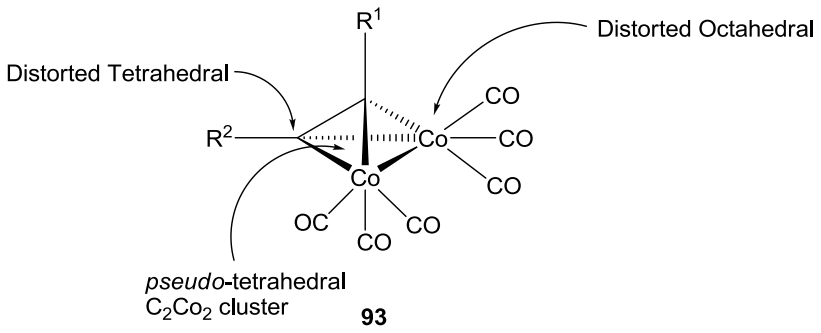


Figure 7. Crystalographic structure of the alkyne-dicobalt complex

At this stage it is important to highlight the critical role that the crystal structure of the alkyne-cobalt complex **93** has played towards the overall understanding of the P-K reaction. It is from this basic model that the fundamentals of subsequent rationalisations have been derived when attempting to explain the complex reactivity observed during product formation.

Beginning with the alkyne component of the complex itself, it is essential to note the changes occurring when moving from the free alkyne state, to that when complexed to the dicobalt system. It was through the understanding of how this subtle change in structural arrangement and electronics occurs, that inferences were made, that begin to explain the observed regioselectivities in isolated products.

The first important characteristic to note is the comparison of the alkyne bonding before and after complexation. Crystallographic studies have shown that C≡C interatomic distances within the complex are increased from ~1.20 Å (typical of C≡C bonding) in the free alkyne, to that of ~1.35 Å after complexation, much closer to that observed in double bonds.[49] This change in bond length is most easily rationalised through the complex metal-alkyne bonding. As the alkyne bonds to the dicobalt system, σ-donation ($\pi \rightarrow d$) from the alkyne into the metal centres promotes complexation. At the same time due to the efficient orbital overlap of the perpendicular complex, simultaneous back donation from the metal to the alkyne ($d \rightarrow \pi^*$) also occurs, reinforcing and strengthening the metal-carbon bonding and stabilising the overall complex.[50] Since back donation from the metal to the alkyne occurs through the π*-orbitals of the alkyne, the overall C≡C bond is lengthened through increased occupancy of the π*-orbital.

A second notable distortion of the alkyne moiety within the complex concerns the observed bond angles. Within the complex, the substituents adjacent to the alkyne moiety deviate from the expected linear arrangement, typical of *sp* bonding. The reasoning behind this effect is much more complex than simple back donation into the π*-orbital of the alkyne, although there appears to be some correlation between the increased deviation from linearity and both the levels of σ-donation and π*-back donation to the alkyne substituent (**Figure 8**).[51]

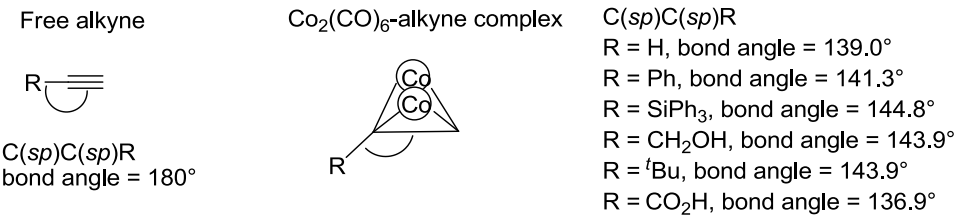


Figure 8. Relative bond angles of various groups within alkyne-Co complexes

Finally, ^{13}C NMR studies of the carbons involved in C-Co bonding show that there appears to be an overall increase in the polarity of unsymmetrical alkynes within the complex. Hence, although the overall complex is stabilised through favourable bonding interactions, the alkyne component appears to be activated towards directed insertion through the increased polarity of the C≡C bond. The extent to which this polarisation occurs is again entirely dependent on the substituents present, but the observed chemical shifts appear to indicate that the larger the electron donation from the substituent to the metal centre, the more deshielded the alkyne carbon becomes.[51]

Up to this point it is clear that the alkyne component within the complex is substantially affected by the extent of alkyne-metal bonding. However, it is also important to note that the bonding within the cobalt component is also subtly changed through this complex bonding arrangement. IR spectral analysis of complexes such as **93** have shown that the observed C≡O stretches are in fact nonequivalent and that the relative position of the CO ligand within the complex directly affects the strength of the observed C≡O bond. It is important to note that σ-donation from the alkyne component of the complex is thought to increase the relative back donation to the CO ligands, strengthening the CO-metal bond and making them harder to remove. Redrawing complex **93** as **94** or **95** illustrates that there are two distinct CO environments within the complex, that of *axial* and *equatorial* positions (**Figure 9**).[52,53]

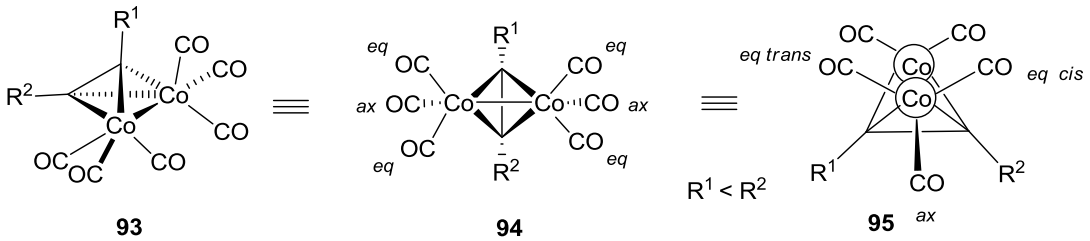


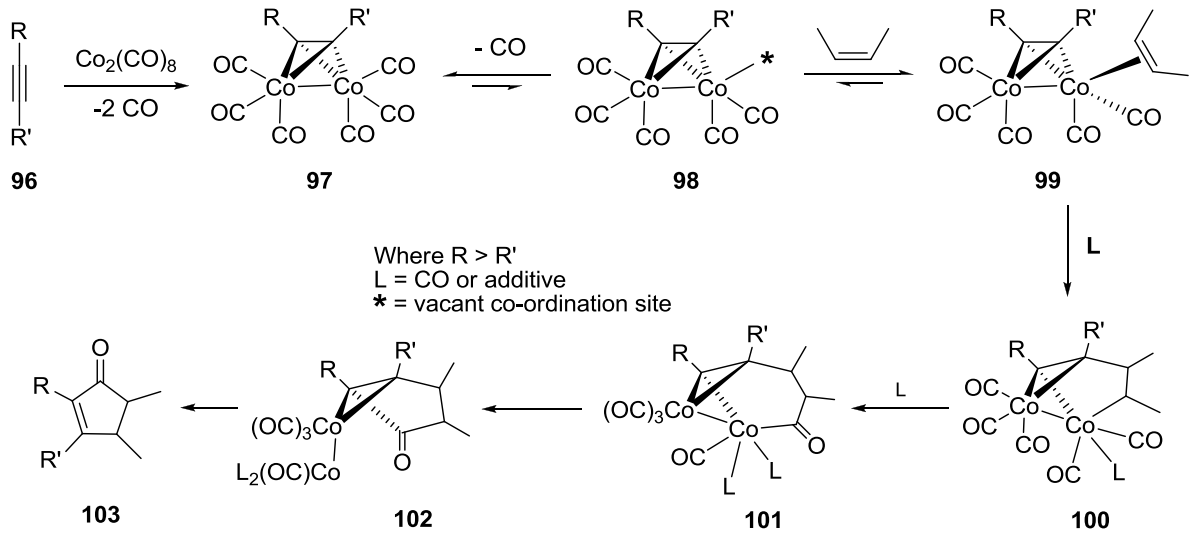
Figure 9. Alternative representations of the dicobalt-alkyne complex

The two distinct environments are a direct consequence of the *pseudo*-octahedral geometry around the central cobalt atom. Furthermore, due to steric interactions and relative back donation within the complex, the *equatorial* positions can be further subdivided into

equatorial cis and *trans* with respect to the higher priority substituent present on the alkyne moiety. Whilst IR studies cannot identify directly which of the CO ligands are affected most by complexation, inferences can be made using DFT computational studies and by monitoring the substitution of CO ligands for Lewis basic additives.[54] The relative ease with which each of the CO ligands can be substituted has direct consequences towards regioselectivity, as will be discussed in **Section 2.10**. Current understanding would suggest that the two *equatorial* positions are more labile than the *axial* position, especially that of the *trans equatorial* CO ligand. However, crystallographic studies of substituted complexes, seem to contradict this, indicating that substitution of CO ligands for Lewis basic compounds, such as phosphines, occurs preferentially at the *axial* position.[49]

2.9 Reaction Mechanism

The conclusive mechanism involved in P-K reaction remains as yet elusive, though in 1985 Magnus proposed the generally accepted mechanism, as shown in **Scheme 30**.[55]

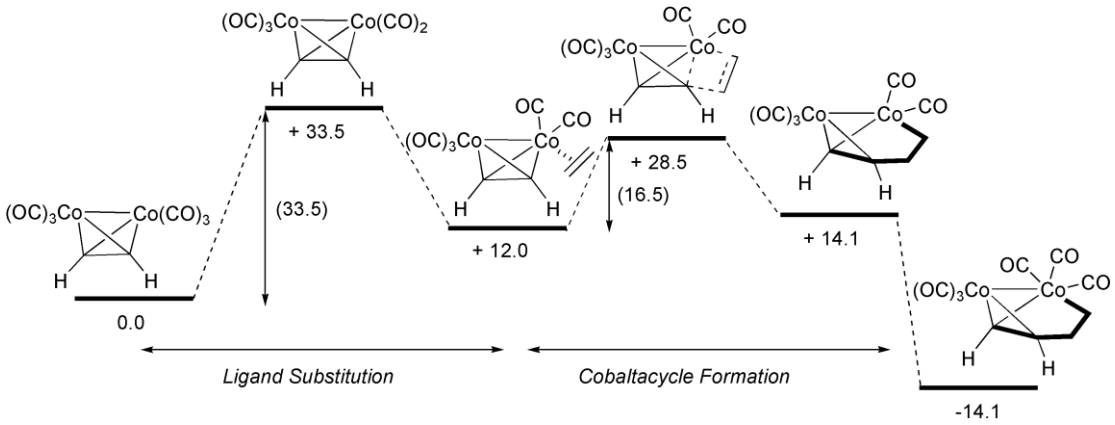


Scheme 30. Proposed mechanism of Pauson-Khand reaction

Starting from the hexacarbonyl complex **97**, the initial step in the reaction mechanism involves the endothermic loss of a CO ligand to form complex **98**. This step is thought to be an equilibrium process favouring the co-ordinatively saturated complex **97**. As dissociation of a CO ligand occurs in complex **97**, a vacant co-ordination site is exposed, which can be reversibly occupied by an alkene, forming complex **99**. Alkene co-ordination was proposed to occur *trans* to the larger group and *cis* to the smaller substituent present on the alkyne, hence developing the regioselectivity observed in product formation with respect to the alkyne

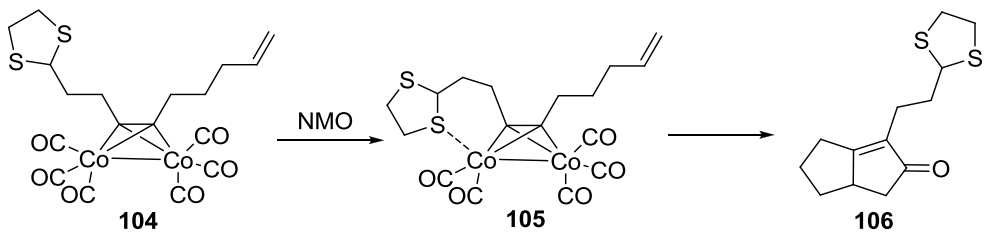
moiety (*vide infra*). From complex **99**, the formation of intermediate **100** is achieved *via* alkene insertion into the alkyne carbon-cobalt bond with the least steric hindrance. Subsequent CO insertion allows the formation of carbocycle **101**, followed by reductive elimination to form **102**. Finally, decomplexation of the cobalt complex furnishes the desired cyclopentenone **103**.

It should be noted that, throughout the description of the reaction mechanism no mention was made of the rate determining step. This is due to the fact that it may change depending on the reaction conditions. With regard to the thermal reaction, DFT calculations have proposed that the loss of CO to form **98**, requires the largest amount of energy in a single step and is the slowest step (**Scheme 31**).[56–58] However, the use of additives may in fact alter the equilibrium and hence change the rate determining step to that of the alkene insertion **100** (*vide infra*).



Scheme 31. DFT analysis of the P-K reaction, Pérez-Castells *et al.*[59]

At present, few, if any, of the reaction intermediates have been isolated and conclusively identified. However, over recent years several pieces of evidence have been discovered to support the described mechanism. In 1993, Krafft and co-workers provided the first structural evidence to support the initial dissociation of a CO ligand. During studies towards the directed intramolecular P-K reaction, the authors isolated an alkyne-$Co_2(CO)_5$ complex **105**, stabilised internally by the alkyl side-chain containing a sulfur atom (**Scheme 32**).[60]



Scheme 32. Structural evidence for CO dissociation in P-K reaction

Further isolation and characterisation of alkyne-$Co_2(CO)_x$ complexes has proven a significant challenge to many groups, due to the inherent instability of the co-ordinatively unsaturated intermediate. However, some success has been accomplished using alternative techniques, such as IR and mass spectroscopy **107** (**Figure 10**).[53,61]

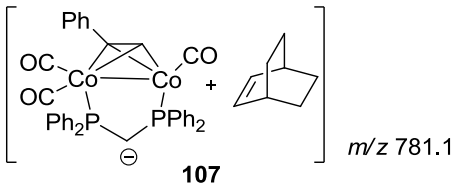
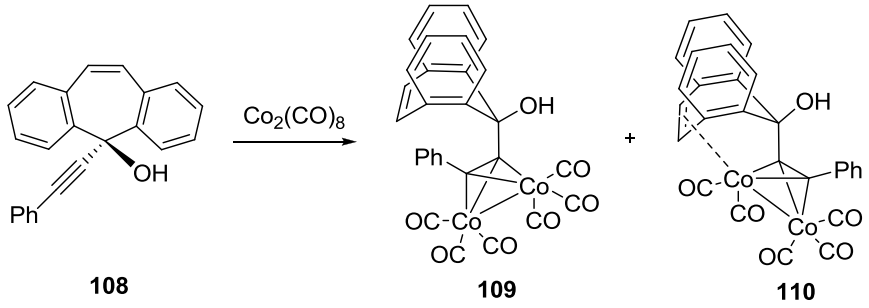


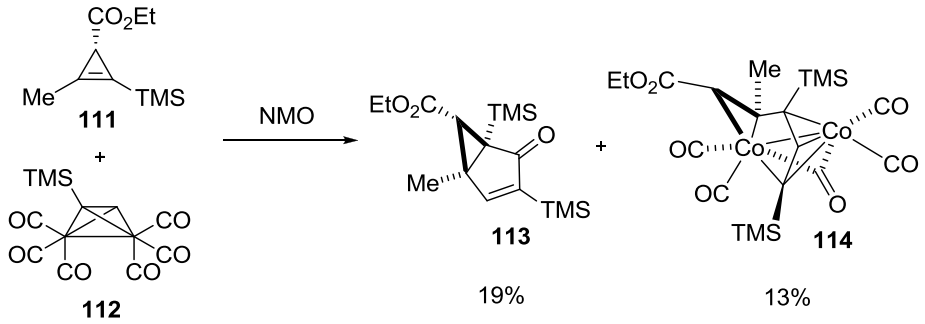
Figure 10. Mass spectroscopy evidence for alkene co-ordination

More recently, Evans and McGlinchey reported the X-ray crystal structure of **110**, an alkyne-$Co_2(CO)_5$ complex involving an intramolecular coordinated alkene (**Scheme 33**).[52] Whilst intermediate **110** lends weight to the proposed co-ordination of alkenes following CO dissociation, the inherent structural arrangement prevents further reaction to allow alkene insertion.



Scheme 33. Structural evidence for alkene co-ordination

Finally, a recent publication by Pallerla and co-workers has elucidated the first proposed intermediate **114** involving alkene insertion (**Scheme 34**).[62]

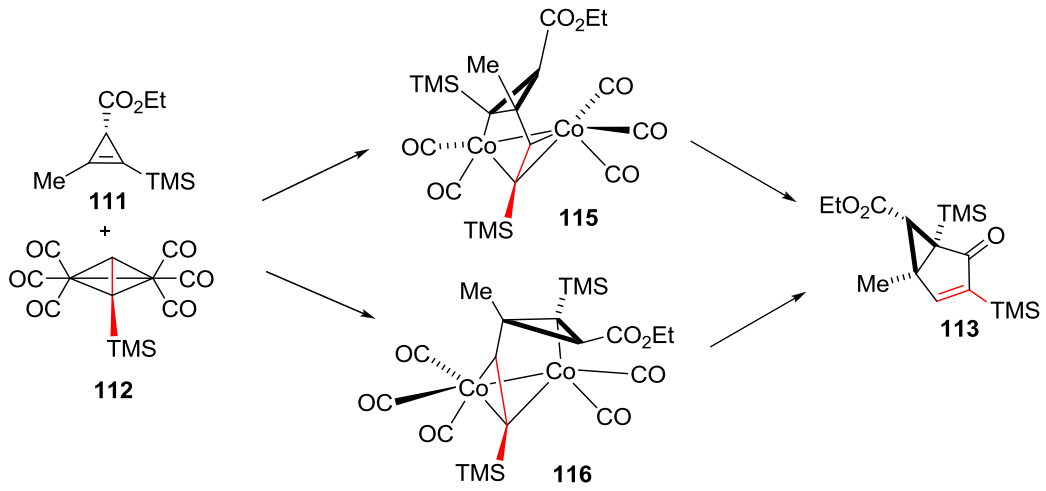


Scheme 34. Products isolated from the intermolecular P-K reaction of 111 and 112

The authors reported the unexpected isolation of **114** during investigations towards the intermolecular P-K reaction of **111** and **112**. Following the general mechanism proposed by

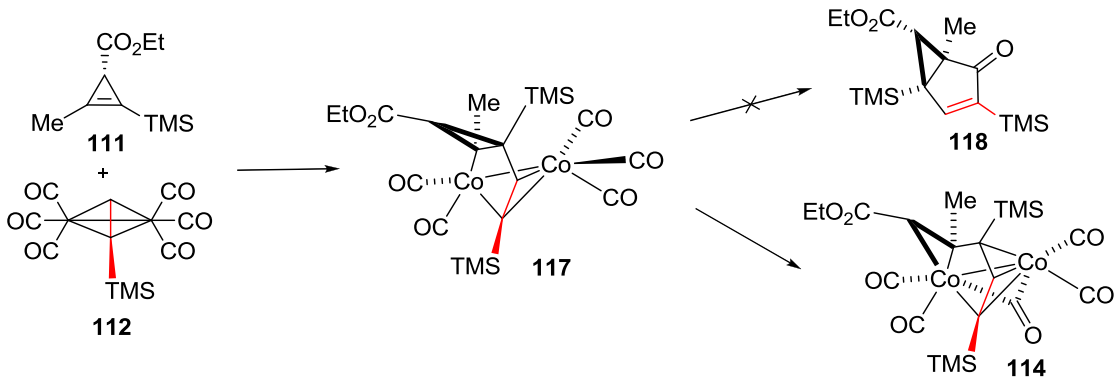
Magnus in **Scheme 30**, the authors state that the formation of **113** and **114** can be depicted as shown in **Schemes 35** and **36**.

With respect to product **113**, following CO dissociation in **112**, alkene co-ordination can occur, in the form of a cyclopropene unit **111**. Subsequent alkene insertion at the least hindered carbon of both the alkene and alkyne components, leads to one of two possible intermediates **115** and **116**. Following this, carbonylation, reductive elimination and decomplexation reveals the expected cyclopentenone product **113** (**Scheme 35**).



Scheme 35. Proposed mechanism towards the formation of 113

However, if regioselectivity was reversed with regard to the alkene component, **114** was formed preferentially (**Scheme 36**).



Scheme 36. Proposed mechanism towards the formation of 114

It was suggested that just as with the formation of **113**, the first two steps of the mechanism proceeded according to the pathway predicted by Magnus, involving CO dissociation and alkene co-ordination. However, following insertion of **111** at the most hindered carbon of the alkene component to form **117**, instead of the reaction following the normal pathway to form regioisomer **118**, an unexpected fragmentation of the cyclopropene unit occurs, leading to the

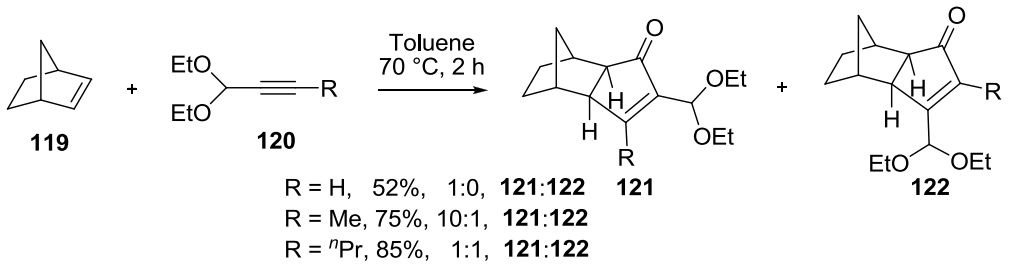
formation of **114**. Whilst the conclusive rational behind this unexpected fragmentation has not been fully elucidated, it was proposed that an inherent stabilisation of the α-carbon adjacent to the silyl group may be responsible.[63]

To date, no further reaction intermediates have been conclusively identified. This is due to the fact that CO dissociation and alkene insertion are the steps requiring the highest activation energy. Accordingly, following alkene insertion, subsequent steps progress largely exothermically, rendering isolation of further intermediates extremely difficult (**Scheme 31**).

2.10 Regioselectivity in the P-K Reaction

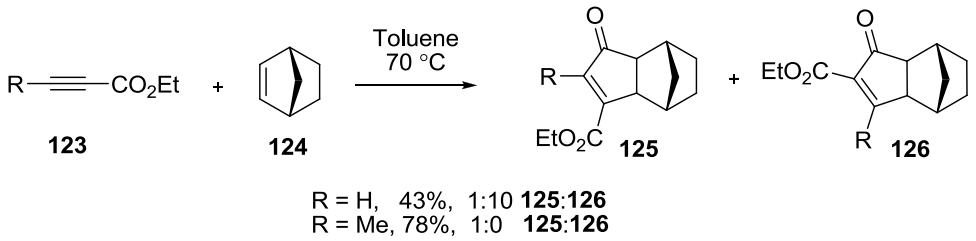
2.10.1 Alkyne Component

In general, the regioselectivity of the P-K reaction is highly predictable with regard to the alkyne component. In most cases, the larger of the two substituents present in the molecule will be incorporated adjacent to the carbonyl of the developing cyclopentenone. It is thought that sterics are the overriding factor determining the observed selectivity, with alkenes such as **119** inserting into the carbon with least hindrance (**Scheme 37**).[64,65]



Scheme 37. Regioselectivty with regard to alkyne component

However, where there is little differentiation in sterics between the two substituents, mixing of alkyne regioselectivity is expected to occur. The most notable examples, where a reversal in regioselectivity has been observed, are when strongly electron-withdrawing substituents are present on the alkyne. As shown in **Scheme 38**, the observed reversal of regioselectivity may suggest that, whilst sterics are typically the overriding factor determining regioselectivity, electronics may also play a role in determining product formation.[66]



Scheme 38. Reversal of regioselectivity due to electron-withdrawing substituents

In an attempt to further rationalise the observed regioselectivity with regards to the alkyne component, many groups have revisited the proposed reaction pathway. In this regard, DFT computational studies have proven extremely useful when attempting to quantify the energetics and determine the order of each of the individual steps within the reaction. It is with this additional computational information that a re-evaluation of the proposed mechanism has been attempted.[56–58]

As previously stated, the CO ligands within the complex are apparently non-equivalent in terms of IR stretching frequency. This indicates that each of the CO ligands are subjected to a varied amount of back donation from the cobalt atoms, depending on their relative position within the complex. The direct consequence of this is that the greater the extent of back donation to the CO ligand, the longer the C≡O bond and hence the stronger the metal-carbon bond to the CO ligand. As the strength of the metal-carbon bond increases between the complex and the CO, exchange of this ligand becomes less facile and hence less activated towards potential substitution with an alkene component.

DFT studies have indicated that, energetically, the two *equatorial* CO ligands incur a lower energy barrier to elimination than the *axial* CO ligand within the complex. As a direct consequence of this, the *equatorial* CO ligands are more likely to be substituted by an alkene, in the first step of the reaction pathway. Importantly, DFT studies have also indicated that the *trans equatorial* CO ligand is the most labile of the two *equatorial* positions, although there appears to be little difference in energy compared to that of the *cis equatorial* CO ligand.[67] It is at this stage that the effects of sterics reinforce the proposed electronic factors in determining the regioselectivity. Accordingly, alkene co-ordination and insertion is more favourable adjacent to the alkyne carbon containing least steric hindrance **127** (**Figure 11**).

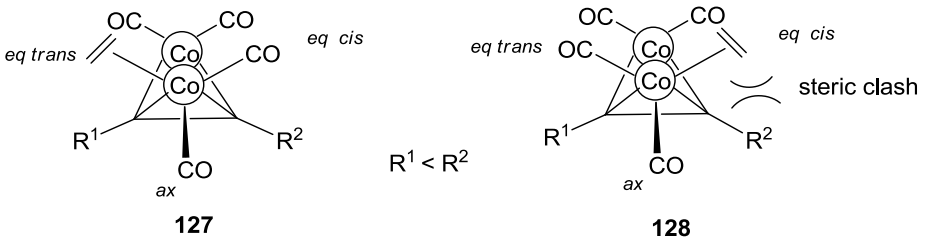


Figure 11. Preferential co-ordination and insertion of alkene in the *trans-equatorial* position

It is important to note that, whilst DFT calculations have provided a quantifiable insight into the relative ease with which each of the CO ligands can be removed from the complex, the mechanism of how this effect is generated is as yet not fully understood. In 2001 Greene and co-workers suggested that it may be due to a *trans*-effect.[68] In that case, back donation to the alkyne component, occurring through the d x^2-y^2 orbitals, simultaneously weakens the bonding to the *pseudo equatorial* CO ligands and hence induces the CO ligands to be more labile **129**-**130** (**Figure 12**). This overall effect is important, as it may well explain the electronic bias determining the reversal in product regioselectivity, when electron-withdrawing substituents are present on the alkyne moiety.

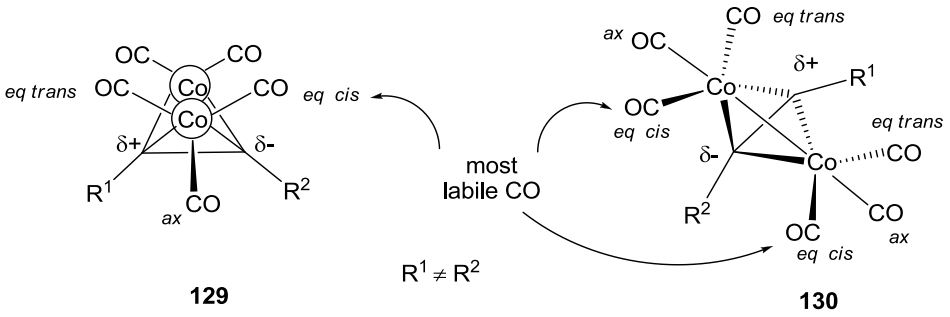


Figure 12. Relative position of most labile CO due to *trans*-effect

In a follow up paper, Greene and co-workers proposed that an alternative *axial* pathway may also be in action.[58] In this regard, it was proposed that although the CO ligands are more labile in the *equatorial* positions, the barrier to *pseudo*-rotation within the complex is relatively low, opening up the possibility of alkene co-ordination occurring in both the *equatorial* and *axial* positions. In fact, when comparing energetics of the various pathways, DFT calculations would suggest that alkene insertion may be more facile from the *axial* position. Furthermore, from the *axial* position, steric discrimination again determines the favourable insertion of the alkene component into the least sterically hindered alkyne carbon **132** (**Figure 13**).

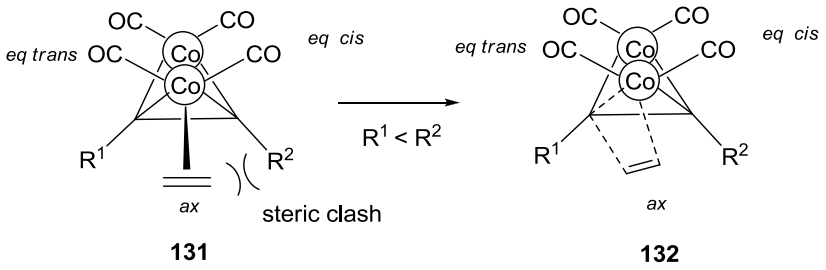
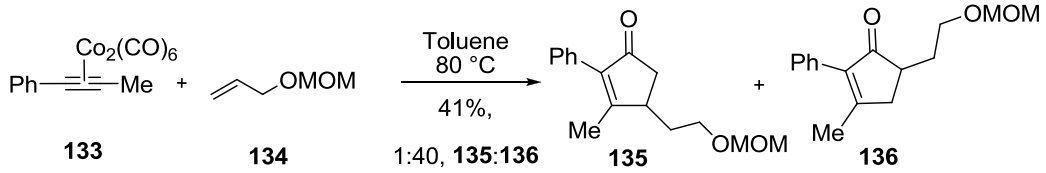


Figure 13. Alternative *axial* pathway

Whilst DFT studies have provided a significant step forward in the understanding of the P-K reaction, they also clearly highlight the levels of complexity involved when attempting to understand the reaction pathway in the absence of known intermediates.

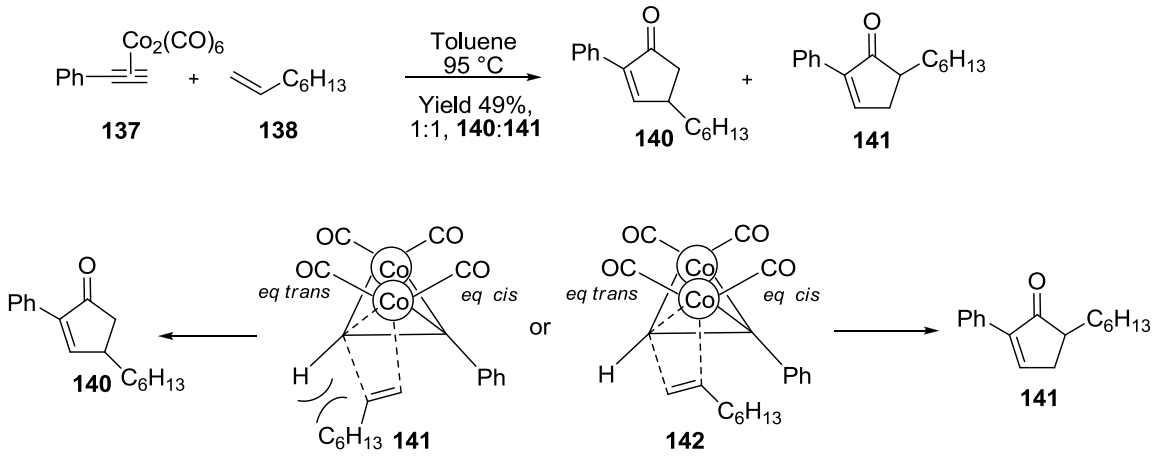
2.10.2 Alkene Component

Regioselectivity is much harder to predict with regard to the alkene component. At the outset it was envisioned that sterics should play a pivotal role in regioselective discrimination. However, alkene regioselectivity is not simply dependent on the substitution pattern of the alkene, but also the alkyne portion. In the example shown, a product mixture of 1:40 **135**:**136** was isolated, following the P-K reaction between **133** and **134** (**Scheme 39**).[69] Importantly, in this case, regioselectivity could be achieved due to the steric bulk present on the internal alkyne. However, as the sizes of the substituents present on alkyne are reduced, a significant mixing of alkene regioselectivity is expected to occur.



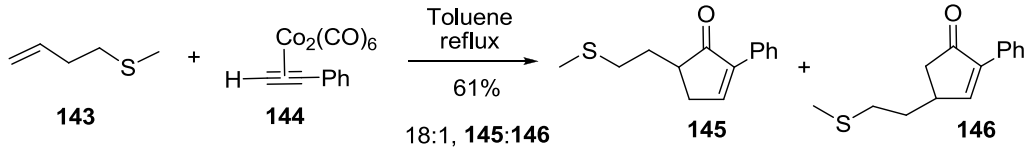
Scheme 39. Alkene regioselectivity in the P-K reaction.

This effect is especially pronounced in terminal alkynes such as **137**, where the structural differences within the alkyne may not be significant enough to induce the predicted steric clashes to control insertion, resulting in 1:1 mixtures of products **140** and **141** (**Scheme 40**).[70]



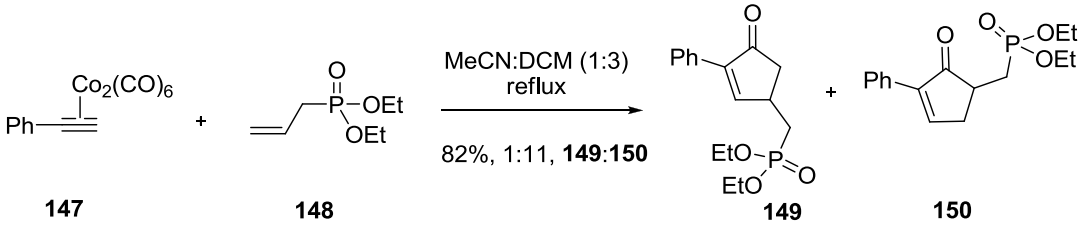
Scheme 40. Regioselectivity with regard to the alkene component

In an attempt to counteract this obvious shortcoming, Krafft and co-workers investigated the use of secondary interactions as a means to control regioselectivity. During their investigations, the authors demonstrated that *homo*- and *bishomo*-allylic sulfide alkenes, such as **143**, almost exclusively formed cyclopentenones, with the heteroatom containing substituent α- to the developing carbonyl **145** (**Scheme 41**).[69,71,72]



Scheme 41. Use of secondary interactions to promote regioselectivity in the P-K reaction

Following the success of this approach, a range of Lewis basic directing groups have been successfully employed, including allyl phosphonates such as **148** (**Scheme 42**),[73] extended phosphonates,[74] and amines[75].



Scheme 42. Allylphosphonate alkenes as directing groups in the intermolecular P-K reaction

To explain this change in regioselectivity, Krafft proposed that a direct co-ordination of the lone pairs, present on Lewis basic groups, was occurring to the cobalt complex. This tethering effect could then direct the alkene for insertion through a preferred orientation within the complex. Evidence for a similar mode of action had already been established through analysis of substituted alkyne complexes containing heteroatoms, such as that shown in complex **104**.[60]

With regard to **104**, crystallographic analysis demonstrated that the co-ordination of the sulfide provided a stabilising effect on pentacarbonyl complexes (**Figure 14**). However, in the case of allylic sulfides, it was clear that coordination of these substrates could occur though one of two possible intermediates, **151** or **152**. Although the structural arrangement in **151** appears to be entirely feasible, current understanding would suggest that mononuclear **152** is most likely to be the reactive species, where there are no physical constraints disfavouring this arrangement.[60,72]

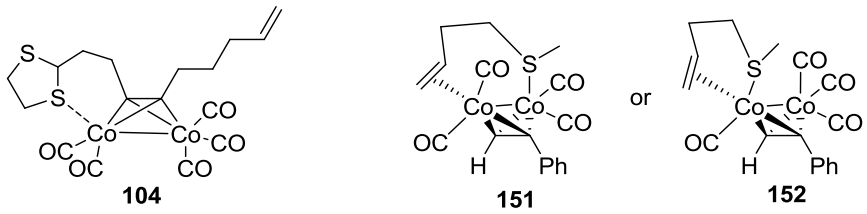
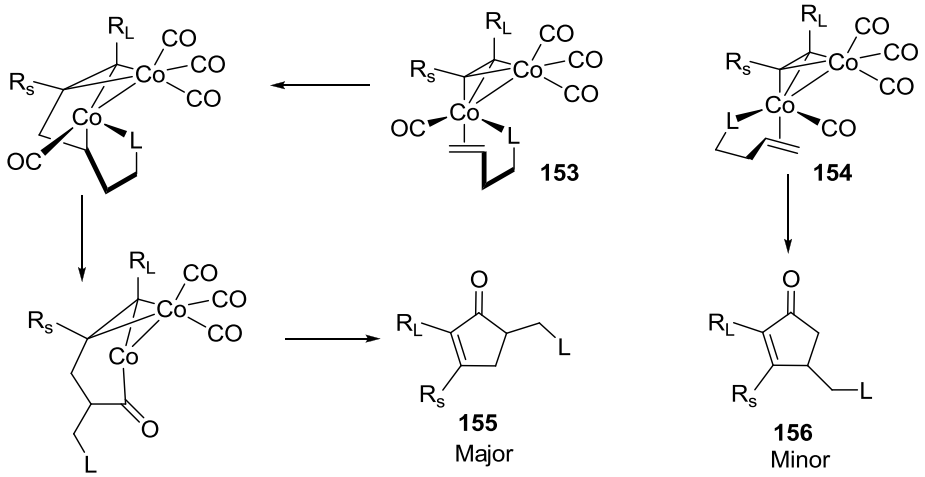


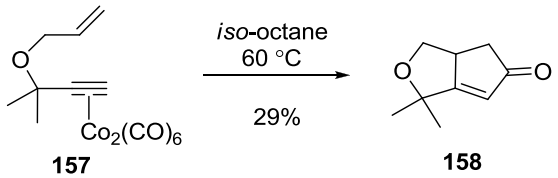
Figure 14. Proposed intermediates involving sulfide containing alkene substrates

Furthermore, Krafft proposed that key to the high levels of selectivity was not only the formation of **152** (**Figure 14**), but also the conformation that the allyl side-chain adopted within the complex itself. From this perspective, the preferred orientation of the allyl side-chain was proposed to be that of intermediate **153**, due to physical and steric constraints (**Scheme 43**).[73]



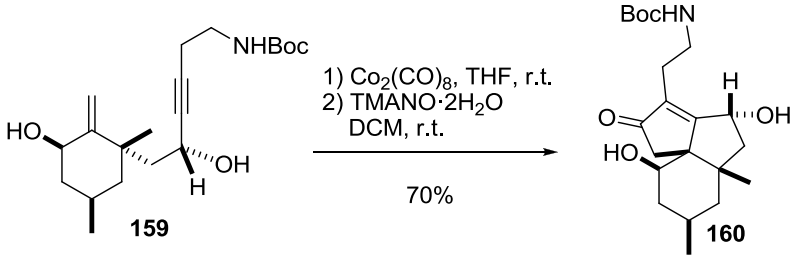
Scheme 43. Proposed mononuclear bidentate arrangement to induce regioselectivity

In general, all issues regarding regioselectivity can be resolved through tethering of the alkene component to the alkyne such as in **157** (**Scheme 44**).[76,77] In this case, structural constraints within the molecule dictate that only one regioisomer can be formed, that of **158**. The clear benefit of this approach is that, not only can a highly controlled and predictable product be formed, but also that the alkyne regioselectivity can be reversed comparative to the intermolecular variant, through the synthesis of a suitable precursor **157**.



Scheme 44. Intramolecular P-K reaction

From a synthetic point of view, the intramolecular P-K reaction has proved to be one of the most important of the early reaction developments. Through incorporation of this strategy relatively rapid access to complex fused ring substrates can be achieved in a single transformation (**Scheme 45**).



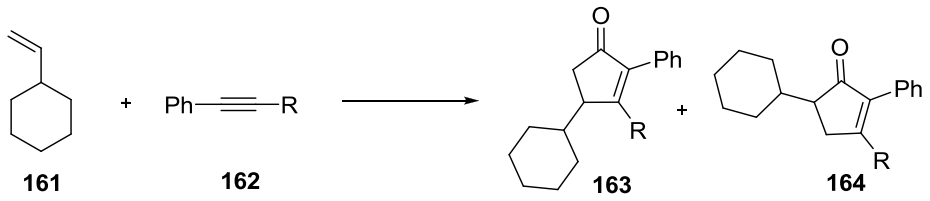
Scheme 45. Synthesis of 160 by intramolecular P-K reaction

In the example shown above, Hoshino and Ishizaki successfully utilised the intramolecular P-K reaction on an internal alkyne **159**, towards the formal total synthesis of Magellanine.[78] Through implementation of the intramolecular P-K reaction, Hoshino and Ishizaki managed to develop an angular fused tricyclic system containing three contiguous chiral centers in a single step.

2.11 General Reactivity of Alkyne and Alkene Components

When designing a synthetic strategy involving a P-K reaction, it is always important to consider the inherent reactivity of both the alkene and alkyne components. In general terms, there does appear to be a subtle change in reactivity, with regards to each component, depending on both the substitution and strain present within the starting materials.[33,34]

With regard to the alkyne portion of the P-K reaction, internal alkynes often appear to exhibit a reduction in reactivity, comparative to the equivalent terminal alkyne system (**Table 2**).[69]



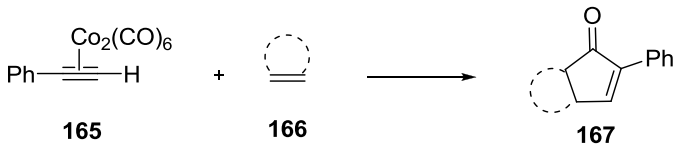
161 162 163 164

Table 2. Reactivity profile of alkynes in the P-K reaction

Entry	R	Yield (%)	Product ratio (**163**:**164**)
1	H	45	1:2.5
2	Me	22	0:1

In the example shown, it was observed that by moving from the terminal alkyne, to the corresponding internal alkyne, a significant reduction in conversion is observed, from 45% to 22% (**Table 2**, Entries 1 and 2). This apparent change in substitution accounts for approximately 50% reduction in reactivity, simply by adding in the extra substituent onto the alkyne component. Whilst this apparent reduction in reactivity initially appears to significantly limit the potential substrate scope of the P-K reaction, any loss in reactivity can often be compensated by employing an intramolecular variant, extending the reaction times, or through the addition of a range of reaction promoters (*vide infra*).

With regards to the alkene component, a similar reactivity pattern is observed, with the least substituted alkenes generally showing the highest reactivity. Furthermore, a recent study by Millet and co-workers has identified a link between the reactivity of the alkene component and both the strain and bond angle generated within the starting material.[67] During their investigations, the authors observe that as the bond angle within the alkene molecule decreases, an apparent increase in reactivity is observed, through lowering of the LUMO energy of the alkene starting material. This observation goes some way to explaining the high levels of reactivity of strained cyclic alkenes such as norbornene derivatives. The results in **Table 3** illustrate that as the bond angle of 107° in norbornene was increased to 128° in cyclohexene, a significant increase in the LUMO energy is observed, corresponding to an appreciable reduction in overall conversions from 59% to 3% yield (**Table 3**, Entries 1 and 3), albeit under a variety of differing reaction conditions.



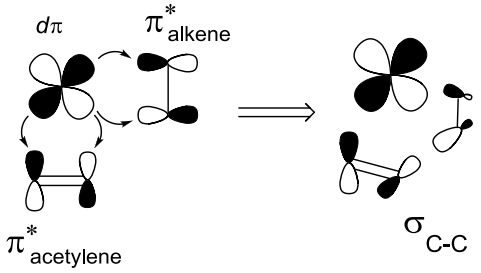
165 166 167

Table 3. Reactivity of various cyclic alkenes in the intermolecular P-K reaction

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

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

DFT calculations have attributed this lowering of the energy of the LUMO and subsequent increase in reactivity, to the fact that alkenes such as norbornene participate in a larger degree of back donation through the π*-orbitals.[57,67] It is believed that this results in a better match of HOMO-LUMO orbital energy levels, increasing their overall reactivity towards alkene insertion. The LUMO (π*-orbital) of the olefin is particularly important, since it is not only involved in back donation from the cobalt complex **168**, but also involved in the formation of the new C-C bond in cobaltacycle **169** (**Figure 15**).

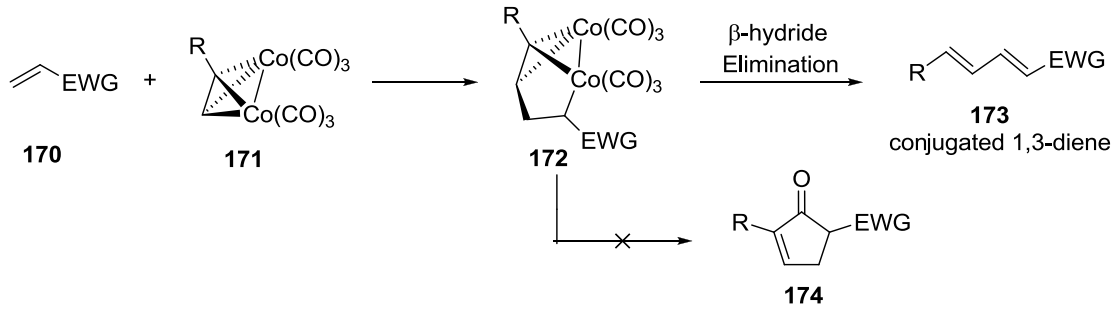


168 169

Figure 15. Orbital interactions during P-K cyclisation

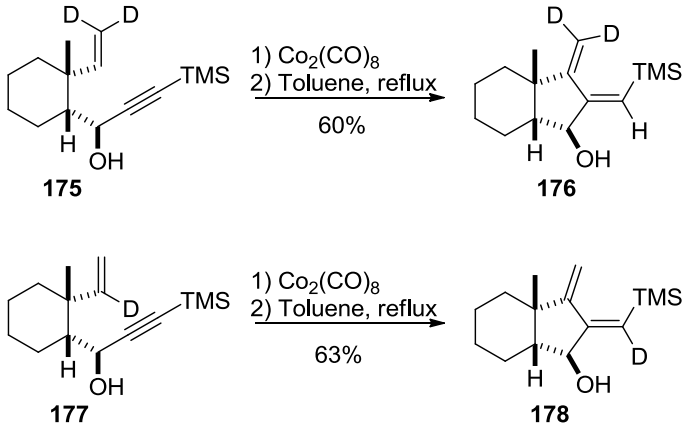
2.11.1 1,3-Conjugated Diene Products

Of all the alkene systems investigated with regard to the P-K reaction, electron-deficient alkenes have proven to be some of the most problematic (**Scheme 46**). Frequently, when these substrates are involved, complex mixtures of products are isolated, of which 1,3-conjugated dienes **173** are often the major component. In these cases, it would appear that a competitive β-hydride elimination pathway is significantly faster than the desired carbonylation step to form the desired cyclopentenone **174**.[79]



Scheme 46. Reactivity of alkenes containing electron-withdrawing substituents in the P-K reaction

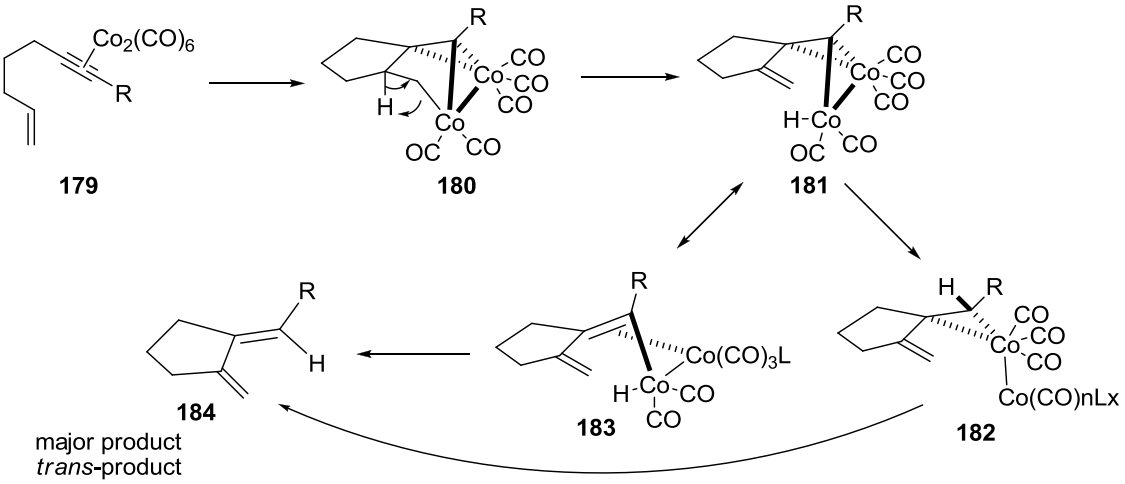
However, despite the fact that 1,3-conjugated dienes are widely accepted as being formed through a β-hydride elimination pathway, the exact mechanism remains as yet unclear. In an effort to elucidate the mechanism, Krafft designed a series of deuteration experiments involving compounds **175** and **177** (**Scheme 47**).[80] It was envisioned that by analysing the different products formed, the resulting positions of the deuterium would help to develop a clearer picture of how the diene products were being formed under reaction conditions. The results of the study showed that when ^{2}D-labelled **175**, with deuterium incorporated on the terminal positions of the starting alkene, was heated, no migration was observed. However, when the deuterium was present on the internal position of the alkene as in **177**, complete transfer was observed to the newly formed alkene in product **178**. Surprisingly, in all of the cases examined, a *cis*-olefin was formed in products **176** and **178**, as opposed to the expected *trans*-olefin (**Scheme 47**).



Scheme 47. Deuterium enriched substrates 175 and 177 to probe elimination pathway

In an effort to explain these findings, Krafft and co-workers proposed that two possible competing pathways may be occurring in the reaction mixture, as depicted in **Schemes 48** and **49**.[80] The generally accepted mechanism towards 1,3-diene formation involves the initial cyclisation of **179** to afford cobaltacycle **180**, followed by β-hydride elimination to regenerate the terminal alkene in **181** (**Scheme 48**). From this point two possible pathways are

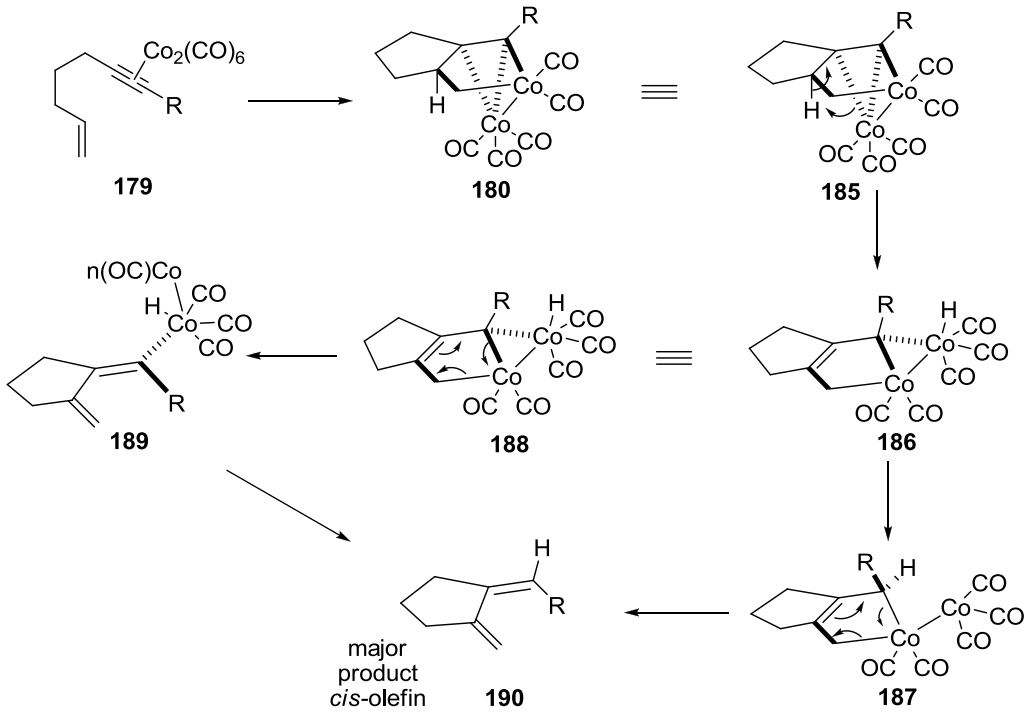
accessible; either through reductive elimination to **182**, followed by decomplexation, or similarly decomplexation to afford **183**, followed by reductive elimination to release the 1,3-diene species **184**. Whilst, the mechanism shown in **Scheme 48** is widely accepted as the pathway explaining the generation of *trans*-selective 1,3-dienes, it does not provide a suitable explanation to account for the formation of compounds **176** and **178**.



Scheme 48. β-Hydride elimination pathway to *trans*-olefin 184

To explain this apparent shift in product formation, Krafft and co-workers began to re-evaluate if this mechanism was the only possible outcome. For effective β-hydride elimination to occur in **180**, the cobalt atom present in carbocycle has to align itself *syn* and parallel to the migrating proton (**Scheme 48**). The authors proposed that due to spatial constrains around the complex, this may not be favoured and that instead an alternative β-hydride elimination and retrocyclisation may be competing to form the *cis*-1,3-diene products, as shown in **Scheme 49**.

Revisiting intermediate **180** it quickly became clear that β-hydride elimination can occur in two possible directions, primarily as described in **Scheme 48**, but also through **185** to form an allylic-type cobaltacycle **186**. Krafft proposed that, in certain cases, substrates may preferentially adopt this conformation, promoting the formation of this alternative intermediate **186**. From **186**, again two possible pathways are accessible; either through retrocyclisation of **188** to provide **189**, followed by reductive elimination; or reductive elimination of **186** to afford **187**, followed by retrocyclisation to afford **190**. Crucially, the mechanism illustrated in **Scheme 49** explains the preferential formation of products such as **176** and **178** containing a *cis*-olefin (**Scheme 47**).



Scheme 49. Alternative retrocyclisation pathway to *cis*-olefin 190

The feasibility of this alternative mechanism provides an important addition to the understanding of the P-K reaction, explaining the formation of 1,3- and 1,4-dienes through conformational restrictions in structural scaffolds that are not electron-deficient, such as **175** and **177**. However, the existence of yet another competing pathway further exemplifies the fact that there are often multiple reaction pathways accessible during the P-K reaction and that product determination is often not as expected and is often substrate dependent.[81]

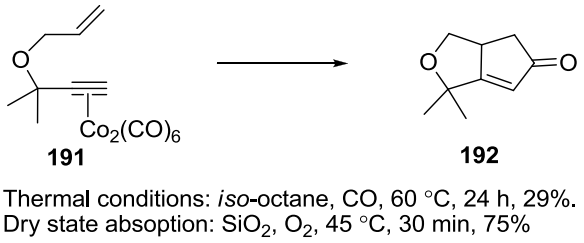
2.12 Reaction Conditions and Promoters of the P-K Reaction

From the original conception of the P-K reaction, promoting cyclisation was based on thermal conditions. Classically this entailed the prolonged heating of the alkyne complex, with excess alkene in hydrocarbon solvents. Unfortunately, in many cases, poor to moderate yields were isolated, with the formation of multiple by-products, requiring lengthy reaction times and purification protocols. Due to the obvious practical difficulties of this approach, many of the recent P-K developments have concentrated on the modification of reaction conditions to improve efficiency and remove the need for complex purification procedures.

2.12.1 Dry-state Adsorption

The first major advance in promoting the P-K reaction involved adsorption of the reagents onto a solid surface such as silica, zeolites, or alumina.[82] Nucleophilic sites on the solid surface, acting as Lewis bases, are thought to co-ordinate to the complex, promoting the initial loss of a CO ligand. Furthermore, these Lewis basic sites were proposed to be involved in subsequent stabilisation of cobalt intermediates, reducing decomposition of the complex prior to reaction completion. The most dramatic reductions in reaction times were observed when a heteroatom was present in the starting material such as in **191** (**Scheme 50**). It was proposed that with these substrates in particular, secondary interactions between the heteroatom and the solid surface aid binding to promote cyclisation.

In the example shown, it was demonstrated that through implementation of dry state adsorption protocols, an appreciable increase in yield to 75% of **192** could be achieved in 30 min, comparative to 29% over 24 h following classical thermal promotion (**Scheme 50**).[83]

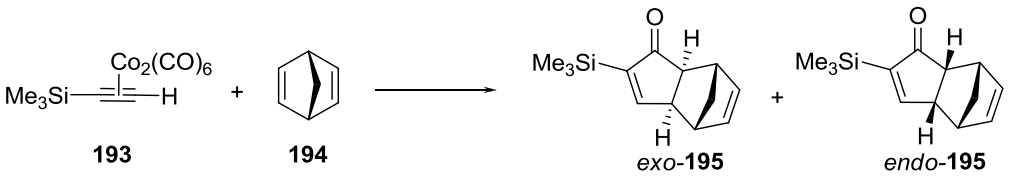


Scheme 50. Promotion of the P-K reaction using dry-state adsorption

2.12.2 Microwave Promotion

Despite the extensive development of microwave technology in modern organic synthesis, it was not until 2002 when Evans and co-workers reported the first microwave promoted P-K reactions (**Scheme 51**).[84] Variations in solvent, alkyne complex, and alkene were all analysed with results in general showing moderate to excellent yields, in remarkably short reaction times. Throughout all of the examples investigated, high temperatures proved critical to attain the desired rate enhancements.

As shown in **Scheme 51**, both polar (DCE) and non-polar (toluene) solvents proved effective in promoting product formation. However, in the majority of cases, toluene proved the most effective solvent, with yields of up to 97% being obtained after just 5 min.

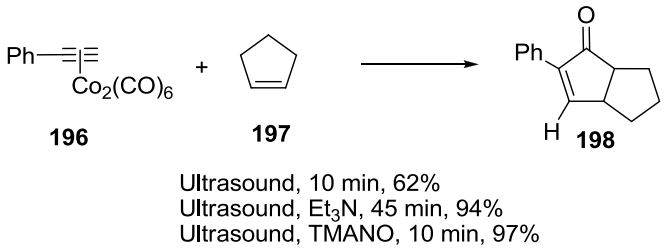


Scheme 51. Microwave promotion of the P-K reaction

2.12.3 Ultrasound Promotion

Exposure of the reaction media to ultrasound (sonication) is thought to form transient, localised areas of high pressure and temperature.[85] It is within these small pockets of high pressure and temperature that the cleavage of metal-CO bonds is thought to occur. Initial investigations by Pauson and co-workers demonstrated that low power ultrasound could be used effectively to induce moderate cyclopentenone conversions.[86]

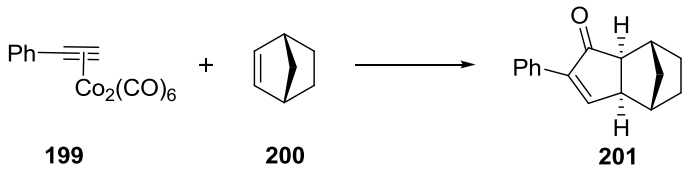
Subsequent developments by Kerr and co-workers utilising high power ultrasound, in conjunction with chemical promoters, have shown remarkable improvements in both yield and reaction time.[87] In the example shown in **Scheme 52**, Kerr *et al*. demonstrated that yields of up to 62% of compound **198** could be achieved simply by sonicating the reaction mixture for 10 min. However, the most dramatic improvements in yields were observed when ultrasound promotion was used in conjunction with amine *N*-oxides, where conversions could be effectively increased to 94-97% of **198** in less than 1 h.



Scheme 52. Effect of ultrasound on the promotion of the P-K reaction

2.12.4 Amine N-Oxides

One of the most important and widely used promoters in modern P-K reactions are amine *N*-oxides.[88,89] Initially used as decomplexation agents to remove the hexacarbonyl cobalt complex from unreacted alkynes, it was envisioned that their addition to the reaction mixture could lead to the irreversible loss of a CO ligand *via* oxidation, to release non-co-ordinating CO_2. Amongst the most popular and commonly used reagents are trimethylamine *N*-oxide (TMANO), and *N*-methylmorpholine *N*-oxide (NMO), which can be used either as the anhydrous or hydrate forms. In general, the hydrated forms of TMANO or NMO appear to be required to avoid premature alkyne decomplexation. Whilst the hydrated forms may reduce the observed rate of reaction, excellent overall yields are often obtained.[90] It is also important to note that the addition of amine *N*-oxides often allows the P-K reaction to be carried out under remarkably mild conditions, with reaction temperatures reduced to ambient temperature (**Scheme 53**).[91]

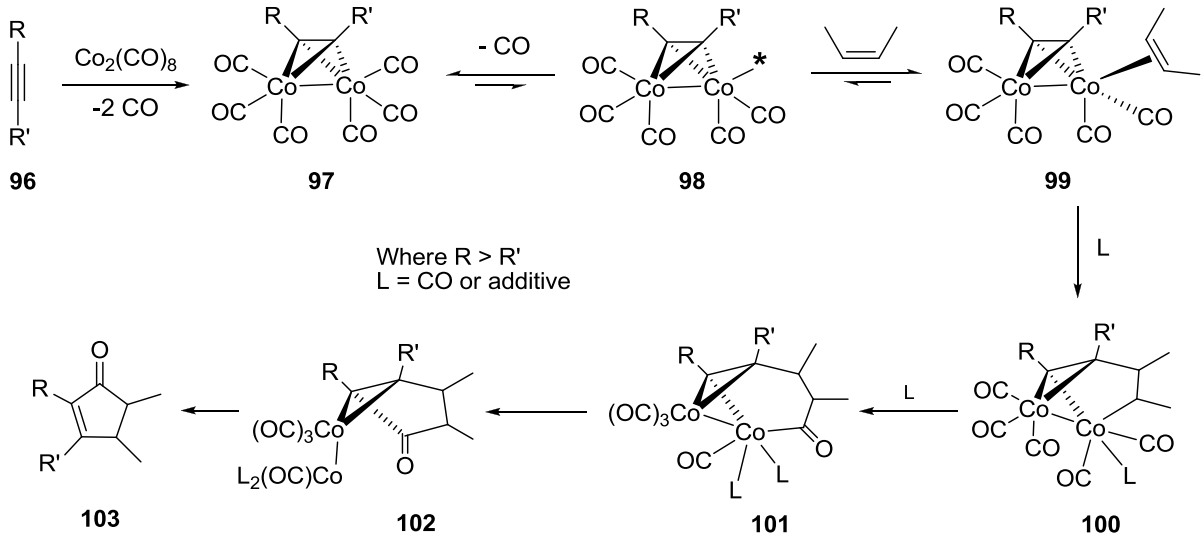


199 **200** **201**

Thermal: toluene, 60 °C, 4 h, 45%
N-oxide: DCM, TMANO·$2H_2O$, r.t., 3 h, 80%

Scheme 53. *N*-oxide promotion of the P-K reaction

Amine *N*-oxide additives are thought to have a dual role within the P-K reaction. Looking more closely at the proposed mechanism, it can be seen that in the conversion of **99→100** and **100→101**, an additional ligand is required to stabilise the complex, to maintain a co-ordinatively saturated configuration (**Scheme 54**). This is normally achieved by re-complexation of a CO ligand or through the donation of a lone pair from an additive ligand. Hence, once the amine *N*-oxide has reacted as an oxidant, releasing CO_2, its reduced form is then free in solution to co-ordinate to the complex to aid the stabilisation of the subsequent Co-intermediates.



Scheme 54. Proposed mechanism of Pauson-Khand reaction

In 1999 Kerr and co-workers demonstrated that this technique could further be incorporated into user-friendly polymer supported resins such as **204** (**Table 4**).[92] Remarkably, it was also noticed that the polymer sequestered most of the cobalt residues formed as by-products in the reaction mixture, simplifying product isolation significantly. Recycling of the desired resins could then be achieved by simple washing, with little or no erosion of activity and yields of **205** consistently remaining above 90% after five cycles (**Table 4**).[93]

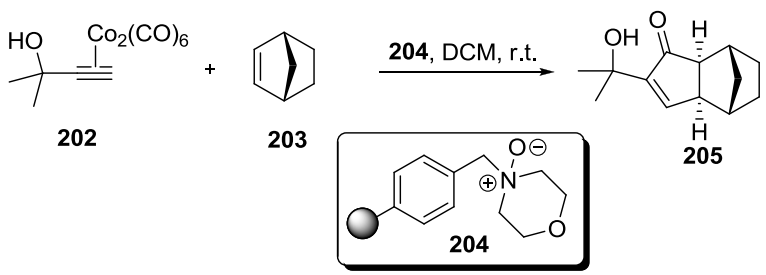


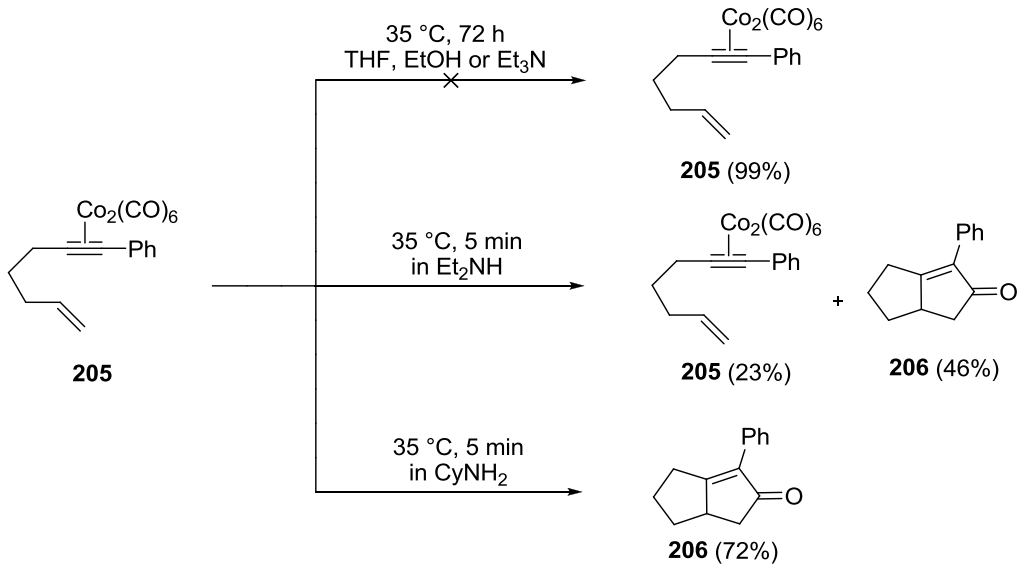
Table 4. Polymer supported amine *N*-oxide promotion of the P-K reaction

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

2.12.5 Amines, Sulfoxides and Sulfides

A third and very important approach towards the promotion of the P-K reaction involves attempted stabilisation of the alkyne-complex intermediates. This approach is somewhat complementary to the dual role that amine *N*-oxides exhibit, only without the initial oxidation of a CO ligand to free up a co-ordination site. Ligands such as sulfides and amines are thought to act as Lewis bases, donating electron density into the complex promoting the loss of CO, providing steric shielding and thus preventing the collapse of complex intermediates as cyclisation occurs.

The development of Lewis basic additives in the P-K reaction is thought to have originated from landmark papers published in the 1970's by Darensbourg and co-workers.[94,95] Through their investigations into ligand effects within low valent transition metals, they successfully showed that hard Lewis bases such as amines and alcohols promoted CO ligand dissociation. It was proposed that the electron donation from the lone pairs on hard Lewis bases increases the electron density on the metal centre, weakening the metal-CO σ-bond. Furthermore, it was also envisioned that due to the *cis*-effect observed in mononuclear transition metals, that addition of Lewis basic additives into the dicobalt complex should promote the dissociation of a CO ligand predominantly on the cobalt atom to which it is co-ordinated (**152**, **Figure 14**, **Section 2.10.2**). Towards this aim, the first examples of Lewis basic additives within the P-K reaction were those of amines, mainly due to their availability and low cost.[96] Adaption of this basic premise into the dicobalt system immediately proved successful, with high levels of conversions readily obtained, even at relatively low temperatures of 35 °C (**Scheme 55**).

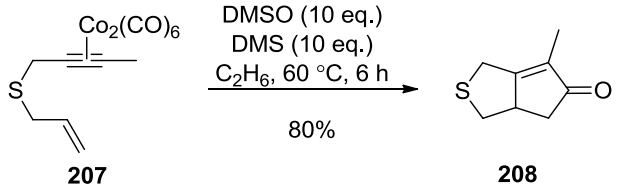


Scheme 55. Amine promotion of the P-K reaction

Initial investigations showed fairly mixed success, with the addition of tertiary amines returning only starting materials. Switching the Lewis basic additive to primary and secondary amines proved more successful with 46% yield of **206** isolated in the presence of Et_2NH and 72% yield with $CyNH_2$.

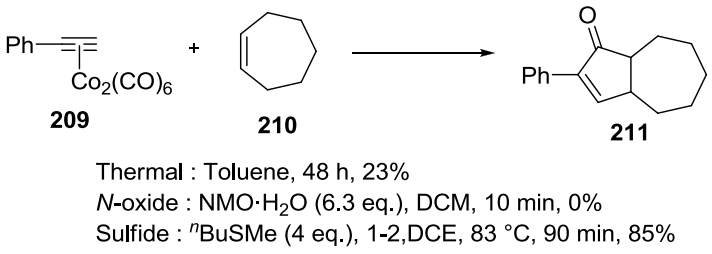
Despite the initial success of cheap and readily available amines such as cyclohexylamine and ammonia in the promotion of P-K reactions, it was still believed that more effective alternatives could be found. The main driving force behind this was the development of catalytic protocols, of which amines (especially primary and secondary), had an inherent disadvantage, in that they were suspected of degrading free $Co_2(CO)_8$ through redox processes.[96] Towards this goal, sulfides were identified as possible alternatives. Sulfides are thought to be poorer σ-donor and better π-acceptor ligands than amines. It was believed that although less electron density would be pushed into the metal centre through σ-donation, the increased π-back donation should have the same overall effect in promoting CO dissociation.

The use of sulfides and sulfoxides as promoters in the P-K reaction was first reported by Jeong and co-workers in 1997 and later by Werz in 2004.[97,98] During investigations towards the ring closure of **207**, it was noticed that the addition of a mixture of DMS and DMSO to the reaction mixture had a positive effect on conversions, with 80% yield of **208** being isolated upon reaction completion (**Scheme 56**).[97]



Scheme 56. Promotion of the P-K reaction using DMS and DMSO

Further investigation and developments by Sugihara *et al*. identified that the presence of alkyl sulfides, such as ^{n}butylmethyl sulfide (^{n}BuSMe), was sufficient to effectively promote the P-K reaction of substrates such as **210** (**Scheme 57**).[99]



Scheme 57. Comparison of sulfide and amine *N*-oxide additives as promoters in the P-K reaction

Importantly, it appears that sulfides often exhibit a complementary effect to that of amine *N*-oxide additives, with sulfides frequently promoting the successful cyclisation of substrates where conversions are poor using amine *N*-oxides. In the example shown in **Scheme 57** Sugihara demonstrated that whilst NMO proved completely ineffective as a promoter in the formation of **211**, the addition of sulfides provided **211** in an excellent 85% yield. In fact, the most recent research would suggest that the co-ordination of sulfides into the complex actually promotes alkene insertion.[54]

Unfortunately, the use of sulfides has some major drawbacks: they are often expensive, require high reaction temperatures, and the distinctive noxious smell makes handling difficult and unpleasant. To address some of these issues, Kerr and co-workers developed two practical alternatives. The first of these was a recyclable and highly efficient polymer-supported sulfide **214**.[100] During investigations towards the promotion of the intermolecular P-K reaction, Kerr *et al*. demonstrated that **214** was capable of multiple reaction cycles with little erosion in activity (88% yield after five cycles), as shown in **Table 5**.

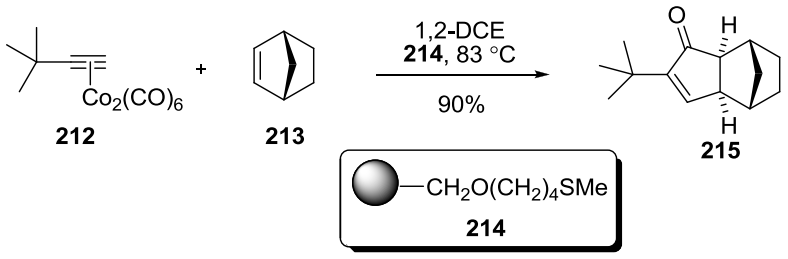
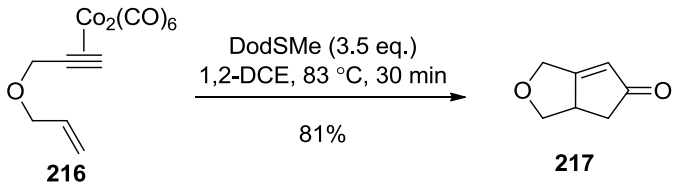


Table 5. Polymer supported sulfide additives in the P-K reaction

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

Complementary to the heterogeneous polymer supported sulfide **214**, was the development of dodecylmethyl sulfide (DodSMe), an odourless solution phase sulfide.[101] As shown in **Scheme 58**, DodSMe proved a highly efficient alternative to conventional sulfide additives, with isolated yields of **217** up to 81% upon reaction completion.



Scheme 58. Odourless DodSMe protocol towards the promotion of the P-K reaction

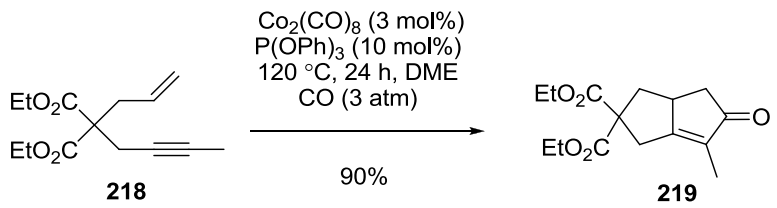
Importantly, the development of DodSMe did not just provide a solution to the noxious smell, but also provided a much more cost effective P-K promoter, since this reagent was significantly cheaper than ^{n}butyl methyl sulfide and easily prepared on a large scale.

2.13 Catalytic Pauson-Khand Reactions

The stoichiometric P-K reaction has proved to be of enormous synthetic versatility, especially when used in conjunction with the recent developments in additives. However, the use of stoichiometric amounts of cobalt, combined with the necessity to pre-form and often purify the hexacarbonyl complex, are major drawbacks to this metal-mediated protocol. However, in recent years, a concerted effort to improve atom efficiency and simplify the reaction to an actual one-pot, catalytic procedure has intensified.

2.13.1 Homogeneous Catalysis

To date, investigations towards the development of a catalytic P-K reaction has covered a wide range of approaches including: screening co-ligands, varying the CO pressure, and changing the form of the cobalt complex within the reaction media.[41,102] However, it was not until 1994 when Jeong and co-workers published the first reliable and user-friendly protocol.[103,104] During their investigations, the authors observed that by increasing the pressure of CO, significant improvements in yields could be achieved (**Scheme 59**). Optimised conditions involved CO pressures of 3 atm, in the presence of $Co_2(CO)_8$ (3 mol%) and triphenyl phosphite (10 mol%), to generate 90% of **219** over a 24 h period.



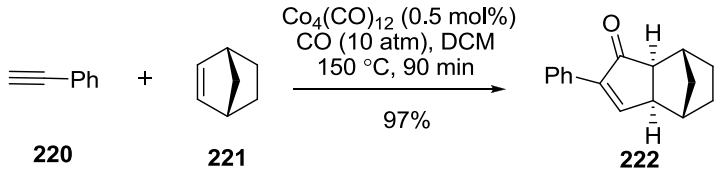
Scheme 59. Catalytic P-K reaction at elevated pressures of CO

With such low catalyst and additive loadings, a CO atmosphere became crucial to maintaining the co-ordinatively saturated complex, to promote catalyst recycling and turnover. However, under current conditions, the rate determining step should also be the

dissociation of a CO ligand from the complex, to facilitate alkene co-ordination. This detail was reflected in the investigations of Jeong *et al*. who discovered that a very delicate balance in CO pressure was required to facilitate reaction progress.[103]

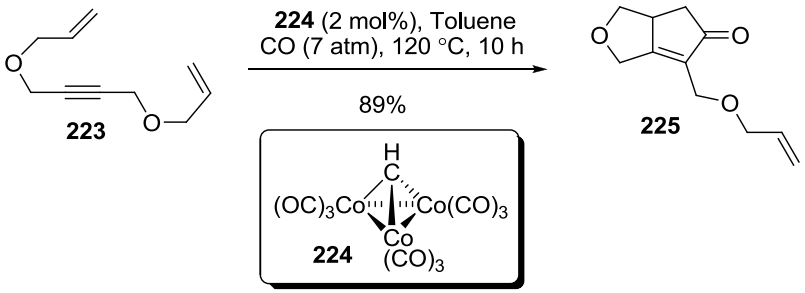
2.13.2 Cobalt Complex Development

Initial investigations, aimed at identifying a suitable catalytic species for the P-K reaction, were based solely on the use of $Co_2(CO)_8$. From the outset, it was proposed that the $Co_2(CO)_8$ complex was the most reactive species and essential to effective turnover. This premise originated from the analysis of reaction mixtures taken from failed P-K reactions. The discovery and identification of higher order cobalt aggregates, such as $Co_4(CO)_{12}$, led to the hypothesis that these species were responsible for the deactivation of the catalytic species. However, subsequent investigations by Krafft[105] and Chung[106] demonstrated that that was not the case and that these higher order clusters could be used as excellent catalysts, capable of highly efficient turnovers under forcing conditions. In the example shown in **Scheme 60** as little as 0.5 mol% $Co_4(CO)_{12}$ proved effective towards the formation of **222** in a yield of 97% under 10 atm of CO.



Scheme 60. Catalytic P-K reaction using $Co_4(CO)_{12}$ cluster

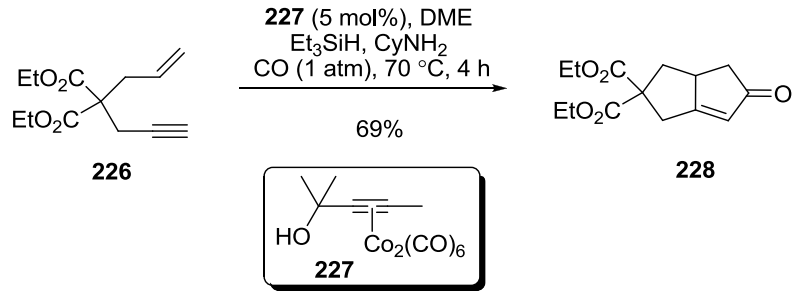
Following on from this pioneering work, Sugihara and Yamaguchi demonstrated that the $Co_4(CO)_{12}$ complex could be further improved through replacement of a $Co(CO)_3$ unit with a methylene bridge, as in complex **224** (**Scheme 61**).[107,108] Remarkably, this subtle change in the structure of the catalyst cluster not only provided efficient catalysis of both the intra- and intermolecular P-K reactions, but also conferred air and moisture stability on the resultant complex.



Scheme 61. Catalytic P-K reaction promoted by stabilised Co cluster 224

Despite the success of various higher order cobalt species in the catalytic P-K reaction, commercially available $Co_2(CO)_8$ remains the most desirable and widely used cobalt source. However, one of the major limitations of this reagent was the need for an ultra-high purity source in order to ensure effective catalytic turnover. In 1999, Krafft provided the solution to this problem, demonstrating that 10 mol% unpurified $Co_2(CO)_8$ could be utilised as an effective catalyst, when prepared in base-washed glassware.[109] Encouraged by the success of this initial protocol, Krafft and co-workers later reported that the addition of 2 equivalents of cyclohexylamine to the reaction mixture was sufficient to ensure efficient catalytic turnover.[110]

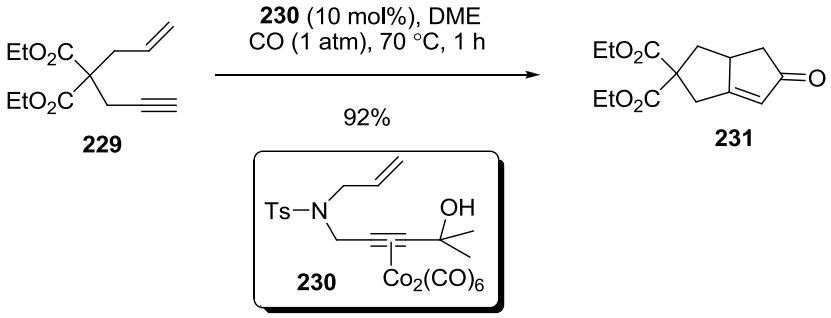
An alternative approach developed by Livinghouse involved the use of a preformed and purified, shelf-stable complex **227** (**Scheme 62**).[111] Livinghouse observed that when **227** was added to the reaction mixture it essentially acted as a pre-catalyst, releasing the active form of the cobalt complex *in situ*. Following the described protocol, Livinghouse demonstrated that up to 69% of **228** could be isolated using as little as 5 mol% pre-catalyst **227**. This approach, though highly desirable, still required the separate formation and purification of the cobalt complex **227**.



Scheme 62. Catalytic P-K protocol developed by Livinghouse and co-workers

Complementary to the Livinghouse approach, Krafft and co-workers confirmed that efficient catalysis could also be achieved using a catalytic amount of sacrificial P-K substrate **230** (**Scheme 63**).[112] It was proposed that following the initial cyclisation of **230**, the residual cobalt complex was released into the reaction mixture *in situ*, providing recyclable amounts

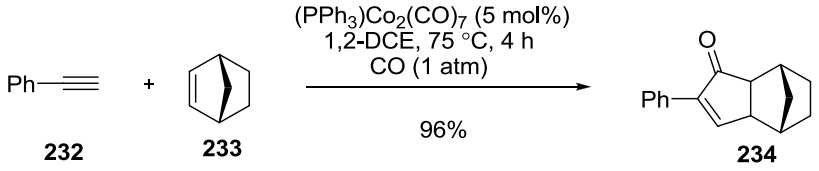
of complex to allow catalytic turnover. Krafft and co-workers designed **230** specifically to maintain a difference in product polarity to facilitate the separation of the two cyclic products under investigation. Through the implementation of this approach Krafft was able to isolate **231** in a yield of 92%, with as little as 10 mol% pre-catalyst **230** within the reaction mixture.



Scheme 63. Catalytic cobalt species in the form of sacrificial P-K substrate 230

Many of the catalytic methods described to date have one major practical difficulty, they all require fairly high pressures of CO, promoting re-incorporation of the CO back into the complex to stabilise intermediates and regenerate the catalyst active species.

Pioneering development of the catalytic P-K reaction by Sugihara,[113] Hashimoto,[114] Joeng,[103] Chen,[115] and Jiang[116] has allowed the incorporation of additives as stabilising ligands to maintain the active catalyst species in solution, whilst requiring only 1 atm of CO. A range of additives have proven fairly successful including tri-*n*-butylphosphine sulfide, DME, H_2O, triphenylphosphate, tetramethylthiourea (TMTU), and triphenylphosphine.[117,118] In the example shown in **Scheme 64**, as little as 5 mol% of a preformed $(PPh_3)Co_2(CO)_7$ complex provided 97% yield of **234** under 1 atm of CO.[117]

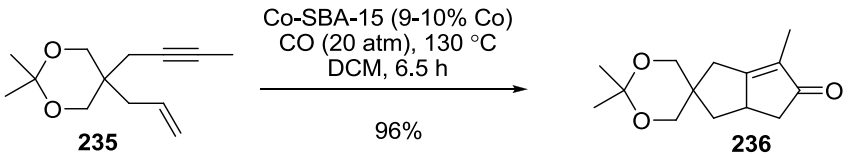


Scheme 64. Additives as promoters of the catalytic P-K reaction

From a practical point of view, it was this incremental reduction in CO pressure which has helped to accelerate subsequent advancements in the catalytic P-K reaction and open its accessibility as a modern synthetic reaction.

2.13.3 Heterogeneous Catalysis

Development of a heterogeneous protocol is clearly desirable from the point of view of purification, scale-up, and recycling of the cobalt source. The first reported system capable of highly efficient conversions was published by Chung *et al*. in 2000 using a cobalt source deposited on mesoporous silica (SBA-15) (**Scheme 65**).[119]

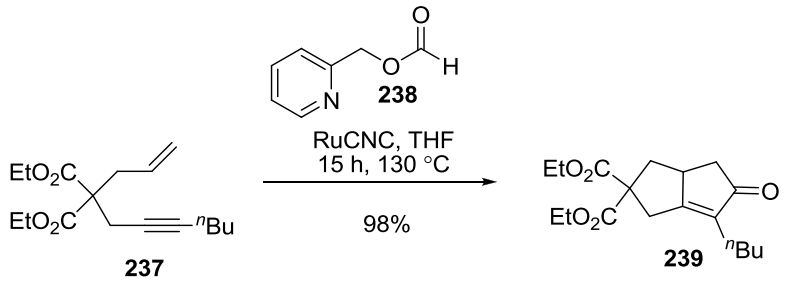


Scheme 65. CoSBA stabilised heterogeneous catalyst in the P-K reaction

The success of this protocol immediately became clear on product isolation, with 96% yield of **236** isolated upon reaction completion. Remarkably, analysis of **236** by ICP-EAS analysis showed that no metal leeching was occurring into the isolated product. Furthermore, following catalyst isolation, repeat experiments demonstrated that the catalyst system incurred no significant loss in reactivity over four separate runs. Unfortunately, the described catalyst system did not prove applicable to the intermolecular P-K reaction, with poor conversions obtained even under elevated temperature and pressures of CO.

With the aim of increasing the accessibility of these systems to large scale synthesis, Chung and co-workers have developed several alternatives based on transition metals loaded on charcoal.[120] This approach proved highly advantageous, with significant reductions in cost, increased air stability and all without any appreciable loss in recyclability or activity.

More recently, with the aim of reducing the high pressures of CO required for efficient cyclisation, Chung and co-workers have developed a hetero-bimetallic Ru/Co co-catalyst supported on charcoal (**Scheme 66**).[121] Although these catalyst systems are capable of moderate to excellent conversions of P-K products (98% yield of **239**), the most important change in the described protocols was the incorporation of alternative sources of CO. Towards this aim, Chung demonstrated that 2-pyridlmethyl formate **238**,[121] and olefinic aldehydes[122] can be effectively added as CO surrogates.



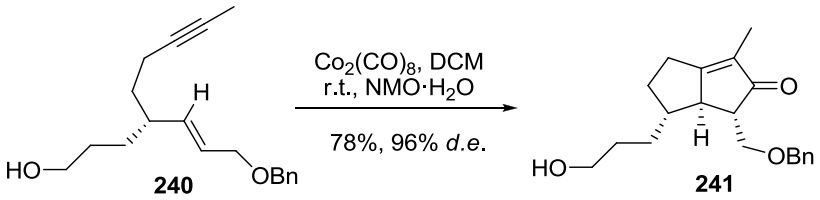
Scheme 66. Alternative Ru/Co heterogeneous catalyst

2.14 Asymmetric Pauson-Khand Reactions

One of the most difficult challenges facing modern organic chemists is the development of efficient synthetic methods to induce high levels of stereoselectivity. The P-K reaction is no exception, with many successful protocols already under development. To date, the asymmetric P-K reaction has been approached from four main synthetic strategies: chiral precursors, chiral auxiliaries, chiral amine *N*-oxides, and through the use of a chiral C_2Co_2 complex core.

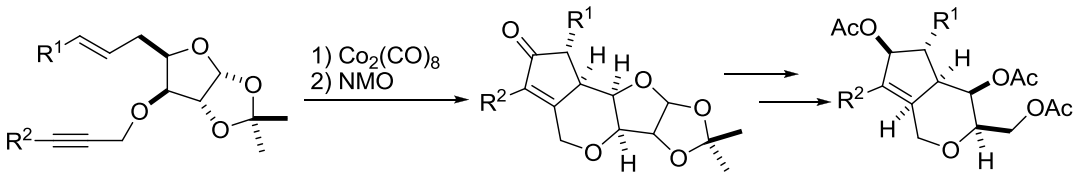
2.14.1 Chiral Precursor Approach

The first and most straight forward strategy towards to the asymmetric P-K reaction is to start from a chiral precursor.[123,124] Hoveyda and co-workers used this approach to excellent effect, creating three contiguous chiral centres in a single step, with excellent levels of diastereoselectivity reported (78% yield of **241**, 96% *d.e.*, **Scheme 67**).[125] It is important to highlight that in the example shown, the established chiral centre in **240** directly influences the diastereoisomeric outcome. Remarkably, high levels of facial selectivity were observed in **241**, despite the relatively free conformation of the initial open chain substrate **240**.



Scheme 67. Synthesis of 241 *via* an asymmetric P-K reaction

Whilst chiral pool substrates such as amino acids have received little attention as potential P-K precursors, carbohydrates have been widely used for the synthesis of chiral targets. An important contribution by Pal and co-workers elegantly incorporates an isopropylidenedioxyfuranoside scaffold in **242**, to promote the exclusive formation of **243**, using NMO promotion (**Scheme 68**).[126] Despite the success of this approach towards a highly selective P-K reaction, the synthesis of subsequent derivatives of the basic scaffold proved variable. During their investigations, the authors observed that the efficiency of the reaction was highly dependent on the levels of substitution present on the alkene moiety, with excellent yields of 87% of **243-C** and 93% of **243-D** attained only when aryl substituents were present on the alkene moiety.



242-A R^1 = H, R^2 = H, 44% **243-A**
242-B R^1 = Me, R^2 = H, 35% **243-B**
242-C R^1 = Ph, R^2 = H, 87% **243-C**
242-D R^1 = (4-OBn-3-OMe)Ph, R^2 = H, 93% **243-D**

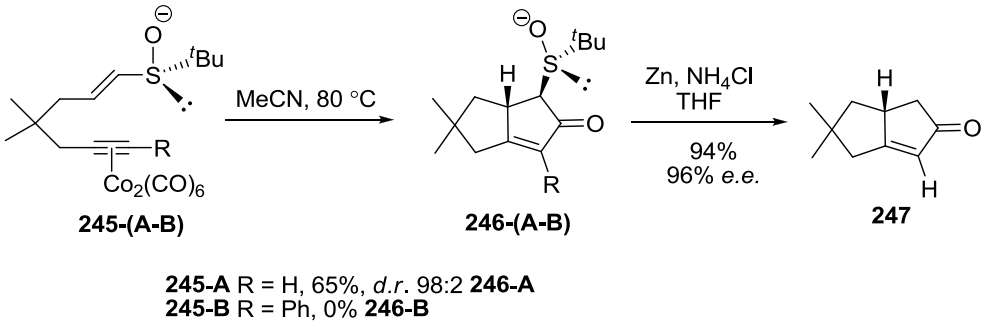
Scheme 68. Synthesis of 244 from carbohydrate chiral precursors

2.14.2 Chiral Auxiliaries

One of the classical approaches to induce asymmetry in modern synthesis is through the use of chiral auxiliaries. However, the success of this approach comes with significant disadvantages: chiral auxiliaries are often expensive and are stoichiometric reagents, requiring additional synthetic steps to both attach and remove the aforementioned group. Thus, any synthetic route utilising auxiliaries must address if the observed selectivities compensate the additional cost and complexity required to access the desired targets.

Many of the first reported uses of chiral auxiliaries in the P-K reaction were applied to the intramolecular variant. When planning this approach it was observed that the highest levels of selectivity were achieved when the chiral auxiliary was in close proximity to the alkyne-cobalt complex. To this extent, both the alkene and the alkyne components of the P-K enyne were identified as feasible sites for the attachment of the auxiliary.[127]

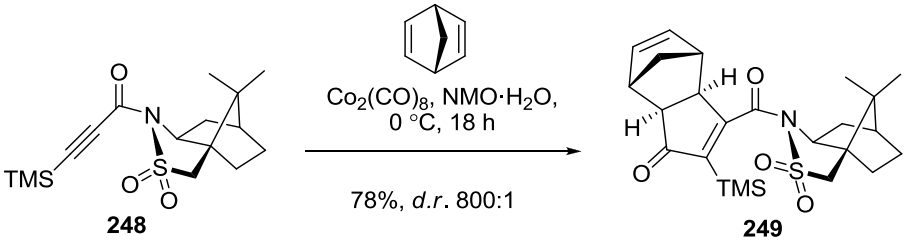
In 1999, Adrio and Careterro successfully utilised the incorporation of a chiral sulfoxide in **245 A-B**, with 65% yield of **246-A** and 98:2 *d.r.* achieved when the terminal alkyne (R=H) was investigated (**Scheme 69**).[128–130] Importantly, **246-B** was not observed when the corresponding internal alkyne (R=Ph) was subjected to identical reaction conditions.



Scheme 69. Incorporation of chiral sulfoxides as directing groups

The results described above highlight an important trend that appears to dominate the overall success of this approach as a synthetic strategy.[131] It would appear that substitution patterns on the alkene and alkyne components affect a critical role in influencing the level of product conversion. From this perspective, an appreciable reduction in yield is often observed as increasing substitution is incorporated into the starting substrate (**Section 2.11**). Despite the potential compromise in yields, the high levels of selectivities achieved to date continue to draw attention to this approach as a feasible strategy towards the selective synthesis of complex targets.

At present, an extensive range of chiral auxiliaries have proven successful, with variety of directing groups employed including functionalities such as ethers, thioethers, sulfoxides, and Evans' and camphor-type ligands.[132–134] In this respect, Pericás and co-workers has highlighted the variety of groups capable of the described transformation, through the elegant incorporation of Oppolzer's bornane 1,2-sultam.[135] In the example shown in **Scheme 70**, Pericás demonstrated that through careful choice of auxiliary, both high yields and selectivities are achievable (78% yield of **249** and a 800:1 *d.r.*).



Scheme 70. Incorporation of Oppolzer's 1, 2-sultam to direct the asymmetric P-K reaction

Despite the relative success reported within this area of asymmetric synthesis, the main challenge facing chemists today continues to be addressing the delicate balance between achieving high levels of selectivity and product conversions.

2.14.3 Chiral C_2Co_2 Core Approach

A third and important method of inducing asymmetry in the P-K reaction involves the formation of a chiral C_2Co_2 complex. As previously mentioned in **Section 2.8**, complexation between $Co_2(CO)_8$ and an unsymmetrical alkyne results in a complex which adopts a *pseudo*-tetrahedral geometry, whereby the complex becomes enantiotopic and each of the $Co(CO)_3$ units become prochiral (**Figure 16**). Redrawing complex **250** as **251** highlights an imaginary chiral centre within the *pseudo*-tetrahedral arrangement.[48]

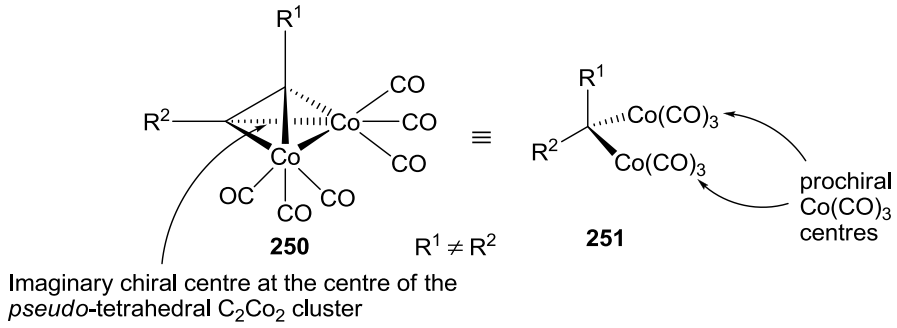


Figure 16. Schematic representation of imaginary chiral centre in C_2Co_2 complexes

As a direct result of this conformation, controlled ligand exchange allows the potential induction of selectivity within the P-K reaction through employment of chiral complexes such as **252** or **253** (**Figure 17**).

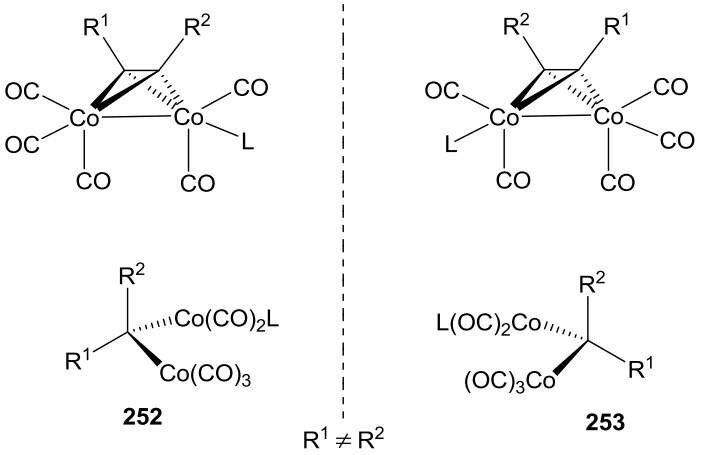
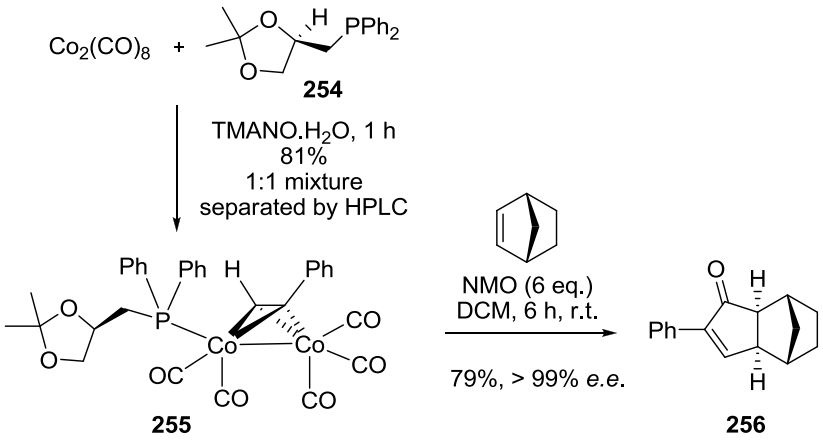


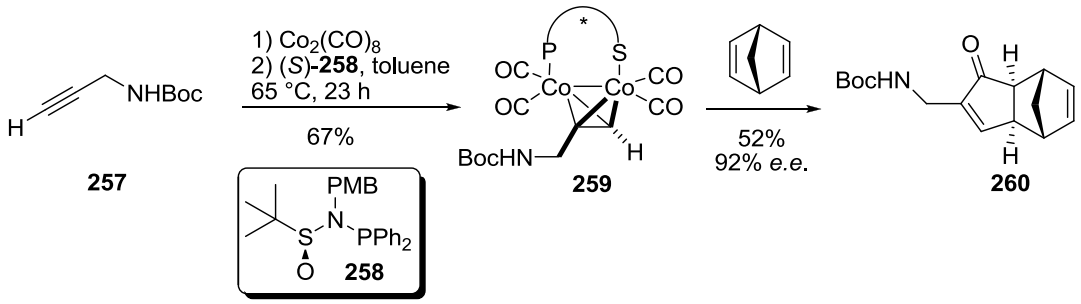
Figure 17. Schematic representation of enantiomers of chiral C_2Co_2 complex

Early development by Pauson and co-workers confirmed this concept by successfully exchanging a single CO ligand with a chiral phosphine (*R*)-(+)-Glyphos, separating the diastereoisomers by crystallisation.[136,137] Subsequent investigations by Kerr *et al*. successfully demonstrated that the synthesis of chiral complexes such as **255**, could be significantly improved the use of amine *N*-oxides (**Scheme 71**). Through the addition of TMANO·H_2O, a racemic Glyphos complex **255** was successfully synthesised, in an excellent 81% yield.[138,139] Following separation of the two diastereomers by HPLC, employment of the enriched complex furnished cyclopentenones **256** in >99% *e.e*. Key to the impressive levels of selectivity in **256** was the additional employment of amine *N*-oxides to promote the asymmetric P-K reaction. Critically, through addition of these newly developed promoters, reaction temperatures could be reduced to room temperature or below, avoiding the elevated temperatures suspected of inhibiting high levels of selectivity.[140,141]



Scheme 71. Asymmetric P-K reaction promoted by chiral C_2Co_2 complex

Since these original findings, a range of novel protocols have emerged exhibiting various degrees of success including NHC replacement of a CO ligand[142] and mixed metal systems.[143–146] One the most successful protocols to have been developed in recent years originated from the laboratories of Verdaguer and co-workers (**Scheme 72**).[147–151] Through the employment of chiral bidentate ligands such as **258**, Verdaguer and co-workers demonstrated that up to 92% *e.e*. can be established in a range of products such as **260**. Unfortunately, just as with the corresponding monodentate systems described in **Scheme 70**, separation of the resultant diastereomeric mixtures of complexes such as **259** proved essential to obtain the desired levels of selectivity in the resultant products.

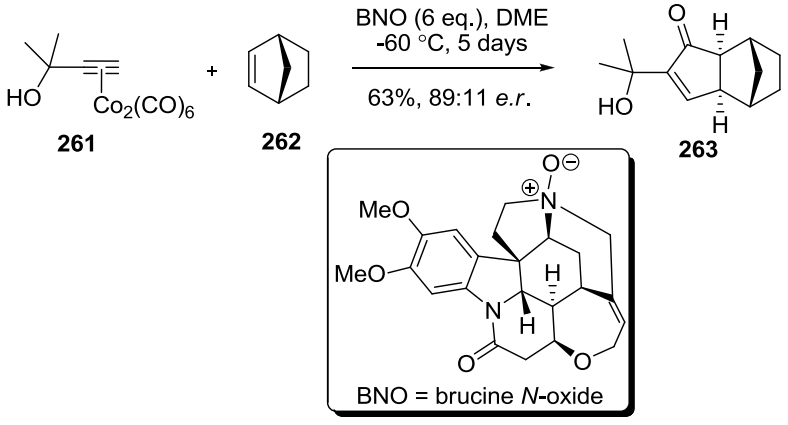


Scheme 72. Asymmetric P-K reaction promoted by a chiral bidentate ligand

2.14.4 Chiral Amine N-Oxides

The final approach discussed here towards the induction of asymmetry in the P-K reaction was through the utilisation of chiral amine *N*-oxides. Previous investigations by Bender and Petrowitsch established that chiral amine *N*-oxides could be successfully utilised to influence the stereochemical outcome of decarbonylation reactions.[152,153] From this perspective, it was envisioned that exposure of a chiral oxidant to a prochiral complex, would result in the selective decarbonylation and *in situ* desymmetrisation of the complex. Furthermore, it was proposed that incorporation of the resultant chiral amine to the complex should not only stabilise cobalt intermediates, but also aid in the enhancement of selective alkene incorporation and product formation.

The introduction of chiral amine *N*-oxides in the P-K reaction immediately showed promise.[154–156] To date, the most successful of the substrates examined was brucine *N*-oxide (BNO), where a selectivity of 89:11 *e.r.* and a 63% yield of **263** was achieved (**Scheme 73**).



Scheme 73. Asymmetric P-K reaction promoted by brucine *N*-oxide (BNO)

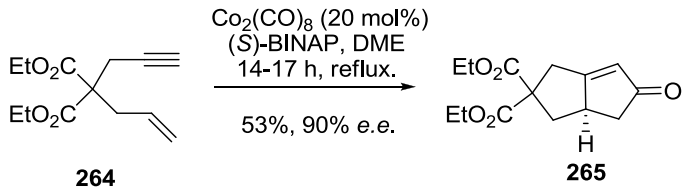
Crucially, the introduction of chiral amine *N*-oxides as promoters in the P-K reaction has provided the first one-pot asymmetric protocol that did not involve the laborious separation of a chiral C_2Co_2 complex, before attempting the desired transformation. Despite a slight

reduction in selectivity comparative to the corresponding enantioenriched complex, amine *N*-oxides represent a clear advancement in the development of an asymmetric process. Furthermore, brucine *N*-oxide has also proved extremely effective in inducing desymmetrisation when preparing chiral complexes, such as phosphine-dicobalt complexes.[48,157]

2.15 Catalytic Asymmetric Pauson-Khand Reaction

From the outset, it was envisioned that the developments in the stoichiometric asymmetric P-K reaction would be adaptable to a catalytic system, improving both atom efficiency and maintaining selectivity for mainstream synthetic use. However, many of the major advances in catalyst development have been achieved through the incorporation of a variety of alternative metals such as rhodium,[158–160] titanium,[161–163] and iridium.[164] From a more classical point of view, the development of the corresponding cobalt-mediated P-K reaction has proved only moderately successful.

Towards this goal, the first highly selective protocol was developed by Hiroi in 2000.[165,166] During investigations towards the catalytic asymmetric P-K reaction, a range of commercially available ligands were screened to determine if selectivity could be achieved. The authors reported that in general the majority of the ligand additives investigated provided poor selectivities. However, significant success was observed when incorporating a catalytic amount of (*S*)-BINAP and $Co_2(CO)_8$, providing **265** in a 53% yield and 90% *e.e.* (**Scheme 74**).



Scheme 74. Asymmetric induction through addition of chiral ligands

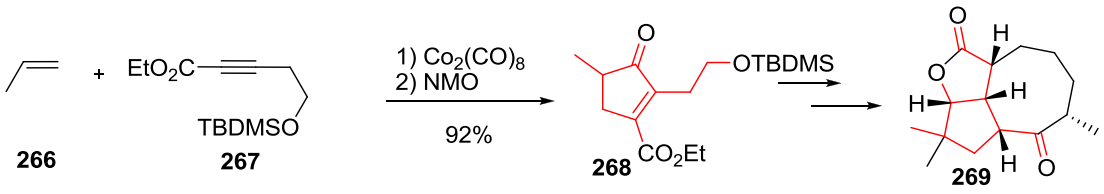
Further developments by Buchwald and Sturla in 2002 reported that chiral diphosphite ligands could also be used to good effect to promote increased yields.[167] Unfortunately, despite the increase in catalyst turnover, a significant erosion in product selectivity was also observed.

To date, inducing asymmetry in the catalytic P-K reaction has proved to be one of the most challenging objectives, with the majority of cobalt catalysed reactions providing only moderate to poor levels of both selectivity and conversion.[168]

2.16 The Pauson-Khand Reaction in Natural Product Synthesis

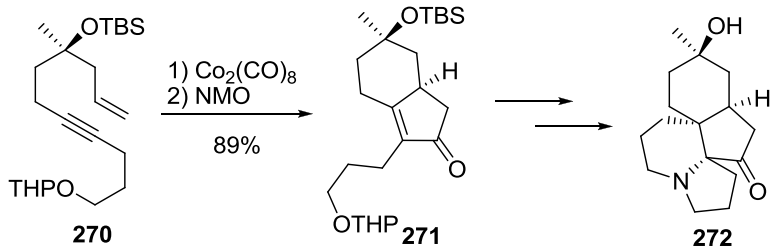
Five-membered rings as independent units, or as part of a complex fused ring system, are common place in naturally occurring molecules. The ability of the P-K reaction to develop complexity and stereospecificity in a single transformation, has increased the popularity of this strategy as a modern synthetic approach.[42,169] When used in combination with the wide ranging protocols currently available (*vide supra*), chemists have discovered that there is normally an efficient protocol available for most substrate functionalities or ring systems investigated. In the following section, a range of natural product targets have been highlighted to exemplify just how far the development of the reaction has progressed and to emphasise the importance of the P-K reaction as a modern synthetic tool.

The first example highlighted is Krafft's synthesis of asteriscanolide **269** (**Scheme 75**). During their investigations, the authors elegantly demonstrate how the P-K reaction could be used to develop a functionalised cyclopentenone **268**, later embedded in a fused ring system **269**.[170] An excellent 92% yield of **268** was achieved through the use of NMO, allowing the formation of a highly functionalised cyclopentenone, which would require multiple linear steps by any other synthetic strategy.



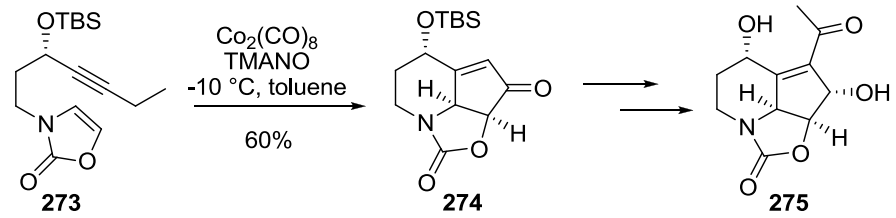
Scheme 75. P-K reaction to build the core cyclopentenone of asteriscanolide 269

In 2002, Zard reported the synthesis of a *lycopodium* alkaloid 13-deoxyseratine **272**, utilising a diastereoselective intramolecular P-K reaction (**Scheme 76**).[171] Through the use of amine *N*-oxide promotion, the authors successfully embedded a highly functionalised [4.3]-fused ring system in **271**. The efficiency demonstrated by the described P-K reaction allowed the total synthesis of **272** to be achieved in an impressive 10 steps with an overall yield of 12%.



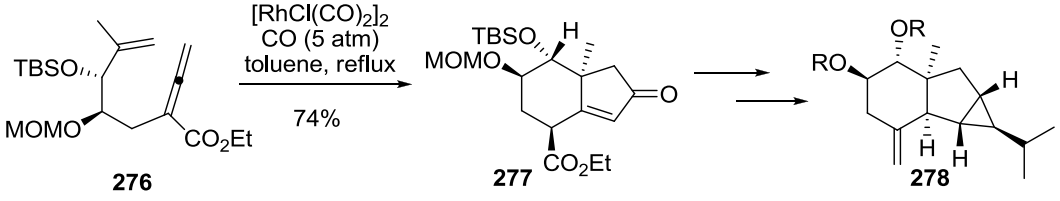
Scheme 76. Synthesis of [4.3]-fused ring system 271 by P-K reaction

Also in 2002, Mukai and co-workers utilised the efficiency and selectivity of the intramolecular P-K reaction to complete the synthesis of 8-α-hydroxystreotazolone **275** (**Scheme 77**).[172] Interestingly, in this specific case the alkene component of the P-K reaction is an oxazolone, further illustrating the versatility and functional group tolerance of this reaction. The formation of a [3.2.2]-fused ring system in **274** also demonstrated the ability of the P-K reaction to embed high levels of complexity in a single transformation.



Scheme 77. Synthesis of core 274 towards the synthesis of 8-α-hydroxystreotazolone 275

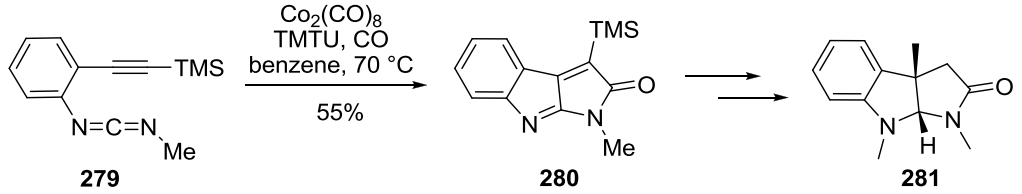
Following on from the successful synthesis of 8-α-hydroxystreotazolone **275**, Mukai and co-workers further demonstrated the functional group tolerance of the P-K reaction, through the ring closure of **276** containing an allene (**Scheme 78**).[173] Using this specific approach, the authors were able to complete the synthesis of uncommon sesquiterpenoids isolated from *Jatropha neopauciflora* **278** with remarkable efficiency. Importantly, in this specific case, the P-K reaction was mediated by a rhodium complex, illustrating that alternative metals are also excellent organometallic systems to facilitate cyclopentenone formation.



Scheme 78. Synthesis of uncommon sesquiterpenes *via* a P-K strategy

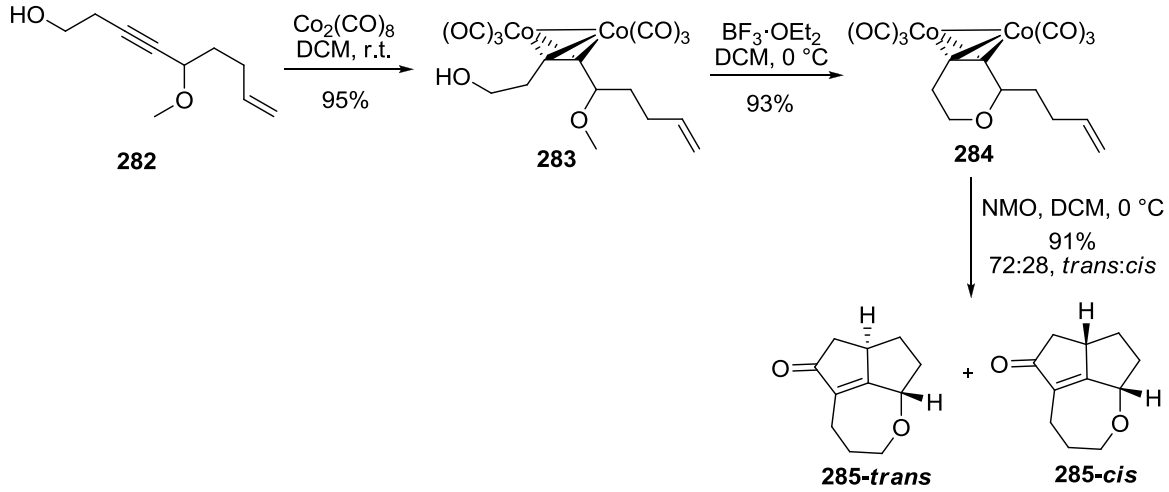
In 2006 Mukai *et al*., continuing the development of P-K methodology towards impressive natural product synthesis, identified alkynecarboiimide **279** as a potential P-K substrate

(**Scheme 79**).[174] During the synthesis of physostigmine **281** the authors not only demonstrated the versatility of the P-K reaction in the formation of complex ring systems, but also expanded the range of known functionality capable of participating in the P-K reaction.



Scheme 79. Synthesis of physostigmine by P-K strategy

In one final example, Shea and co-workers completed the synthesis of several novel oxygen containing heterocycles such as **285** (**Scheme 79**).[175] Analysing the route taken towards the target molecules identifies two key transformations delivered by the cobalt complex in **283**. The first of these involved intramolecular ring closure of complex **283**, only possible because of the deviation from *sp* linearity developed within the complex. Following this, **284** underwent an intermolecular P-K reaction to provide **285** in a yield of 91% and a ratio of 72:28 *trans*:*cis*. In this example, Shea and co-workers not only provided an elegant route to the target molecules, but clearly demonstrated the stability of the alkyne complex and its tolerance for functional group transformations without degradation.



Scheme 79. Synthesis of 285 *via* a P-K strategy

2.17 The Challenges Ahead

From the preceding literature review it is clear that what started in its conception as an ingenious, if inefficient, organometallic transformation, the P-K reaction has developed into an important and powerful tool in organic synthesis. Key to this development was the

expansion of the fundamental knowledge of each of the individual steps through intermediate isolation and DFT studies. It was from this basis that subsequent model systems were identified to expand the boundaries and scope of the reaction.

Despite all of the advancements and in-depth investigations pursued to date, many challenges still remain. The most important of these are the identification of a catalytic system and a reliable asymmetric variant. Key to future developments of the P-K reaction is the stability and versatility of the cobalt complex. Whilst significant advances have been made towards stabilising the cobalt source, the lack of commercial availability of these alternative systems often deters wide-spread use. Compounding the problem is the need to use an atmosphere of highly toxic CO. Although this can be avoided through the use of CO surrogates, access to the CO within these systems requires the use of rhodium, significantly increasing the cost of any reaction. The future of the reaction must lie in the formation of a stabilised complex capable of catalytic turn over without significant degradation. Whilst this still appears to be some time away, the development of its application remains important.

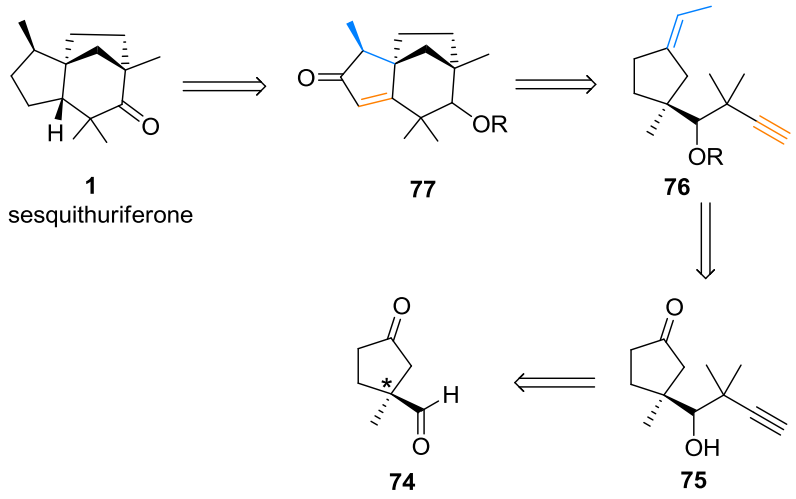
However, it should be noted that whilst the use of stoichiometric amounts of cobalt is not ideal, the atom economy provided by many of the described transformations certainly justifies the incorporation of a P-K strategy into the reaction sequence. It is towards this aim that we hope to demonstrate that significant enhancements of certain synthetic approaches can be achieved through adopting a P-K strategy towards the synthesis of sesquithuriferone **1**.

3 Towards the Synthesis of Sesquithuriferone

3.1 Retrosynthetic Analysis

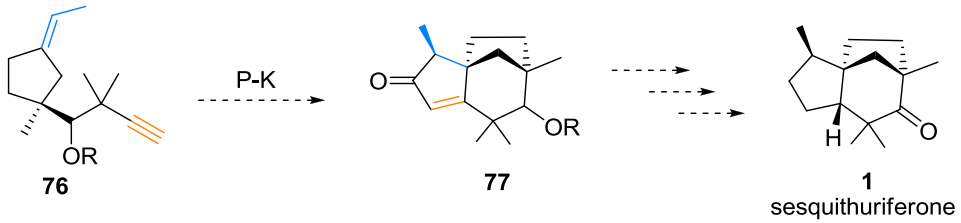
As previously described in **Section 2.5**, a significant amount of precedent has been established towards the synthesis of the related fused-ring systems of cedrene **4** and 3-*epi*-cedren-3-one **6**, incorporating a P-K strategy.[12,176] It was anticipated that by following a similar approach towards the synthesis of sesquithuriferone, many of the identified techniques could be applied, to promote selectivity. Additionally, by adopting this approach we hoped to assess if the identified sequence was applicable as a general strategy to access the various structural manifolds contained within the entire family of natural products.

With these aims in mind, it was envisioned that sesquithuriferone **1** could be quickly built up from the enone motif present in **77**, which in turn is accessible *via* a P-K reaction from **76**. Preparation of **76** was proposed through a *Z*-selective olefination of ketone **75**, ultimately synthesised from the chemoselective addition of the alkynyl side-chain to **74** (**Scheme 85**).



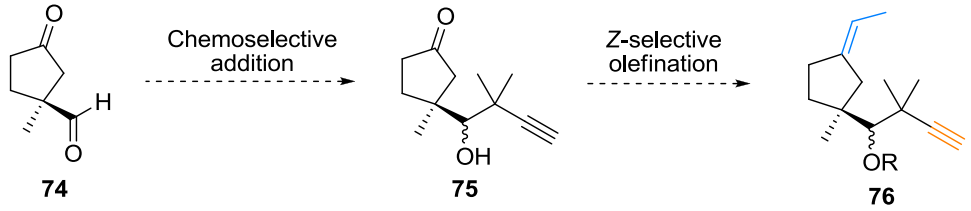
Scheme 85. Retrosynthetic analysis of sesquithuriferone

From the outset of this project it was recognised that key to the success of this approach was the introduction of high levels of complexity at an advanced stage of the synthetic sequence. Towards this goal, the P-K reaction is ideal, embedding two additional stereogenic centres in the formation of **77**, from a relatively simple and accessible compound **76** (**Scheme 86**).



Scheme 86. Proposed Pauson-Khand cyclisation

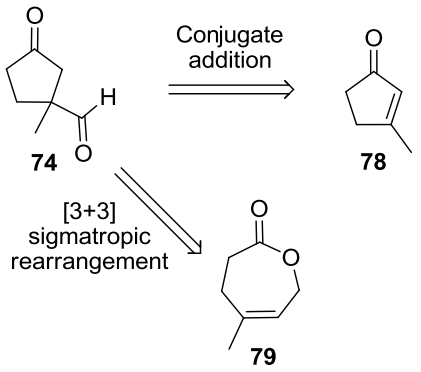
The benefit of this approach is that the early stages of the synthetic sequence would not be encumbered by high levels of complexity, allowing a rapid construction of the basic framework. Additionally, from an asymmetric point of view, the quaternary centre established in **74** should promote a diastereoselective P-K reaction to embed the desired chiral configuration in **77**. However, from a synthetic point of view, a potential problem was also identified concerning chemoselectivity, upon addition of the side-chain to **74** (**Scheme 87**).



Scheme 87. Proposed strategy towards 76

Although aldehydes are inherently more electrophilic than ketones, the relatively high steric demand around this site may not promote the predicted reactivity profile. Secondly, following the addition of the side-chain, it was recognised that if high levels of Felkin-Ahn control could not be achieved, structural and analytical analysis of the resultant product **75** could be hindered by diastereomeric mixtures. This in turn, would make analysis of the *Z*:*E* ratio increasingly difficult, following the olefination of **75**. However, it should be noted, that the alkanol stereogenic centre in **75-77** would ultimately be removed by oxidation at a later stage in the synthetic sequence and hence, any loss of selectivity would mainly be of analytical concern, rather than synthetic. Despite these underlying questions surrounding the synthetic sequence, the described strategy was seen as an excellent starting point to construct the basic structural framework in **77**.

With a general strategy in hand, attention turned towards the synthesis of **74**, both in a racemic and enantioenriched form. Retrosynthetic analysis of **74** identified two main synthetic approaches (**Scheme 88**).



Scheme 88. Proposed strategies to access 74

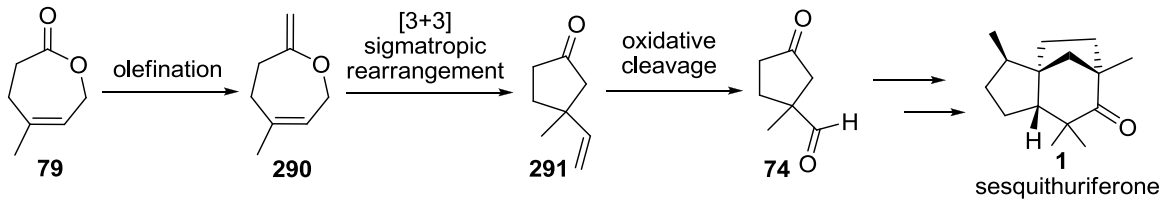
The first and most favoured approach, involved the conjugate addition of an umpolung reagent. Through the use of this technique, the addition of what is essentially an electrophilic functionality could be achieved as a masked reagent, before revealing it at a later stage. This should not only allow for a concise synthesis, but also potentially provide an asymmetric variant and a level of synthetic flexibility.

A second and much more elaborate strategy was also identified, involving a Claisen rearrangement to generate the desired quaternary centre in **74**. A literature search quickly identified that this route was much more speculative, complex, and certainly appeared to provide a greater challenge when developing a highly selective asymmetric variant. Importantly though, this route did provide the opportunity to develop novel methodologies, not only towards the synthesis of 3,3-substituted cyclopentanones such as **74**, but also towards unsaturated ε-lactones such as **79**.

The following sections will provide an overview of the synthetic strategies applied when attempting to synthesise compound **74** by both these approaches. It is important to note that investigations towards both of these routes were carried out simultaneously, although they will be presented as individual sections.

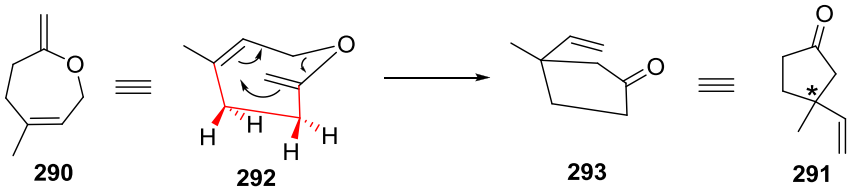
3.2 Claisen Rearrangement Strategy Towards the Synthesis of 74

The first approach presented towards the synthesis of **74** involved a Claisen rearrangement strategy (**Scheme 89**). It was envisioned that, following the olefination of lactone **79**, a Claisen rearrangement of enol ether **290** would furnish cyclopentanone **291** containing the desired quaternary centre. To complete the sequence, keto-aldehyde **74** would be revealed *via* oxidative cleavage, to provide the desired starting material required to continue the synthesis of sesquithuriferone.



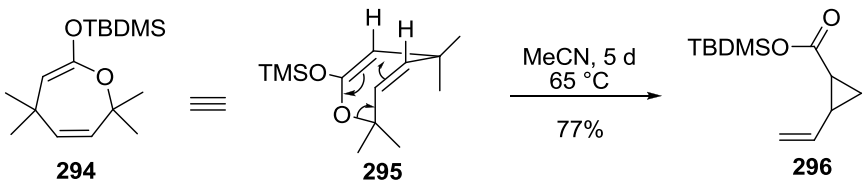
Scheme 89. Proposed synthesis of key keto-aldehyde 74

Based on the substrate adopting a chair-like transition state **292**, the sigmatropic rearrangement can be depicted as shown in **Scheme 90**. However, a closer examination of the transition state reveals that for **290** to attain the desired chair conformation in **292**, significant eclipsing of the C-C and C-H bonds in the bridging section must occur. Having stated this, when taking into account the energetic driving force, due to the formation of a carbonyl, combined with the release in strain when moving from an unsaturated seven-membered ring, it was anticipated that conditions could be found to promote the desired transformation.



Scheme 90. Proposed Claisen rearrangement of 290

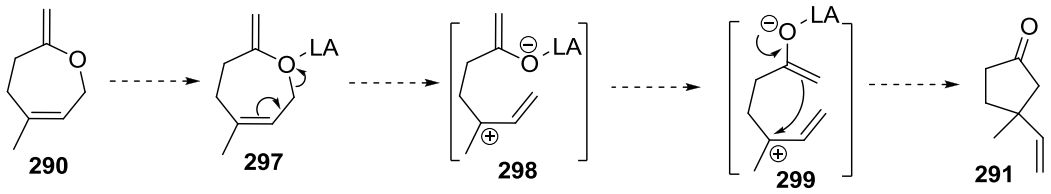
To date there is no literature precedent for the proposed transformation. However, Ireland-Claisen rearrangements of seven-membered rings are often thought to occur through boat transition states, where C-C and C-O eclipsing effects are also observed (**Scheme 91**).[177–182] Care must be taken, when comparing the transition state in **295** with that of our desired transformation, since the proposed transition state (**292**, **Scheme 90**) was not predicted to adopt a boat configuration and the eclipsing effects are significantly different to those observed in the example shown (**295**, **Scheme 91**). Despite this, it was hoped that the tolerance of eclipsing effects observed in boat transition states could offer some limited evidence that the proposed transformation could still be possible.



Scheme 91. Proposed boat transition states of seven-membered enol ethers

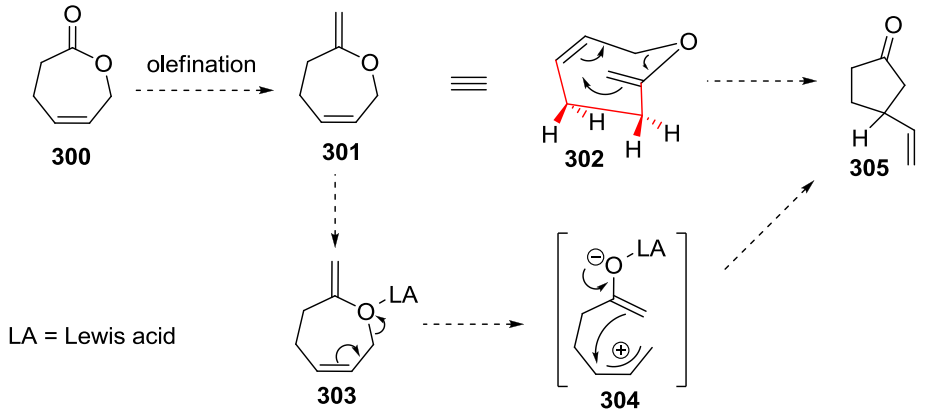
Alternatively, whilst the chair-like transition state provides a suitable model to depict the proposed transformation, the inherent transannular strain generated from rotating the *exo*-

olefin back into the ring system, combined with the resulting eclipsing effects, may render this model unrealistic. Should this be the case, a more disconcerted mechanism may be more plausible. From this perspective, the formation of a tertiary carbocation **298** would facilitate the partial fragmentation of the ring, before kinetically favoured formation of cyclopentanone **291** through intramolecular attack of enolate **299**, as depicted in **Scheme 92**.



Scheme 92. Alternative transition state in the formation of 291

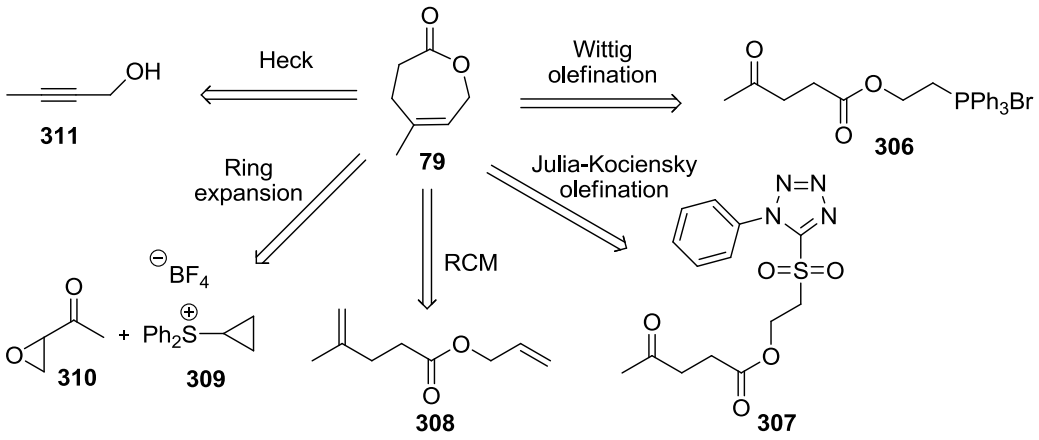
With the aim of gaining insight into which of the presented mechanisms would predominate, a second lactone **300** was identified as an interesting target (**Scheme 93**). It was envisioned that by exposing **300** to identical rearrangement conditions, changes in reactivity would be observed to provide some insight into the mechanistic pathway. In this regard, the absence of the methyl functionality on the olefin would result in a secondary carbocation **304** (as opposed to the more stabilised tertiary carbocation **298**, **Scheme 92**). It was proposed that this should have a greater effect on the rate of reaction of the disconcerted mechanism than on the chair-like transition state.



Scheme 93. Comparison of proposed mechanistic pathways to 305

It should be noted, that it is unlikely that this reaction would conclusively indicate which of the two proposed mechanisms were more probable. However, it was anticipated that through this initial examination the substitution pattern on the olefin, some indication of how to design subsequent derivatives more capable of differentiating between the mechanisms could be elucidated.

With two potential working models for the proposed transformation, attention turned towards accessing the required starting materials **79** and **300**. From this perspective, a number of strategies had been envisioned involving both intra- and intermolecular processes (**Scheme 94**).

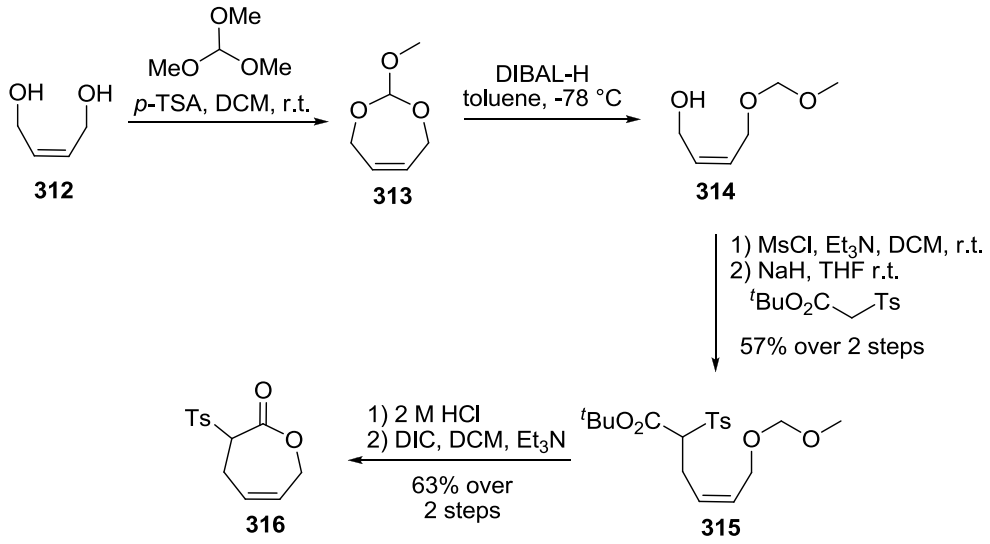


Scheme 94. Synthetic strategies towards 79

3.3 Synthesis of ε-Lactones

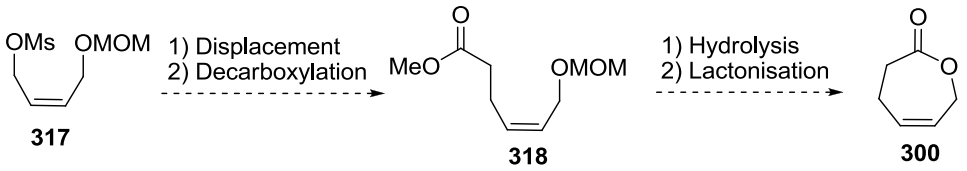
With a preliminary set of synthetic targets identified, attention turned towards the development of methodologies for the preparation of **79** and **300** on a multi-gram scale. A comprehensive literature search revealed few suitable methods for the preparation of unsaturated seven-membered lactones, similar to those under investigation (*vide infra*). With this in mind, it was decided that the preparative strategy should begin with the synthesis of lactone **300**. Indeed, from a synthetic point of view, the disubstituted olefin appeared to be a more facile target to access.

Pleasingly, a recent publication by the Craig group highlighted a step wise route towards the synthesis of α-substituted ε-lactones (**Scheme 95**).[182] The published procedure involved an initial desymmetrisation of *cis* diol **312** through reaction with trimethyl orthoformate and DIBAL-H, to form key compound **314**. It was from this point that a sequential 3-step protocol involving mesylation, displacement, and lactonisation provided access to lactone **316**. Preliminary analysis of this strategy identified that this approach would be ideal to gain access to ε-lactone **300**, due to the reported high yields and the simple starting materials involved in the described transformations. It was also recognised that relatively few alterations to the synthetic sequence would be required to provide the desired target **300**.



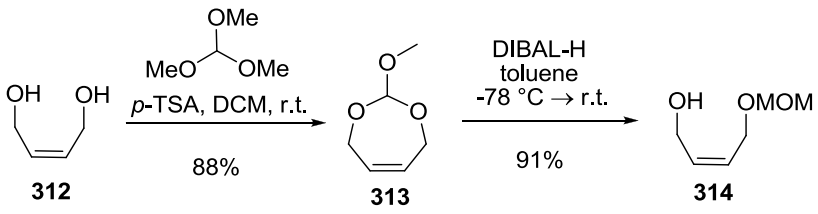
Scheme 95. Synthesis of α-substituted ε-lactones by Craig and co-workers.

Towards this aim, a modified protocol was quickly designed that involved an alternative malonate displacement, followed by Krapcho decarboxylation. It was from this point that **300** could be isolated, through sequential hydrolysis and lactonisation, as shown in **Scheme 96**.



Scheme 96. Proposed synthesis of 300

Following the procedures described by Craig and co-workers, compound **314** was synthesised by condensation of *cis* diol **312**, with trimethyl orthoformate under acidic conditions in a yield of 88%. Subsequent desymmetrisation, through low temperature reduction with DIBAL-H provided **314** in an excellent yield of 91% (**Scheme 97**).[183,184]



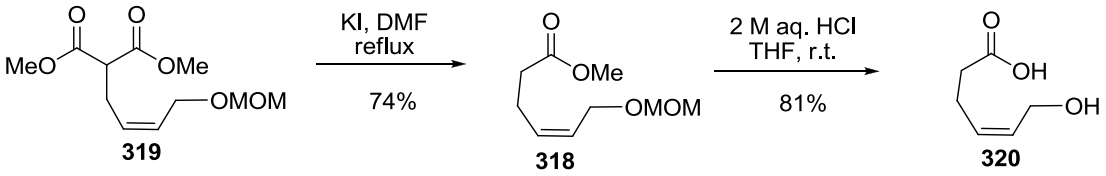
Scheme 97. Desymmetrisation of *cis*-diol 312

The next task involved the synthesis of malonate derivative **319**. To begin the sequence, an initial mesylation was carried out according the procedure described by Craig *et al*.[182] It was at this point that the synthetic route began to deviate from the published protocols. The crude mesylate of **314**, was then added to a preformed solution of dimethyl malonate and NaH,

facilitating the efficient displacement of the mesylate group to provide **319** in an 82% yield over the two steps (**Scheme 98**).

Scheme 98. Synthesis of dicarbonyl compound 319

With significant quantities of **319** in hand, initial attempts to isolate **320** could be attempted. Preliminary investigations indicated that Krapcho decarboxylation was an ideal approach for the synthesis of **318**, with yields in excess of 70% being isolated. Optimised conditions involved refluxing **319** in a suspension of KI in DMF to provide **318** in a reproducible 74% yield (**Scheme 99**). To complete the sequence, compound **320** was obtained through the double hydrolysis of both the MOM and ester functionalities under acidic conditions to provide **320** in an excellent 81% yield.



Scheme 99. Synthesis of compound 320

From the outset of this approach, the synthetic strategy had always been to complete the synthesis of **300** using a coupling agent; therefore a screening of conditions was performed to optimise the desired ring closure (**Table 6**).

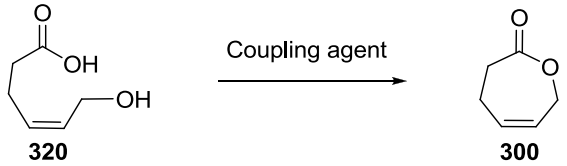


Table 6. Attempted ring closing of acid alcohol 320

Entry	Coupling agent	Solvent	Yield (%)
1	*p*-TSA	Toluene	/
2	DIC	DCM	81
3	DCC	DCM	45
4	Py_2S_2	benzene	0
5	HATU	DCM	83

The first set of conditions explored towards the synthesis of **300** was through acid-catalysed condensation (**Table 6**, Entry 1). Unfortunately, despite numerous attempts, this approach proved somewhat problematic. Although the desired product was isolated in low quantities, a representative yield could not be determined due to the low boiling point of **300**. Conformation of the successful formation of **300** was achieved through GCMS analysis of the crude reaction mixture. To avoid these isolation issues all future attempts to synthesise **300** were carried out in a lower boiling point solvent.

Following the DIC procedure set out by Craig and co-workers towards the synthesis of **316**, a significant increase in yield of **300** was immediately observed (**Table 6**, Entry 2). Furthermore, by carrying out the reaction in DCM, product isolation proved much more facile with an isolated yield of 81% obtained. Subsequent attempts using DCC and the Corey-Nicolaou coupling reagent[185] proved somewhat disappointing, with significantly reduced yields observed in both cases (**Table 6**, Entries 3 and 4). However, a slight improvement in yield to 83% of **300** was observed when using the coupling agent HATU (**Table 6**, Entry 5).

Having identified a suitable set of conditions to facilitate the synthesis of **300**, the remaining material was brought through in a reproducible yield of 83% using the HATU-based protocol, providing significant quantities of material to attempt the subsequent olefination reactions.

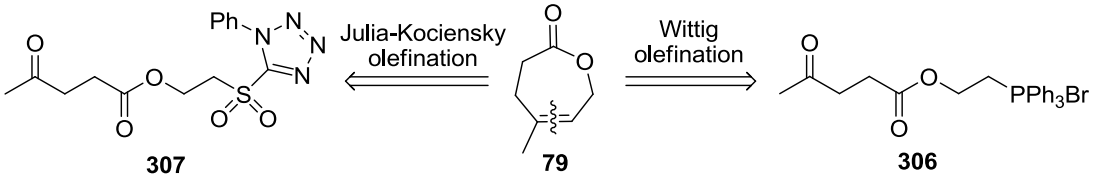
Whilst the early success towards the synthesis of lactone **300** showed promise, two key faults were recognised with this approach. Firstly, from a practical point of view, the strategy required a linear sequence of seven steps, and whilst each of these individual transformations proved to be fairly robust and reproducible, it was too long a sequence to be desirable as a general approach to ε-lactones. Secondly, the initial steps of the reaction sequence involved the desymmetrisation of a C_2 symmetrical diol **312**, significantly reducing the possibilities of diversification into other derivatives such as **79**.

To overcome these issues, a re-evaluation of the approach had to be pursued. Key to the success of any new approach would not only be a reduction in the linear sequence of synthetic steps, but also the identification of a method that would provide several points of diversity.

The following sections will provide a brief outline of each of the synthetic strategies pursued towards the synthesis of **79**.

3.4 Olefination Strategies Towards the Synthesis of Lactone 79

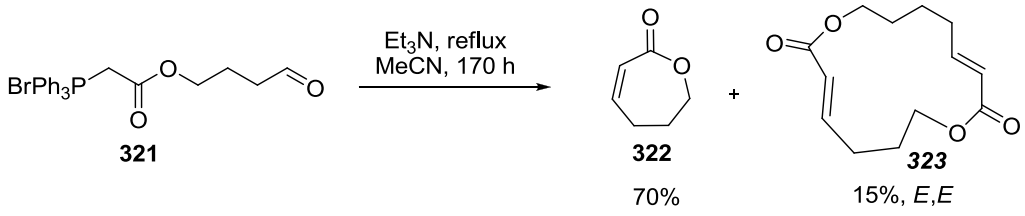
From the outset of these investigations, the primary aim was to develop a route that required the minimum number of synthetic steps, with high levels of selectivity. To achieve this, an intramolecular reaction was envisioned involving *Z*-selective intramolecular olefination from precursors **306** or **307** to deliver lactone **79** (**Scheme 100**).



Scheme 100. Olefination strategy to access 79

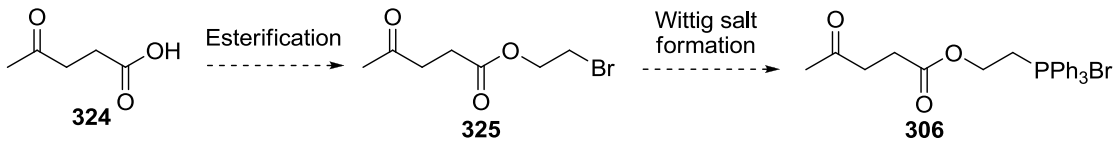
3.4.1 Wittig Olefination Strategy Towards the Synthesis of Lactone 79

With regard to this approach, there was limited literature precedent. In 1989 Le Floc'h and co-workers published a preliminary study describing the relationship between chain length and product oligomerisation, towards the formation of α,β-unsaturated cyclic lactones (**Scheme 101**).[186] The results of the study demonstrated that the intramolecular closure of seven-membered rings by Wittig olefination was favoured, with a 70% yield of **322** isolated. Importantly, the authors observed that as the alkyl portion was systematically increased in length beyond **321**, an appreciable decrease in the formation of the monomeric species was observed, resulting in preferential dimerisation and oligomerisation thereafter. To achieve these impressive results an 'infinite dilution' type approach was used, whereby a solution of phosphonium salt was slowly dripped into a refluxing solution of Et_3N in MeCN. It was hoped that by following a similar approach to the described procedure the synthesis of **79** could be achieved.



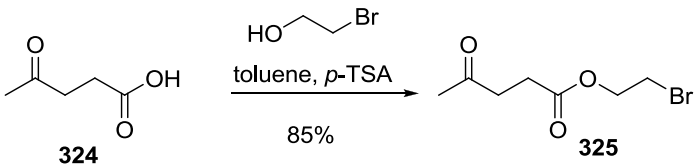
Scheme 101. Wittig ring closing strategy by Le Floc'h *et al.*

To synthesise the desired Wittig precursor a two-step protocol was envisioned (**Scheme 102**). The proposed sequence would involve an initial esterification, followed by reaction with triphenylphosphine to furnish the desired Wittig salt **306**.



Scheme 102. Proposed synthesis of Wittig precursor 306

Accordingly, a solution of leuvilinic acid **324** and 2-bromoethanol were refluxed under Dean Stark conditions, in the presence of a catalytic amount of *p*-TSA. Upon workup and purification, a yield of 85% of **325** was obtained (**Scheme 103**).



Scheme 103. Synthesis of bromo-ester 325

With gram quantities of **325** now in hand, attention could be turned to the synthesis of the requisite Wittig salt **306**. Towards this aim, a range of conditions were explored, including thermal and microwave promotion (**Table 7**).

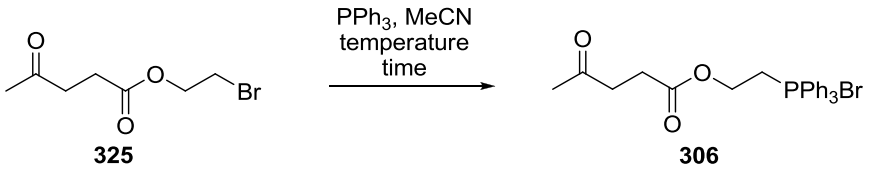


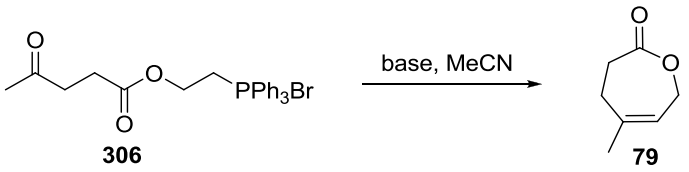
Table 7. Synthesis of Wittig salt 306

Entry	Solvent	Promotion	PPh_3 (eq.)	Temperature (°C)	Time (h)	Yield (%)
1	Toluene	thermal	1.2	reflux	12	15
2	MeCN	thermal	1.2	reflux	12	33
3	MeCN	thermal	2	reflux	12	81
4	MeCN	microwave	2	80	2	36
5	MeCN	microwave	2	100	4	78
6	MeCN	microwave	2	110	4	0

Initial investigations began with the formation of the desired phosphonium salt **306** in a non-polar solvent (toluene). It was expected that as **325** was refluxed in the presence of a slight excess of PPh_3, the phosphonium salt would crash out of solution, allowing the straightforward isolation of **306**. Rather unexpectedly, all attempts to form Wittig precursor **306** by this method proved largely unsuccessful (**Table 7**, Entry 1). However, it was observed that by increasing the polarity of the solvent to MeCN, a slight increase in isolated yield could be achieved, *via* a homogeneous reaction mixture (**Table 7**, Entry 2). Significantly, yields increased dramatically when a larger excess of PPh_3 was added to the reaction mixture providing **306** in an 81% yield (**Table 7**, Entry 3).

Despite an appreciable increase in the yield of **306**, it was felt that further improvements to the procedure could be made, to bring through the gram quantities of material required to investigate the proposed ring closure. In an effort to increase conversions, microwave promotion was investigated. Accordingly, a solution of PPh_3 and **325** in MeCN were heated under microwave promotion conditions for various lengths of time. Heating the solution at 80 °C for 2 h immediately showed some success, with a moderate 36% yield isolated upon trituration of the reaction mixture (**Table 7**, Entry 4). However, a significant increase in yield was observed when increasing the temperature to 100 °C for 4 h, with a 78% yield of **306** isolated (**Table 7**, Entry 5). Unfortunately, no further increases in product conversion could be achieved, with degradation of the reaction mixture occurring above 100 °C (**Table 7**, Entry 6). Although microwave promotion provided a significantly faster reaction time, the improvements in yield and efficiency that were initially desired could not be achieved. It was with these results in mind that all further attempts to optimise the reaction further were suspended.

With the requisite phosphonium salt **306** prepared in acceptable yields, the intramolecular cyclisation could now be attempted. Towards this aim, a range of conditions were investigated as shown in **Table 8**.



306 **79**

Table 8. Attempted ring closure of 306 by Wittig olefination

Entry	Base	Temperature (°C)	Time (h)	Solvent	Yield (%)
1	Et_3N	reflux	216	MeCN	0
2	KO^tBu	r.t.	60	THF	0
3	^{n}BuLi	0 → r.t.	48	THF	0

To begin the screening of reaction conditions, an initial attempt was carried out following the procedures set out by Le Floc'h and co-workers (**Table 8**, Entry 1).[186] Accordingly, a solution of **306** was added by syringe pump to a refluxing solution of Et_3N in MeCN over 48 h and then refluxed for a further 7 days. Unfortunately, after this time lactone **79** could not be detected within the reaction mixture. Instead, a complex range of products was formed, of which triphenylphosphine oxide was present in small quantities.

In a second attempt to promote the desired ring closure, an alternative protocol was envisioned. This adapted approach involved the simultaneous addition of separate solutions of KO^tBu and **306** into a reaction vessel containing a large volume of THF, over a 48 h period (**Table 8**, Entry 2). It was envisioned that the increased strength of the base would enhance the rate of deprotonation, whilst high dilution would avoid competitive oligomerisation. Unfortunately, lactone **79** was not detected even after a prolonged reaction period. Importantly, triphenylphosphine oxide was again detected within the complex mixture, indicating that Wittig olefination was occurring within the reaction.

In the final attempt, ^{n}BuLi was used as the base (**Table 8**, Entry 3). Following the protocol described for Entry 2, separate solutions of ^{n}BuLi and **306** were dripped into a large volume of THF at 0 °C over 36 h. Disappointingly, as with the previous two attempts, a complex mixture of products was formed, in which lactone **79** was not detected.

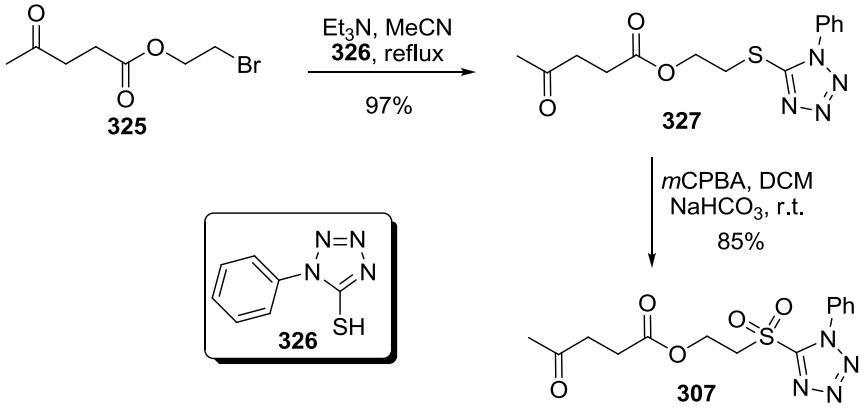
Clearly, the results presented in **Table 8** indicate that phosphonium salt **306** is not a suitable precursor for the synthesis of lactone **79** by intramolecular ring closure. However, throughout the reaction conditions investigated, the isolation of triphenylphosphine oxide would suggest that Wittig olefination was taking place. Despite this, the complex range of products formed indicated that even if lactone **79** was formed in low yields, the efficiency of the proposed ring

closure was too low to justify further examination. At this point alternative and more viable routes towards the synthesis of key intermediates were prioritised.

3.4.2 Julia-Kociensky Olefination Strategy Towards the Synthesis of Lactone 79

Concurrent and complementary to the intramolecular Wittig strategy, a second olefination approach was also investigated involving the corresponding Julia-Kociensky reagent **307**. Whist this olefination technique has enjoyed a wealth of success throughout literature, it is only more recently that this strategy has increased in popularity as a ring closing methodology.[187] Importantly, to date most of the examples within the literature have involved the closing of larger macrocycles, with no direct precedent available for smaller cyclic systems such as **79**.[188,189]

Using common intermediate **325**, the synthesis of **307** was envisioned following a similar approach to Wittig salt **306**. Accordingly, from **325** it was proposed that the corresponding sulfide **327** could be synthesised through S_N2 displacement and subsequent oxidation to provide sulfone **307** (**Scheme 104**). This should provide a simple and scalable route through to gram quantities of **307**, required for further investigations towards the proposed intramolecular ring closure.



Scheme 104. Julia-Kociensky strategy to access lactone 307

Synthesis of the corresponding sulfide proved relatively facile under basic conditions, with a 97% yield of **327** isolated. Subsequent oxidation with excess *m*CPBA provided sulfone **307** in an excellent yield of 85%.

Following the successful synthesis of **307**, a short screening of olefination conditions was carried out to assess the suitability of **307** towards intramolecular ring closure (**Table 9**).

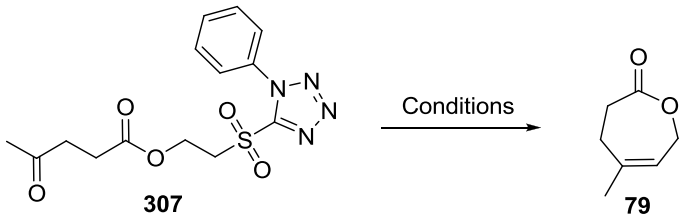
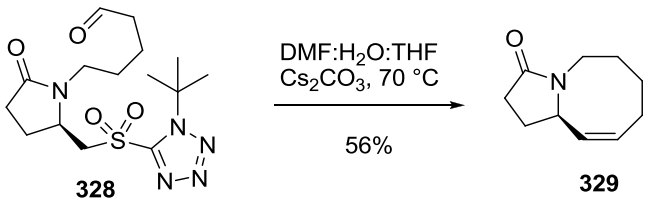


Table 9. Attempted synthesis of 79 by Julia-Kociensky olefination

Entry	Solvent	Base	Temperature (°C)	Yield (%)
1	DMF:THF:H_2O	Cs_2CO_3	70	0
2	THF	^{n}BuLi	-20 → r.t.	0
3	THF	KHMDS	-20 → r.t.	0

When attempting to identify a suitable set of reaction conditions to complete the synthesis of lactone **79**, attention was drawn to a recent example developed by the Dixon group.[188] During investigations towards the synthesis of Nakadomarin A, the authors successfully utilised a *Z*-selective Julia-Kociensky olefination to provide an eight-membered ring system **329** (**Scheme 105**).



Scheme 105. Z-selective synthesis of 329 by Dixon and co-workers

The conditions used to achieve this impressive result involved a mild base, combined with a highly polar solvent, in an 'infinite dilution' type approach. Despite the structural differences between **329** and **79**, these conditions appeared to be an excellent starting point for these investigations. Importantly, the polar reaction media should help to promote *Z*-selectivity, whilst the high dilutions shift the effective molarity towards an intramolecular reaction. Accordingly, following the protocols set out by the Dixon group, a solution of **307** was added to a refluxing solution of Cs_2CO_3 over 10 h (**Table 9**, Entry 1). Unfortunately, an extremely complex range of unknown products was formed, with no individual component isolated in significant quantities.

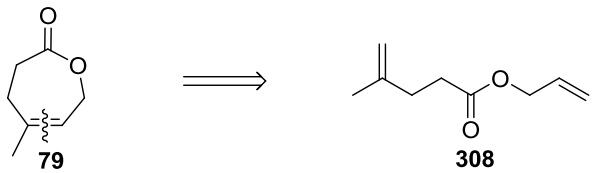
In two further attempts to promote cyclisation, slight adaptions of the reaction conditions were pursued. This alternative protocol involved the separate and simultaneous addition of bases ^{n}BuLi or KHMDS and **307** to a large volume of THF at -20 °C, before warming to r.t. (**Table 9**, Entries 2 and 3). However, a complex mixture of compounds was again formed, in which lactone **79** was not detected by ^{1}H NMR, TLC or GCMS analysis.

Despite the identification of an efficient route to **307**, all further investigations towards the formation of **79** proved unsuccessful. Importantly, a subsequent publication by Blakemore and co-workers following a similar approach towards the synthesis of medium sized lactones, concluded that monomeric ring closure appears to be disfavoured, with dimerisation identified as the most likely result.[190]

It was clear from the results described in **Section 3.4** that accessing lactone systems such as **79** by an intramolecular olefination was not a feasible option. At present it is unclear why the intramolecular reaction is so disfavoured and all attempts to rationalise the outcome have not led to a definite conclusion. However, current thinking points towards a combination of an unfavourable increase in transannular strain during the formation of the transition state, combined with an unfavourable conformational bias, as will be described in the next section.

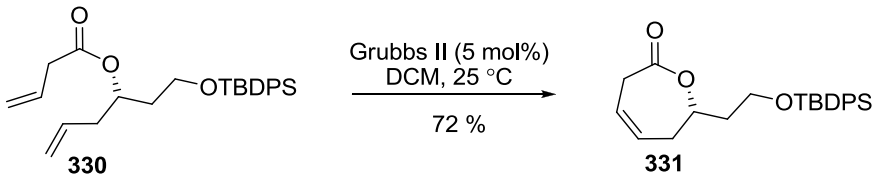
3.5 Ring Closing Metathesis (RCM) Strategy Towards the Synthesis of Lactone 79

Following the unsuccessful attempts to synthesise **79** by intramolecular olefination, an alternative strategy had to be pursued. This required the re-evaluation of the retrosynthetic approach from the target lactone **79**. In this regard, RCM was identified as a potential and concise approach (**Scheme 106**).



Scheme 106. RCM strategy towards the synthesis of 79

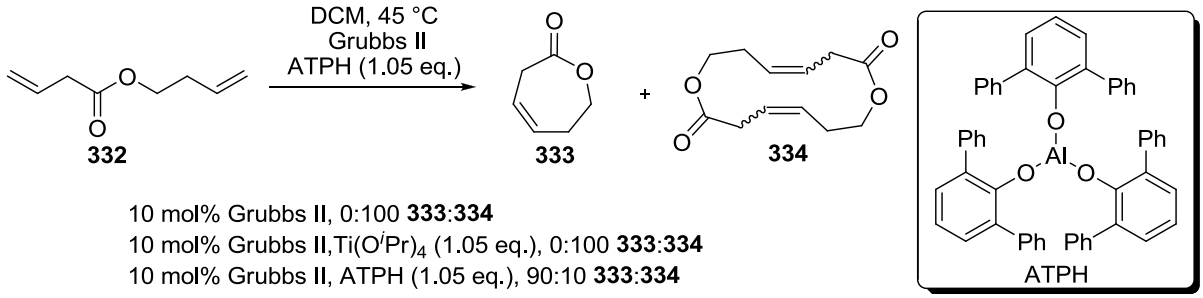
Having stated this, a literature search aimed specifically at determining the suitability of the proposed RCM strategy identified important, if seemingly contradictory results. In 2006, the Yadav group reported the successful synthesis of an unsaturated seven membered lactone **331** using Grubbs II catalyst.[191] The transformation was performed under dilute conditions with no adverse dimerisation or side products reported (**Scheme 107**).



Scheme 107. Yadav's RCM strategy towards the synthesis of 331

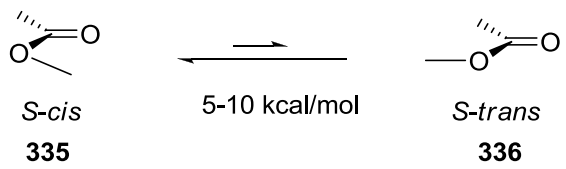
Further investigation identified a number of additional groups that had published similar findings, indicating that yields of 51-72% were possible with similar substrates.[192–196] In several of the reported syntheses however, competitive oligomeristion was also described, indicating that high dilution was critical to the success of this approach, with concentrations of 0.05-0.002 M proving optimal for these systems.

Conversely, in 2008 Pentzer and co-workers published the synthesis of several examples of medium sized cyclic lactones, of comparable structural similarity to **79**.[197] In their landmark paper, the authors propose that when attempting the ring closure of substrates such as **332**, that dimerisation to **334** is the most probable outcome, rather than the formation of monomeric product **333** (**Scheme 108**).



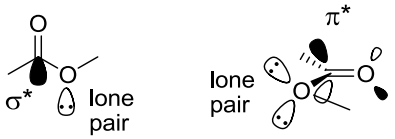
Scheme 108. Encapsulation-RCM by Pentzer and co-workers

In an attempt to rationalise their findings the authors proposed that dimerisation was a direct consequence of conformational bias, resulting from the open chain ester preferentially adopting the *S-cis* conformation **335** (**Scheme 109**).[198,199]



Scheme 109. Proposed *S-cis* and *S-trans* conformations of esters

DFT analysis has shown that the extra inherent stability of the *S-cis* conformation is thought to be generated by favourable orbital interactions between the lone pairs on the oxygen and both the σ* and π* orbitals of the carbonyl unit (**Figure 18**).[200]



337 338

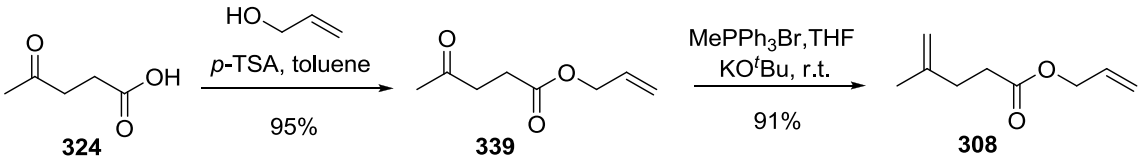
Figure 18. Orbital interactions involved in determining ester conformation

Although this orbital interaction provides extra stabilisation, the difference in energy between the *S-cis* and *S-trans* conformations was estimated at around 5-10 kcal/mol, which is easily overcome at room temperature. However, as proposed by Pentzer, this conformational pre-organisation may be sufficient to shift the effective molarity away from an initial intramolecular reaction and hence reduce the overall yield of the monomeric species, to promote dimer and oligomer formation. In 2002, a publication by Jansen and co-workers also seemed to concur with these findings, stating that when attempting the ring closure of medium sized lactams, the same conformational bias was sufficient to prevent effective ring closure.[201]

Despite the varied reported success of the closure of seven-membered lactones of similar structure to **79**, it was felt that an initial exploration of reaction conditions could quickly identify the suitability of **308** for this synthetic approach. In the event that direct RCM of the proposed precursor **308** could not be achieved, two options remained: firstly, modification of the substrate to activate the olefins for ring closure (relay-RCM); and secondly, an encapsulation-RCM process described by the Pentzer group (**Scheme 108**).

3.5.1 Synthesis and Screening of RCM Precursors

With three direct methods identified to facilitate the proposed ring closure, substrate synthesis and reaction screening could be initiated. The first substrate of choice was compound **308** (**Scheme 110**). Synthesis of this substrate was proposed through a two step protocol involving an initial esterification, followed by Wittig olefination to embed the second olefin. From the outset, the described reaction sequence proved highly efficient, with both the esterification of **324** under Dean Stark conditions to provide **339** and the subsequent Wittig reaction to afford **308**, achieved in excess of 90% yield.



Scheme 110. Two step protocol to synthesise diene 308

With significant quantities of **308** in hand, preliminary attempts at ring closure could be attempted. A search through the vast array of literature covering the field of RCM immediately highlighted that a huge range of variables were capable of determining the outcome of the reaction, including: solvent, functionality, temperature, concentration, and additives.[202–207] With this in mind, a systematic study was initiated.

Due to the suspected volatility of the target molecule **79** (inferred from the volatility of **300**), preliminary investigations were carried out in DCM (**Table 10**). It was also noted that mass analysis of the products would be crucial, since cyclic monomers and dimers would show little or no differentiation in the NMR spectra, provided they were head to tail products. Taking these factors into account, both the crude and purified reaction products were examined by GCMS to confirm the identity of the compounds formed.

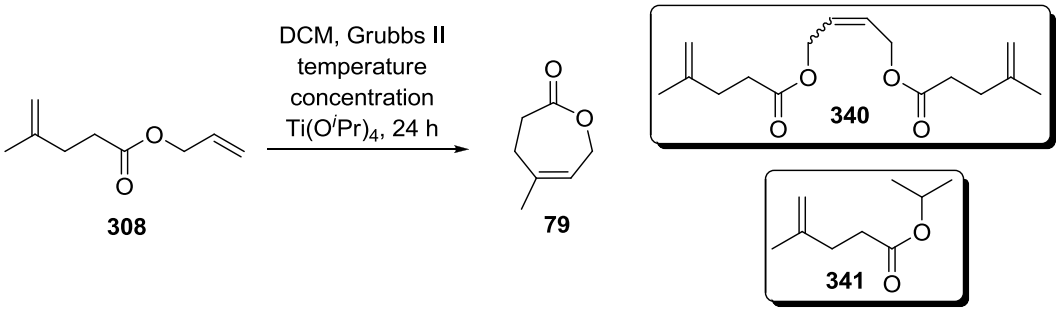


Table 10. Attempted synthesis of 79 by RCM in DCM

Entry	Catalyst (mol%)	Temperature (°C)	Dilution (mmol)	$Ti(O^iPr)_4$ (eq.)	**79** (%)	Side product **340** or **341** (%)
1	5	r.t.	0.1	/	0	**340** (67)
2	10	r.t.	0.02	/	0	**340** (63)
3	10	r.t.	0.02	0.3	0	**340** (62), **341** (26)
4	10	r.t.	0.02	3	0	**340** (34), **341** (57)
5	10	reflux	0.02	/	0	**340** (62)
6	10	reflux	0.02	0.3	0	**340** (55), **341** (28)
7	10	reflux	0.02	3	0	**340** (21), **341** (71)
8[a]	20	reflux	0.002	/	0	**340** (58)

[a] 20 mol% catalyst added as four separate batches of 5 mol% every 6 h.

From the preliminary results shown in **Table 10**, several general trends became apparent. Crucially, despite a wide range of conditions examined, no desired product **79** was isolated (**Table 10**, Entries 1-8). Following a closer examination of the reaction mixtures, **340** or **341** were identified as the major components formed under all of the conditions examined.

The isolation of **340** was not entirely unexpected, since it was the result of head-to-head dimerisation of the monosubstituted olefin. However, the fact that it was present in such substantial amounts was alarming. Interestingly, concentration did not seem to have a significant effect on the formation of **340**, with isolated yields consistently in the range of 58-67%, despite dilutions varying from 0.1-0.002 M (**Table 10**, Entries 1, 2, 5 and 8). Similarly, temperature did not appear to affect yields significantly (**Table 10**, Entries 2 and 5). These results suggest that one, or all, of three critical factors were responsible in determining product formation: (a) the allylic functionality was having an activating effect on the olefin, promoting head-to-head dimerisation, (b) the substitution pattern on the reacting olefins was influencing product formation, or (c) monomeric ring closure was inhibited by the conformational effects proposed by Pentzer.[197]

However, the isolation of **341** was completely unexpected (**Table 10**, Entries 3, 4, 6 and 7). The large quantities of **341** isolated would suggest that in the presence of $Ti(O^iPr)_4$ an unexpected transesterification was occurring, largely shutting down the RCM process through removal of the second olefin. Importantly, these effects appeared to be much less prevalent where 0.3 equivalents of $Ti(O^iPr)_4$ was present in the reaction mixture (26-28% **341**, **Table 10**, Entries 3 and 6). However, a significant increase in **341** was observed when 3 equivalents of $Ti(O^iPr)_4$ was added to the reaction mixture (57-71%, **Table 10**, Entries 4 and 7). Furthermore, it would appear that the transesterification process was further promoted at higher temperatures, with yields increasing from 57% of **341** at room temperature, to 71% of **341** at reflux (**Table 10**, Entries 4 and 7). At present, the reasoning behind this unexpected transesterification process remains unclear and to date, to the best of our knowledge, no literature precedent for similar transformations exists.

Following the disappointments of the reaction in DCM, a comparative study was carried out in toluene (**Table 11**). The benefit of switching to toluene was that significantly higher temperatures could be reached under reaction conditions. It was envisioned that by increasing the overall energy within the reacting system any potential conformational effects would be reduced, promoting monomeric ring closure.

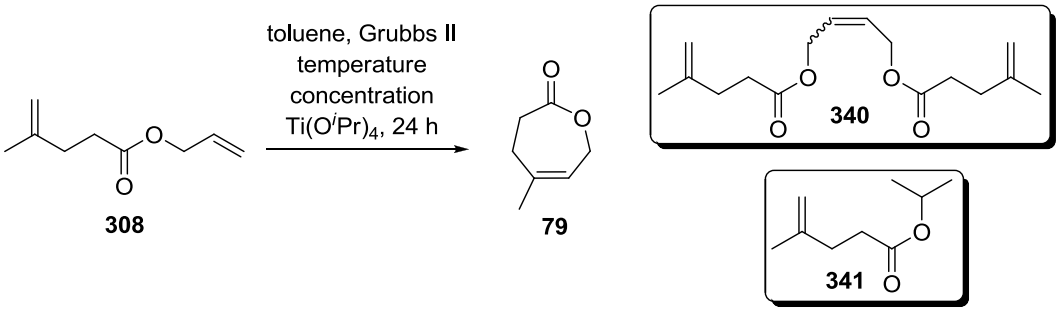


Table 11. Attempted synthesis of 79 by RCM in toluene

Entry	Catalyst (mol%)	Temperature (°C)	Dilution (mmol)	Ti(O^{i}Pr)$_4$ (eq.)	**79** (%)	Side product **340** or **341** (%)
1	5	r.t.	0.1	/	0	**340** (58)
2	10	r.t.	0.02	/	0	**340** (52)
3	10	r.t.	0.02	0.3	0	**340** (57), **341** (23)
4	10	r.t.	0.02	3	0	**340** (22), **341** (56)
5	10	reflux	0.02	/	0	**340** (54)
6	10	reflux	0.02	0.3	0	**340** (56), **341** (28)
7	10	reflux	0.02	3	0	**340** (9), **341** (88)
8[a]	20	reflux	0.002	/	0	**340** (59)

[a] 20 mol% catalyst added as four separate batches of 5 mol% every 6 h.

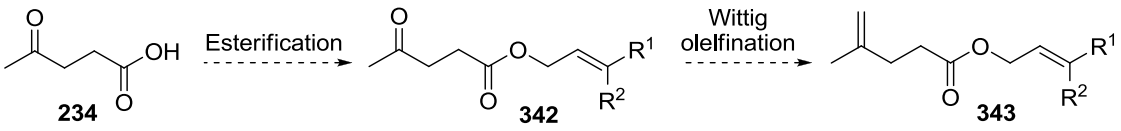
Unfortunately, as with the previous DCM protocol (**Table 10**), in all of the cases examined lactone **79** was not detected and in general, a similar reactivity profile was observed (**Table 11**, Entries 1-8). Again, concentration seemed to have little effect on product formation, with the head-to-head dimer **340** isolated as the major product in the absence of Ti(O^{i}Pr)$_4$ (52-59%, **Table 11**, Entries 1, 2 and 8). Temperature also seemed to have little effect on isolated yields, with 52% of **340** isolated at room temperature compared to 54% of **340** at reflux (**Table 11**, Entries 2 and 5). Importantly, isolated yields of **340** were observed to be approximately 5% lower in toluene, when compared to the previous DCM system investigated (**Tables 10** and **11**).

The addition of Ti(O^{i}Pr)$_4$ to the reaction mixture had a similar effect to those observed in the DCM protocols, with the formation of both the dimeric species **340** and the transesterification product **341** being the only products detected throughout. Furthermore, the ratio of products followed a similar trend, with the dimeric product **340** isolated in higher yields from reactions containing 0.3 equivalents of Ti(O^{i}Pr)$_4$ and temperature having little effect on these results (**Table 11**, Entries 3 and 6). However, temperature again had a significant effect on the formation of **341** in the presence of a large excess of Ti(O^{i}Pr)$_4$. It was observed that at reflux

88% of **341** was formed, compared only 56% at room temperature (**Table 11**, Entries 4 and 7). To put this into further context, the temperature effect becomes more pronounced when compared to the isolated yields of **341** in refluxing DCM. This shows that as reflux conditions rise from 45 °C in DCM, to 110 °C in toluene, yields of **341** rise appreciably from 71% to 88% (**Table 10**, Entry 7, **Table 11**, Entry 7).

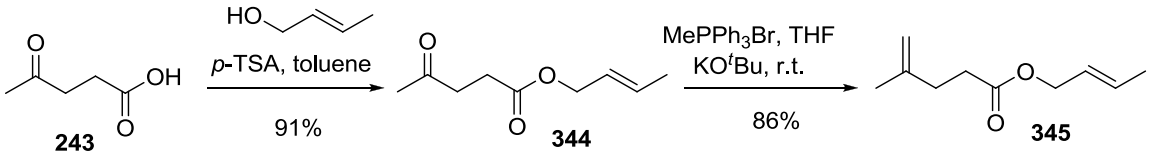
As demonstrated by the results shown in **Tables 10** and **11**, diene **308** is not a suitable precursor to facilitate effective ring closure under the conditions investigated. However, one final trend in reactivity could be determined through careful examination of the products formed. Namely that, in all cases, no cyclic dimerisation or oligomerisation was observed, only head-to-head dimerisation product **340**. Importantly, this would indicate that the 1,1-disubstituted olefin remained unreactive in the presence of Grubbs II catalyst throughout all of the conditions examined.

In an attempt to indirectly address this problem without deviating from the current strategy, an initial solution was proposed that involved varying the substitution pattern on the allylic olefin. It was envisioned that by increasing the number of substituents on this olefin, a reduction in the activity of this moiety would be observed, slowing the rate of head-to-head dimerisation and hence, promote monomeric ring closure. Towards this aim, a modified substrate **343** was proposed (**Scheme 111**). To synthesise **343**, an identical strategy to the previous synthesis of **308** was envisioned, involving an initial esterification with an alternative allylic alcohol, followed by Wittig olefination. In this way a range of allylic substitution patterns could be accessed without increasing the complexity of the synthetic sequence.



Scheme 111. General two step protocol to synthesise substituted dienes

Esterification of **243** with the corresponding crotyl alcohol proved facile, with an excellent 91% yield of **344** isolated under Dean Stark conditions. Following this, olefination with $MePPh_3Br$ and KO^tBu provided the corresponding RCM precursor **345** in an 86% yield (**Scheme 112**).



Scheme 112. Two step protocol to synthesise diene 345

Having completed the synthesis of **345**, a comparative study to the ring closure of **308** was initiated, to determine if the additional substituent in the olefin had a significant influence on monomeric ring closure (**Table 12**).

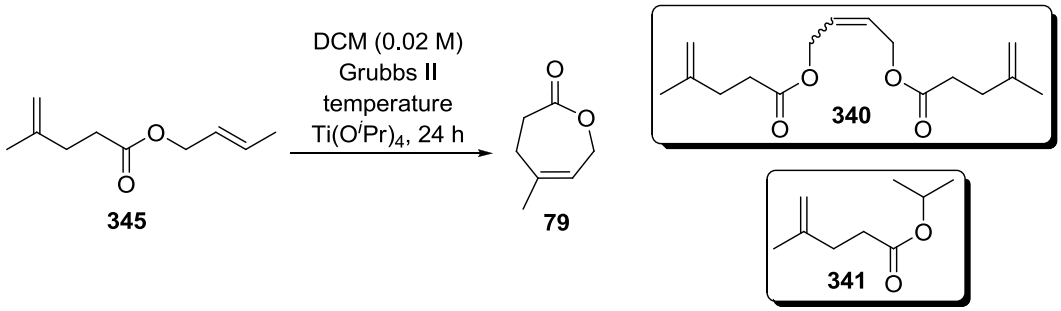


Table 12. Attempted synthesis of lactone 79 by RCM in DCM

Entry	Grubbs II (mol%)	Temperature (°C)	$Ti(O^iPr)_4$ (eq.)	**79** (%)	Side product **340** or **341** (%)
1	10	r.t.	/	0	**340** (59)
2	10	r.t.	0.3	0	**340** (61), **341** (27)
3	10	r.t.	3	0	**340** (32), **341** (55)
4	10	reflux	/	0	**340** (63)
5	10	reflux	0.3	0	**340** (57), **341** (28)
6	10	reflux	3	0	**340** (21), **341** (69)
7[a]	20	reflux	/	0	**340** (61)

[a]20 mol% catalyst added as f separate batches of 5 mol% every 6 h. Reaction concentration 0.002 M.

Unfortunately, the results in **Table 12** indicate that the addition of an extra methyl on the allylic olefin had no positive effect on the formation of **79**. Furthermore, the additional substitution appeared to result in no appreciable change in reactivity, with the ratio of products remaining fairly consistent compared to the corresponding allylic system **308** (**Tables 10** and **11**). In this regard, the major product in the absence of $Ti(O^iPr)_4$ was the head-to-head dimer **340** (**Table 12**, Entries 1, 4 and 7). Additionally, increasing yields of **341** were observed with increasing amounts $Ti(O^iPr)_4$ and elevated temperatures (**Table 12**, Entries 2, 3, 5 and 6).

Despite these disappointing results, compound **345** was also subjected to similar conditions in toluene (**Table 13**).

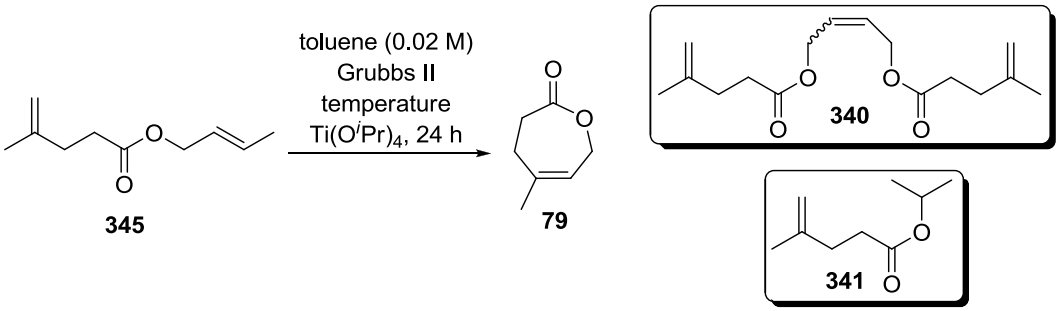


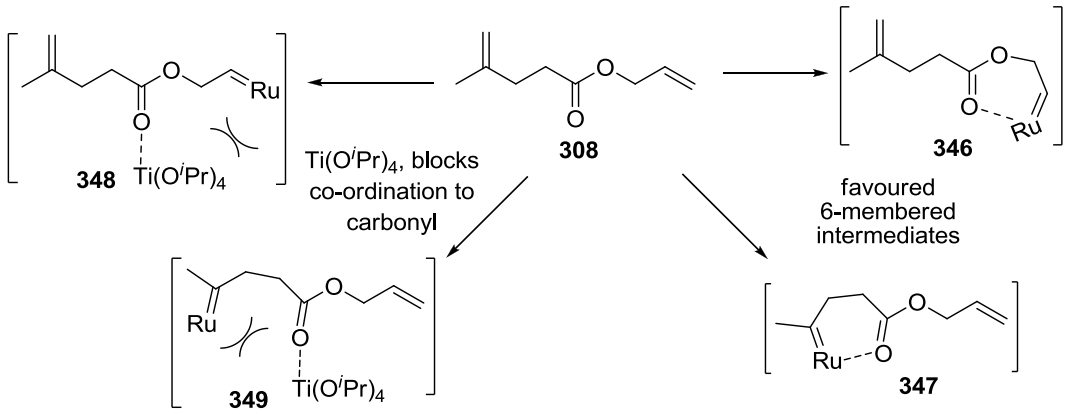
Table 13. Attempted synthesis of lactone 79 by RCM in toluene

Entry	Grubbs II (mol%)	Temperature (°C)	Ti(O^{i}Pr)$_4$ (eq.)	**79** (%)	Side product **340** or **341** (%)
1	10	r.t.	/	0	**340** (54)
2	10	r.t.	0.3	0	**340** (57), **341** (25)
3	10	r.t.	3	0	**340** (26), **341** (62)
4	10	reflux	/	0	**340** (57)
5	10	reflux	0.3	0	**340** (53), **341** (29)
6	10	reflux	3	0	**340** (11), **341** (86)
7[a]	20	reflux	/	0	**340** (61)

[a] 20 mol% catalyst added as four separate batches of 5 mol% every 6 h. Reaction concentration 0.002 M.

Unfortunately, as **Table 13** clearly demonstrates **79** was not detected throughout the various RCM conditions examined in toluene. Once again, a similar reactivity profile was observed when compared to the corresponding unsubstituted system **308** (**Table 11**). With regards to the product distribution, **340** was the major product in the absence of Ti(O^{i}Pr)$_4$ (**Table 13**, Entries 1, 4 and 7) and upon addition of 0.3 equivalents of Ti(O^{i}Pr)$_4$ **341** began to be detected as the minor product (**Table 13**, Entries 2 and 5). Again, as the equivalents of Ti(O^{i}Pr)$_4$ were increased a corresponding rise in **341** was observed, with 62% at room temperature and 86% at reflux observed (**Table 13**, Entries 3 and 7).

Before continuing any further, additional investigation into the formation of side product **341** was required. Theoretically, Ti(O^{i}Pr)$_4$ was proposed to act as a Lewis acid, co-ordinating to the carbonyl and preventing the formation of potentially non-reactive carbenoid intermediates **346** and **347** (**Scheme 113**).[208,209]



Scheme 113. Proposed co-ordination of Ti(O^{i}Pr)$_4$ in RCM reactions

However, throughout all of the conditions examined, containing either substoichiometric or excess amounts of Ti(O^{i}Pr)$_4$, side product **341** was observed. To further understand if this was simply a result of the reaction of **308** or **345** with Ti(O^{i}Pr)$_4$, or some unknown process in the presence of Grubbs II catalyst, a series of control reactions were carried out. Towards this aim, RCM precursors **308** and **345** were stirred separately in refluxing solutions of Ti(O^{i}Pr)$_4$, monitoring product change after 6 h in order to determine the stability of the RCM precursor in the presence of the additive.

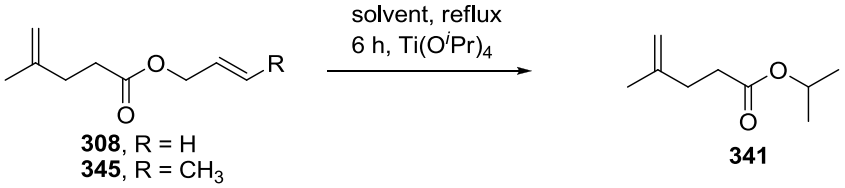


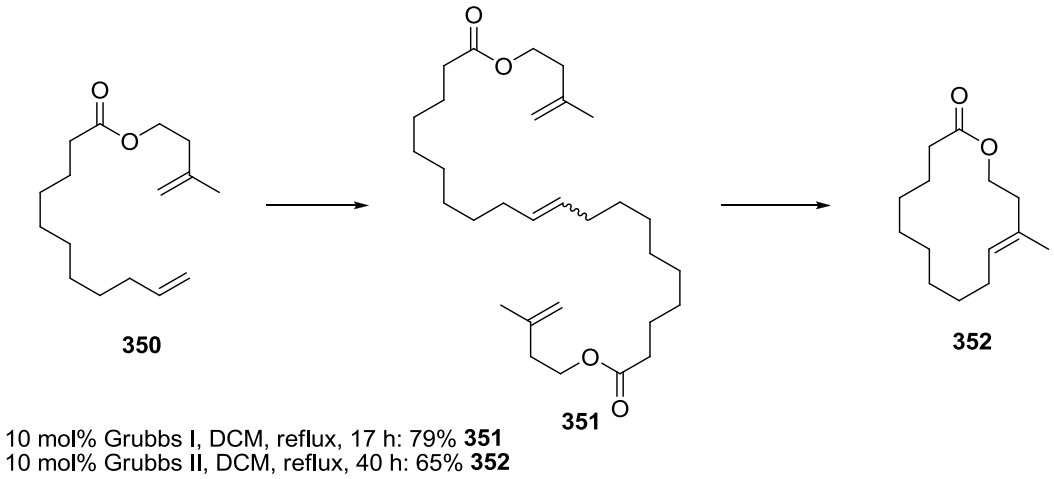
Table 14. Control reactions to determine effect of Ti(O^{i}Pr)$_4$

Entry	R	Solvent	Ti(O^{i}Pr)$_4$ (eq.)	Yield (%)
1	**308**	DCM	3	28
2	**308**	Toluene	3	41
3	**345**	DCM	3	27
4	**345**	Toluene	3	45

From the results shown in **Table 14**, it immediately becomes clear that dienes **308** and **345** are unstable in the presence of Ti(O^{i}Pr)$_4$ at reflux. Closer analysis of the levels of conversion to **341** reveals an increase in the transesterification process at higher temperatures (**Table 14**, Entries 2 and 4). Additionally, these results appear to concur with the product distributions observed in previous examples containing both the additive and Grubbs II catalyst (**Tables 10-13**). Interestingly, the substitution pattern on the allylic olefin did not significantly

influence the rate of formation of **341**. Crucially, this effect was sufficiently pronounced to justify the removal of $Ti(O^iPr)_4$ as an additive in all future investigations to synthesise **79**.

With the formation of **341** attributed to the presence of $Ti(O^iPr)_4$, attention turned towards the formation and reactivity of head-to-head dimer **340**. In 2001, Fürstner and co-workers observed that when attempting to close large macrocycles such as **352**, an initial head-to-head dimerisation was occurring to form **351**, which upon prolonged reaction time, formed the desired ring closing product **352** (**Scheme 114**).[210]



Scheme 114. Intermediate dimer 351 detected during the ring closure of 352, Fürstner *et al.*

Whilst the presence of **79** had never been detected, it could not be ruled out that dimerisation to **340** was simply an intermediate compound and that prolonged reaction times may produce the desired monomeric ring closing to deliver **79**. To ascertain if this process was occurring, acyclic dimmer **340** was subjected to extended reaction times in the presence of Grubbs II catalyst to verify if the desired bite back could occur (**Table 15**).

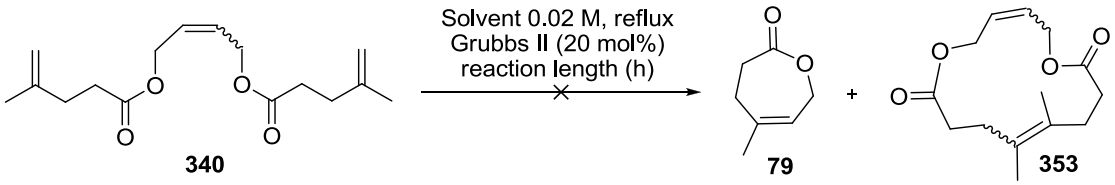


Table 15. Attempted ring closure of asymmetric dimer 340

Entry[a]	Solvent	Reaction length (h)	**79** or **353** (%)
1	DCM	24	0
2	DCM	48	0
3	Toluene	24	0
4	Toluene	48	0

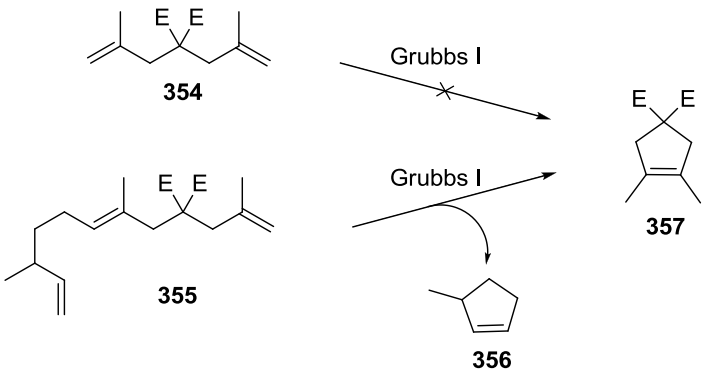
[a] In all cases 20 mol% of catalyst was added over 24 h at 6 h intervals.

Unfortunately, all of the conditions investigated failed to promote the formation of **79**. Additionally, no dimerisation to form the larger 14-membered macrocycle **353** was detected and in all cases, a quantative return of the starting dimer **340** was observed. These results indicated that the formation of **79** (or **353**) was likely to be unfavourable due to a combination of the proposed *S-cis* conformational bias and the steric demand of forming a tri- or tetra-substituted olefin.

Disappointingly, despite a wide range of conditions investigated to date, all attempts to form **79** by RCM have proved unsuccessful. However, some important questions were answered. Firstly, head-to-head dimer **340** was the major product formed in the absence of additives. Secondly, the addition of $Ti(O^iPr)_4$ to the reaction mixture caused the formation of an unexpected transesterification product **341**, altering the initial RCM precursor and largely shutting down the reactive system. Thirdly, the proposed RCM reaction did not form an intermediate dimer **340**, before subsequent monomeric ring closure to **79**. Finally, in all instances, the 1,1-disubstituted olefin remained unchanged or unreactive to the catalyst system. It was this final key point that determined the direction of further investigations. Whilst it was recognised that there remained a huge variety of substitution patterns that could be added to the allylic olefin in order to change the reactivity of the system, it was felt that activation of the 1,1-disubstituted olefin could be more beneficial.

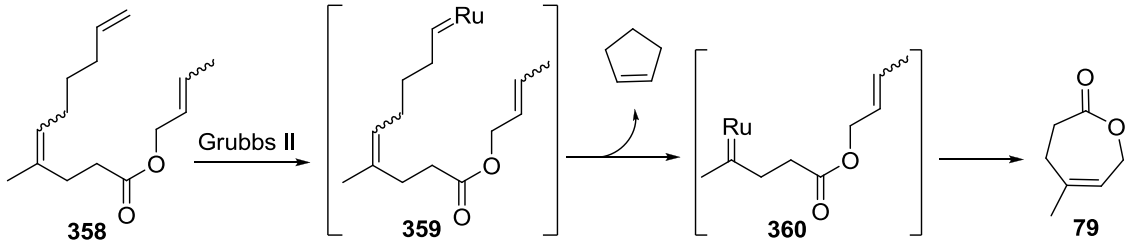
3.5.2 Relay-RCM Approach

With the aim of promoting reaction at the 1,1-disubstituted olefin, a subtle change of approach was envisioned, through the incorporation of relay-RCM. In 2004, Hoye and co-workers demonstrated that this strategy could be effectively employed to promote the ring closure of particularly unreactive systems such as **354** (**Scheme 115**).[211] Mechanistically, it was proposed that an initial highly favoured five-membered ring closure promotes incorporation of the ruthenium catalyst onto the most sterically demanding olefin, before affecting ring closure to **357**.[212]



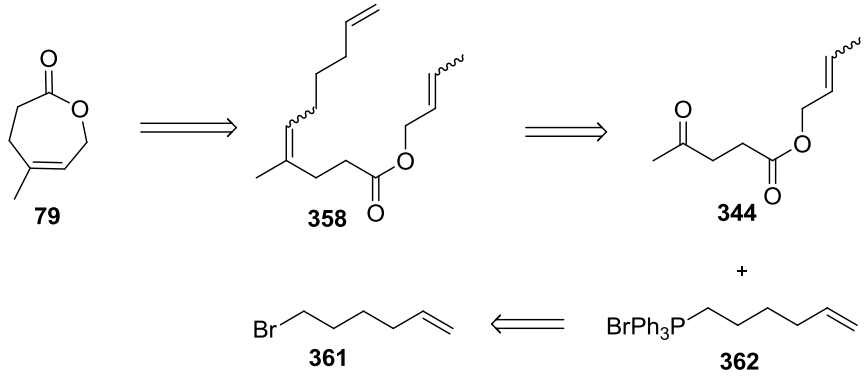
Scheme 115. 1,1-disubstituted olefin activation by relay-RCM, by Hoye and co-workers

It was envisioned that by following a similar strategy towards the synthesis of **79**, the reactive ruthenium species could be effectively directed onto the 1,1-disubstituted olefin **360**, promoting RCM through substrate activation (**Scheme 116**).



Scheme 116. Relay RCM strategy to access lactone 79

It was also recognised that if ring closure was still unsuccessful by this method, it was likely that the proposed ring closure was limited by the unfavoured *S-cis* ester conformation, as opposed to the substitution patterns present on the olefins hindering catalyst incorporation. A synthetic strategy was immediately designed with the aim of utilising the common intermediates synthesised in the previous routes under investigation (**Scheme 117**).



Scheme 117. Proposed synthetic strategy to access 358

It was envisioned that the relay substrate **358** could be synthesised from **344** *via* a Wittig olefination with phosphonium salt **362**, ultimately synthesised from the commercially

available alkyl halide **361**. From the outset, the length of side-chain was chosen specifically to ensure the formation of a cyclopentene side product. By following this approach, the formation of a five-membered ring should be sufficiently favourable to promote access to the sterically demanding trisubstituted olefin in **358**. The volatility of the cyclopentene by-product was also ideal, since its low boiling point should ensure that it was effectively removed from solution under reflux conditions, thus maintaining an entropic driving force. Intermediate **358** was initially chosen as the most suitable starting point, since the differences in substitution patterns present on the separate olefins, should ensure that the side-chain was the most reactive site, slowing any potential competitive macrocyclisation or dimerisation.

The first step towards the synthesis of **358** involved the formation of phosphonium salt **362**. From previous experience in synthesising simple alkyl phosphonium salts, it was known that **362** should be readily accessible by refluxing the alkyl halide **361** in the presence of PPh_3 (**Table 16**).

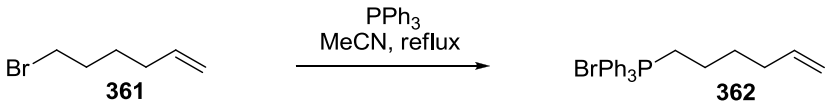


Table 16. Synthesis of Wittig salt 362

Entry	PPh_3 (eq.)	Yield (%)
1	1.1	84
2	1.5	93
3	2.0	99

An initial attempt using stoichiometric amounts of PPh_3 proved successful, with a yield of 84% of **362** isolated (**Table 16**, Entry 1). Upon further investigation, the conversion of **362** could be effectively increased to 99%, by increasing the relative amount of PPh_3 within the reaction mixture (**Table 16**, Entry 3). Unfortunately in all cases, isolation of the desired product proved problematic, with repeated trituration of the product required to remove all of the excess PPh_3.

With the requisite phosphonium salt **362** now in hand, preliminary investigations towards the addition of the side-chain through Wittig olefination was attempted (**Table 17**). Initial attempts involved the reaction of 1.1 equivalents of phosphonium salt **362** with **344**, to provide **358** in a moderate yield of 43% (**Table 17**, Entry 1). However, by increasing the relative amount of ylide in the reaction mixture to 2 equivalents, the yield was significantly improved to an acceptable 68% (**Table 17**, Entry 3).

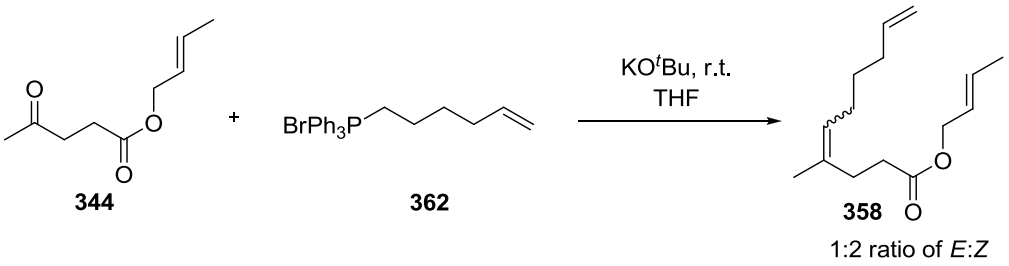
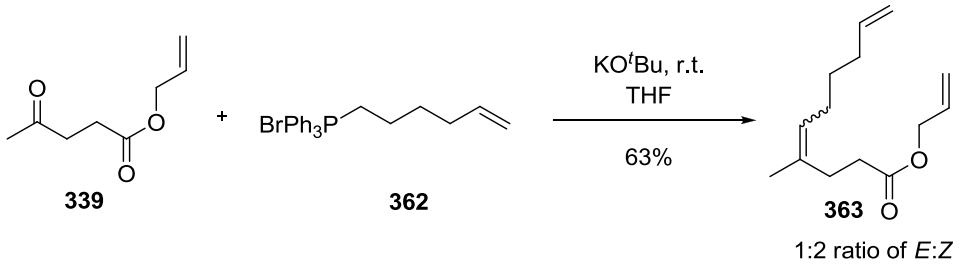


Table 17. Synthesis of triene 358 by Wittig olefination

Entry	**362** (eq.)	Yield (%)
1	1.1	43
2	1.5	56
3	2.0	68

It should be noted that, since both the *E*- and *Z*-isomer of the trisubstituted olefin **358** should exhibit similar reactivity, no attempts were made in the preparatory phase to control selectivity and hence, an inseperable mixture of 1:2 *E*:*Z* geometric isomers was obtained. Whilst isolation of the desired compound proved relatively straightforward, spectroscopic characterisation of the compound proved somewhat more challenging. Due to the mixtures of compounds formed, mass characterisation became essential to confirm the correct product was present.

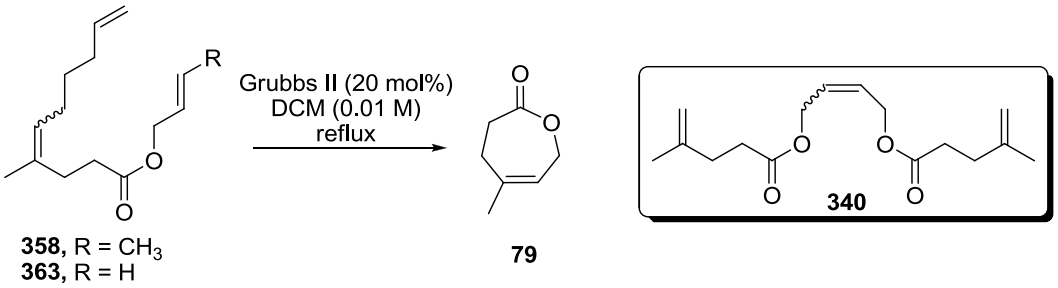
Towards the outlined relay-RCM strategy, compound **363** was also synthesised. It was envisioned that by comparing the products formed in this reaction to that of the equivalent relay-RCM involving **358**, any changes in overall reactivity due to the substitution pattern on the allylic olefin could be observed. Accordingly, compound **363** was synthesised in a yield of 63% from the Wittig reaction of **339** with 2 equivalents of **362**, as shown in **Scheme 118**.



Scheme 118. Synthesis of triene 363 by Wittig olefination

Having successfully synthesised the two relay substrates **358** and **363**, initial investigations towards the proposed relay-RCM process could be attempted. Knowledge obtained from previous RCM investigations (**Section 3.5**) indicated that despite the proposed activation of the 1,1-disubstituted olefin, the second intramolecular cyclisation was likely to be slow, with

the ADMET (acyclic diene methatesis) pathway predominating at higher concentrations. In an attempt to address this potential problem, high dilutions of 0.01 M were initially identified as a suitable starting point (**Table 18**).



358, R = CH_3
363, R = H

79

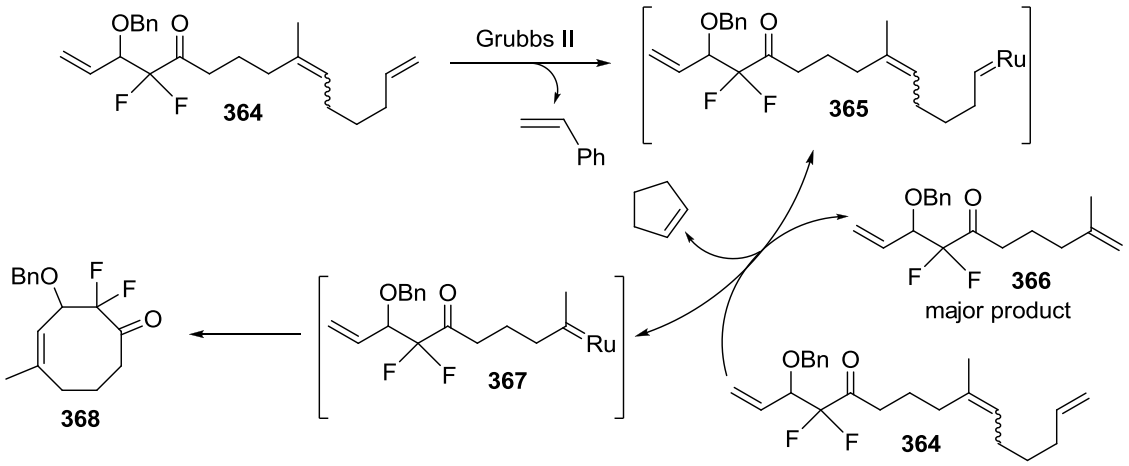
Table 18. Attempted synthesis of lactone 79 by relay RCM

Entry[a]	Triene	**79** (%)	**340** (%)
1	**358**	0	58
2	**363**	0	56

[a] Catalyst added in 5 mol% portions every 6 h.

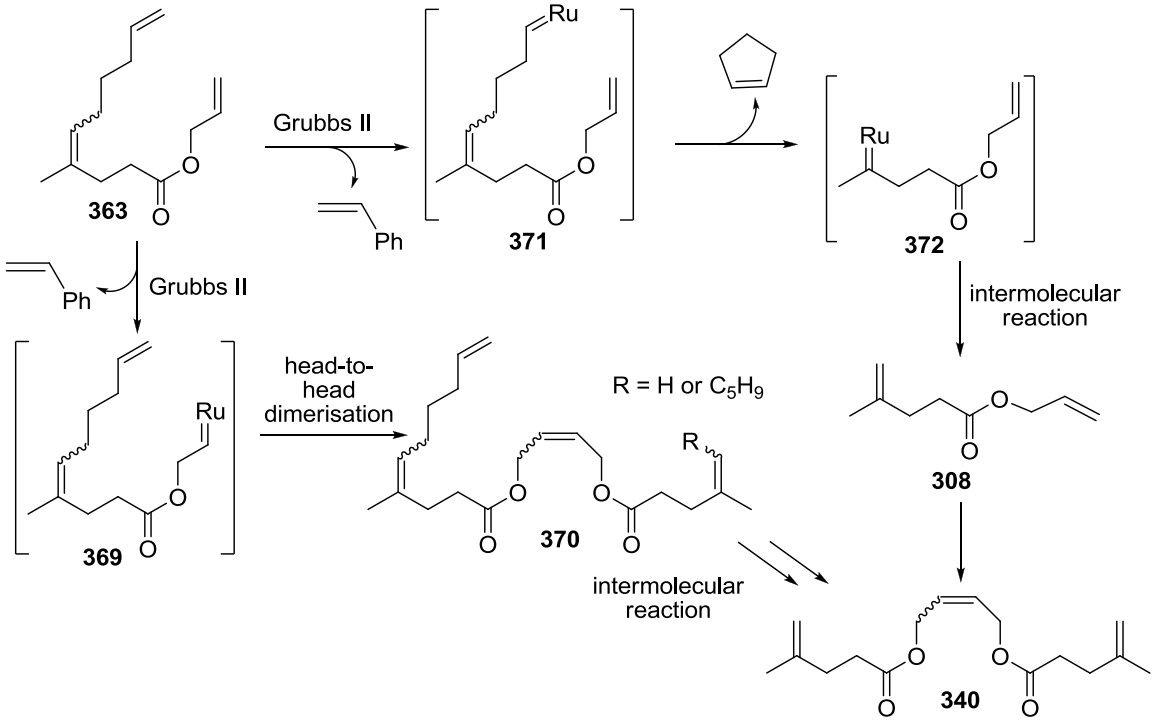
Accordingly, a solution of **358** or **363** was added in a single portion to a refluxing solution of 5 mol% of Grubbs II catalyst in DCM. The resulting solution was then refluxed for 24 h. During the 24 h period an additional 3 portions of 5 mol% Grubbs II were added to the solution after 6 h, 12 h and 18 h, to ensure catalyst degradation was not hindering reaction progress. Disappointingly, all attempts to form **79** *via* the relay-RCM protocol failed, with acyclic dimer **340** identified as the major component upon reaction completion (**Table 18**, Entries 1 and 2).

A similar result was observed by Percy and co-workers in 2009 when attempting the cyclisation of a fluorinated eight membered ketone **368** (**Scheme 119**).[213] During their investigations, the authors describe a capping-off effect to rationalise the unexpected regeneration of the non-relay starting material **366**. It was proposed that the initial five-membered ring closure occurred as expected, to promote olefin activation **365→367**. However, subsequent ring closure of the less favoured eight-membered ring to **368** was thought to be sufficiently slow that an intermolecular reaction was instead favoured, capping-off the activated olefin **367→366**. Effectively, this resulted in the removal of the additional side-chain, to regenerate the non-relay substrate **366** *in situ*.



Scheme 119. Proposed *in situ* regeneration of non relay diene 366

From this premise and the fact that the acyclic dimer **340** was formed throughout, it is believed that two possible pathways may be occurring in the reaction mixture (**Scheme 120**). Firstly, an initial reaction of the side-chain in **363**, to regenerate **308** *in situ* (**371→372→308**), which then forms the acyclic dimer **340**. Alternatively, the allylic functionality may have an activating effect, promoting the head-to-head dimerisation (**369→370**), before a secondary capping-off of the side-chain occurs to form **340**. It is unclear from the results, if one or both of these proposed pathways are responsible for the resultant formation of **340**. However, failure to form any of the desired lactone **79** would suggest that despite attempted substrate activation, the conformational bias of the ester was the predominant barrier to the RCM process.



Scheme 120. Synthesis of 340 through two proposed competing mechanistic pathways

In one final attempt to promote the relay-RCM closure of compound **358** and **363**, the trienes were reacted under 'infinite dilution' (**Table 19**). It was recognised that the intramolecular (RCM) and intermolecular (ADMET) processes are competitive and that dilution can directly affect the relative rate of each of these reactions. Thus, by following the principles often used in macrocyclisations,[214] a slow addition of the triene to a dilute solution of catalyst, over a prolonged period of time, should change the effective molarity in favour of the intramolecular RCM process.

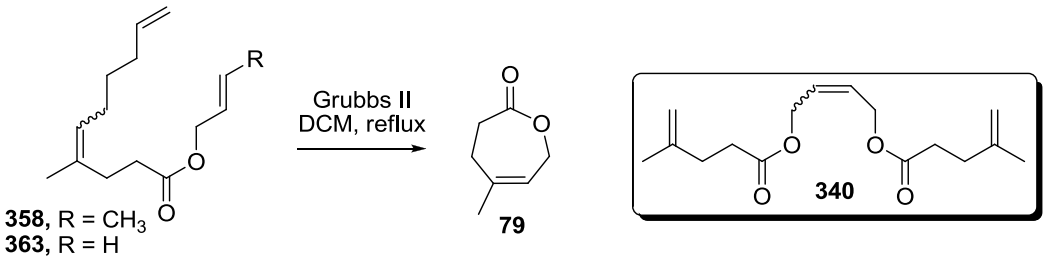


Table 19. Attempted synthesis of lactone 79 by relay RCM

Entry[a]	Triene	Yield **79** (%)	Yield **340** (%)
1	**358**	0	41
2	**363**	0	43

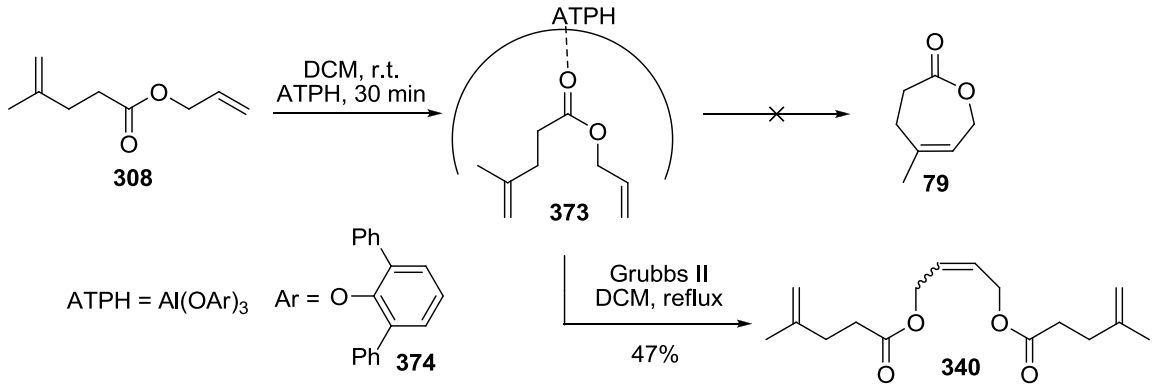
[a] 25 mol% of catalyst was added in 5 mol% portions.

Accordingly, a solution of Grubbs II catalyst was refluxed in a large volume of DCM, before the slow addition of trienes **258** or **363**, over a 36 h period. As in previous attempts, additional portions of 5 mol% Grubbs II were added to ensure an active catalyst system was present in the reacting mixture. In these cases, portions of catalyst were added after 6 h, 12 h, 24 h and finally 36 h, bringing the total catalyst loading to 25 mol% over the analysed period. Unfortunately, product **340** was again isolated as the major reaction component in yields of 41-43% regardless of the triene starting material added (**Table 19**, Entries 1 and 2).

3.5.3 Encapsulated-RCM

To conclude the RCM investigations, it was necessary to attempt the synthesis of **79** utilising an encapsulation protocol described by Pentzer *et al*. (**Scheme 121**).[197] From a series of crystal structures by Yamamoto it was elucidated that the aluminium ligand system (ATPH) surrounds the diene in a propeller-like arrangement as in **373**.[215] Co-ordination of the ligand was proposed to shield the RCM precursor from potential intermolecular reaction, whilst

disrupting the *S-cis* ester conformation, pushing the two reacting olefins together, increasing the probability of monomeric ring closure.



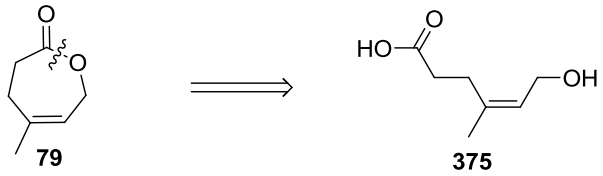
Scheme 121. Attempted synthesis of lactone 79 by RCM encapsulation

Accordingly, diene **308** was stirred in a solution of the aluminium ligand (ATPH) at room temperature prior to the addition of Grubbs II catalyst in a single portion. Disappointingly, all attempts to facilitate the ring closure of **308** proved unsuccessful, with **340** isolated as the major product in a yield of 47%. This result was rather surprising since it was envisioned that the encapsulation system described by Pentzer and co-workers should effectively promote the monomeric ring closure of **308**. Importantly however, in all of the systems described within this publication, no trisubstituted olefin products were ever synthesised. The failure of this approach may indicate that the steric demand of **79** is simply too high for the investigated catalyst systems.

It was at this stage that investigations towards synthesis of **79** by RCM were concluded. From all of the results shown in this section, RCM is not a viable approach towards the synthesis of **79**. In the majority of conditions investigated, dimeric product **340** was isolated as the major product. Additionally, the substrates under investigation did not appear to be stable to the presence of $Ti(O^iPr)_4$, with an unexpected transesterification product **341**, formed throughout. Although a conclusive explanation for the failure of this approach remains as yet elusive, it was likely that a combination of unfavourable *S-cis* conformational effects and the challenging steric demand of both incorporation of the catalyst into a 1,1-disubstituted olefin and the formation of the desired trisubstituted olefin were responsible.

3.6 Ring Expansion Strategy Towards the Synthesis of 79

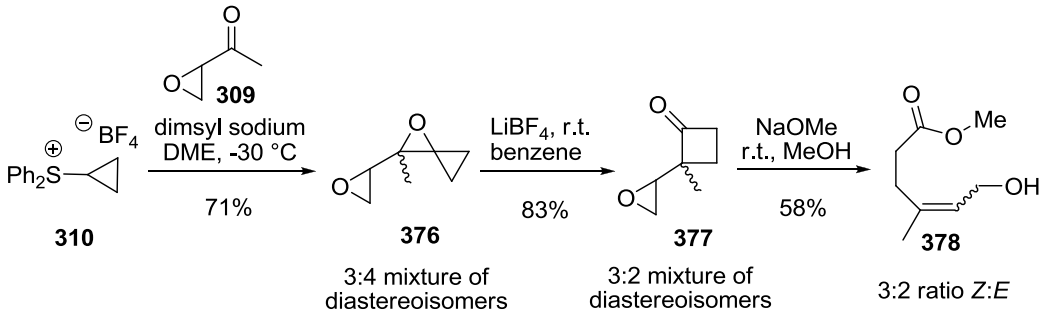
Following the disappointments of the olefination and RCM strategies to provide a concise synthesis of **79**, a new approach had to be taken. Since it was clear that all attempts to synthesise the olefin in **79** as a final ring closing step was too problematic, it was proposed that lactonisation from precursor **375** may be a viable alternative (**Scheme 122**).



Scheme 122. Lactonisation strategy to access 79

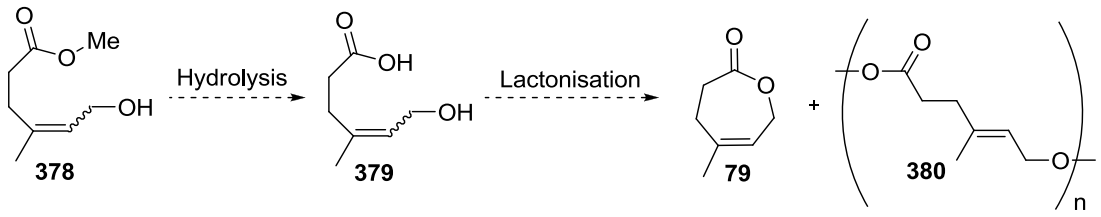
From a synthetic point of view, this strategy provided two main challenges: (a) intramolecular ring closure and (b) selective formation of a *Z*-olefin. With regard to these issues, it was recognised that the intramolecular ring closure of **375** containing a *Z*-olefin should be significantly faster than intermolecular transesterification. However, failure to develop high levels of *Z*-selectivity at the alkene moiety, could lead to increasingly complex mixtures of products formed at this key step, rather than the desired ring closure. In the knowledge that the selective synthesis of **375** was not going to be facile, it was decided that a much more precedented route should be attempted.

Following a comprehensive literature search, a novel and much more elaborate approach to the synthesis of **79** was discovered, utilising a ring expansion and Grob fragmentation protocol.[216] Initially developed by Trost *et al.*, this route provided a concise pathway towards unsaturated ester **378** (**Scheme 123**).



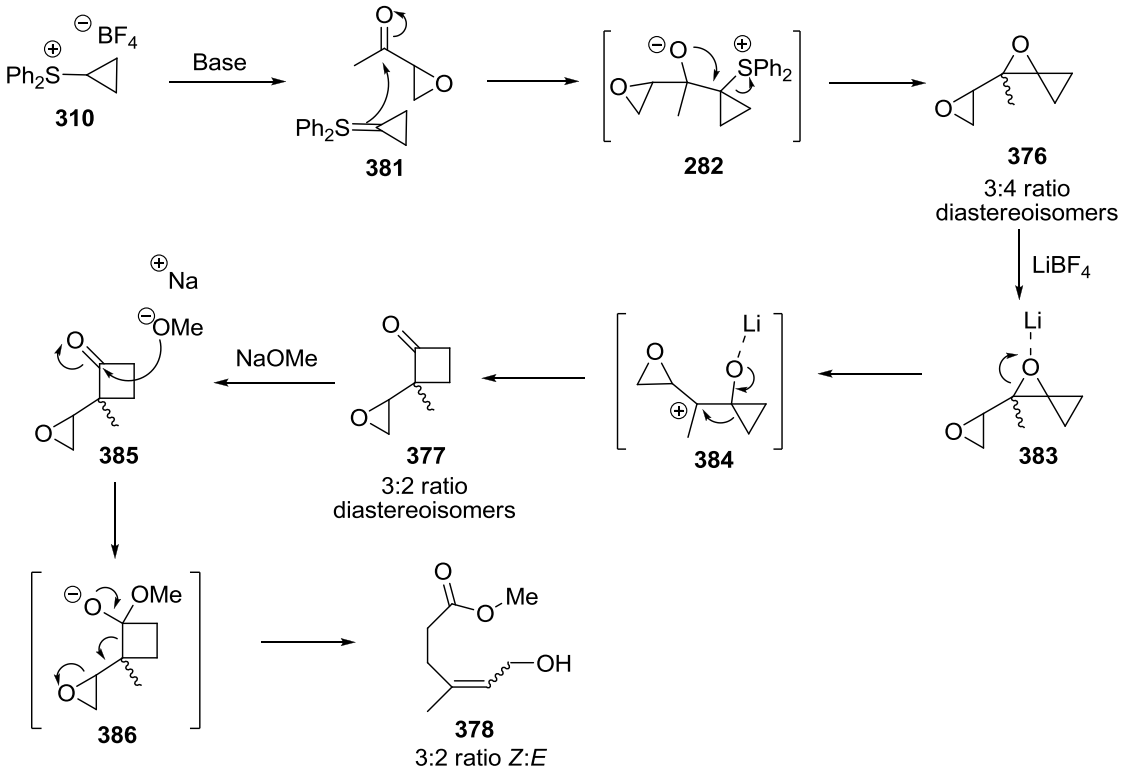
Scheme 123. Synthesis of 378 by ring expansion/Grob fragmentation, Trost *et al.*

It was envisioned that from ester **378**, hydrolysis and subsequent ring closure with a coupling agent, would provide **79** (**Scheme 124**).



Scheme 124. Proposed strategy to access 79 from ester 378

In the original paper, Trost and co-workers described that **376** could be accessed through Corey-Chaykovsky reaction between **310** and **309**, to provide **376** as a 3:4 mixture of diastereomers (**Scheme 125**).[216] Upon exposure of **376** to $LiBF_4$, a Lewis acid-promoted ring expansion was observed, to afford **377** as a 3:2 mixture of diastereomers. Finally, addition of an alkoxide nucleophile to **377** promoted a Grob-type fragmentation, to provide **378** as an inseperable 3:2 mixture of *Z*:*E* isomers.

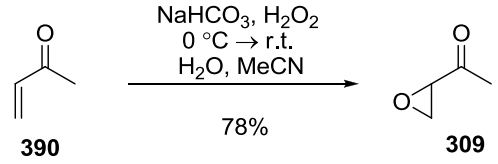


Scheme 125. Proposed mechanism of ring expansion/Grob fragmentation protocol

Although this route provided access to **378**, the overall selectivity was poor, with a 3:2 mixture of *Z*:*E* geometric isomers observed. It was proposed that this lack of selectivity was due to the creation of tertiary carbocation intermediate **384** (**Scheme 125**). Clearly, any future attempts to modify the described protocols to develop increased *E*:*Z* selectivity would be hindered by this suspected key intermediate. However, despite the apparent disadvantages of this strategy, it was felt that this approach would allow the evaluation of the final lactonisation step and hence determine if lower levels of *Z*:*E* selectivity could be tolerated.

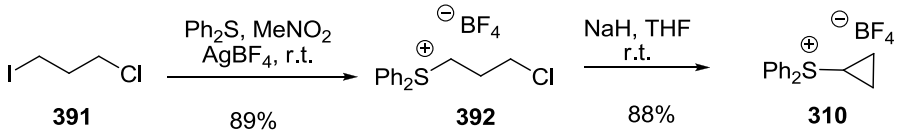
Before attempting the described synthetic sequence, starting materials **309** and **310** had to be synthesised in gram quantities. Following a literature search, two direct methods were identified.

The first of the two starting materials synthesised was epoxy ketone **309**. Isolation of significant quantities of **309** proved relatively straightforward, following the literature procedure described by Yao and co-workers.[217] Accordingly, methyl vinyl ketone (MVK) **390**, was added to a basic solution of H_2O_2 to afford **309** in a 78% yield (**Scheme 127**).



Scheme 127. Synthesis of epoxy ketone 309

With gram quantities of **309** in hand, attention turned to the synthesis of cyclopropyl sulfide salt **310**. Accordingly, a two-step protocol was initiated involving an initial silver salt-promoted halide displacement with diphenyl sulfide, followed by base-induced cyclisation (**Scheme 128**). Following the procedures described by Trost and co-workers, the synthesis of **310** was achieved on a significant scale, to provide gram quantities of the desired sulfide salt.[218]

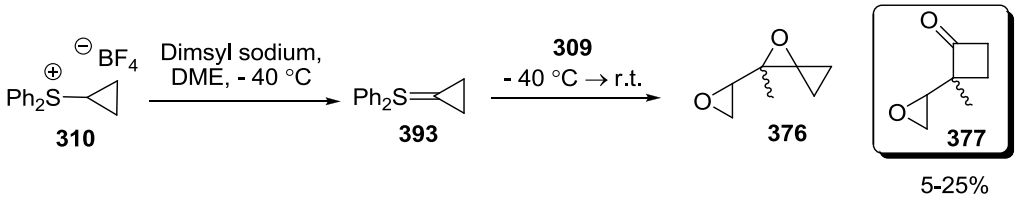


Scheme 128. Two step protocol to synthesise 310

With reagents **309** and **310** successfully prepared, synthesis of oxaspirane **376** could be attempted**.** Towards this aim, two separate sets of deprotonation conditions were investigated to facilitate the formation of the sulfinium ylide **393**.

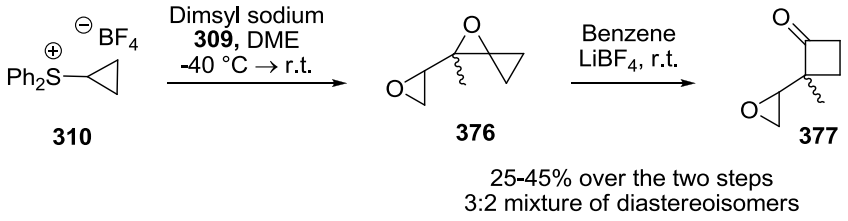
Following the literature procedures set out by Trost and co-workers, a preliminary attempt to form oxaspirane **376** was performed using dimsyl sodium. Accordingly, to a stirred suspension of **310** at -40 °C in DME, was added dimsyl sodium (**Scheme 129**). Immediately a colour change was observed indicating the suspected formation of the ylide. A solution of **309** was then added, before allowing the reaction mixture to rise to room temperature. Unfortunately, despite ^{1}H NMR conformation that **376** had been successfully formed all attempts to isolate oxaspirane **376** using silica gel chromatography proved unsuccessful, with **376** not detected. In all cases the major compound obtained was cyclobutanone **377**, in yields

of 5-25%. It appeared that oxaspirane **376** was not stable to the Lewis-acidic silica, with the described ring expansion occurring during chromatography. Whilst this could have been an extremely favourable outcome, removing the need for a second reaction to promote the desired ring expansion to **377**, isolated yields proved to be too low and variable to justify the synthesis of **377** in this manner.



Scheme 129. Attempted synthesis of oxaspirane 376

To overcome these isolation issues, a modified protocol was envisioned to access **377** without purification. Accordingly, following the formation of oxaspirane **376**, the crude mixture was diluted with benzene and stirred in an excess of $LiBF_4$ (**Scheme 130**). Importantly, by following this approach the yields of **377** could be effectively increased to 25-45% over the two steps. Unfortunately, throughout all of reactions investigated, reproducibility proved problematic and an alternative procedure was required, to provide a robust method to access **377**.

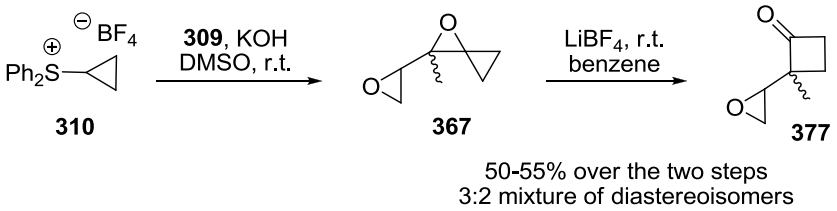


Scheme 130. Modified protocol to access 377 using dimsyl sodium

In the original 1978 publication, Trost and co-workers also describe an alternative deprotonation protocol to access **376**, involving sulfinium ylide formation in the presence of KOH in DMSO.[216] From previous experience gained through the formation **376** using dimsyl sodium, it was envisioned that a similar modified protocol could be used to isolate **377** (**Scheme 131**). Accordingly, to a solution of **309** and **310** in DMSO, was added KOH in a single portion at room temperature. Almost immediately, the solution turned to a brown suspension, slowly darkening over a 4 h reaction period. Upon isolation, the crude mixture was diluted with benzene before the addition of $LiBF_4$, monitoring progress by ^1H NMR.

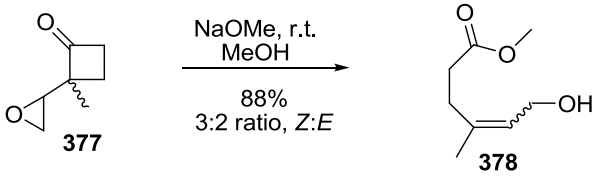
Initial investigations following the described procedure attempted to wash out all of the DMSO from the first step, before the addition of $LiBF_4$ to promote the desired ring expansion to **377**. Towards this aim, yields of 30-45% **377** were isolated, with suspected losses

occurring to the aqueous phase. Subsequently, it was discovered that the presence of DMSO in the crude mixture did not significantly hinder the desired formation of **377**. Furthermore, when this protocol was repeated without the rigorous removal of DMSO, an appreciable increase in the yield of **377** was isolated, albeit in a significantly longer reaction period. Following this modified protocol, reproducible yields of 50-55% **377** could be isolated over the two steps as a 3:2 mixture of diastereoisomers. It was using this method that subsequent batches of **377** were synthesised, bringing through the desired quantities of material to complete the proposed synthesis of lactone **79**.



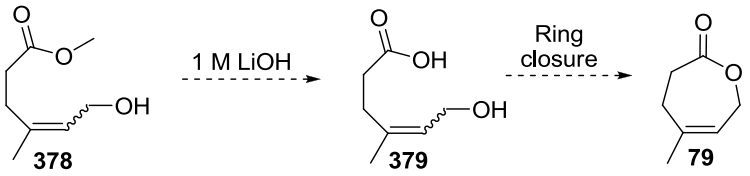
Scheme 131. Modified protocol to access 377 using KOH

With a successful procedure for the synthesis of **377** established, the formation of **378** could be pursued. Remarkably, cyclobutanone **377** readily formed open chain ester **378** when stirred in a solution of sodium methoxide at room temperature (**Scheme 132**). Unfortunately, as reported by the Trost group, **378** was isolated as a mixture of geometric isomers (3:2 ratio, *Z*:*E*).[216] Regardless of this, the reliability of this protocol represented a significant step forward towards the synthesis of lactone **79**.



Scheme 132. Synthesis of 378 by Grob-type fragmentation

As previously described, it was envisioned that **379** could be synthesised from **378** following a two-step protocol involving an initial hydrolysis, followed by ring closure with a coupling agent (**Scheme 133**).



Scheme 133. Proposed synthesis of 379

In this regard, hydrolysis of ester **378** under acidic conditions proved relatively facile, with complete consumption of the starting materials detected after 2 h. However, purification of **379** by column chromatography proved somewhat problematic, with separation of the highly polar products proving difficult and suspected product losses leading to poor isolated yields of **379**. It was with this in mind, that all future attempts at the final ring closure were pursued using crude product **379**.

Due to the structural similarity between **379** and **320** (**Table 6**, **Section 3.3**), it was decided that investigations towards the ring closure of **379** should be primarily limited to DIC and HATU, where the highest yields were observed. However, one further option was identified as an interesting alternative, ring closure *via* a Mitsunobu reaction. These procedures, in combination with previous studies (**Table 6**, **Section 3.3**) represented a reasonably complete screening of approaches to establish whether activation of the acid or alcohol functionality was the most efficient strategy to promote ring closure. It was with this set of conditions that the synthesis of **79** was attempted (**Table 20**).

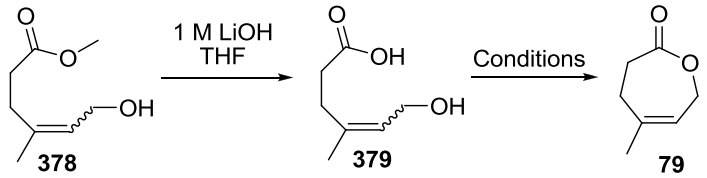


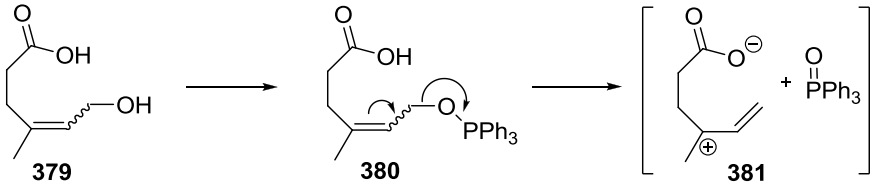
Table 20. Synthesis of 79 by intramolecular ring closure

Entry	Solvent	Conditions	Temperature	Yield (%)[a]
1	Toluene	PPh_3, DEAD	reflux	0
2	DCM	DIC, Et_3N	r.t.	36
3	DCM	HATU, Et_3N	r.t.	43

[a] Yield based over two steps

From the outset, it was recognised that Mitsunobu activation of the alcohol functionality was slightly speculative, with no notable examples to close small or medium sized rings within the literature. However, this method had been used with some significant successes in the closure of larger macrocycles.[214,219–221] It was from these literature examples that a set of conditions were chosen.[221] Accordingly, **379** was treated with PPh_3 and DEAD, to yield a complex mixture of compounds in which lactone **79** was not detected (**Table 20**, Entry 1). It was unclear at this stage, whether this was a direct result of the *E*:*Z* mixture of isomers in solution, or the result of an S_N1 type elimination process due to the activated allyl alcohol

(**Scheme 134**).[222] Closer analysis of **379** reveals that the formation of a tertiary carbocation **381** could be entirely feasible, promoting the elimination pathway. If this is in fact the case, then the substitution pattern on the olefin under investigation, may actually be hindering effective ring closure, rather than promoting the synthesis of **79** by this method.



Scheme 134. Proposed tertiary carbocation formation during Mitsunobu reaction

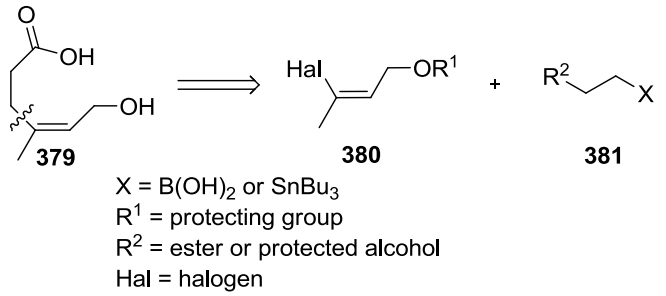
Following the failure of a Mitsunobu approach to activate the alcohol functionality, it was decided that all further approaches would follow previous investigations (**Table 6**, **Section 3.3**). Towards this aim, the coupling agents DIC and HATU were investigated. Accordingly, **379** was treated with DIC and Et_3N to afford a modest 36% yield of **79** (**Table 20**, Entry 2); an acceptable yield considering only the *Z*-isomer was capable of ring closure. Importantly, the relative success of this protocol indicated that the initial mixture of *E*:*Z* isomers present in **379** was not entirely inhibitory towards the formation of the desired lactone **79**. In one final attempt to increase the yield of **79**, carboxylic acid **379** was treated with HATU and Et_3N in DCM at room temperature (**Table 20**, Entry 3). Pleasingly, **79** was isolated in a yield of 43% (72% yield relative to the 60% of *Z*-isomer present).

With the identification of a suitable set of conditions to form **79**, it was recognised that this route could be scaled up and used as a viable, if unselective, route through to **79**. However, for this strategy to be truly desirable, an increased level of *Z*-selectivity had to be developed. Towards this aim, a range of ideas were considered. However, the challenges of trying to adapt the current reaction protocols to generate increased *Z*-selectivity were deemed too difficult. The relative success of this route answered two important questions regarding the synthesis of **79**. Firstly, it indicated that **379** was capable of ring closure, and secondly that **379** could tolerate a lack of *Z*-selectivity at the alkene moiety. It was from this point that studies into this route were concluded, with all future investigations concentrating on the development of a *Z*-selective strategy.

3.7 Heck Strategy Towards the Synthesis of 79

Although the ring expansion protocol described in **Section 3.6** was relatively successful, this approach clearly had significant disadvantages in terms of selectivity. With this in mind, it was decided that any final attempts to synthesise **79** should afford four key features: (a) *Z*-olefin selectivity, (b) multiple points of diversity, (c) a potential asymmetric variant, and (d) limited number of synthetic steps. Whilst it was recognised that this list of key attributes was an extremely challenging set of prerequisites, it was still believed that a solution could be found through a specific combination of documented methodologies.

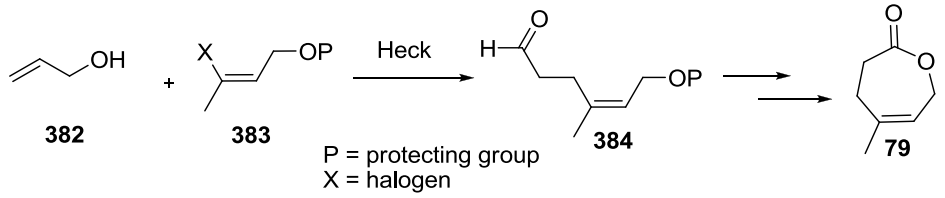
From this perspective, it was recognised that using lactonisation as the final step in previous routes had allowed the first, if unselective, synthesis of **79**. Hence, this key step should be included in the retrosynthetic design of any improved route. This meant that all further investigations should concentrate specifically on embedding a Z-selective olefin. Towards this aim, an organotransition metal approach appeared ideal. This strategy involved cutting the C-C bond connecting the olefin to the alkyl-acid portion of the molecule in **379** to reveal two possible starting materials; a vinyl halide **380** and an alkyl portion **381** containing a coupling partner (**Scheme 135**).



Scheme 135. Proposed direct disconnection strategy towards the synthesis of 379

Importantly, the proposed organotransition metal approach would allow the synthesis of **379** as a catalytic system, with the inclusion of chiral ligands providing a potential asymmetric variant. However, whilst this strategy initially appeared desirable, one major problem persisted: organotransition metal coulpings between sp^2 and sp^3 partners are notoriously difficult to achieve. To overcome this issue, an alternative sp or sp^2 substrate had to be considered as a surrogate coupling partner. By approaching the transformation in this way, the design of the coupling partner must provide a product that would either result in the formation of a sp^3 centre, or allow the simple and selective transformation of the product to a sp^3 centre, such as that within **379**. Following a comprehensive literature search one such

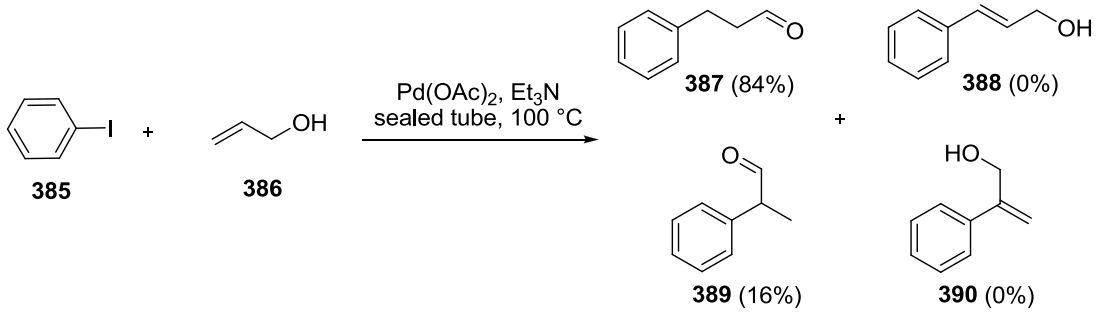
potential method was proposed involving the palladium-catalysed Heck reaction of an allyl alcohol such as **382** and a vinyl halide **383** (**Scheme 136**).



Scheme 136. Proposed Heck strategy to synthesise 79

In the early 1970's, Heck and co-workers had used this approach to access aldehydes similar to that desired from the proposed transformation (**Scheme 137**).[223,224] A short review on these investigations will now follow outlining the results of important mechanistic studies and asymmetric modifications.

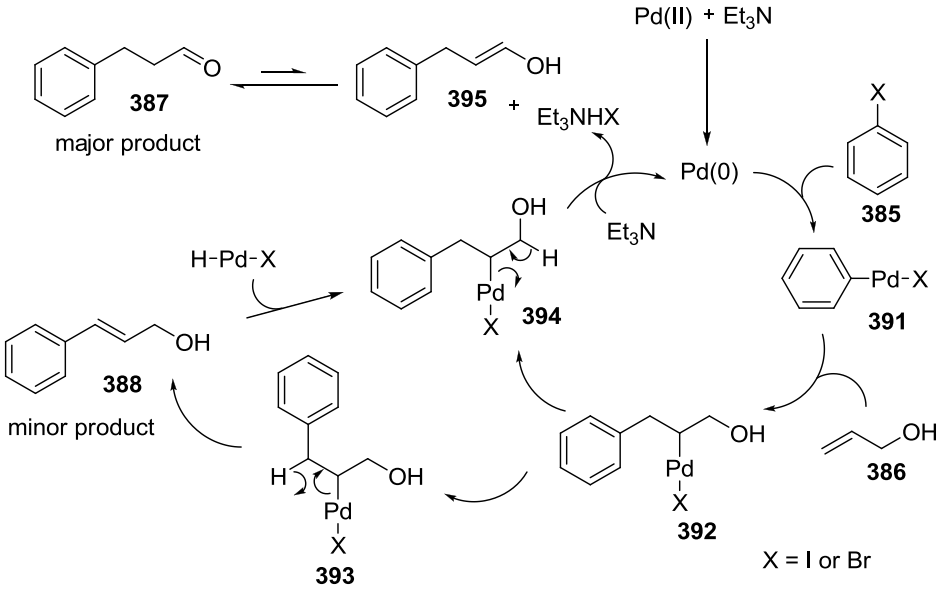
In landmark papers, Heck and co-workers report that when a mixture of allyl alcohol and aryl halides are refluxed in a sealed vessel containing catalytic amounts of palladium, aldehyde **387** was the major component isolated in nearly all instances. However, despite the apparent efficiency of this system, up to four separate compounds were detected within the reaction mixture, depending on the conditions investigated (**Scheme 137**).



Scheme 137. Product distribution from Heck reaction between 385 and 386, Heck *et al*.

To fully understand how the various products are formed under the described reaction conditions, a closer look at the mechanism was required (**Scheme 138**). It was proposed that the first step of the reaction involved the oxidative addition of Pd(0) to the aryl halide substrate **385**. Following this, the organopalladium complex **391** then co-ordinates and inserts into the olefin of the allyl alcohol **386**, to form intermediate **392**. However, at this point in the reaction sequence it can be seen that β-hydride elimination can occur in one of two directions, forming two separate and distinct products. If the elimination occurs towards the aryl portion of the intermediate as in **393**, the resultant product is allyl alcohol **388**, where the re-established olefin is in conjugation with the aryl ring. Conversely, if the β-hydride elimination occurs towards the alcohol functionality as in **394**, the result is the enol **395**,

which can readily tautomerise to provide aldehyde **387** (**Scheme 138**). The addition of this extra pathway means that even if the β-hydride elimination resulted in the formation of the allylic alcohol product **388**, subsequent reaction with a palladium hydride source can effectively isomerise this product through to enol ether **395** and ultimately to the observed aldehyde **387**. Hence the formation of the carbonyl acts as the driving force to promote the formation of the aldehyde as the major component.



Scheme 138. Proposed mechanism of Heck coupling/isomerisation of allyl alcohols

However, in nearly all cases at least low yields of aldehyde **389** were also isolated (**Scheme 137**). Explaining the formation of **389** under the reaction conditions required a reworking of the mechanistic pathway and the inclusion of a competitive isomerisation cycle (**Schemes 138** and **139**). The effect of this competitive pathway is best illustrated through the formation of aldehyde **389**, as shown in pathway A (**Scheme 139**). In this case, even though C-2 arylation results in the initial formation of **390**, this product is thought to react further with a palladium hydride source to generate **389** as the major component.

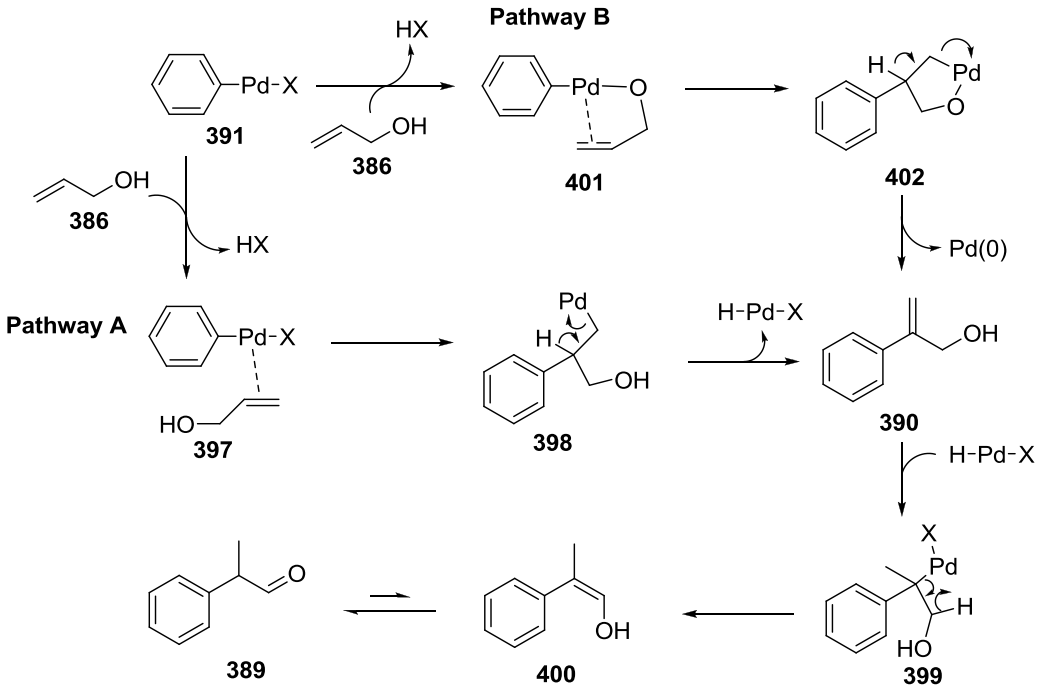


Figure 139. Two plausible pathways to facilitate the formation of compounds 389 and 390

Furthermore, it cannot be ruled out that in some instances the alcohol functionality of **386** could be acting as a directing group such as in **401** to produce regioisomer **390**, as in pathway B. Importantly, the described oxo-palladium interaction in **401** explains the increased formation of **390** and **389**, where stronger bases are used, through increased tethering of the allyl alcohol portion **386**.[225]

With a general mechanistic understanding, Heck and co-workers went on to investigate if the substitution pattern of the allylic alcohol was a key factor in determining product formation. Through this study they hoped to highlight, not only where the limitations of the reaction occurred, but also if the described system could be extended into the preferential formation of the corresponding ketone systems (**Table 21**).[224]

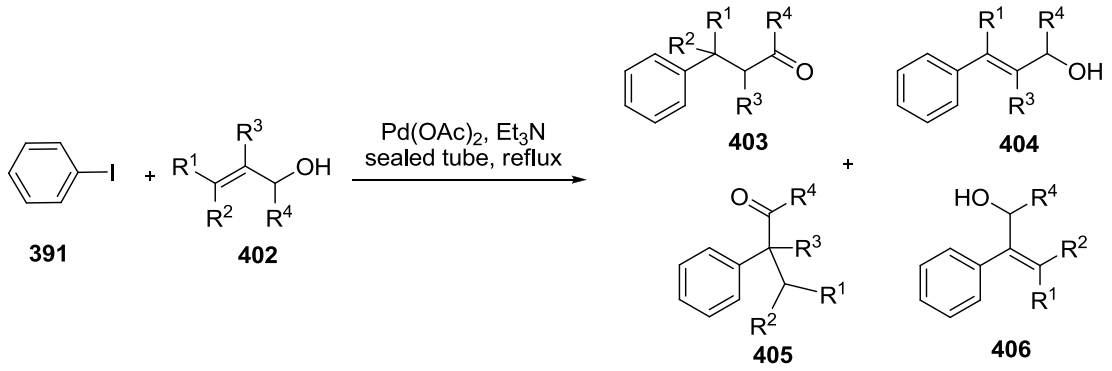


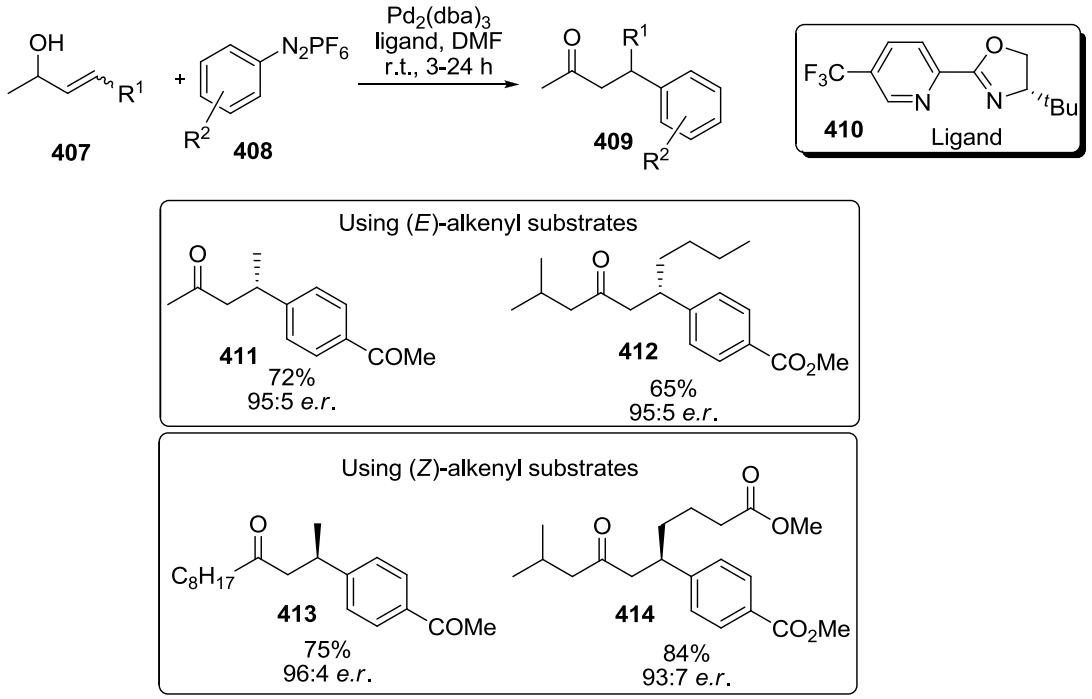
Table 21. Product distributions of Heck reaction of aryl halides and substituted allyl alcohols, Heck *et al*.

Entry	R^1	R^2	R^3	R^4	**403** (%)	**404** (%)	**405** (%)	**406** (%)	Total yield (%)
1	H	H	H	H	84	0	16	0	71
2	Me	H	H	H	74	0	26	0	84
3	H	H	H	Me	90	0	10	0	95
4	H	H	Me	H	96	0	4	0	95
5	Me	Me	H	H	62	0	19	3	51

Analysing the results in **Table 21** provides some important insights into the efficiency of the reaction and the factors that determine product formation. Firstly, the reaction appeared to be largely regioselective, with arylation occurring preferentially at the C3-position of **402**, to afford **403** (**Table 21**, Entries 1-5). However, inclusion of an additional methyl group at the R^1 position demonstrated that sterics played a more significant role in influencing product formation, with increased arylation at the C2-position of **402** observed, to provide **405** (**Table 21**, Entry 2). This trend in regioselectivity was further exemplified in Entry 5, where **402** containing two methyl groups on the terminal positions (R^1 and R^2 = Me), resulted in both increased C2-arylation of **402**, and an appreciable reduction in overall yield. Finally, the described reaction protocols appeared to tolerate additional substitution at the R^3 and R^4 positions of **402**, resulting in C3-arylation product **403** almost exclusively in both these cases (**Table 21**, Entries 3 and 4).

The initial results of this study appeared to suggest that this approach was fairly robust and generic, although questions were beginning to be raised concerning how effective this method could be in terms of regioselectivity and conversions, when incorporating increasingly bulky substituents.

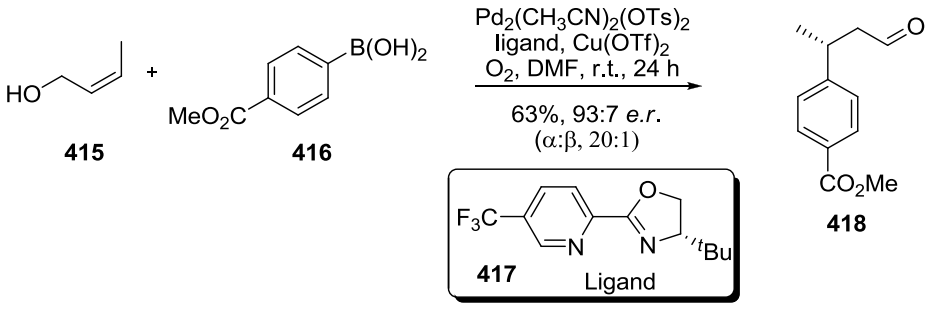
From an asymmetric point of view, recent publications by the Sigman[226] and Correia[227] groups have successfully demonstrated that access to highly enantioenriched systems could be possible, through the inclusion of chiral ligands such as **410** (**Scheme 140**). During investigations towards the formation of ketones such as **409**, Sigman and co-workers reported moderate to excellent yields of 65-84% and excellent levels of enantioselectivity (up to 95:5 *e.r.*) on substrates containing a range of substitution patterns at the C3-position of the allyl alcohol **407**.



Scheme 140. Asymmetric induction through the addition of ligands. Sigman *et al*.

Despite having identified a possible approach that provided a catalytic transformation, variable substitution patterns, and an asymmetric variant, two key issues remained. Crucially, in all of the examples published to date, the reactions were carried out using aryl coupling partners, with no examples of vinyl substrates having been examined. It was not known if this was due to competitive side product formation, with the resultant products reacting further in a subsequent Heck reaction, or if vinyl systems had not yet been investigated. Additionally, with regard to the asymmetric variant, the examples highlighted in **Scheme 140** concerned the exclusive use of aryl diazonium salts such as **408**, as opposed to the corresponding halide derivatives. Whilst this was not ideal for the synthesis of lactone **79** by the proposed strategy (**Scheme 142**), literature precedent would suggest that iodides are not only capable, but excellent candidates for asymmetric induction, especially in the presence of silver salts to sequester the halide in the reaction mixture.[228,229] Furthermore, the most recent examples reported by the Sigman group have indicated that boronic acids such as **416** are suitable

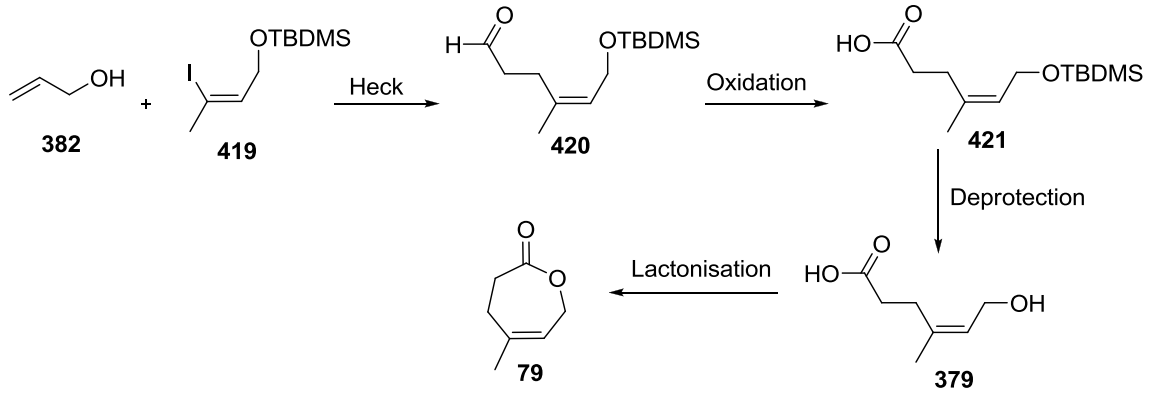
alternative substrates to allow a highly selective asymmetric protocol to be achieved (**Scheme 141**).[230] Whilst conversion of the vinyl iodide substrates to diazonium salts may not be feasible, access to the corresponding vinyl boronic acids could be a reasonable alternative.



Scheme 141. Synthesis of 418 *via* asymmetric Heck of boronic acids

Despite the fact that there appeared to be several underlying questions as to whether the proposed system was capable of delivering all of the desired prerequisites to provide a generic methodology towards the synthesis of ε-substituted lactones, it was envisioned that the proposed strategy should at least allow the rapid and selective synthesis of lactone **79**.

Inclusion of the Heck reaction into the general synthetic strategy revealed that the synthesis of lactone **79** could be accessible *via* a four-step protocol (**Scheme 142**). The proposed sequence of reactions would involve the initial formation of aldehyde **420** *via* a Heck reaction, followed by oxidation to provide acid **421**. The synthesis of **79** could then be completed by deprotection and subsequent ring closure.



Scheme 142. Proposed Heck strategy to synthesise 79

With regard to the design of the identified route, it was envisioned that following the formation of the 3,3-disubstituted product **420**, a significant reduction in overall reactivity of the resultant olefinic moiety should be observed, as was reported in the initial study carried out by Heck and co-workers.[224] This in turn, should inhibit any potential subsequent reaction of **420** towards the formation of unwanted side products (**Figure 19**). It was also proposed

that through protection of the free alcohol in **420** with TBDMS, that a level of secondary steric bulk may inhibit further reaction of the resultant product olefin. Furthermore, it was proposed that by protecting the free alcohol as the corresponding silyl ether this should prevent the formation of the unwanted oxo-palladium interactions resulting in the formation of unwanted regioisomers (*vide supra*). The TBDMS protecting group was seen as ideal for this process, since it should be readily removed using a fluoride source, whilst stable enough to survive the fairly harsh conditions of the Heck reaction.

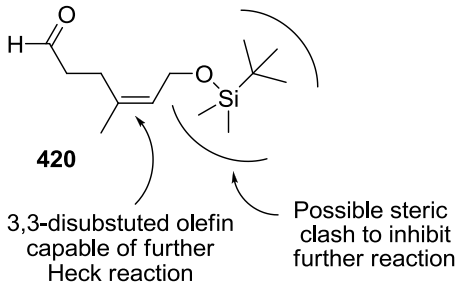
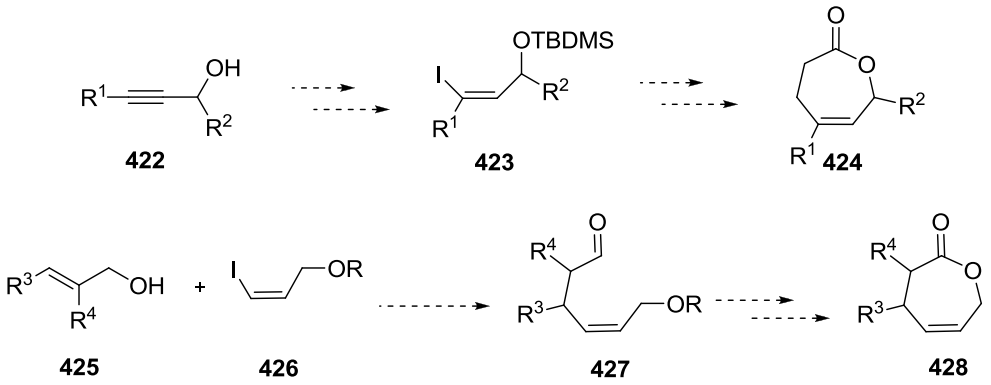


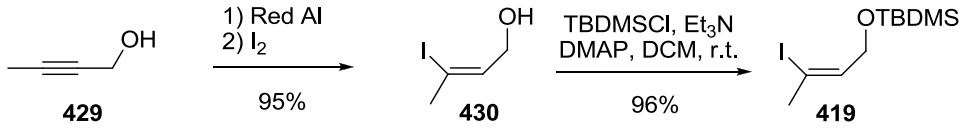
Figure 19. Resultant product from proposed synthetic strategy

Through the implementation of this strategy it was also recognised that four points of diversity could be incorporated into the synthesis of ε-lactones such as **424** and **428**, ideal for a generic strategy (**Scheme 143**).



Scheme 143. Proposed diversity synthesis through variation of the starting materials

With a plausible route through to aldehyde **420** identified, attention turned towards the synthesis of vinyl iodide **430**. Following a literature search, a reliable one pot procedure was identified involving the reduction of alkynes through sequential reduction with a hydride source, followed by quenching with iodine, to afford **430** in a yield of 95% (**Scheme 144**).[231] Following the successful selective synthesis of **430**, the free alcohol was protected as the corresponding TBDMS ether **419**, in a yield of 96%.



Scheme 144. Two-step protocol to synthesise 509

With **419** now in hand, attention turned towards the proposed Heck reaction. Towards this aim, a range of conditions were investigated, including under thermal and microwave promotion (**Table 22**).

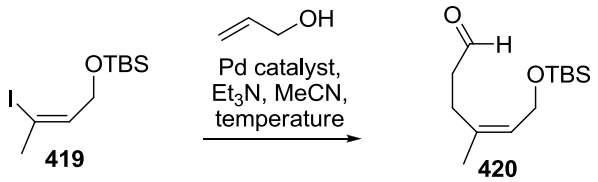


Table 22. Synthesis of aldehyde 420 *via* a Heck protocol

Entry	Pd	Catalyst (mol%)	Promotion	Temperature (°C)	Yield (%)
1	$Pd(OAc)_2$	5	thermal	100	43
2	$Pd(OAc)_2$	2.5	thermal	100	45
3	$Pd_2(dba)_3$	5	thermal	100	31
4	$Pd_2(dba)_3$	2.5	thermal	100	33
5	$Pd(OAc)_2$	5	microwave	110	56
6	$Pd(OAc)_2$	2.5	microwave	110	57
7	$Pd_2(dba)_3$	2.5	microwave	110	39

Initial attempts to synthesise aldehyde **420** were based on the reaction conditions set out by Heck and co-workers (**Table 22**, Entries 1-4).[224] Accordingly, a solution of vinyl iodide **419**, Et_3N, and excess allyl alcohol was reflux in MeCN in a sealed vessel, in the presence of palladium catalyst, to yield aldehyde **420** in yields of 43-45%. Importantly, it would appear that a higher loading of catalyst was not critical to promote the reaction (**Table 22**, Entries 1 and 2). However, switching the palladium source did appear to have an appreciable effect on product formation. Repeating the reaction using $Pd_2(dba)_3$ as the catalyst source, with loadings of both 5 and 2.5 mol%, afforded 31-33% of **420** (**Table 22**, Entries 3 and 4).

In an attempt to increase yields and reduce the overall reaction time, microwave promotion was investigated (**Table 22**, Entries 5-7). Through the implementation of this technique, yields could be increased significantly to 56-57% of **420**, when using $Pd(OAc)_2$ as the

catalyst source (**Table 22**, Entries 5 and 6). Similarily, just as with the thermally promoted reaction, yields remained consistent regardless of the catalyst loading. Again, through switching the palladium source to $Pd_2(dba)_3$, a significant reduction in yield was observed with 39% of **420** isolated (**Table 22**, Entry 7).

Importantly, through the use of microwave promotion, the overall reaction length could be reduced from 24 h in a sealed vessel, to 3 h under microwave conditions. Whilst it was recognised that **Table 22** did not represent a comprehensive optimisation programme, the decision was made to move on through the proposed reaction sequence to determine if the strategy was indeed viable.

Towards this aim, the next step in the reaction sequence involved the oxidation of aldehyde **420** to the corresponding acid **421**. Whilst several methods were available to achieve this transformation, it was felt that the mild Pinnick oxidation conditions should not only provide a rapid reaction, but also allow a relatively simple isolation of the resultant product. From this perspective, a short screening of reaction conditions was investigated (**Table 23**).

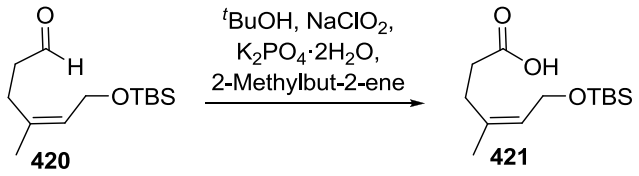


Table 23. Attempted oxidation of aldehyde 510

Entry	Equivalents of oxidant	Temperature (°C)	Reaction length (h)	Yield (%)
1	7	r.t.	12	/
2	4	0	1	/
3	1.5	r.t.	3	/

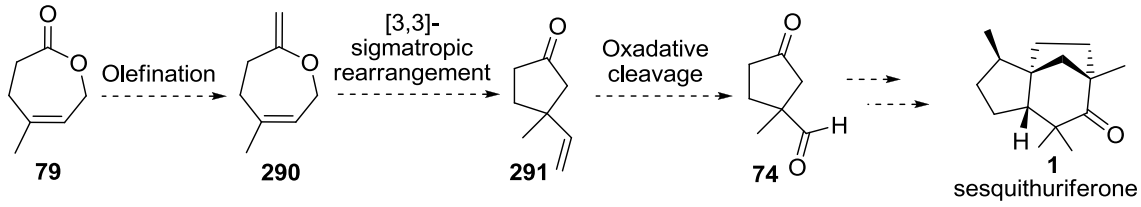
As the results presented in **Table 23** illustrate, oxidation of aldehyde **420** to the corresponding carboxylic acid **421** proved unsuccessful, with the desired product never having been conclusively isolated (**Table 23**, Entries 1-3). Initial attempts involved stirring a solution of **420** with a large excess of oxidant at room temperature. Unfortunately, analyses of the resultant mixture indicated that whilst no starting material was detected after the allotted time period, no product **421** could be conclusively isolated by column chromatography (**Table 23**, Entry 1). In a second attempt to isolate **421**, the aldehyde was stirred for 1 h at 0 °C, with an excess of oxidant in a mixed solvent system (**Table 23**, Entry 2). Following work-up, a significant quantity of starting aldehyde **420** was detected, with no

421 conclusively isolated following column chromatography. In one final attempt to isolate the carboxylic acid, **420** was stirred in a slight excess of oxidant at room temperature for 3 h. Analyses of the crude mixture again indicated the complete consumption of starting material had occurred. However, consistent with all of the previous attempts to synthesise **421**, the carboxylic acid could not be isolated from the complex mixture of compounds returned from the reaction (**Table 23**, Entry 3). Unfortunately, due to time constraints a systematic study could not be completed in order to identify a reliable set of conditions to generate **421**.

To date, the described Heck approach is still at an early stage of development and significant investigation is required to complete the synthesis of **421**. However, an optimised set of conditions has been established towards the synthesis of **419**, with significant progress made towards the development of a novel Heck protocol for the synthesis of **420**. Additionally, whilst not completed, the described Heck strategy appears to be a viable selective route to synthesise lactone **79**, if not further substituted derivatives.

3.8 Summary

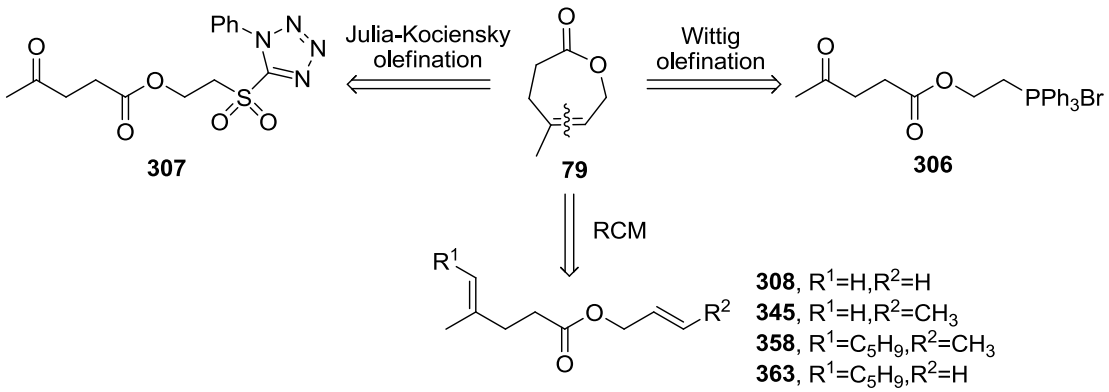
A novel synthetic strategy has been devised to access 3,3-disubstituted cyclopentanones, involving the proposed sigmatropic rearrangement of seven-membered enol ethers such as **290**. The identified strategy was envisioned to provide a key intermediate towards the total synthesis of a complex natural product target sesquithuriferone **1** (**Scheme 145**).



Scheme 145. Synthetic strategy to sesquithuriferone

Before attempting the proposed Claisen rearrangement, a robust and potentially generic route towards the synthesis of lactone **79** and substituted derivatives of this type was pursued. Towards this aim, a range of synthetic strategies were implemented to affect the synthesis of **79**. These included olefination, RCM, ring expansion, and Heck- based protocols.

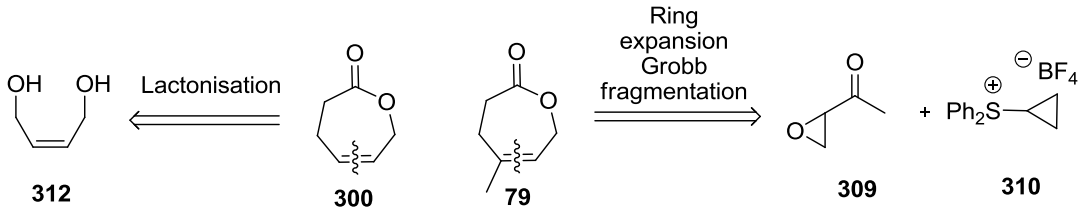
Unsuccessful strategies:



Scheme 146. Unsuccessful olefination and RCM strategies towards the synthesis of 79

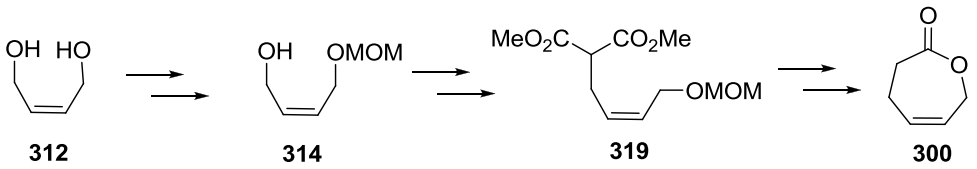
The synthesis of precursors **306** and **307** to effect monomeric ring closure through Wittig and Julia-Kociensky olefination has been completed. However, following a series of ring closure studies, these substrates proved to be ineffective towards the synthesis of lactone systems such as **79** (**Scheme 146**). A further set of compounds **308**, **345**, **358** and **363** were synthesised with the aim of accessing **79** through RCM. Towards this approach, a range of conditions and strategies were pursued including high dilution, relay-RCM, and encapsulation methods. The results of this study indicated that monomeric ring closure using these substrates was not a viable option, with the formation of a head-to-head dimer **340** the most likely product under the conditions examined.

Successful strategies:



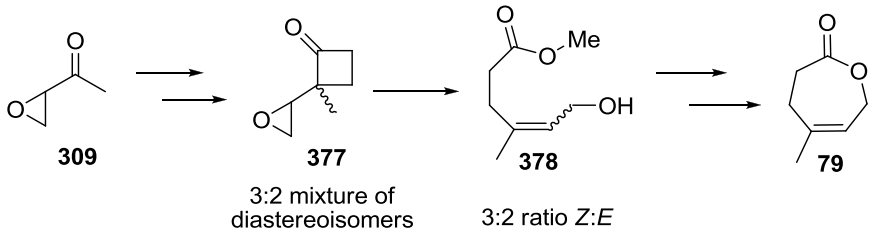
Scheme 147. Successful strategies towards the syntheses of 300 and 79

The synthesis of lactone **300** has been completed, with significant quantities isolated to date. Lactone **300** was synthesised according to a step-wise approach involving the desymmetrisation of *cis*-diol **312**, followed by displacement of an activated alcohol. From this key compound, **300** was isolated through decarboxylation, hydrolysis and lactonisation with a coupling agent (**Scheme 148**). Despite the success of this synthetic route, divergence into a range of substituted derivatives has proved prohibitive.



Scheme 148. Synthesis of 300 from *cis*-diol 312

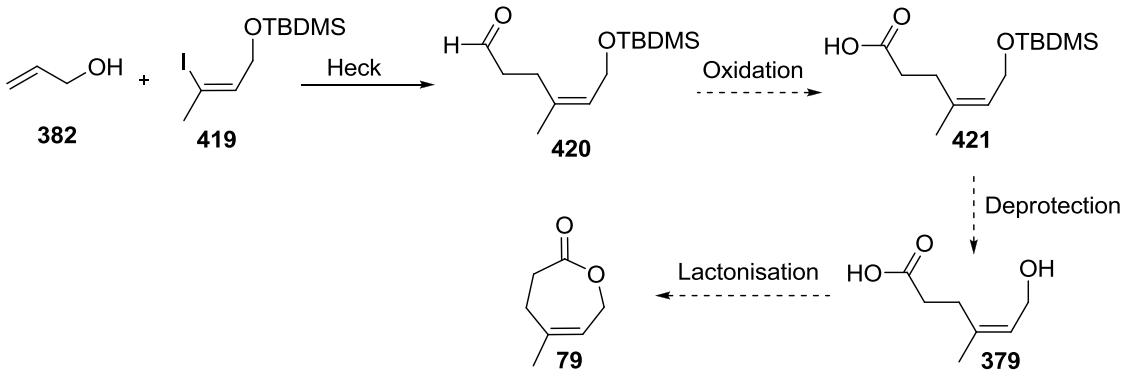
The successful synthesis of target lactone **79** was achieved through the implementation and development of a ring expansion/Grob fragmentation protocol. Whilst this strategy provided rapid access to **79**, and potentially other derivatives, this method lacked the level of selectivity required for a generic methodology to access substituted lactones such as **79** **(Scheme 149)**.



Scheme 149. Synthesis of 79 through consecutive ring expansions and Grob-type fragmentation

Strategy for Future Development:

With the aim of providing a selective route through to **79**, one final synthetic strategy was initiated, but requires future development to determine the viability of this approach (**Scheme 150**).



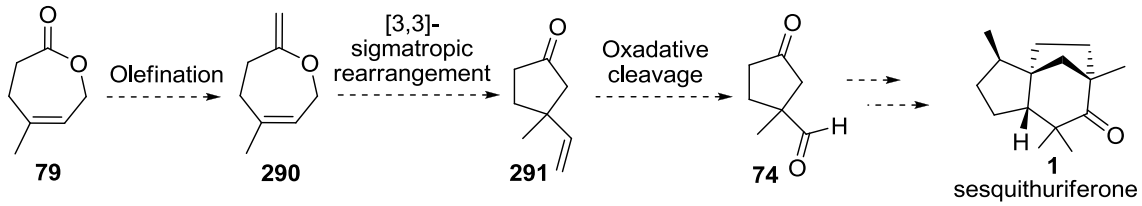
Scheme 150. Proposed synthesis of 79 *via* a Heck protocol

Key to the success of this approach was the embedding of a *Z*-selective olefin early in the synthetic sequence *via* a Heck reaction. Following this, a sequential oxidation/deprotection and lactonisation protocol has been envisioned. Significant progress has been made towards the synthesis of **79** by this strategy, with the successful synthesis of aldehyde **420** to date. Future work surrounds isolation of compound **421**, with a series of optimisation programmes

planned to increase the synthetic efficiency of each of the individual steps. Additionally, a series of experiments have been planned to determine the suitability of this method to provide further derivatives of **79**.

Future work

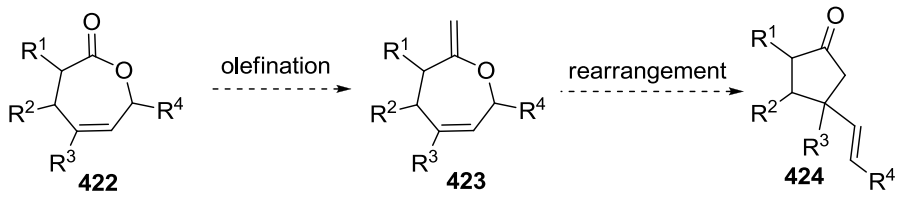
Undoubtedly, the primary goal of all future efforts regarding this project should surround the scale up and synthesis of gram quantities of lactone **79**. It is only from this point, that a comprehensive examination of reaction conditions can be attempted, to first provide enol ether **290** and ultimately determine if the proposed rearrangement is possible (**Scheme 151**).



Scheme 151. Proposed strategy to access 74 from 79

Should the proposed rearrangement of **290** prove successful, a range of derivatives of **79** should be synthesised to attempt a comparative rate study to determine which of the proposed rearrangement mechanisms predominate. With respect to the synthesis of further derivatives of **79**, the Heck protocol provides an excellent opportunity to synthesise both the racemic and asymmetric variants, and identify a generic strategy towards the synthesis of substituted ε-lactones.

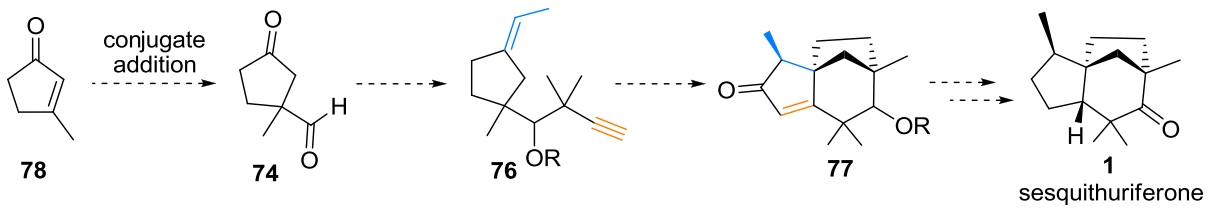
A retrospective overview of the project recognises that substituted cyclopentenones such as **424**, are of more synthetic importance within organic synthesis than the described ε-lactones investigated (**Scheme 152**). However, if the proposed rearrangement is in fact feasible, the development of a selective and potential asymmetric route to lactones such as **422** becomes all the more important. Crucially, the development of an asymmetric variant of the Claisen rearrangement has proved extremely challenging over the years, with no generic systems currently available to provide high levels of enantioenrichment in a range of products. From this perspective, it was recognised that an asymmetric rearrangement of **290** to **74** was unlikely. However, the corresponding diastereoselective Claisen rearrangement is a much more realistic target. Hence, if a method can be found to access enantioenriched forms of compounds such as **422**, this may allow the development of synthetic routes through to complex products such as **424**, not currently accessible in a concise manner (**Scheme 152**).



Scheme 152. Proposed transformation of substituted lactones 422 to cyclopentanones 424

4 Conjugate Addition Strategy

Given the relative problems incurred when attempting the synthesis of keto-aldehyde **74** *via* the proposed [3+3]-sigmatropic rearrangement (**Section 3**), it was clear that a definite simplification of the proposed route also had to be investigated. The main issue attributed to the previously described synthetic strategy, was the high levels of complexity incorporated early in the synthetic sequence i.e. the synthesis of novel lactone **79** (*vide supra*). In an attempt to avoid over complexity, a second synthetic strategy was simultaneously investigated involving the proposed conjugate addition approach (**Scheme 155**). This subtle adaption would not only provide a significant reduction in the number of synthetic steps, but also provided access to **74** from an inexpensive and commercially available starting material 3-methylcyclopentenone **78**.

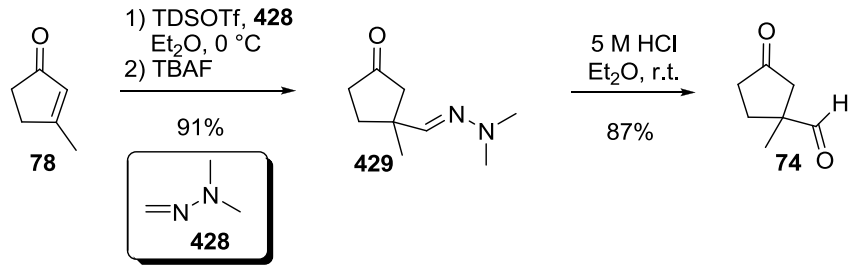


Scheme 155. Proposed conjugate addition strategy to access sesquithuriferone

Formyl groups are inherently electrophilic in character and to date no methods are available to directly introduce these groups into α,β-unsaturated systems such as **78**. With this in mind, it was perceived that an umpolung approach could be used, whereby the formyl group was masked as a nucleophilic reagent, before transforming it to the desired electrophilic functionality further downstream. The masking of formyl groups as umpolung reagents is a common practice within organic synthesis and in this case, a number of options were available, including vinyl groups, 1,3-dithianes, and formylhydrazones.[232]

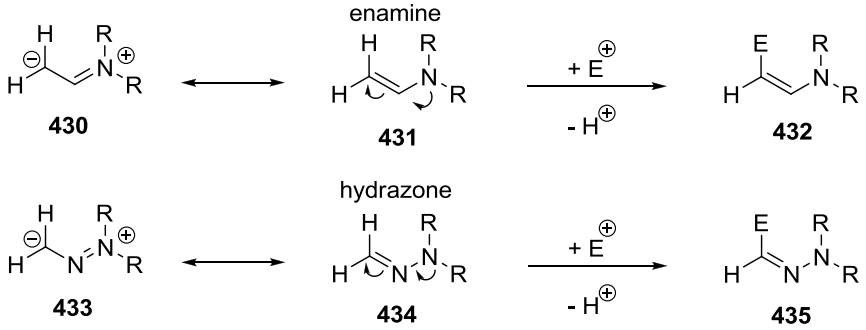
Following a comprehensive literature search, an ideal approach was quickly identified involving the nucleophilic addition of formaldehyde dialkylhydrazones such as **428** (**Scheme 156**).[233–238] To date, a large body of work has been completed in this area demonstrating the versatility of this approach, with excellent yields and selectivites reported throughout.[233] The benefit of this approach was clear in that the synthetic sequence could begin from a commercially available starting material, avoiding a complex synthetic sequence before reaching late stage intermediates. Additionally, detailed experimental procedures and structural data were currently available that should allow rapid progress towards the key P-K reaction; and most importantly, a potentially high yielding and selective asymmetric variant

was already in place that did not require the development of an analytical method to determine the selectivity attained.[233]



Scheme 156. Proposed synthesis of 74 through the use of formyl hydrazones

The success of dialkylhydrazones as nucleophilic reagents has been attributed to an inherent aza-enamine type reactivity (**Scheme 157**). A closer examination of the dialkylhydrazones indicates that they bear a striking resemblance to enamines in terms of both the mesomeric structure and reactivity.[238]



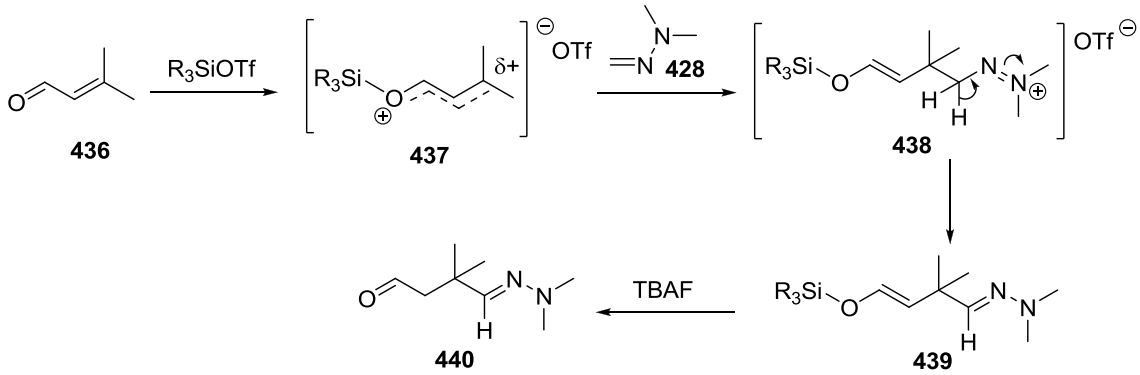
Scheme 157. Azaenamine reactivity of formyl hydrazones

Just as with enamines **431**, it was proposed that the observed nucleophilicity of these hydrazone reagents **434** was derived from the conjugated lone pair present on the amine nitrogen adjacent to the double bond. Hence, the relative reactivity is dependent on the availability of this lone pair to push through and create an effective δ-negative charge on the β-carbon, such as in **433**. It should be noted however, that due to the higher electronegativity of the imine nitrogen adjacent to this nucleophilic site, an overall reduction in reactivity would be observed comparative to its enamine equivalent.

Additionally, it has been shown that the substitution pattern on the β-carbon of the hydrazone plays a significant role in determining the overall reactivity of these reagents. Consequently, as groups other than hydrogen are added to the β-carbon, an appreciable decrease in nucleophilicity was subsequently observed. Investigations indicate that with regard to the substituted derivatives, a high level of reactivity is still maintained with electrophilic substrates such as the Vilsmeier reagent and trifluoroacetic anhydrides.[239–241] However, the

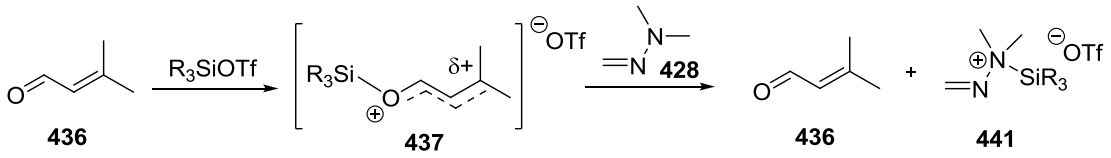
nucleophilicity was sufficiently reduced to prevent reaction with less electrophilic substrates such as carbonyls and Michael acceptors. This fact is particularly important when considering our synthetic strategy, since it would prevent any further reaction with the ketone functionality in **429** once the 1,4-hydrazone addition has occurred.

Importantly, a sufficient level of nucleophilicity was still maintained in the formyl dialkylhydrazone reagents such as **428** to allow their successful use as umpolung synthetic equivalents. It should be noted, however, that despite the comparative increase in nucleophilicity, no spontaneous reaction was observed with Michael acceptors in the absence of reaction promoters. Hence, to access the desired reactivity of these specific reagents, a pre-activation of the enone was critical to increase the relative electrophilicity of this functionality. A comprehensive screening of reaction promoters by Lassaletta and co-workers demonstrated that conventional Lewis acids such as $TiCl_4$, $BF_3{\cdot}Et_2O$, and $ZnCl_2$ were ineffective in promoting the desired reaction.[233] However, it was subsequently discovered that the addition of various silyltriflates resulted in a significant level of conversion to the desired product **440** (**Scheme 158**). In particular, the most bulky silyltriflates (TDSOTf) proved most effective, with a significant decrease in the 1,4-addition product **440** observed as the steric environment around the silyl group was systematically reduced.



Scheme 158. Proposed activation/addition pathway

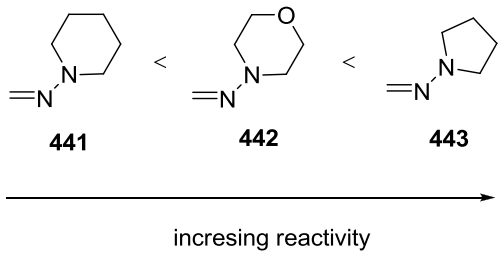
Crucially, it was noticed that when sufficient steric bulk was not present around the silyl group, an appreciable level of **441** was observed (**Scheme 159**). This was primarily thought to be due to a competitive side reaction, whereby the lone pair of the nitrogen on the alkyl portion of the hydrazone was preferentially attacking the silyltriflate, rather than facilitating product formation through the proposed 1,4-addition pathway.



Scheme 159. Proposed competitive side product formation

As previously mentioned, TDSOTf was identified as the most effective reagent towards the promotion of 1,4-addition. However, at present, this reagent is no longer commercially available and an accessible alternative had to be identified for the purposes of the synthetic strategy proposed. Pleasingly, an examination of the results published by Lassaletta and co-workers indicated that moderate to excellent yields of **440** were achievable using the commercially available reagent, TBDMSOTf, although reduced yields were observed comparative to the optimised system.[233]

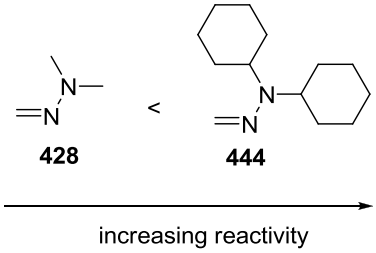
Furthermore, with regard to the alkyl component of the hydrazone, there does appear to be a direct correlation between the aza-enamine reactivity of the reagent and the substitution pattern present on the amine nitrogen (**Scheme 160**). Investigations have shown that the pyrrolidine derivative **443** exhibits a high level of aza-enamine reactivity, with a reduction in nucleophilicity at the terminal azomethine carbon observed as the piperidine **441** and morpholine **442** systems are applied.[238]



Scheme 160. Structural variants of hydrazone reagents and their relative reactivity

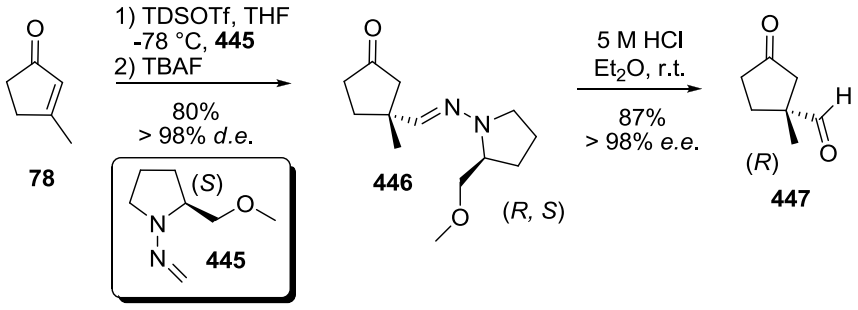
Several theories have been proposed to explain this apparent change in reactivity with structure, though none have been conclusively proved. One such rationalisation attributes the relative conjugative contribution to the hybridisation state of the amine nitrogen present within the ring system.[238,242] In this regard, it was proposed that variations of the valence angle within the ring system have a direct correlation with the level of *n*-π overlap, and ultimately the resultant aza-enamine reactivity of the hydrazone reagent. From this perspective, it was proposed that six-membered rings such as **441** and **442** incur a less effective *n*-π overlap comparative to the pyrrolidine equivalent **443**, accounting for their reduced reactivity. In contrast, open chain hydrazones such as **428** and **444** have proved to be

very effective aza-enamines (**Scheme 161**). The high level of reactivity observed by these reagents has been attributed to the wide valence angle which allows the maximum *n*-π overlap to occur. With regard to these reagents, **444** has shown a remarkable level of activity and is a more effective reagent than **428**. In the case of **444**, steric shielding of the amine nitrogen was believed to be occurring, effectively blocking the competitive nucleophilicity of the amine nitrogen and promoting the desired reactivity through the terminal azomethine carbon. Furthermore, it is also likely that there is an increased stabilising effect on the iminium intermediate due to the electron-donating cyclohexyl groups.



Scheme 161. Open chain hydrazone reagents and their relative reactivity

Importantly, this synthetic approach readily adapts itself to an asymmetric variant, with excellent levels of selectivity reported to date (> 98% *d.e.*) (**Scheme 162**). In particular, it was through the use of Ender's proline derived hydrazone **445**, that the highest levels of selectivity were achieved.[233] Although the relevant examples published in current literature were towards the formation of the opposite enantiomer (*R*) comparative to the desired target, the commercial availability of both enantioenriched forms of the chiral dialkylhydrazines (*R* and *S*) indicated that this was still a feasible approach.



Scheme 162. Asymmetric variant of conjugate addition strategy

At present it is believed that the high levels of diastereoselectivity are generated through a tight chair transition state, whereby clashes between the side-chain (OMe) on the pyrrolidine ring and the CH_2 portion of the enone, promote a minimum energy conformation **448** as shown in **Figure 20**.

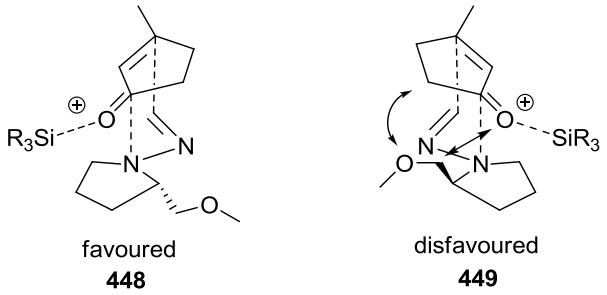
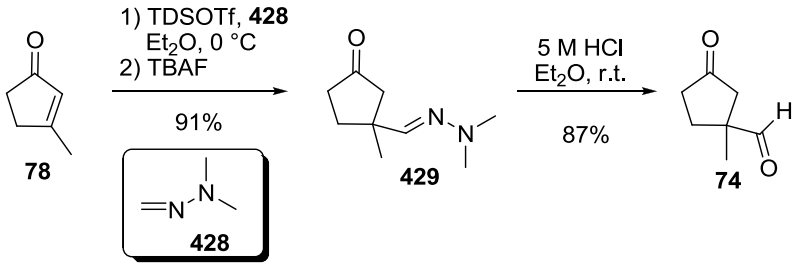


Figure 20. Proposed transition states of the asymmetric variant

After comprehensively reviewing the information available, it was decided to proceed towards the racemic synthesis of **74** *via* the conjugate addition strategy using formyl hydrazone **428** and TBDMSOTf.

4.1 Conjugate Addition Strategy Towards the Synthesis of 74

Towards the formation of racemic **74**, preliminary investigations surrounded the conjugate addition of formyl dimethylhydrazone **428** to 3-methylcyclopentenone **78**, as described by Lassaletta and co-workers (**Scheme 163**).[233] As previously discussed, TDSOTf is no longer commercially available and TBDMSOTf was to be substituted in its place. Due to this subtle change in silyl triflate, it was recognised that minor modifications of the reaction protocols may be required to obtain the desired quantities of **74** required to complete the synthesis of sesquithuriferone. With this in mind, a preliminary screening of reactions conditions was carried out to identify which of the protocols described by Lassaletta and co-workers was optimal using this alternative reagent.



Scheme 163. Synthesis of keto-aldehyde 74 by the Lassaletta group

Prior to attempting the proposed synthetic sequence, the requisite dimethylhydrazone **428** had to be prepared (**Table 23**). The initial synthesis of **428** was carried out following the procedure of Class and co-workers, to afford **428** in a modest 58% yield (**Table 23**, Entry 1).[243] Despite the successful formation of **428**, it was perceived that the presence of water in the reaction mixture may be hindering complete conversion of hydrazine **450** to the desired

product **428**. A literature search identified an alternative preparative protocol for the synthesis of the corresponding piperidinehydrazone, under anhydrous conditions.[244] Pleasingly, by following this procedure an 81% yield of **428** was isolated after distillation, significantly improving conversions (**Table 23**, Entry 2).

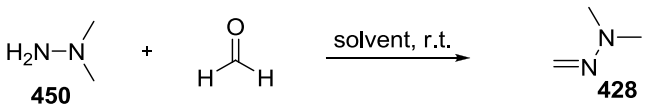
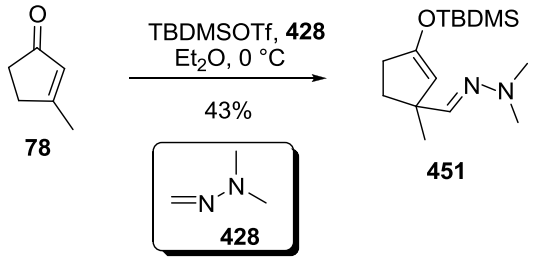


Table 23. Synthesis of formyl hydrazone 428

Entry	Solvent	Yield (%)
1	Et_2O, H_2O	58
2	Et_2O	81

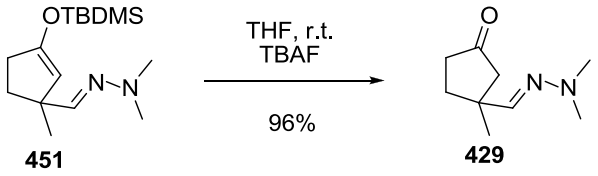
With **428** now in hand, an initial screening of reaction conditions was attempted to gain insight into the described conjugate addition process. To begin the reaction sequence the synthesis of silyl enol ether **451** was investigated (**Scheme 164**). By following a step-wise approach, the efficiency of each of the individual steps could be determined, before attempting any optimisation programmes, if required. Following the procedures described by Lassaletta and co-workers a yield of 43% of **451** was isolated, with 26% **78** also recovered.



Scheme 164. Synthesis of silyl enol ether 451

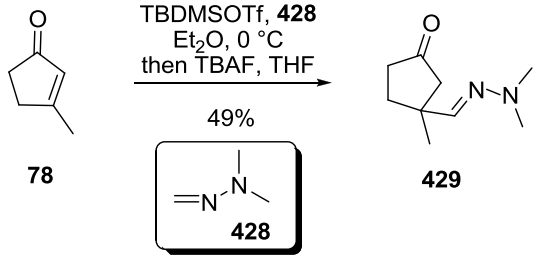
Whilst this result was rather disappointing, it was not entirely surprising since no representative yields of **451** were reported in the original paper by Lassaleta, due to its suspected high volatility. However, more concerning was the large quantities of residual starting enone **78** detected.

Treatment of the resultant silyl enol ether **451** with a solution TBAF successfully formed **429** in an excellent yield of 96% after purification (**Scheme 165**). The high yields observed in this step, combined with the apparent ease of isolation, indicated that a one-pot procedure would be the most advantageous future approach to minimise any potential loss of silyl enol ether **451**.



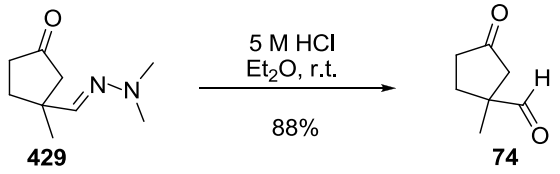
Scheme 165. Synthesis of keto hydrazone 429

With the knowledge of how to monitor the reaction, an initial attempt at a one-pot procedure was pursued (**Scheme 166**). Accordingly, following this alternative protocol a modest yield of 49% of **429** was observed. Crucially, these initial results indicated that under current reaction conditions, the exchange of TDSOTf for TBDMSOTf resulted in a significant reduction in conversion of **429**, comparative to the 91% yield reported by Lassaletta and co-workers.[233] Additionally, these initial investigations also indicated that the reduction in overall yield was primarily due to the conjugate addition process to form **451**, rather than the subsequent deprotection to provide **429**. Throughout all of the initial syntheses of **429** incorporating TBDMSOTf, 20-30% of the starting enone **78** was recovered upon reaction completion.



Scheme 166. Synthesis of 429 by one pot protocol

With the successful synthesis and identification of **451** and **429** completed, removal of the hydrazone in **429** was attempted under acidic conditions (**Scheme 167**). Reaction progress proved to be fairly rapid, with complete deprotection observed by TLC analysis after 4 h.

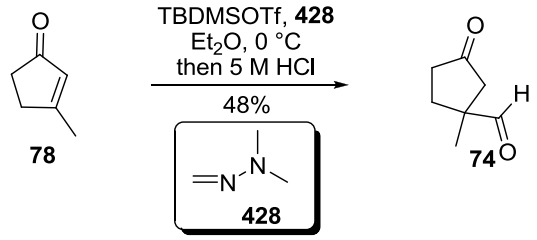


Scheme 167. Acid mediated deprotection of 429

Even though an encouraging 88% yield of **74** was isolated from this reaction, hydrolysis of hydrazone **429** was believed to be quantitative (*via* TLC analysis). Crucially, the removal of **74** from the acidic media proved problematic, with a laborious extraction process required due to the high aqueous solubility of **74**. Despite repeated attempts to modify the extraction

protocol, no successful conditions were identified to facilitate the complete extraction of **74**, with the partial loss of the product to the aqueous phase deemed unavoidable.

In order to fully explore the initial reaction sequence before attempting optimisation, an additional one-pot procedure was identified to directly access the target molecule **74** from **78** (**Scheme 168**). Accordingly, following completion of the conjugate addition, the reaction was quenched with a solution of aqueous 5 M HCl and allowed to stir until complete deprotection was observed by TLC analysis. The described one-pot protocol successfully delivered keto-aldehyde **74** in a modest 48% yield.



Scheme 168. Synthesis of 74 by one-pot protocol

Although the simplicity of this procedure towards the synthesis of **74** was extremely desirable, two major drawbacks were observed when following this approach. Firstly, product extraction again proved challenging, with product losses to the aqueous phase observed; and secondly, the complete separation of **74** from the residual starting enone **78** proved almost impossible due to co-elution.

Following the completion of the initial set of reactions, a series of short optimisation programmes were designed to identify an efficient protocol, before attempting a scale-up of the reaction. Due to the ease of access, the two-step procedure to form **429** was chosen to begin the optimisation process. Towards this aim, the first variables examined were the effects of solvent and reaction length (**Table 24**).

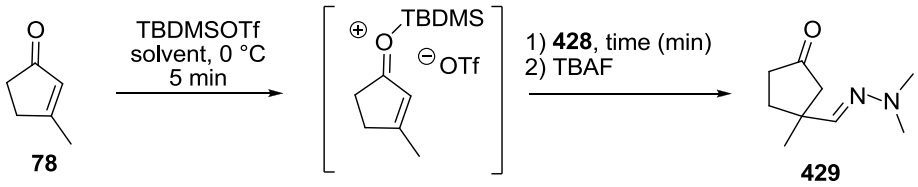


Table 24. Effect of solvent and reaction length on the synthesis of 429

Entry	Solvent	Time (min)	Yield (%)
1	Et_2O	15	43
2	Et_2O	30	48
3	DCM	15	49
4	DCM	30	53
5	THF	15	48
6	THF	30	58
7	THF	60	56

From the results presented in **Table 24** it was observed that product conversions could be improved slightly through the use of more polar solvent systems and prolonged reaction times. Closer analysis of the isolated yields indicates that, by extending the reaction length from 15 min (based on the published protocol) to 30 min, a 5-10% increase in the yield of **429** could be achieved, regardless of the solvent under investigation (**Table 24**, Entries 2, 4 and 6). Additionally, further extension of the reaction length to 60 min appeared to have little or no significant effect on conversions (**Table 24**, Entry 7). More importantly, switching the solvent system provided an appreciable effect on isolated yields, with THF proving to be the most effective solvent. This subtle change in solvent polarity allowed yields as high as 58% of **429** to be isolated, compared to 48% with the equivalent Et_2O system (**Table 24**, Entries 2 and 6).

In a further extension of the optimisation process, the effect of temperature was also examined in a range of solvents (**Table 25**).

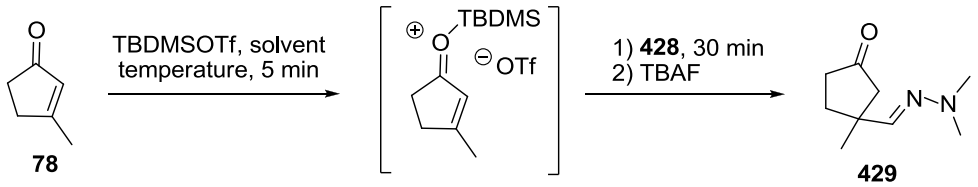


Table 25. Effect of temperature and solvent on the synthesis of 429

Entry	Solvent	Temperature (°C)	Yield (%)
1	Et_2O	0	46
2	Et_2O	-78	49
3	DCM	0	45
4	DCM	-78	49
5	THF	0	56
6	THF	-78	61
7[a]	THF	-78	60
8	Et_2O	r.t.	32

[a]Reaction length of 60 min.

The results in **Table 25** illustrate that by carrying out the reaction sequence at -78 °C a slight increase in yield could be achieved, comparative to the equivalent system at 0 °C (**Table 25**, Entries 2, 4 and 6). The general trend in reactivity was also followed, with the highest product conversions observed in THF, with an isolated yield of 61% of **429** (**Table 25**, Entry 6). Importantly, the efficiency of the reaction was not significantly affected by the reduced temperatures, with extended reaction times proving ineffective in increasing reaction conversions (**Table 25**, Entry 7). However, it was observed that any increase in temperature above 0 °C resulted in an appreciable decrease in the yield of **429** upon reaction completion (**Table 25**, Entry 8).

In a final attempt to increase yields, the effect of complexation time was analysed (**Table 26**). From this perspective, it was proposed that the relatively high levels of starting enone **78** recovered from these reactions may be due to incomplete complexation of the silyl group to the enone. To determine if this was in fact the case, a range of complexation times were examined.

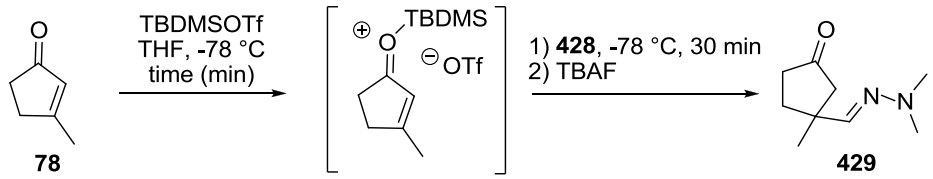


Table 26. Effect of complexation on the synthesis of 429

Entry	Complexation time (min)	Yield (%)
1	5	52
2	10	53
3	20	54
4	30	62
5	60	62

The results obtained from this study appeared to indicate that the length of time required to affect enone complexation was significant at low temperature (**Table 26**). In this regard, reduced product conversions were observed when a complexation time of less than 30 min was examined (**Table 26**, Entries 1-3). However, an appreciable increase in isolated yield of **429** to 62% was observed when the length of time to complete the complexation process was extended to 30 and 60 min (**Table 26**, Entries 4 and 5). Crucially, whilst an extended complexation period of 30 min proved beneficial, extension beyond this did not appear to provide any further advantage (**Table 26**, Entry 5).

In an alternative attempt to improve product conversions, the effect of the silyl reagent was analysed (**Table 27**). In this regard, representative reactions were attempted to ascertain if any advantage could be gained through the use of TESOTf. To obtain an overall understanding of exactly how much the substitution pattern on the silyl promoter effects conversions, TMSOTf was also examined.

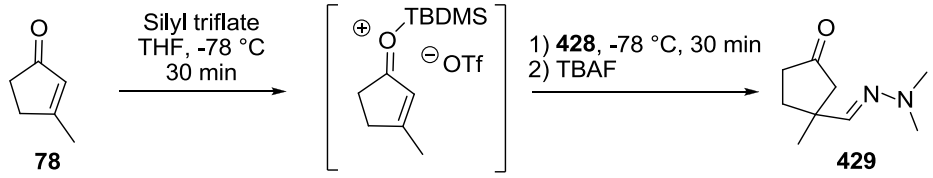


Table 27. Effect of silyl triflate on the synthesis of 429

Entry	Silyl triflate	Yield (%)
1	TMSOTf	28
2	TBDMSOTf	60
3	TESOTf	42

Analysis of the results presented indicated that, as expected, reduced conversions of **429** were observed using TMSOTf as a promoter, with a yield of 28% observed (**Table 27**, Entry 1). Unfortunately, it also appeared that TESOTf did not represent the comparative increase in steric bulk required to promote increased product formation, with a yield of 42% of **429** recovered (**Table 27**, Entry 3).

Despite the isolation of moderate yields of **429**, it was decided that scale-up of the reaction should be pursued in order to bring through the quantities of material required to continue forward through the proposed reaction sequence (**Table 28**).

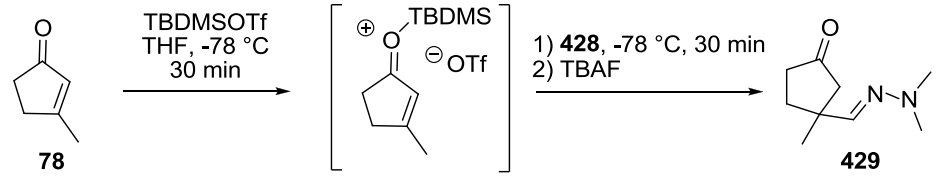


Table 28. Attempted scale up of 429

Entry	Scale (mmol)	Concentration (M)	Yield (%)
1	2	0.2	59
2	4	0.2	41
3	4	0.1	40
4	4	0.4	42
5	6	0.2	37
6	6	0.4	38
7	6	0.1	37

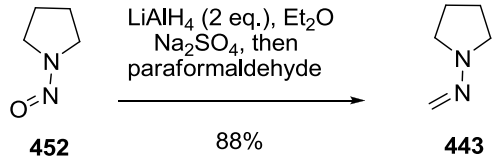
From the results shown in **Table 28**, a sharp decrease in conversion to **429** was immediately observed upon scale-up of the reaction. Most notably, the observed yields dropped from 59% to 41% of **429**, when increasing the scale to 4 mmol (**Table 28**, Entries 1 and 2). Increasing the scale further to 6 mmol, provided a similar reduction in yield with 37% of **429** isolated (**Table 28**, Entry 5).

In order to determine if this surprising effect was due to concentration, the dilutions of the reaction mixtures were adjusted to either 0.1 M or 0.4 M (**Table 28**, Entries 3, 4, 6 and 7). Unfortunately, concentration did not have a significant effect on the conversions of **429**, with isolated yields remaining fairly consistent regardless of the concentrations examined.

As demonstrated by the results in **Table 28**, the reaction protocol under investigation was not suitable to provide **429** at an increased scale. Crucially, this surprising outcome represented a significant barrier towards progression through the synthetic sequence.

Since no clear advantage could be gained by varying the current reaction conditions, the next logical step was to address the reactivity of the dialkyhydrazone involved in the conjugate addition. From this perspective, literature precedent would suggest that dimethylhydrazone **428** was not as reactive as the corresponding pyrrolidine derived hydrazone **443**.[237,244] In an attempt to increase the yields of the desired keto-hydrazone and identify a suitable set of reaction conditions for scale-up, the corresponding pyrrolidine derivative **443** was first synthesised and then examined under conjugate addition protocols.

Towards this aim, a literature search identified a suitable one-pot procedure to synthesise **443** involving the reduction of nitroso pyrrolidine **452**, followed by condensation with paraformaldehyde (**Scheme 169**).[237] Pleasingly, through careful control of the reaction conditions, isolation of the desired product **443** was achieved in an excellent 88% yield, on a significant scale.



Scheme 169. Synthesis of formyl hydrazone 443

With **443** in hand, an initial set of reactions were carried out to directly compare the reactivity of **428** and **443**, under both Lassaletta's standard reaction conditions, as well as the current optimised conditions (**Table 29**).

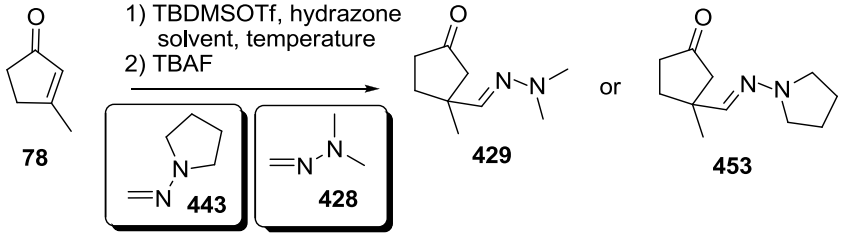


Table 29. Comparison of the reactivity of hydrazone reagents 428 and 443

Entry	Solvent	Temperature (°C)	Hydrazone	Yield (%)
1	Et_2O	0	**443**	**453** (65)
2	THF	-78	**443**	**453** (78)
3	Et_2O	0	**428**	**429** (48)
4	THF	-78	**428**	**429** (59)

From the results shown in **Table 29**, it was immediately recognised that through the subtle change in hydrazone reagent to **443**, a significant increase in the yield of **453** could be achieved. Following the published protocols set out by Lassaletta at 0 °C,[233] an encouraging 65% yield of **453** was isolated, representing a 17% increase in the yield comparative to hydrazone **428** (**Table 29**, Entries 1 and 3). Further examination of **443** under current optimised conditions provided **453** in an improved yield of 78% (**Table 29**, Entry 2). However, despite this marked improvement in reactivity, it should be noted that 10-20% starting enone **78** continued to be isolated from these reactions.

Before attempting to increase the scale of the reaction using **443**, one final attempt to optimise the reaction conditions was pursued. This final examination of reaction conditions involved a systematic variation of the stoichiometry of each of the reagents involved in the transformation (**Table 30**).

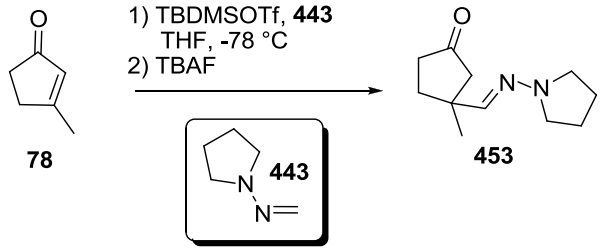


Table 30. Attempted optimisation of pyrrolidine system to form 453

Entry	TBDMSOTf (eq.)	**443** (eq.)	Yield (%)
1	1	1	58
2	1	1.5	77
3	1	2	78
4	1.2	1	53
5	1.2	1.5	81
6	1.2	2	84
7	1.5	2	88
8	0.9	1.2	88

Crucially, the results obtained from this short study indicated that further improvements in the conversions of **453** could be achieved, with yields as high as 88% isolated (**Table 30**, Entries 7 and 8). Importantly, one major trend was identified throughout this process; the highest yields of **453** were isolated when an excess of **443** was present, comparative to the silyl triflate (**Table 30**, Entries 2, 3 and 5-8). Furthermore, significant improvements in the

conversion of **78** to **453** were achieved when a large excess of both the silyl triflate and hydrazone **443** were added to the reaction mixture (**Table 30**, Entries 5-7). However, the corresponding reaction involving sub-stoichiometric amounts of TBDMSOTf proved just as effective, providing an excess of hydrazone **453** was present (**Table 30**, Entry 8). Crucially, this final adaption of reaction conditions proved the most useful from a practical point of view, since it provided the greatest level of atom economy, with regard to the reagents within the reaction mixture.

Due to the fact that hydrazone **443** had to be synthesised, as opposed to the commercial availability of enone **78** and TBDMSOTf, the optimised conditions taken forward for scale-up were those identified above (**Table 30**, Entry 8). With the identification of a suitable protocol to synthesise **453**, a range of scales were examined to determine the viability of the reaction sequence to provide **453** in sufficient quantities (**Table 31**).

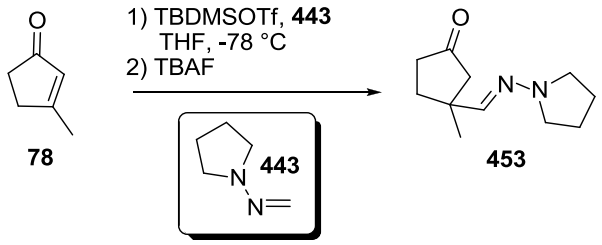
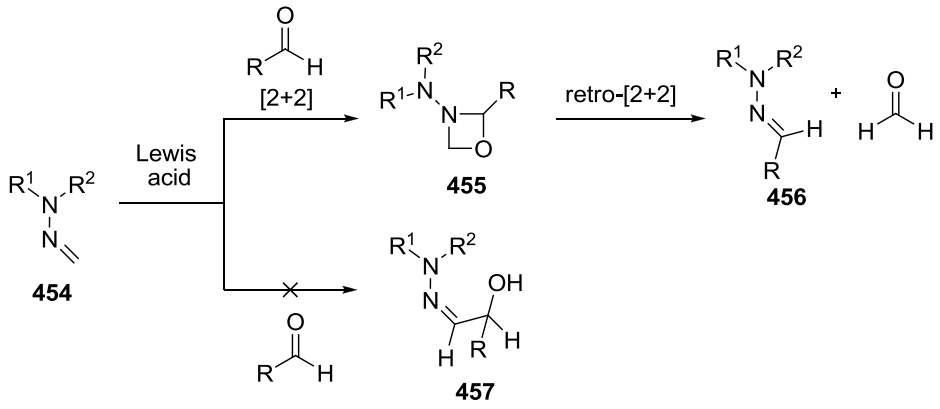


Table 31. Attemped scale-up of the synthesis of 453

Entry	Scale (mmol)	Yield (%)
1	2	88
2	5	84
3	10	78
4	30	76

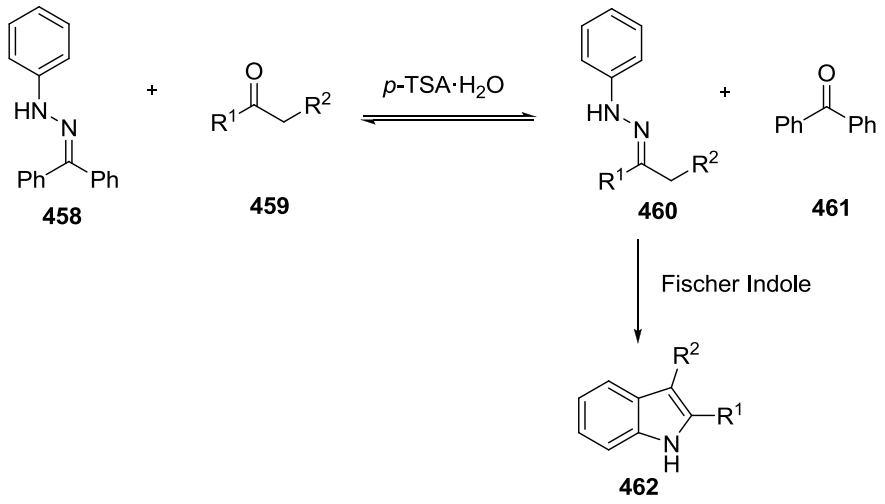
Pleasingly, the results in **Table 31** illustrate that the synthesis of **453** on a significant scale proved extremely successful, providing **453** in a yield of 76%, on a 30 mmol scale (**Table 31**, Entry 4). It should be noted that just as with the dimethyl formyl hydrazone **428**, a reduction in yield was observed as the scale was systematically increased (**Table 31**, Entries 1-4). However, through the use of the newly developed protocol the reductions in reaction conversions were not as significant as previously observed, allowing the multi-gram synthesis of **453**, to provide the material required for later steps (*vide supra*).

With significant quantities of **453** in hand, one final problem required attention: the deprotection of the **453** to **74**. Previously, established conditions for this transformation involved the hydrolysis of **429** under aqueous acidic conditions (**Scheme 167**). However, this required a lengthy extraction process, with the partial loss of **74** to the aqueous phase. To address this problem, a new protocol was envisioned involving the dynamic exchange of the hydrazone with an alternative carbonyl source (**Scheme 170**). Inspiration for the incorporation of this process originated from previous investigations by Lassaletta and co-workers.[234,245] During their investigations towards the synthesis of α-hydroxy hydrazones **457**, the authors reported that many of the hydrazones under investigation did not have the inherent nucleophilicity to form the desired target molecules **457**. Instead they underwent a [2+2]-cycloaddition and reversion, exchanging the hydrazone functionality for the more thermodynamically stable product **456**.



Scheme 170. Proposed [2+2]-cycloaddition and reversion to furnish 456, by Lassaletta *et al*.

Following a further literature search, a second example of this process was identified towards the synthesis of indoles, by Buchwald and co-workers.[246,247] During their investigations, the authors reported that a similar process could be successfully incorporated to facilitate the exchange of a phenyl hydrazone **458** onto substituted ketones such as **459**, in the presence of *p*-tolylsulfonic acid monohydrate (*p*-TSA·H_2O) (**Scheme 171**).



Scheme 171. General strategy for the synthesis of indoles by Buchwald and co-workers.

Towards the synthesis of **74**, a similar protocol was proposed involving switching the hydrazine portion of **453** onto acetone (**Table 32**). This approach should not only allow the use of an inexpensive, low boiling point carbonyl surrogate, but also allow the reaction to be carried out under largely anhydrous conditions. With the aim of identifying a suitable set of conditions to provide **74**, various amounts of *p*-TSA·H_2O were added to a solution of **453** in acetone.

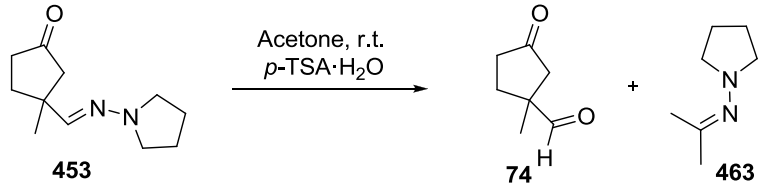


Table 32. The synthesis of 74 in acidified acetone

Entry	*p*-TSA (eq.)	Yield (%)
1	1	56
2	1.5	78
3	2	86
4[a]	2	94

[a]1.0 equivalent of H_2O added to the reaction mixture

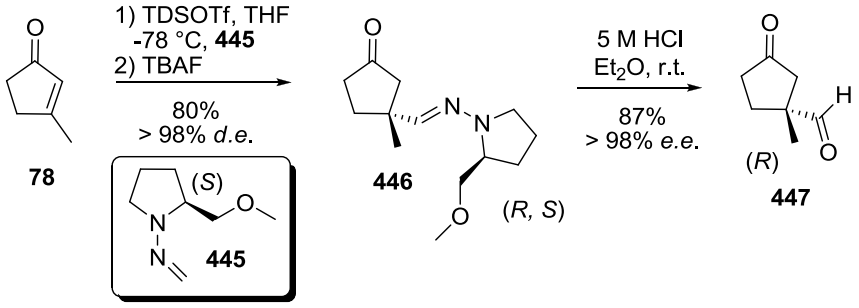
The results presented in **Table 32** indicated that whislt the proposed strategy proved successful towards the deprotection of **453** to **74**, complete conversion of **453** could not be achieved in the presence of stoichiometric or excess amounts of *p*-TSA·H_2O (**Table 32**, Entries 1-3). Optimised conditions required the addition of a large excess of *p*-TSA·H_2O, combined with a stoichiometric volume of H_2O, to provide **74** in a yield of 94% (**Table 32**,

Entry 4). Despite the fact that the optimised deprotection protocol required the addition of excess H_2O to the reaction mixture, product isolation proved to be relatively straightforward, with no obvious product losses observed.

The success of this adapted deprotection protocol marked an important point towards the synthesis of sesquithuriferone. With a scalable, concise route through to key racemic compound **74**, attention was turned towards the development of an asymmetric variant.

4.2 Asymmetric Variant

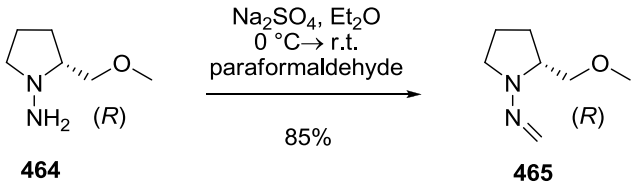
As previously stated, a large body of work has been completed by Lassaletta adn co-workers towards the synthesis of an enantioenriched form of **447**. To date, the most successful reported protocol has involved the conjugate addition of Ender's proline derived hydrazone SAMP **445**, to embed the corresponding (*R*)-enantiomer in **447** (**Scheme 172**).[233]



Scheme 172. Asymmetric variant of the conjugate addition strategy, Lassaletta *et al.*

However, in the case of sesquithuriferone an (*S*)-selective process was essential, requiring the addition of the corresponding opposite enantiomer, RAMP-derivative **465** (**Table 33**). The commercial availability of both the SAMP and RAMP hydrazine forms of this ligand further increased the desirability of this approach, avoiding a lengthy synthetic sequence to access the desired enantioenriched ligand.[248]

Furthermore, synthesis of the corresponding formyl RAMP hydrazone **465** proved relatively facile following the procedures set out by Lassaletta and co-workers, to provide **465** in a yield of 85% (**Scheme 173**).[236] Analyses of the purified hydrazone **465** indicated that the product contained a comparable level of enantioenrichment and opposite stereoconfiguration to the corresponding SAMP derivative **445**.



Scheme 173. Synthesis of the formyl RAMP hydrazone 465

Following the detailed procedures set out by Lassaletta and co-workers, an initial set of trial reactions were attempted to synthesise **466** and **467** (**Table 33**).

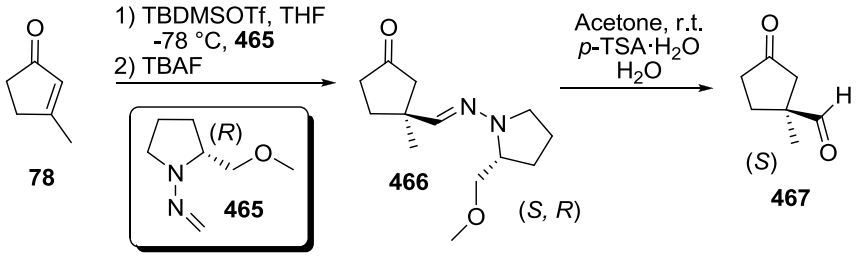


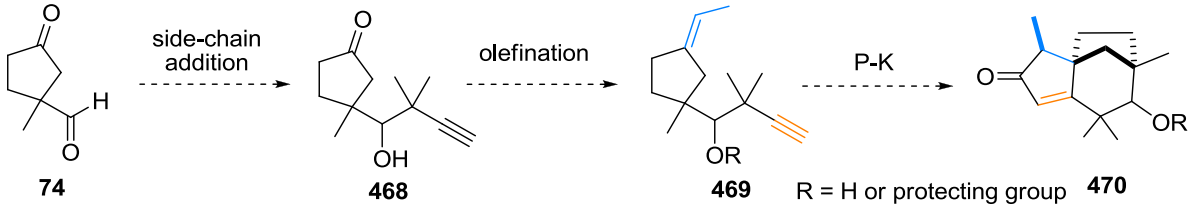
Table 33. Synthesis of the asymmetric variant 467

Entry	Scale (mmol)	Yield of **466** (%)	*d.e.* (%)	Yield of **467** (%)	*e.e.* (%)
1	2	78	> 98	90	> 98
2	6	76	> 98	92	> 98
3	10	77	> 98	92	> 98

The results presented in **Table 33** illustrated that the protocols described by Lassaletta and co-workers could be successfully adapted to the corresponding RAMP derivative **465**. Following product isolation, yields as high as 78% of **466** were achieved on a 2 mmol scale (**Table 33**, Entry 1). Crucially, scale-up of the reaction protocols appeared to have little or no effect on conversions, with the yields of **466** maintained at 76-78% throughout (**Table 33**, Entries 1-3). Following the successful synthesis of **466**, each of the individual products were deprotected to the corresponding keto-aldehyde **467** in yields in excess of 90% (**Table 33**, Entries 1-3). Furthermore, spectroscopic analyses and optical rotations confirmed that the selectivities embedded in **466** and **467** were equal and opposite to the stereoconfigurations identified in the published data towards the corresponding opposite enantiomer.[233]

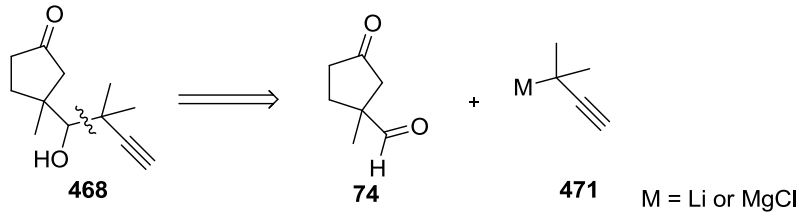
4.3 Addition of Alkynyl Side-Chain to 74

Following the successful isolation of **74**, both in its racemic and enantioenriched form, further progress towards the synthesis of sesquithuriferone could be attempted. Towards this aim, the next goal was the isolation of key P-K precursor **469**. As previously stated, this was proposed through the chemoselective addition of an alkynyl side-chain to **74**, followed by *Z*-selective olefination, to form **469** (**Scheme 174**).



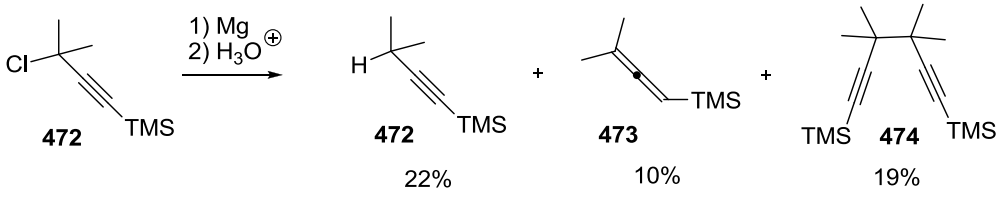
Scheme 174. Proposed synthesis of P-K precursor 76

From the outset of the synthesis towards sesquithuriferone, a clear emphasis had been placed on the development of a concise route. In this respect, initial efforts concentrated upon the addition of the entire side-chain through the use of an organometallic reagent **471** (**Scheme 175**).



Scheme 175. Retrosynthetic strategy towards the synthesis of 468

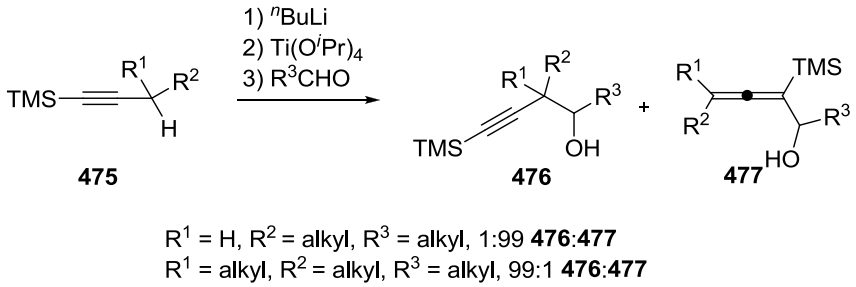
Literature precedent for the formation of organometallic reagents from compounds such as **472** suggested that regioisomeric mixtures of products were likely, due to an *in situ* rearrangement of the reactive species (**Scheme 176**).[249] Indeed, metallated species of this kind are prone to tautomerisation, whereby the reactive species may react either as the metallated alkyne, or the allenic species, forming separate and distinct products **472-474**.



Scheme 176. Tautomeric products formed by Grignard reagent of 472

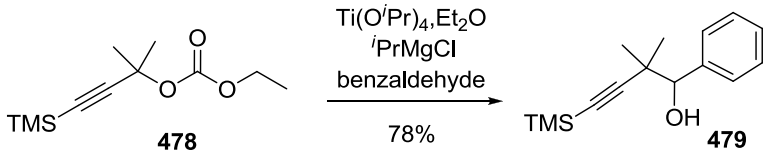
In contrast, the corresponding titanium species showed more promise as a nucleophilic reagent (**Scheme 177**).[250] Through transmetallation of an alkyllithium species onto Ti(O^{i}Pr)$_4$,

the regioselectivity was predictable and entirely dependent on the substitution pattern present in the reactive species. In this regard, it would appear that increased levels of substitution at the reactive centre resulted in the preferential formation of the alkynic product **476**, whereas the less substituted equivalent formed the allenic product **477**.



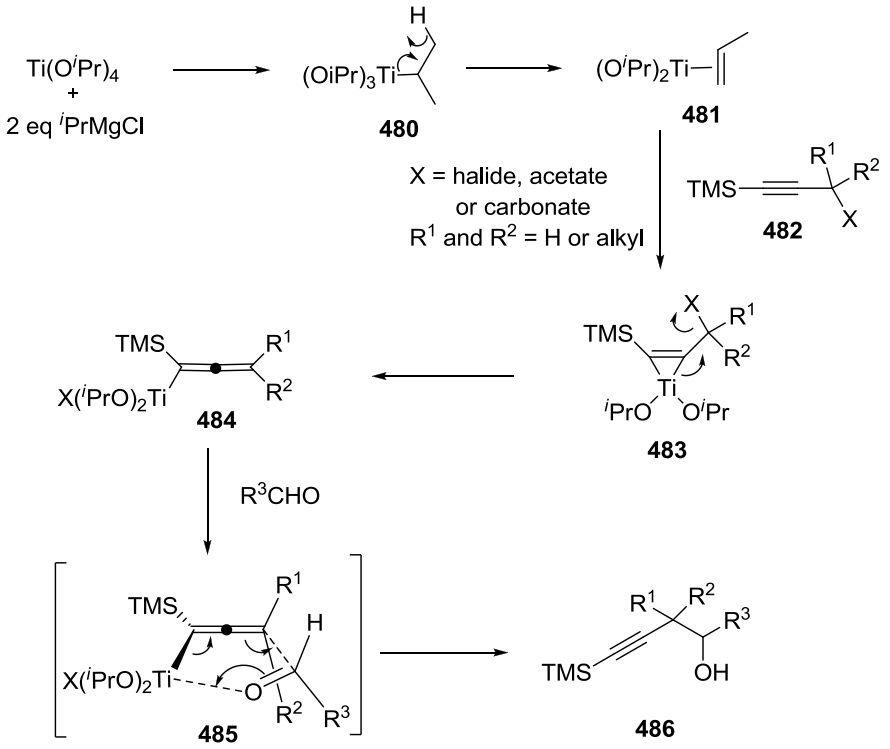
Scheme 177. Predictable reactivity of an organotitanium species

A further literature search identified a much more user-friendly approach, avoiding lithiation and transmetallation (**Scheme 178**). Investigations pioneered by Sato and co-workers reported that by treating the corresponding propygylic halide or carbonate **478** with $Ti(O^iPr)_4$ and ^{i}PrMgCl, the addition of the propygylic unit could be achieved with almost complete regioselectivity.[251,252]



Scheme 178. Propargylic addition to aldehydes *via* titanium mediated methodology, by Sato *et al*.

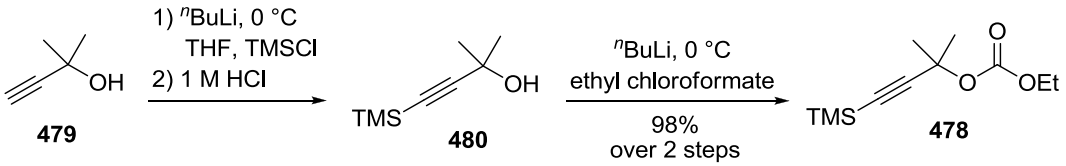
Closer analysis of the reaction mechanism revealed that the addition of ^{i}PrMgCl to $Ti(O^iPr)_4$ causes an initial ligand exchange, followed by β-hydride elimination to form titanium alkene complex **481** (**Scheme 179**). Exchange of the alkene moiety for the more electron-rich triple bond of the alkyne, then facilitates the elimination of a leaving group in **483** to form a reactive titanium allene species **484**. It was proposed that from this intermediate, controlled nucleophilic attack occurs through a five-membered transition state **485**, reinstating the alkyne moiety in the resultant product **486**.



Scheme 179. Proposed mechanism for alkyne side-chain addition, Sato *et al*.

A review of the various substrates investigated by Sato and co-workers revealed that trisubstituted variants, such as **478**, were expected to form the alkyne product preferentially.[252] Furthermore, due to the inherent steric bulk of these substrates, the reactive species was thought to be effectively unreactive in the presence of ketones. With regard to the proposed synthetic strategy in question, this innate selectivity appeared ideal. Crucially, this would not only promote the selective addition of the side-chain to the aldehyde exclusively, but also allow an excess of nucleophile to be added to the reaction mixture.

With a suitable synthetic approach identified, synthesis of the requisite alkyne carbonate **478** was pursued (**Scheme 180**). Accordingly, from commercially available propargyl alcohol **479**, double protection with TMSCl under basic conditions, followed by aqueous acidic work-up provided **480**. Subsequent reaction of **480** with ethylchloroformate under basic conditions, provided the desired carbonate **478** in an excellent 98% yield over the 2 steps.



Scheme 180. Synthesis of alkyne side-chain 478

With all of the required reagents now in hand, a range of conditions were investigated towards the synthesis of **482** (**Table 34**).

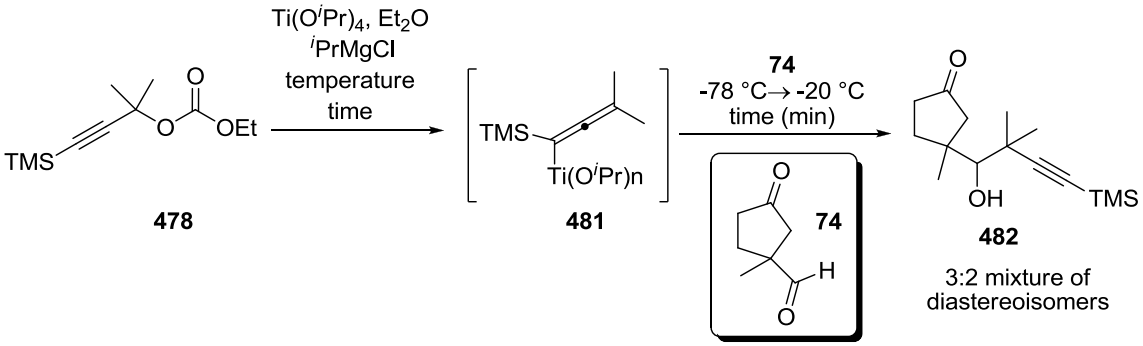


Table 34. Synthesis of 482 *via* a titanium-mediated side-chain addition

Entry	Complexation temperature (°C)	Complexation time (min)[a]	Time at -20 °C (min)[b]	Yield (%)
1	-40	60	30	43
2	-40	90	30	48
3	-40	90	60	58

[a]Represents the length of time to pre-form the titanium allene species, before addition of **74** at -78 °C.
[b]Following addition of **74** at -78 °C, the reaction mixture was warmed to -20 °C where it was maintained to promote side-chain addition.

To begin the screening process, an initial attempt was made following the procedures described by Sato *et al.*, providing **482** in a yield of 43%, as a 3:2 mixture of diastereoisomers (**Table 34**, Entry 1).[252] Despite the success of this initial protocol, reproducibility of this procedure proved problematic with isolated yields varying considerably. Additionally, the physical characteristics of the reaction mixture were observed to change quite significantly depending on the source of the ^{i}PrMgCl and Ti(O^{i}Pr)$_4$. In an effort to overcome these issues, an extended complexation time was investigated (**Table 34**, Entry 2). Through this critical extension of the time period allotted to allow the formation of the titanium allene species **481**, yields of **482** not only increased to 48%, but became more reliable, with little variation observed. In one final adaption to the described protocol, the length of time that the reaction mixture was held at -20 °C following the addition of **74** was also investigated (**Table 34**, Entry 3). Pleasingly, by extending this time to 60 min, isolated yields of **482** increased to 58%.

Whilst this preliminary set of results appeared entirely positive, it was felt that further improvements to the described protocol could be achieved (**Table 35**). Towards this aim a short solvent screen was carried out using the optimised conditions developed in **Table 34**, Entry 3.

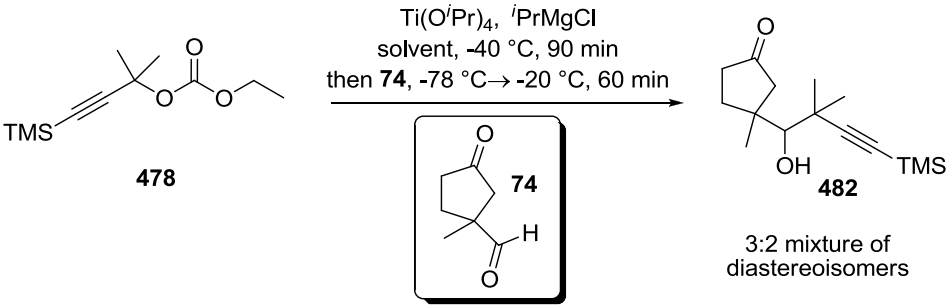


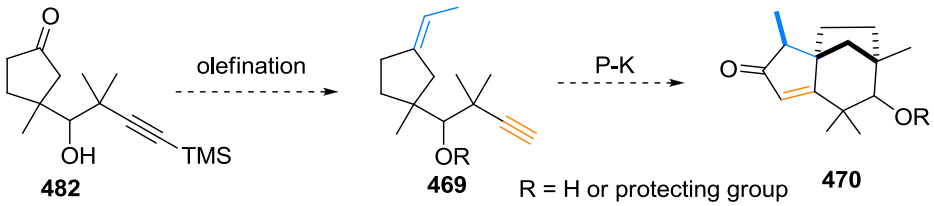
Table 35. Effect of solvent towards the synthesis of 482.

Entry	Solvent	Yield (%)
1	Et_2O	58
2	DCM	63
3	THF	45

The results shown in **Table 35** indicate that by switching the reaction solvent to DCM, an overall increase in the yield of **482** to 63% could be achieved (**Table 35**, Entry 2). Whilst this represented only a moderate 5% improvement in the yield of **482** comparative to the standard Et_2O system, fewer side-products were detected, simplifying purification. Unfortunately, further improvements in the yield of **482** could not be achieved by exchanging the solvent to THF, with a moderate 45% yield isolated (**Table 35**, Entry 3).

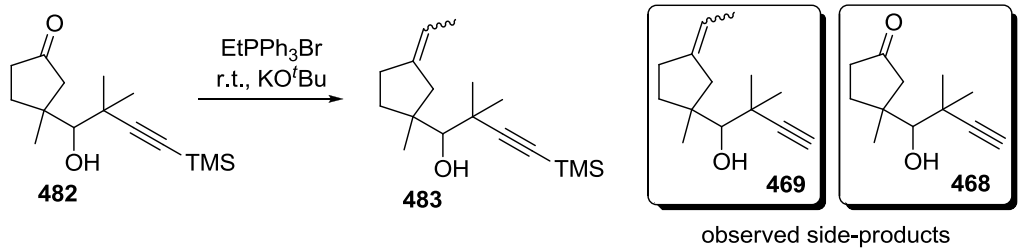
Importantly, in all of the reaction conditions examined to date, **482** was obtained as a complex 3:2 mixture of diastereoisomers, with little variation observed. As a result, it was recognised that future progress though the proposed synthetic sequence would prove challenging, due to the complex mixture of products carried through to subsequent steps. However, due to the relative success of this transformation, no further attempts to identify a more selective process were pursued, in favour of determining whether the proposed P-K reaction could be achieved.

Following the successful synthesis of **482**, olefination of the ketone functionality could now be attempted (**Scheme 181**). From the outset, it was recognised that a *Z*-selective olefin had to be embedded within **469**, to attain the required methyl orientation in the P-K product **470**.



Scheme 181. Proposed strategy towards the synthesis of 470

Towards this aim, a preliminary set of olefination reactions were carried out to determine whether **482** was a suitable substrate to continue through the proposed synthetic sequence (**Scheme 182**).

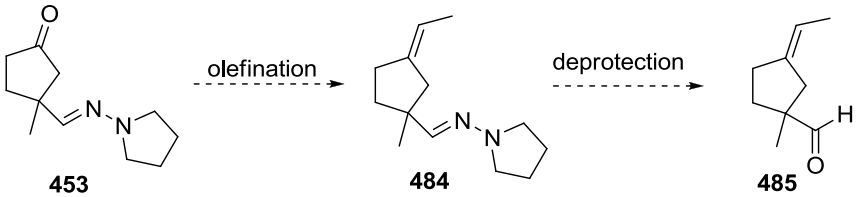


Scheme 182. Attempted synthesis of 483 by Wittig olefination

Initial attempts to synthesise **483** with a slight excess of ylide, proved largely unsuccessful. Upon complete consumption of the ylide, the resulting mixture contained predominantly starting material **482**. Purification of the resultant products also proved extremely difficult, with complex mixtures obtained throughout. GCMS analysis of the crude mixture identified starting material **482**, product **483** and the unexpected formation of **468** and **469**. It would appear that under the reaction conditions investigated, partial deprotection of the terminal TMS group was also occurring. Increasing the excess of phosphonium ylide to 5 equivalents, had a positive effect on reaction conversions, with a significant decrease in starting material **482** observed. However, the resultant mixture continued to be too complex to accurately quantify or purify the resultant mixtures.

Importantly, subsequent ^{1}H NMR analyses of a small quantity of purified **469** obtained from column chromatography, revealed that the overall *E*:*Z* selectivity of the resultant olefin could not be determined. Clearly, the initial mixture of diastereoisomers, further complicated by geometric isomers, was a significant barrier to obtaining an accurate *E*:*Z* ratio of products.

In order to address this issue, a simplification of the starting material **482** was required. Returning to the various products isolated to date provided one such potential solution, involving the olefination of **453** (**Scheme 183**). Through this subtle simplification of the starting material, determination of *E*:*Z* ratios should be possible either as the hydrazone **484**, or as the resultant aldehyde **485**. However, by simplifying the starting material **453** further, it was not clear if the induction of *Z*-selectivity could be achieved.



Scheme 183. Proposed alternative olefination protocol

On the other hand, previous research from within our own laboratory, had demonstrated that an appreciable level of *Z*-selectivity could be embedded through a systematic reduction in reaction temperature.[14] Crucially, these investigations revealed that whilst the olefination process was largely unselective at room temperature, providing **487** in a 2:1 *Z*:*E* ratio, selectivities of up to 9:1 (*Z*:*E*) could be achieved at -196 °C to -90 °C, to provide **487** in a yield of 95% (**Table 36,** Entries 1 and 3).

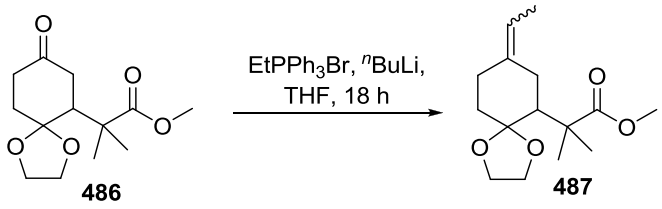


Table 36. Olefinic selectivity through temperature control, Kerr and co-workers

Entry	Temperature (°C)	Yield (%)	*Z*:*E* Ratio
1	r.t.	92	2:1
2	-78	99	4:1
3	-196 → -90	95	9:1

Following a similar approach, a series of reactions were designed to detect whether temperature could effectively influence the *Z*:*E* ratio during the olefination of **453** (**Table 37**). *Z*:*E* ratios were determined by ^{1}H NMR analysis of diagnostic peaks within both the hydrazone product **484** and the resultant aldehyde **485**. By approaching the analysis in this way, any scrambling of the trisubstituted olefin in **485** could be detected following the acid promoted deprotection.

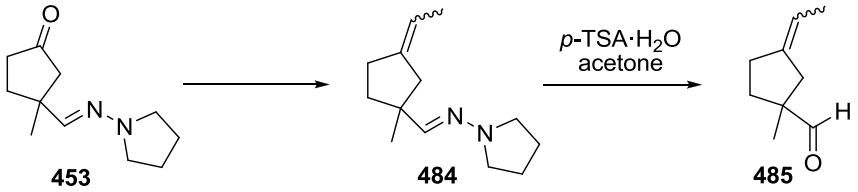
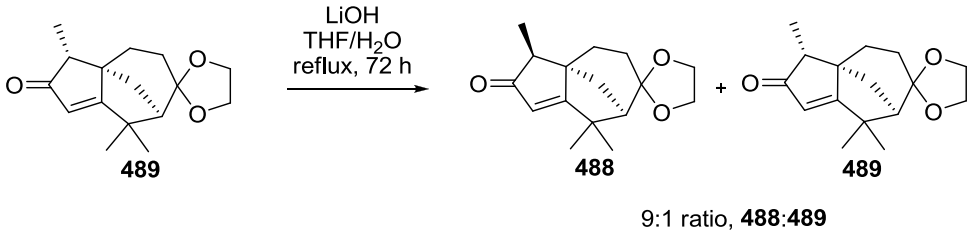


Table 37. Temperature study towards the olefination of 453

Entry	Temperature (°C)	Base	Time (h)	Yield of **484** (%, *Z*:*E*)	Yield of **485** (%, *Z*:*E*)
1	r.t.	KO^{t}Bu	12	94 (1:1)	95 (1:1)
2	0	KO^{t}Bu	36	54 (5:2)	94 (5:2)
3	-30	^{n}BuLi	72	42 (4:1)	94 (4:1)
4	-78	^{n}BuLi	120	32 (7:1)	95 (7:1)

The results in **Table 37** illustrate that significant levels of selectivity could be achieved through a systematic reduction of the reaction temperature. Importantly, when the reaction was carried out at room temperature no significant *Z*:*E* discrimination was observed, with a 1:1 ratio of **484** isolated in a yield of 94%. However, as the reaction temperature was systematically reduced to -30 °C and below, significant levels of *Z*:*E* selectivity were observed, with a 7:1 ratio obtained at -78 °C (**Table 37**, Entries 3 and 4). Crucially, the results in **Table 37** also highlighted that despite the large excess of ylide within the reaction mixture, as the temperature was reduced below room temperature, conversions to **484** were reduced appreciably from 94% to 32% at -78 °C (**Table 37**, Entries 1 and 4). Following the successful synthesis of **484**, each of the individual mixtures were deprotected under acidic conditions, providing the corresponding aldehyde **485** in yields in excess of 90%. Importantly, no change in the *Z*:*E* ratio was observed following the deprotection protocol.

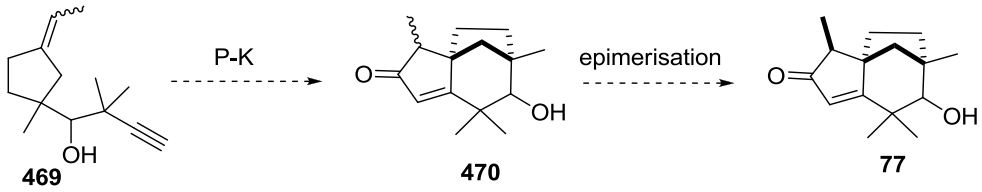
Although achieving high levels of olefin selectivity was preferable, both towards future product identification and the selective formation of the desired P-K precursor **469**, it was also recognised that a large quantity of material would be required to allow progress through subsequent steps and that the low yields were a significant barrier to progress at this early stage. With this in mind, a re-evaluation of the overall strategy had to be pursued before beginning a systematic screening of conditions to promote the required yields at -78 °C. Following a review of previous investigations from within the group, it was recognised that an epimersation process may provide a potential solution. More specifically, when attempting the synthesis of β-cedrene, Kerr *et al*. demonstrated that epimerisation could be used effectively to install the desired methyl geometry, when a selective olefination could not be achieved.[13] In this specific case, stereoisomer **489** was converted to a 9:1 ratio of **488**:**489** in the presence of excess LiOH in THF at reflux (**Scheme 184**).



Scheme 184. Successful implementation of epimerisation process towards the synthesis of *β*-cedrene

Subsequent examination of the proposed route towards the synthesis of sesquithuriferone highlighted that an analogous approach could be possible, following the P-K reaction of precursor **469** (**Scheme 185**).[176] It should be noted however, that the fused ring system **470** under current investigation was sufficiently different to **488** and **489**, raising the question

whether any enrichment of this site could be achieved, and if it could, would it result in the correct orientation in **77**?.

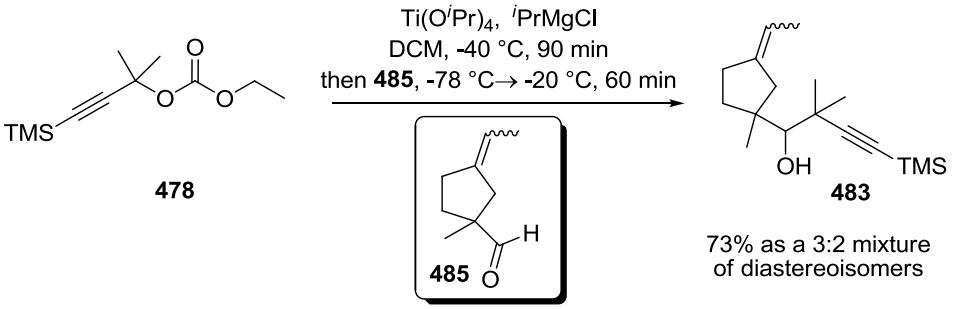


Scheme 185. Proposed epimerisation of 470

Despite the obvious questions surrounding this approach, it was decided that subsequent investigations would incorporate the higher yielding and unselective room temperature olefination process, to provide **484** in a 1:1 *Z*:*E* mixture of isomers (**Table 37**, Entry 1). Whilst it was recognised that the resultant complex mixtures of compounds could make the identification of subsequent intermediates problematic, it was felt that proof of concept was more important at this stage, to show the proposed route was a viable one, before returning to address any issues regarding selectivity.

With significant quantities of **485** now available, a subtle change in the reaction sequence was envisioned, involving the addition of the alkynyl side-chain **478** to the alternative aldehyde substrate **485**. Through this slight adaption of the described synthetic route it was proposed that all issues involving partial deprotection of the terminal TMS group could be avoided (*vide supra*).

The first step in this process involved the addition of the alkyne side-chain using the previously identified optimised conditions in DCM (**Scheme 186**).

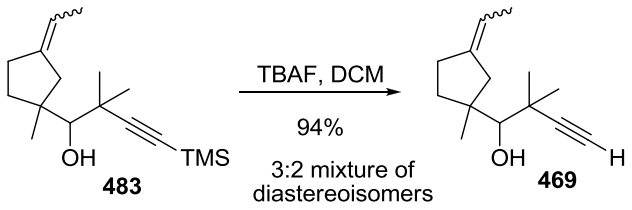


Scheme 186. Addition of side-chain to aldehyde 485

From the outset, this new approach proved successful, with isolated yields of **483** immediately increasing to 73%. Importantly, it would appear that the addition of the alkynyl side-chain was slightly more favoured in the absence of the free ketone. Furthermore, ^{1}H NMR analyses of the resultant product **483** would appear to suggest that the side-chain addition was again incorporated as a 3:2 mixture of diastereoisomers in the resultant product.

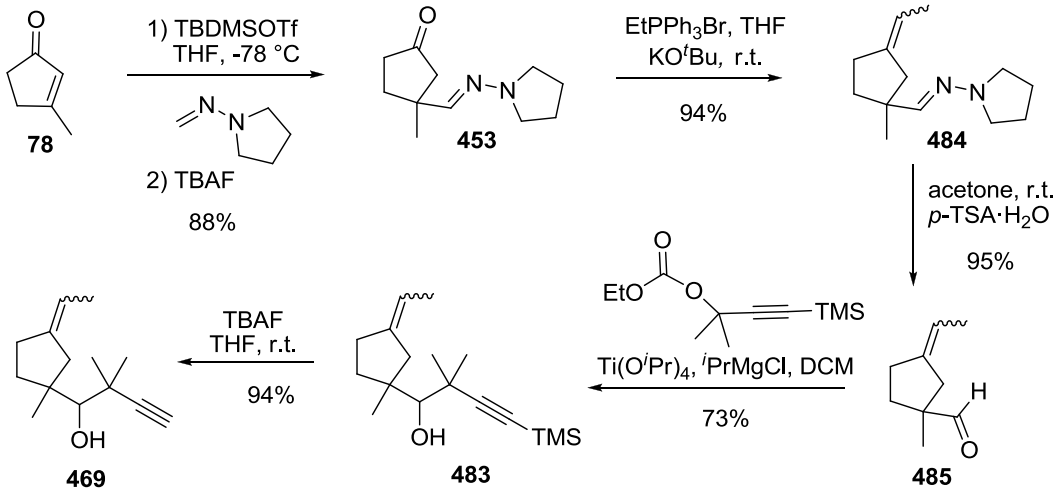
In the interests of time further optimisation of this reaction was deferred, awaiting the success of the key P-K reaction.

To complete the synthesis of **469** one final step was required: the removal of the terminal TMS group present on the alkynyl portion of the molecule (**Scheme 187**). Pleasingly, deprotection proved relatively facile through the addition of a solution of TBAF, to provide **469** in an excellent yield of 94%, as a 3:2 mixture of diastereoisomers.



Scheme 187. Synthesis of P-K precursor 469 through deprotection of terminal TMS group

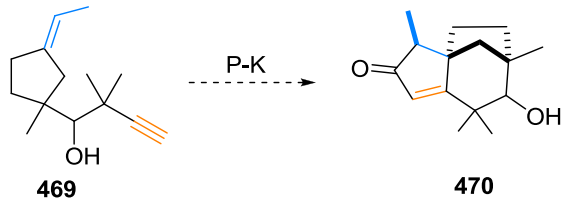
With the completion of this final step it was recognised that a reasonably concise route had been developed towards the construction of key compound **469** (**Scheme 188**). Whilst the described route was completely unselective at present, key points within the synthetic strategy had been identified to allow a selective process to be attempted at a later stage.



Scheme 188. Summary of the optimised route through to P-K precursor 469

4.4 Investigations Towards the Pauson-Khand (P-K) Reaction of 469

With the P-K precursor **469** now in place, a systematic screening of the reaction conditions could be initiated to identify a suitable protocol to promote the formation of **470** (**Scheme 189**).

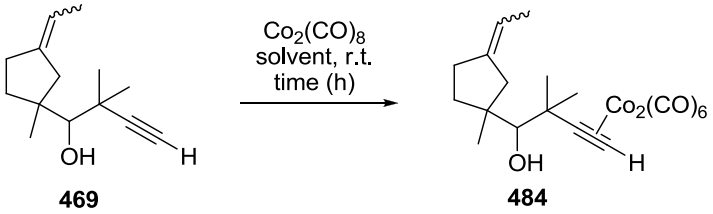


469 **470**

Scheme 189. Proposed synthesis of 470 *via* the P-K reaction

From this perspective, all attempts to promote the desired P-K reaction were pursued using cobalt-mediated methodologies, more specifically, with dicobalt octacarbonyl ($Co_2(CO)_8$). Whilst alternative metal protocols exist, the emphasis was on the development of an initial stoichiometric $Co_2(CO)_8$ promoted transformation, before continuing to investigate whether a catalytic system could be employed.

As such, efforts turned towards the preparation of the requisite cobalt hexacarbonyl complex **484** (**Table 38**).



469 **484**

Table 38. Attempted formation of cobalt complex 484

Entry	Solvent	Time (h)	Yield (%)
1	Petrol	12	57
2	Petrol	24	72
3	DCM	6	95
4	DCE	6	94

The results in **Table 38** illustrate that whilst not all of the solvents investigated proved to be entirely effective towards the formation of complex **484**, yields of up to 95% could be achieved (**Table 38**, Entry 3). Initial attempts to form the stoichiometric complex **484** in petrol proved problematic, with 57% of **484** isolated after 12 h (Table **38**, Entry 1). Further

extension of the reaction length to 24 h had a positive effect on yields, however complete conversion to **484** was still not observed (**Table 38**, Entry 2). Switching the solvent system, to DCM or DCE, proved to be key to promoting the desired transformation, with the observed yields increasing significantly to 94-95% of **484** (**Table 38**, Entries 3 and 4).

Following the successful isolation of complex **484**, a range of conditions were examined to promote the identified P-K reaction in one-pot (**Table 39**). Initial investigations involved varying temperature, solvent and the addition of various additives.

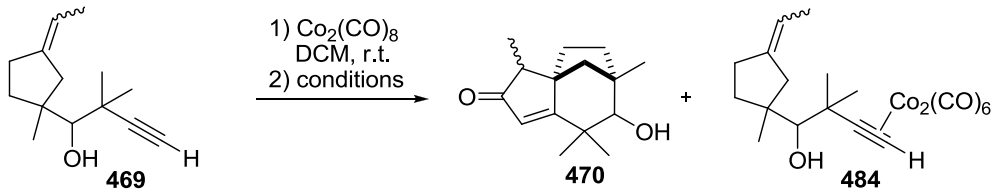


Table 39. Attempted P-K reaction of 484

Entry	Additive	Temperature (°C)	Solvent	Time (h)	Yield of **470** (%)
1	/	reflux	DCE	72	0
2	DodSMe	reflux	DCE	72	0
3	TMANO·$2H_2O$	r.t.	DCM	24	0
4	TMANO·$2H_2O$	0	DCM	24	0

To begin the screening of reaction conditions, an initial thermal reaction was attempted (**Table 39**, Entry1). Unfortunately, following 72 h at reflux, **470** was not detected within the resultant mixture. Instead complex **484** and a small quantity of decomplexed enyne **469** was obtained. Subsequent addition of the P-K promoter DodSMe to the reaction mixture also proved ineffective, with **484** and **469** again recovered as the major components (**Table 39**, Entry 2). Finally, all attempts to promote the desired transformation using TMANO·$2H_2O$, both at room temperature and 0 °C proved ineffective, with no **470** detected (**Table 39**, Entries 3 and 4). However, through the addition of TMANO·$2H_2O$ to the reaction mixture, no **484** was detected upon reaction completion, instead a quantitative return of the starting material **469** was observed.

With an initial trail of reaction conditions proving unsuccessful, attention focused on accessing **470** *via* microwave promotion (**Table 40**).

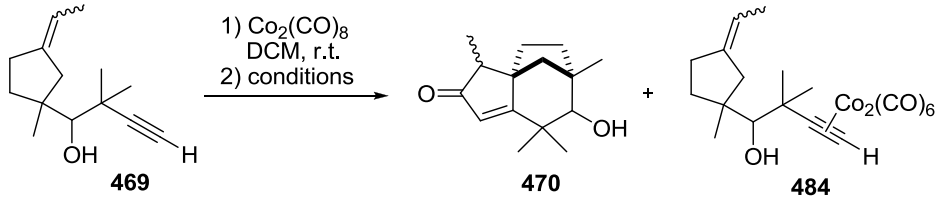
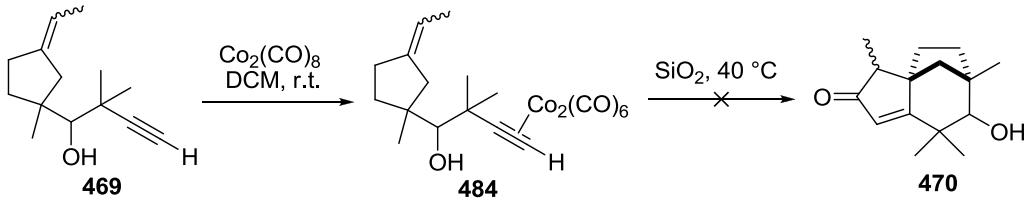


Table 40. Attempted P-K reaction of 470 using microwave promotion

Entry	Solvent	Additive	Temperature (°C)	Yield (%)
1	Toluene	/	90	0
2	DCE	/	90	0
3	DCE	DodSMe	90	0

As the results in **Table 40** illustrate, conditions could not be established to promote the desired transformation of **469** to **470**. From this perspective, initial attempts surrounded the protocols set out by Evans and co-workers involving the heating of complex **484** at elevated temperatures in a sealed microwave tube (**Table 40**, Entries 1 and 2).[84] However, in both cases complex **484** was recovered as the major component, with traces of starting material **469** also detected. In addition to these published procedures, the use of DodSMe in DCE at 90 °C was also investigated (**Table 40**, Entry 3). Unfortunately, this had little or no effect on the outcome of the reaction with complex **484** returned almost exclusively.

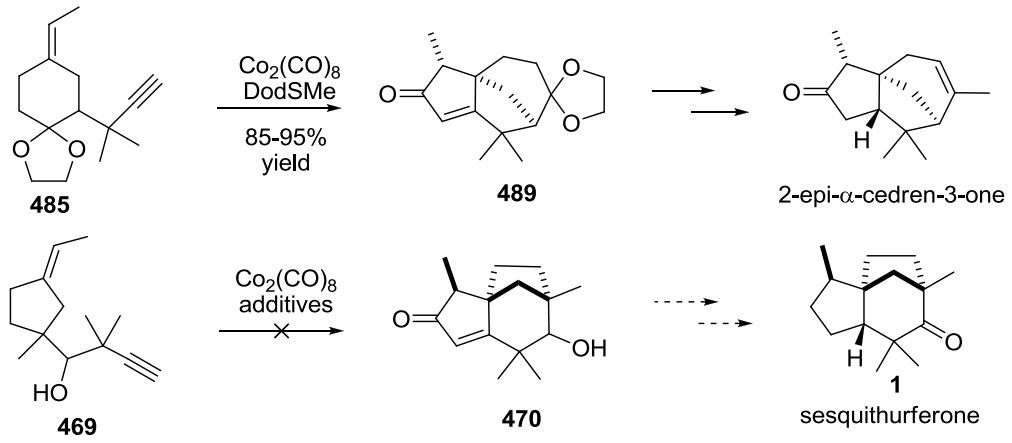
In one final attempt to promote the formation of **470**, dry-state conditions were investigated (**Scheme 190**). It was envisioned that the presence of an oxygen atom in the side-chain, may facilitate an increased interaction with the silica gel to promote the transformation. Unfortunately, this alternative approach proved completely ineffective, with the rapid decomplexation of **484** observed within 15 min, to provide enyne **469** exclusively.



Scheme 190. Dry state absorbed promotion of P-K reaction

4.5 Structural Analysis of the P-K Substrate

Following the disappointments of the initial attempts to form **470** by the P-K reaction, it was clear that **469** was not a suitable substrate to achieve the proposed transformation. With the aim of establishing how to proceed from this point, a careful and systematic analysis of the basic structural scaffold was pursued. By following this approach, it was envisioned that several points of diversity could be established, in order to identify which of the key structural characteristics of **469** were preventing the effective formation of **470**. Ultimately, it was hoped that a suitable derivative of **469** could be identified that would allow the synthesis of sesquithuriferone, without adding too much complexity to the synthetic route. To begin this process, **469** was compared to the precedented system **485**, previously developed within our laboratory (**Scheme 191**).[14]



Scheme 191. Comparison of established P-K precursor 485 to 469

A closer examination of the two P-K precursors **469** and **485** illustrates just how different these two substrates are in terms of basic structural scaffold (**Figure 21**). Crucially, the key discernible similarities were the presence of a trisubstituted olefin, two carbon units away from the side-chain and the presence of a *gem*-dimethyl group adjacent to the alkyne moiety.

Figure 21. Structural comparison of P-K precursors

However, apart from these two key attributes, substrates **485** and **469** appeared to be significantly different. Firstly, precursor **485** contained a six-membered ring, as opposed to a five-membered ring present in **469**. Whilst this may not initially appear important, this subtle

change in ring size could contribute to an entirely different conformational bias when attempting to form the desired transition state required for effective product formation. Secondly, **485** had a trisubstituted carbon where the side-chain is attached to the ring system, as opposed to the quaternary centre in **469**. It was expected that this would not only affect conformational flexibility of the side-chain, but also increase a potential restricted rotation due to intramolecular steric clashes. Thirdly, the proposed system **469** has an extra carbon in the side-chain comparative to **485**. Importantly, this extra carbon not only contained an additional heteroatom, but also a stereogenic centre. From this perspective, it was entirely feasible that the two orientations of the heteroatom at this position could lead to match/mismatch conformational bias when attempting to form the proposed product. Further details of these effects will be discussed in the following sections as each of the various structural scaffolds were synthesised and examined under the pretext of developing a suitable P-K precursor to complete the synthesis of sesquithuriferone.

4.6 Structural Modification of P-K Precursor 469

The most logical point to begin the modification of **469** was through the implementation of protecting group chemistry, to mask the free hydroxyl present in the side-chain. With regards to the oxygen heteroatom, one key factor was identified as crucial: the lone pairs present on the oxygen atom could be capable of forming an intramolecular interaction, to co-ordinate into the cobalt complex through a five-membered intermediate **487**, as shown in **Figure 22**.

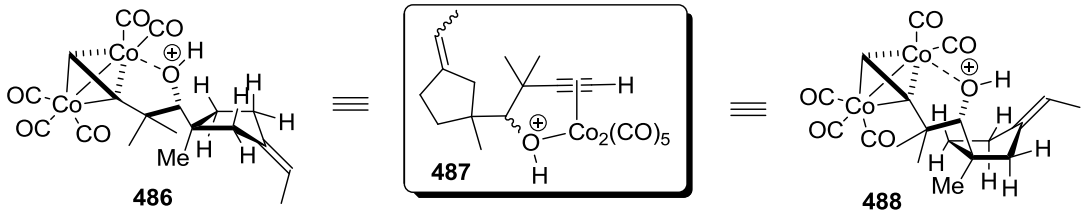


Figure 22. Proposed co-ordination of free hydroxyl to alkyne cobalt complex

If in fact the hydroxyl was forming the identified intermediate **487**, it was proposed that this could lead to one of two contradictory effects. The proposed interaction could be activating the complex for alkene co-ordination, in which case, the formation of **487** would promote the intramolecular removal of a CO ligand, known to be the rate-determining step in the P-K reaction.[59] It was from **487** that one of two processes were expected to occur. Firstly, if the heteroatom co-ordination is reversible, this would then free-up a co-ordination site to allow incorporation of an alkene into the complex, promoting the formation of **470**. However, if the rate of alkene co-ordination is slow or disfavoured, the overall effect could be that the

complex becomes destabilised, due to the free co-ordination site, resulting in the decomplexation of the alkyne. Furthermore, it was also recognised that this intramolecular lone-pair interaction could result in an unfavourable conformation such as **486**, preventing the alkyne complex from rotating into a suitable position that would allow alkene co-ordination to occur, especially if the ligation of the heteroatom is highly favoured or not readily reversible. Importantly, due to the apparent stability of the alkyne-cobalt complex in the first set of P-K reactions, it was likely that if this co-ordination was occurring, the result was an unfavourable conformation rather than a destabilising effect on the resultant complex.

To determine the effect of protecting groups on the formation of **470**, three separate groups were chosen: OMe, OTMS and OTBDMS (**Table 41**). It was envisioned that by examining the relative rate of reaction with these three groups incorporated, information could be gathered regarding not only whether the free hydroxyl group was inhibiting reaction progress, but also establish if increasing the steric bulk around the heteroatom had a significant effect on the rate of formation of **470**.

As can be observed from the results presented in **Table 41**, protection of the free hydroxyl group in **469** proved challenging. Initial attempts involving the addition of MeI to form the corresponding methyl ether **489**, proved unsuccessful with starting material **469** recovered in all cases (**Table 41**, Entries 1 and 2). However, the addition of a TMS group proved successful under basic conditions, providing **490** in a yield of 94% (**Table 41**, Entry 3). Importantly, the reaction required 48 h to reach completion. The extremely slow rate of reaction was thought to be reflective of the high levels of steric congestion generated around the heteroatom of the side-chain in **490**. Unfortunately, all subsequent attempts to synthesise the TBDMS derivative of **491** proved unsuccessful, using either TBDMSCl/imidazole or TBDMSOTf/DMAP protocols (**Table 41**, Entries 4 and 5). It would appear that the addition of such a bulky protecting group was disfavoured due to the close proximity of both the methyl at the ring junction, as well as the *gem*-dimethyl adjacent to the heteroatom.

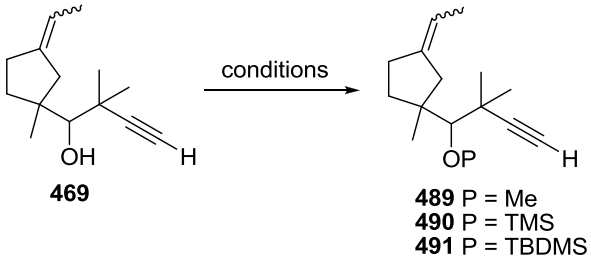


Table 41. Attempted formation of 489-491

Entry	Electrophile	Base	Temperature (°C)	Yield (%)
1	MeI	K_2CO_3	0 → r.t.	0
2	MeI	NaH	0 → 40	0
3	TMSCl	Et_3N	0 → r.t.	**490** (94)
4	TBDMSCl	Imidazole	r.t.	0
5	TBDMSOTf	DMAP, Et_3N	0 → r.t.	0

With **490** successfully synthesised, attention turned towards the proposed P-K reaction (**Table 42**). Towards this aim, a range of conditions were screened to determine if the addition of a TMS protecting group was sufficient to promote the formation of **492**, or if further manipulation of the basic structural scaffold was required.

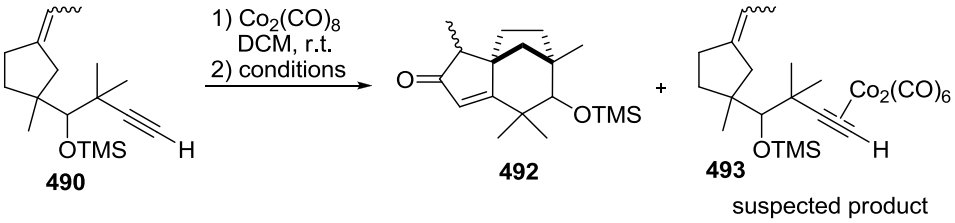


Table 42. Attempted P-K reaction of 490

Entry	Additive	Temperature (°C)	Solvent	Time (d)	Yield (%)
1[a]	/	reflux	DCE	3	0
2[a]	DodSMe	reflux	DCE	3	0
3	TMANO·$2H_2O$	r.t.	DCM	1	0
4	TMANO·$2H_2O$	0	DCM	1	0

[a] Starting material was recovered *via* decomplexation with TMANO

To begin the screening process an initial thermal reaction was attempted (**Table 42**, Entry 1). Following 3 d at reflux, no product conversion was detected. Furthermore, the addition of promoters such as DodSMe and TMANO·$2H_2O$ to the reaction mixture also proved

unsuccessful, with no product **492** detected after prolonged reaction periods (**Table 42**, Entries 2, 3 and 4). With regard to the thermal and DodSMe promoted P-K reactions, little or no decomplexation of **493** was observed by TLC analysis (**Table 42**, Entries 1 and 2). However, in the case of the TMANO·$2H_2O$ promoted P-K reactions, starting enyne **490** was returned exclusively (**Table 42**, Entry 3). Importantly, due to cobalt residues formed during the reaction and co-elution of the cobalt-complex with DodSMe, the isolation of **493** could not be achieved by column chromatography (**Table 42**, Entries 1 and 2). In both of these cases the resultant product was stirred in a large excess of TMANO·$2H_2O$ to effect decomplexation to allow the recovery of the starting material **490**.

Following the failure of **490** to undergo the proposed P-K reaction to form **492**, alternative substrate **494** was identified as a suitable synthetic target (**Figure 23**). This approach was favoured as the formation of the corresponding ketone derivative **494** should provide a significant simplification of the P-K substrate, through removal of a stereogenic centre. In this regard, it was envisioned that an appreciable reduction in the number of conformations that **494** could access would be observed, increasing the probability of alkene co-ordination through the conformations shown in **Figure 23**.

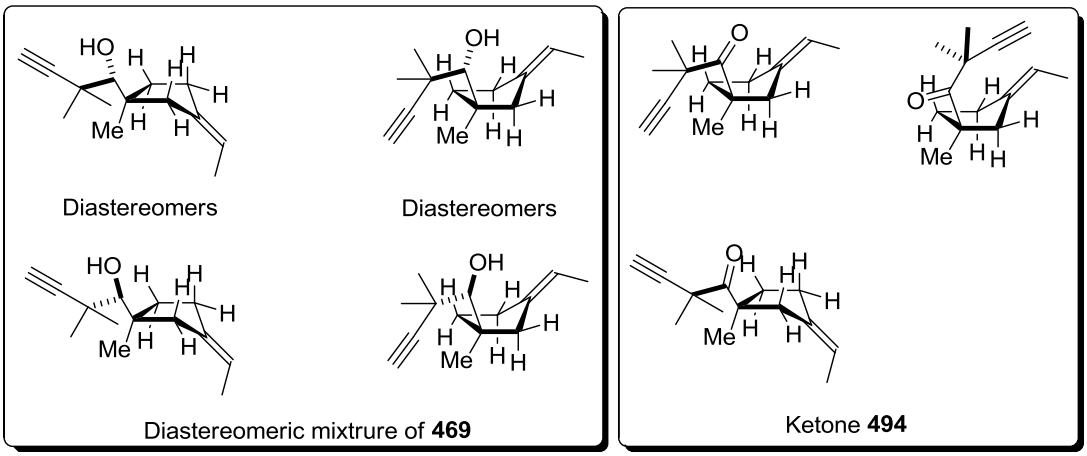
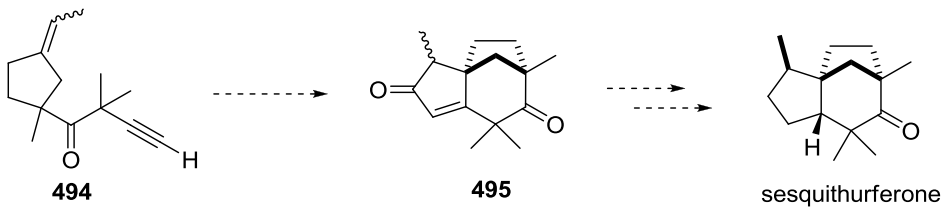


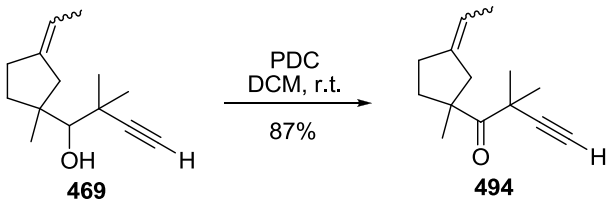
Figure 23. Proposed conformational differences between P-K precursors 469 and 494

Crucially, the inclusion of the ketone moiety in **494** at this stage in the sequence would allow a significant simplification of the synthetic route towards sesquithuriferone (**Scheme 192**).



Scheme 192. Proposed synthesis of sesquithuriferone from ketone derivative 494

Whilst a wide range of oxidation methods were available to achieve the desired transformation, initial investigations proved highly successful using PDC, providing **494** in a yield of 87%.



Scheme 192. Synthesis of 469 by oxidation with PDC

With significant quantities of **494** available, a short study was initiated to determine whether removal of the identified stereogenic centre was critical to the formation of **495** (**Table 43**).

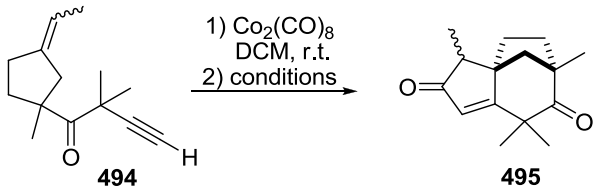


Table 43. Attempted P-K reaction of 495

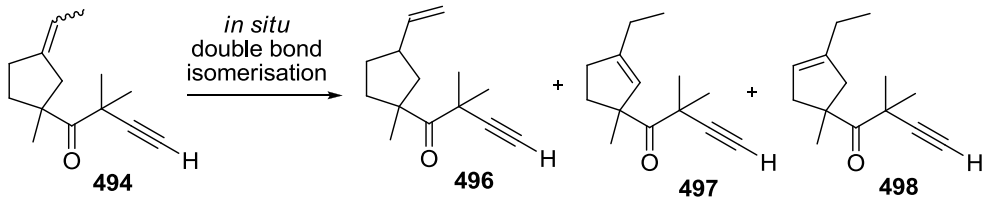
Entry	Additive	Temperature (°C)	Solvent	Time (d)	Yield (%)
1	DodSMe	reflux	DCE	3	0
2	TMANO·$2H_2O$	r.t.	DCM	1	0
3	TMANO·$2H_2O$	0	DCM	1	0

Initial attempts to promote the desired P-K reaction using DodSMe proved unsuccessful (**Table 43**, Entry 1). Importantly however, analysis of the resultant reaction mixture revealed that starting enyne **494** was not the major component returned, instead, an inseparable mixture of unknown compounds was obtained in all cases. Subsequent attempts using TMANO·$2H_2O$ promotion also proved unsuccessful and in these cases, starting enyne **494** was recovered as the major component (**Table 43**, Entries 2 and 3).

Separation of the individual components isolated from the DodSMe promoted reaction by column chromatography proved unsuccessful due to co-elution. The one clear interpretation that could be made from the ^{1}H NMR data was that the number of olefinic peaks was observed to increase. GCMS analysis of the complex mixture appeared to indicate that whilst the number of detected peaks increased, the mass was consistent with that of the starting enyne **494**. Furthermore, IR analysis indicated that the diagnostic terminal alkyne signal was not present in the final mixture of compounds. Whilst conclusive identification of these

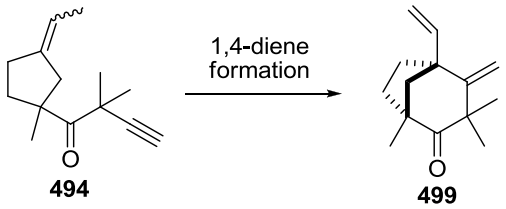
products remains as yet elusive, two processes that explain the formation of these side products are proposed (**Schemes 193** and **194**).

The first explanation involves double bond isomerisation, to account for structures such as **496**-**498** (**Scheme 193**). Whilst, this process was entirely unexpected due to the trisubstituted nature of the starting olefin in **494**, this would account for the increased complexity in the olefinic range of the ^{1}H NMR spectra. In this regard, subsequent investigations observed that this process can occur *in situ* to result in entirely distinct products (*vide infra*).



Scheme 193. Proposed structures formed following double bond isomerism of starting enyne 494

However, the formation of compounds such as **496**-**498** would not account for the disappearance of the terminal alkyne signal. A alternative explanation for this could come through the formation of a 1,4-diene system such as **499** (**Scheme 194**). The formation of structures such as **499** would appear to offer a reasonable explanation of the observed data, with increased olefinic peaks, removal of the terminal alkyne and a mass consistent with the starting enyne **494**. The formation of 1,4-dienes under similar conditions are not without precedent within the literature and are thought to result from a β-hydride elimination pathway similar to those described by Krafft and co-workers.[80] It should be noted however, that all of the proposed structures are provided as a tentative assignment, with no specific confirmation of structure achieved to date.



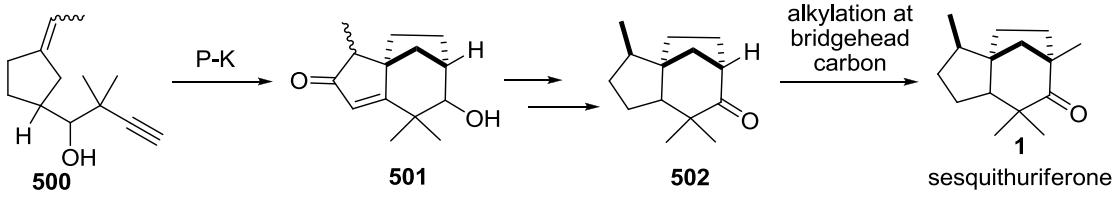
Scheme 194. Proposed structure of side product 499 formed *via* β-hydride elimination

The formation of suspected products such as **496**-**499** indicates that the stereogenic centre containing the heteroatom does appear to have a significant effect on the progress of the P-K reaction. However, due to the limited success of this approach to facilitate the formation of **495**, the removal of this chiral centre was not considered critical to access a high yielding and reproducible process.

With the knowledge that slight modifications of the original substrate **469** did not facilitate the formation of the desired P-K products, it was recognised that a significant alteration of the basic structural scaffold was required. Towards this aim, several points of diversity within the basic structure were identified and systematically examined in order to identify a suitable substrate to complete the key P-K transformation. Details of these investigations are provided in the following sections.

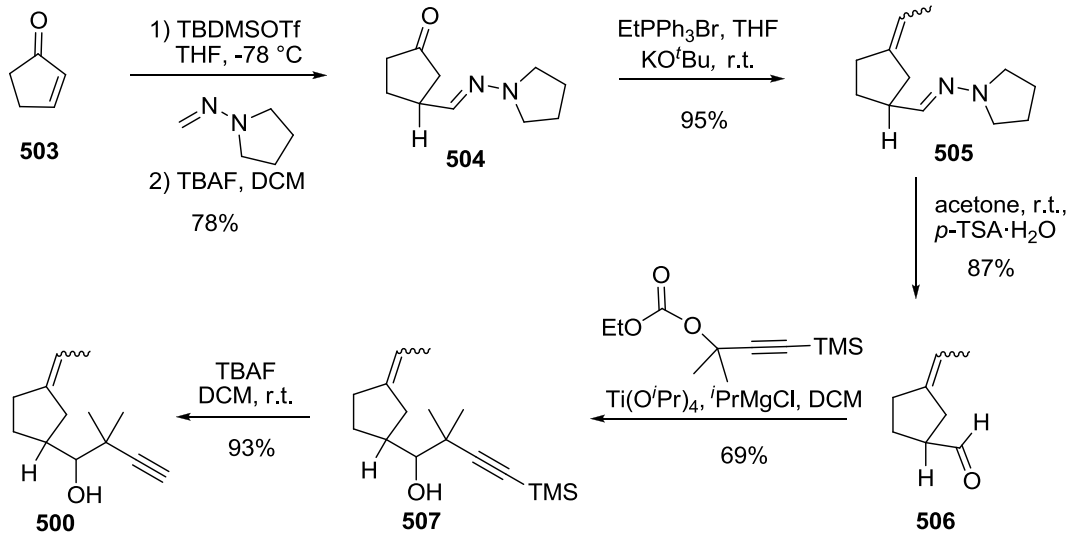
4.6.1 Synthesis and Investigation of Tertiary Derivative 500

As previously described, a significant amount of restricted rotation was believed to be occurring within the basic scaffold of **469** due to the close proximity of the heteroatom and the methyl groups adjacent. In order to remove one of these interactions and attempt to provide extra flexibility and rotation about this centre, the formation of the corresponding tertiary derivative **500** was proposed (**Scheme 195**). However, at this stage it was also recognised that should this substrate prove successful in the synthesis of **501** through the P-K reaction, completion of the synthesis of sesquithuriferone would require a challenging alkylation at the bridgehead carbon. Whilst deprotonations at these positions have been achieved, it was not an ideal step to incorporate into the synthetic sequence.[253–255]



Scheme 195. Proposed deprotonation/alkylation at the bridgehead carbon of 502

Nevertheless, adaption of the previous synthetic route to provide **500** proved relatively facile through switching of the enone substrate to cyclopentenone **503** (**Scheme 196**). From this point, all of the previously developed methodologies could be used to provide **500**.



Scheme 196. Synthetic route to access the corresponding tertiary derivative 500

Accordingly, keto-hydrazone **504** was synthesised following the optimised conjugate addition protocols previously established, to provide **504** in a yield of 78%. Following this, Wittig olefination provided **505** in a yield of 95%, as a 1:1 (*Z*:*E*) mixture of geometric isomers. Subsequent deprotection and side-chain addition also proved accessible with yields of 87% of **506** and 69% of **507**, respectively. Finally, following removal of the terminal TMS group on the alkyne portion, **500** was isolated in a yield of 93%. Importantly, the overall success of this general strategy clearly highlights that the designed route was in fact robust and readily adaptable to provide a range of substituted derivatives key to synthesising other members of the same family of natural products.

Following the successful synthesis of **500** a range of conditions were investigated to establish the suitability of this substrate towards the proposed P-K reaction (**Table 44**).

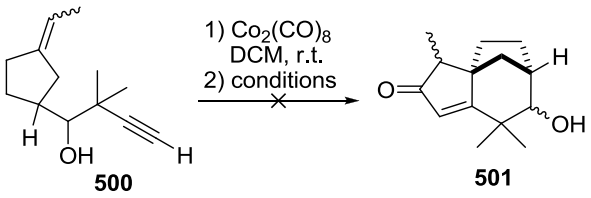
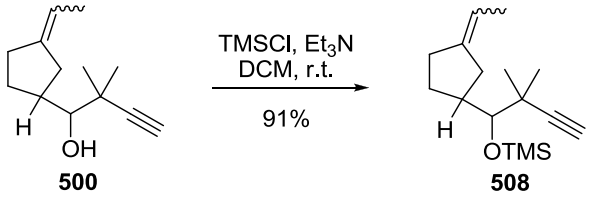


Table 44. Attempted P-K reaction of 500

Entry	Additive	Temperature (°C)	Solvent	Time (d)	Yield (%)
1	DodSMe	reflux	DCE	3	0
2	TMANO·2H$_2$O	r.t.	DCM	1	0
3	TMANO·2H$_2$O	0	DCM	1	0

The results in **Table 44** illustrate that incorporation of a tertiary centre into the starting material **500** had no significant effect on product conversions, with **501** remaining undetected under all of the conditions examined. In terms of reactivity profile, the starting material **500** was recovered as the major product in all cases, regardless of whether DodSMe or TMANO·$2H_2O$ were used to promote the reactions (**Table 44**, Entries 1-3). Importantly however, throughout all of the conditions examined, a significant amount of degradation was observed, with less than 60% of **500** returned throughout.

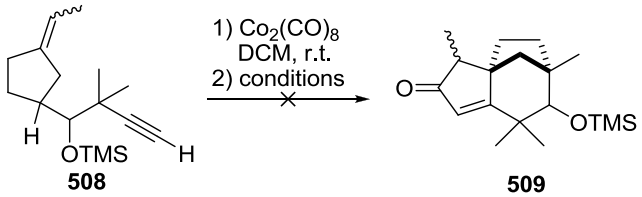
Following the failure of **500** to provide the desired P-K product **501**, the corresponding TMS derivative **508** was synthesised and examined under current reaction conditions (**Scheme 197** and **Table 45**). The synthesis of **508** proved relatively facile under basic conditions, with an isolated yield of 91% obtained. Importantly, unlike the quaternary derivate **469**, the rate of reaction was significantly faster, with complete conversion of **500** to **508** observed after 30 min, indicating that a significant amount of steric hinderance had been removed through the exclusion of the methyl substituent.



500 **508**

Scheme 197. Synthesis of TMS derivative 508

With **508** now in hand, a standard screening of P-K reaction conditions was initiated (**Table 45**). The results presented in **Table 45** indicate that in all cases, P-K product **509** was not obtained. Importantly, the major component recovered from the reaction mixtures was starting material **508**, regardless of whether DodSMe or TMANO·$2H_2O$ was used to promote the reaction (**Table 45**, Entries 1-3).



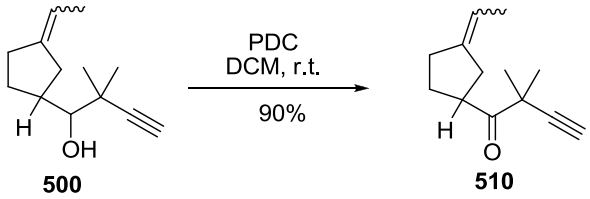
508 **509**

Table 45. Attempted P-K reaction of 508

Entry	Additive	Temperature (°C)	Solvent	Time (d)	Yield (%)
1	DodSMe	reflux	DCE	3	0
2	TMANO·$2H_2O$	r.t.	DCM	1	0
3	TMANO·$2H_2O$	0	DCM	1	0

Additionally, it would appear that the removal of the methyl at the bridging position of **508** resulted in an overall decrease in the stability of not just the alkyne-cobalt complex, but also the starting material **508**. Under all of the conditions examined to date, less than 70% of the original starting material **508** was recovered following purification.

In one final attempt to facilitate product formation, ketone derivative **510** was investigated (**Scheme 198**). Following the previous protocols set out towards the synthesis of **494**, an excellent yield of 90% of **510** was isolated using PDC as the oxidising agent.



Scheme 198. Synthesis of ketone derivative 510 *via* oxidation with PDC

To complete investigations involving the tertiary scaffolds, substrate **510** was examined under a range of P-K reaction conditions (**Table 46**). Unfortunately, as the results in **Table 46** demonstrate, the P-K reaction of ketone derivative **510** failed to provide the desired target **511**. Importantly, as with the previously examined tertiary derivatives **500** and **508**, ketone **510** was returned as the major component throughout in yields of 60-65%, regardless of whether DodSMe or TMANO·$2H_2O$ was used to promote the reaction (**Table 46**, Entries 1-3). This final result highlights that in all the cases investigated to date, the removal of the extra methyl substituent appears to result in an inherent instability of both the cobalt complex and the enyne substrates.

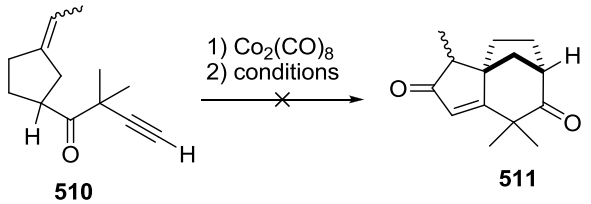


Table 46. Attempted P-K reaction of 510

Entry	Additive	Temperature (°C)	Solvent	Time (d)	Yield (%)
1	DodSMe	reflux	DCE	3	0
2	TMANO·$2H_2O$	r.t.	DCM	1	0
3	TMANO·$2H_2O$	0	DCM	1	0

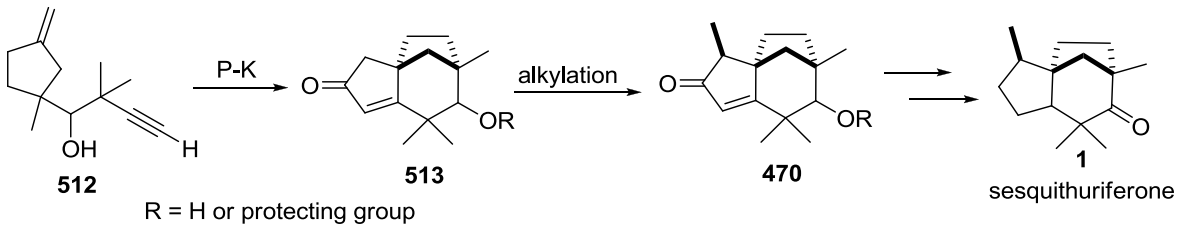
With the completion of this study it was clear that varying the substitution pattern on the carbon centre containing the side-chain was not key to the success of the proposed P-K

reaction. Furthermore, whilst it appeared that some steric hinderance had been relieved around the side-chain, this did not provide the desired change in reactivity required for the completion the synthesis of the identified tricyclic core. To date, no obvious explanation has been established as to why substrates **500**, **508** and **510** appear to degrade under the reaction conditions examined.

4.6.2 Reduced Substitution on the Alkene Moiety

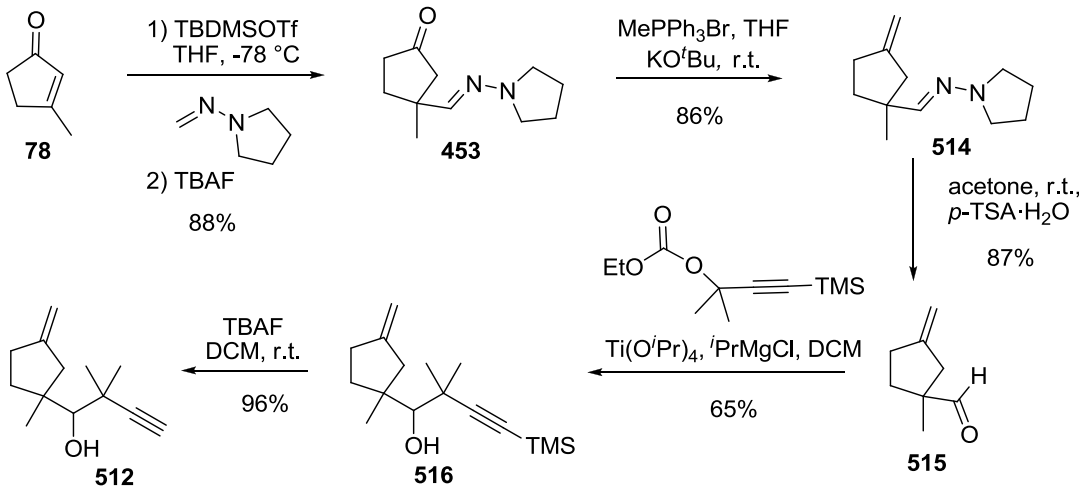
In order to establish a robust set of conditions towards the synthesis of the P-K product, two additional points of diversity required investigation: (a) the substitution pattern on the alkene moiety, and (b) the effect of the *gem*-dimethyl group.

With an obvious synthetic strategy in place to vary the substitution pattern on the alkene, structural derivative **512** was identified as the next candidate with which to attempt the P-K reaction. This approach was favoured since the reduced substitution pattern on the alkene moiety could potentially increase the overall reactivity of the P-K substrate through a reduction in the steric environment upon alkene co-ordination to the cobalt complex. In this regard, should **512** prove successful, no significant alterations to the synthetic route towards sesquithuriferone would be required (**Scheme 199**). Accordingly, common intermediate **470** would be accessed through alkylation of the α-position of the resulting protected enone **513**. From this perspective, the selective addition of the methyl substituent could be achieved due to the different steric environments created by the fused ring system adjacent, which would remove the need for an additional epimerisation process.



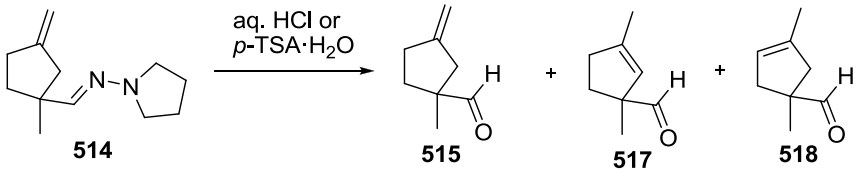
Scheme 199. Adapted synthetic strategy based on terminal methylene derivative 512

From a synthetic point of view, common intermediate **453** underwent Wittig olefination with the corresponding methylphosphonium salt to provide **514** in a yield of 86%. Subsequent deprotection of **514** in acidified acetone provided **515** in a yield of 87%. Finally, the synthesis of **512** was completed through side-chain addition in a yield of 65% of **516**, followed by TMS removal in an excellent 96% yield of **512**.



Scheme 200. Synthesis of methylene derivative 512

However, despite the relative ease with which **515** was synthesised, careful monitoring of the reaction conditions proved essential due to a competitive isomerisation process (**Scheme 201**).



Scheme 201. Complex mixture of products isolated upon extended reaction times in the presence of acid

Following the successful synthesis of **512** a range of conditions were investigated to determine if the substitution pattern on the alkene portion was critical to effective product formation (**Table 47**).

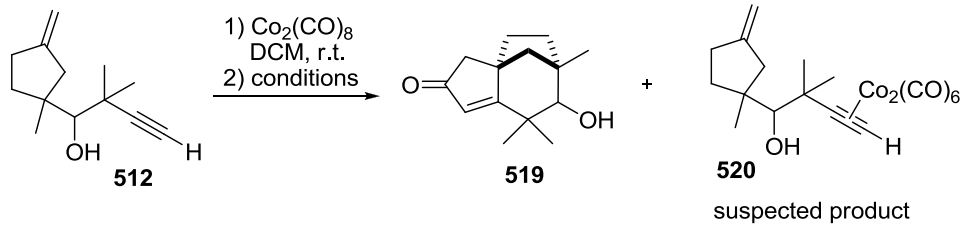


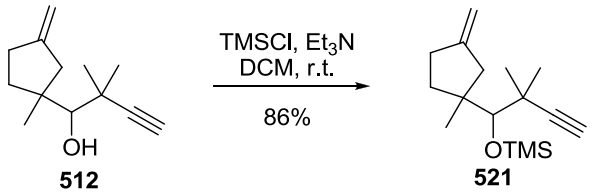
Table 47. Attempted P-K reaction of 512

Entry	Additive	Temperature (°C)	Solvent	Time (d)	Yield (%)
1[a]	DodSMe	reflux	DCE	3	0
2	TMANO·2H$_2$O	r.t.	DCM	1	0
3	TMANO·2H$_2$O	0	DCM	1	0

[a] Starting material recovered *via* decomplexation with TMANO·2H$_2$O

As the results in **Table 47** demonstrate, the terminal methylene derivative **512** proved ineffective towards the formation of the P-K product **519**. Initial attempts to promote the formation of **519** with DodSMe resulted in what appeared to be a mixture of starting enyne **512** and complex **520** (**Table 47**, Entry 1). Unfortunately, due to co-elution of **520** with DodSMe conclusive isolation of the complex could not be achieved. Starting material **512** was recovered from this mixture of products through decomplexation with TMANO·$2H_2O$. Subsequent investigations utilising TMANO·$2H_2O$ also proved ineffective, with the quantitative recovery of starting enyne **512** in all cases (**Table 47**, Entries 2 and 3). These results were consistent with all previous attempts to form the desired product containing a free alcohol (*vide supra*). Importantly however, throughout all of the conditions examined no significant degradation or isomerisation of the starting material **512** was observed.

Following the failure of **512** to provide the desired P-K product **519**, the corresponding TMS derivative **521** was synthesised and examined under current reaction conditions (**Scheme 202** and **Table 48**). The synthesis of **521** proved facile under basic conditions with 86% of **521** isolated upon reaction completion. However, once again due to the increased steric environment around the oxygen heteroatom, the reaction required 48 h to reach completion.



Scheme 202. Synthesis of TMS derivative 521

With **521** in hand, the substrate was investigated under a range of conditions to promote the key P-K reaction (**Table 48**).

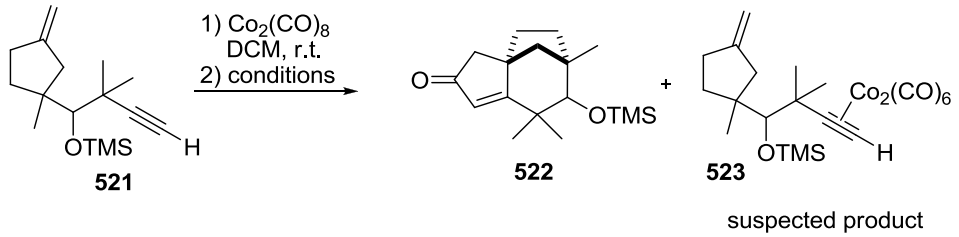


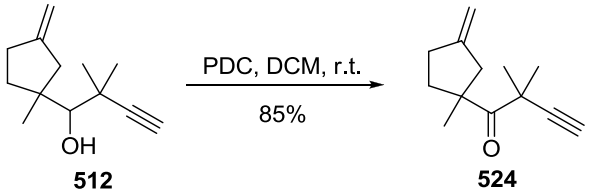
Table 48. Attempted P-K reaction of 521

Entry	Additive	Temperature (°C)	Solvent	Time (d)	Yield (%)
1[a]	DodSMe	reflux	DCE	3	0
2	TMANO·$2H_2O$	r.t.	DCM	1	0
3	TMANO·$2H_2O$	0	DCM	1	0

[a] Starting material recovered through decomplexation with TMANO·$2H_2O$

Unfortunately, just as with all of the substrates examined to date, no product **522** was detected within the reaction mixture (**Table 48**, Entries 1-3). Initial attempts to promote the P-K reaction using DodSMe returned **523** as the major product, with trace amounts of **521** also isolated (**Table 48**, Entry 1). Subsequent reactions under TMANO·$2H_2O$ promotion provided only starting enyne **521** (**Table 48**, Entries 2 and 3). Importantly, just as with the free alcohol substrate **512**, no significant degradation or isomerisation was observed under the reaction conditions examined.

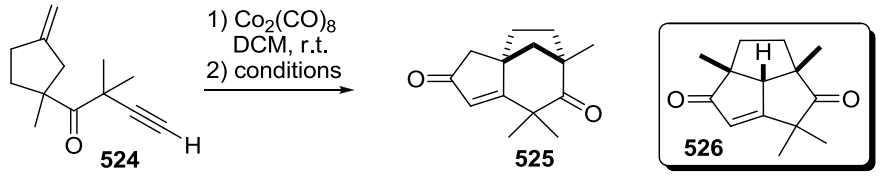
In one final attempt to facilitate product formation, ketone derivative **524** was investigated (**Scheme 203**). Following the protocols set out towards the synthesis of **500**, an excellent yield of 85% of **524** was isolated using PDC as an oxidising agent.



512 **524**

Scheme 203. Synthesis of ketone derivative 524

Following the successful isolation of significant quantities of the final methylene derivative **524**, the substrate was examined under the established set of conditions to determine whether the P-K reaction could be achieved (**Table 49**).



524 **525** **526**

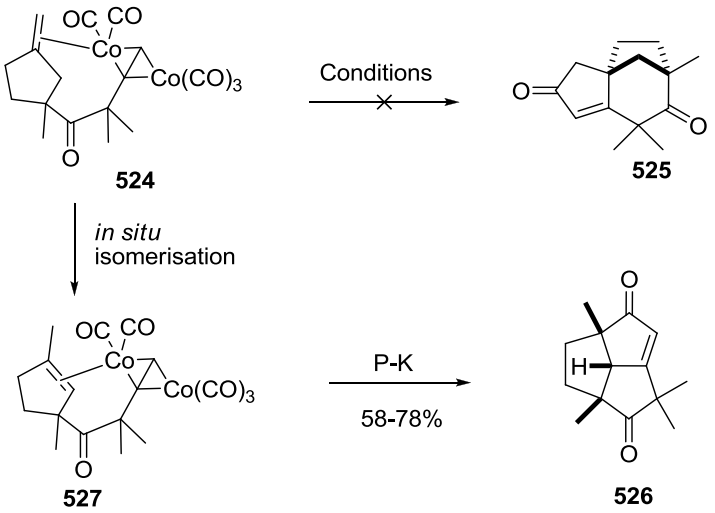
Table 49. Attempted P-K reaction of 524

Entry	Additive	Temperature (°C)	Solvent	Time (h)	Yield of **525** (%)	Yield of **526** (%)
1	DodSMe	reflux	DCE	12	0	58
2	TMANO·$2H_2O$	r.t.	DCM	5	0	75
3	TMANO·$2H_2O$	0	DCM	8	0	78

From the outset of the investigations involving the P-K reaction of **524**, it was clear that a substantial change in reactivity had taken place. Upon reaction completion, TLC analysis indicated that complete consumption of the starting material **524** had occurred, with IR anaylsis indicating the formation of an enone. However, subsequent ^{1}H NMR analyses of the resulting product confirmed that **525** had not been formed under the conditions examined.

Instead, the corresponding [5,5,5]-tricyclic compound **526** was isolated in all cases (**Table 49**, Entries 1-3). In this regard, the isolated yields of **526** varied significantly depending on the promoter added to the reaction mixture, with DodSMe affording **526** in a yield of 58%, as opposed to isolated yields of 75-78% using $TMANO{\cdot}2H_2O$.

The formation of **526** was proposed to be the result of an *in situ* isomerisation process occurring within the reaction mixture (**Scheme 204**). Whilst the exact mechanism for the formation of **526** under the conditions investigated has not been determined, the relative stability of the previous substrates **512** and **521** would suggest that **526** was formed as a result of a cobalt mediated hydride shift.[256] Importantly, it would also appear that this rearrangement of the alkene moiety was more favoured under amine *N*-oxide promotion, with yields approximately 20% higher than under the corresponding sulfide promoted reaction.

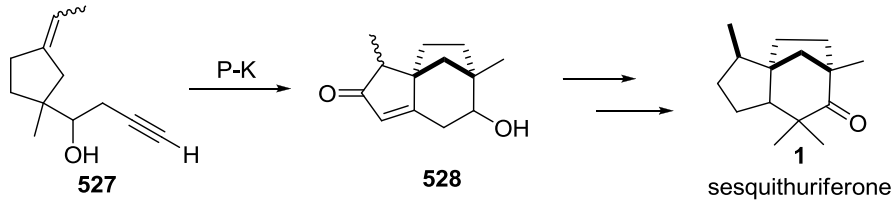


Scheme 204. Proposed isomerisation/P-K reaction to provide compound 526

Importantly, the formation of **526** did highlight some key features about the proposed P-K transformation. Firstly, the removal of the stereogenic centre in **494** and **524**, in the presence of both the *gem*-dimethyl and the quaternary centre were crucial to increasing the reactivity of the substrate under investigation. Whilst these two substrates formed completely different products to the desired tricyclic core in **470**, it did provide some limited evidence that the subtle change in conformational freedom was promoting increased interaction between the alkyne-cobalt complex and the alkene moiety within the substrate. However, failure of both these substrates to form the desired systems **495** and **525** indicated that further manipulation of the basic structural scaffold was required to promote the desired P-K transformation.

4.6.3 Removal of the gem-Dimethyl Substituent

In one final attempt to promote the P-K reaction, substrate **527** was identified as a suitable candidate (**Scheme 205**). The key structural difference in **527** compared to the previous systems investigated was the absence of the *gem*-dimethyl group adjacent to the alkyne moiety. It was envisioned that the removal of such a large group within the side-chain would significantly reduce the steric environment around the heteroatom, resulting in an increased level of conformational freedom, to facilitate alkene co-ordination and ultimately reaction progress to deliver enone **528**.



Scheme 205. Modified strategy towards the synthesis of sesquithuriferone

However, from a synthetic point of view, the removal of the *gem*-dimethyl group in **527** presented two key problems. Firstly, the current titanium-mediated process to embed the alkynyl side-chain could prove unsuitable towards the synthesis of substrates such as **527**, with the allene product potentially being delivered instead (*vide supra*). Secondly, conversion of **528** to sesquithuriferone would require an alternative reaction sequence to incorporate the formation of a suitable compound which would allow the regioselective double alkylation of the six-membered ring.

Before investigations towards the titanium-mediated formation of **527** could begin, identification and synthesis of a suitable alkynyl substrate had to be pursued. Towards this aim, three potential candidates were indentified to facilitate the proposed transformation: propargyl bromide **529** and carbonates **530** and **531** (**Figure 24**).

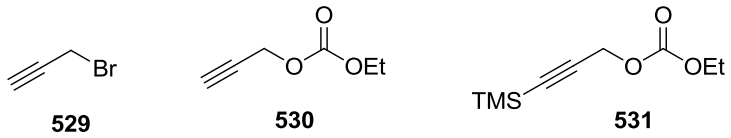
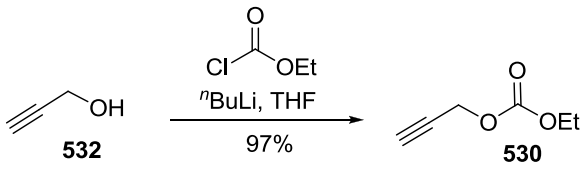


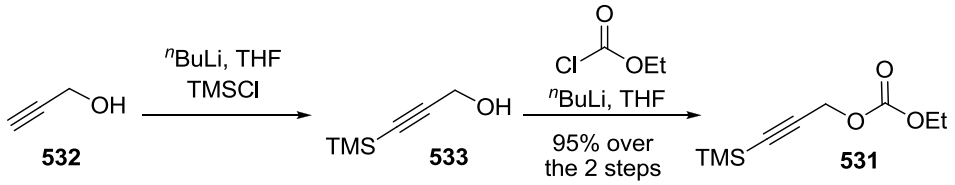
Figure 24. Potential alkynyl substrates towards the addition of the side-chain

Fortunately, the synthesis of the two carbonate substrates proved relatively facile using an analogous approach to the previous synthesis of **478**. Accordingly, **530** was afforded in a yield of 97%, through the exposure of propargylic alcohol **532** to ethyl chloroformate under basic conditions (**Scheme 206**).



Scheme 206. Synthesis of the alternative carbonate side-chain 530

The formation of **531** was achieved following the established protocols towards the synthesis of **478**, to provide the corresponding TMS protected substrate **531** in a yield of 95% over the two steps (**Scheme 207**).



Scheme 207. Synthesis of the TMS protected carbonate 531

With each of the three separate alkynyl candidates **529**-**531** available in significant quantities preliminary investigations towards the synthesis of **527** could be attempted (**Table 50**). Accordingly, each of the separate alkynyl reagents were examined under the optimised conditions established to date.

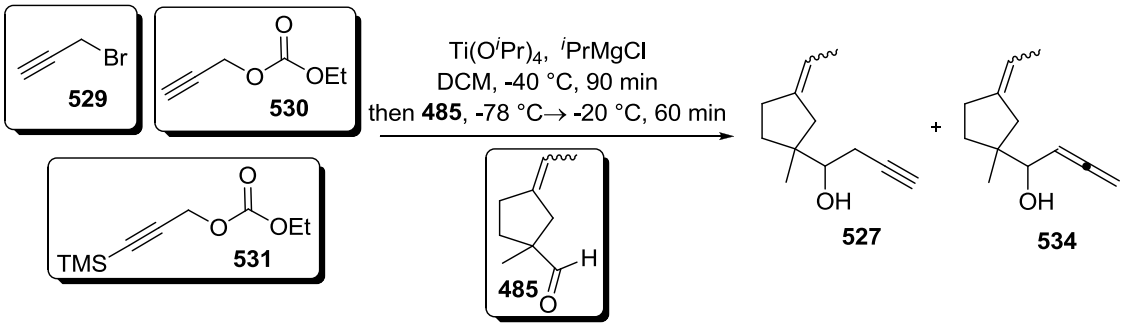


Table 50. Attempted formation of 527 through the established titanium-mediated methodology

Entry	Side-chain	Yield (%)	Ratio of **527**:**534**
1	**529**	44	2:1
2	**530**	41	2:1
3[a]	**531**	41	2:5

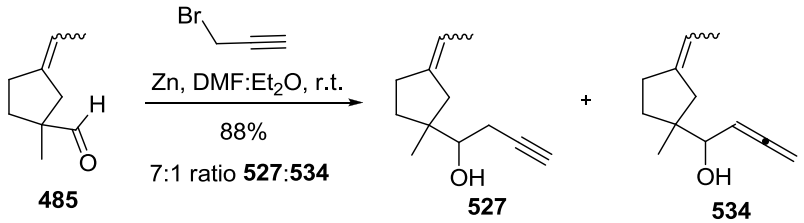
[a] Following the allotted time the resultant product was deprotected using TBAF to provide products **527** and **534**.

The results in **Table 50** demonstrate that although the three substrates under investigation successfully provided **527**, the selectivity and yields observed throughout proved disappointing. In this regard, an initial attempt was pursued using propargylic bromide **529**,

which resulted in the formation of an inseparable 2:1 mixture of **527**:**534** in a yield of 44% (**Table 50**, Entry 1). Whilst the alkyne product **527** was observed to be the major product within this mixture, the poor levels of selectivity achieved were inhibitive to further progress. Switching the alkynyl reagent to **530** provided no clear advantage, with an inseparable 2:1 mixture of **527**:**534** also formed, in a slightly reduced yield of 41% (**Table 50**, Entry 2). In one final attempt to access **527**, the TMS protected substrate was examined under the current optimised conditions, to provide an inseparable mixture of **527**:**534** in a 2:5 ratio and a yield of 42% following removal of the silyl unit. Importantly, in this case a definite swich in regioselectivity was observed with the allene product **543** now observed as the major component.

Whilst it was recognised that a short optimisation programme may provide higher yields from the described transformation, the ratio of alkyne:allene products **527**:**534**, were such that the identification of an alternative process was deemed more beneficial. Towards this aim, a short literature search identified a potential solution through the use of an organozinc reagent.[257]

Accordingly, following the procedures described within the literature a yield of 88% was isolated, as an inseperable 7:1 mixture of **527**:**534** (**Scheme 208**). Importantly, this improved process not only allowed a significant increase in yield, but also an appreciable change in the ratio of products, with **527** obtained as the major product.



Scheme 208. Alternative protocol towards the synthesis of 527

Since the mixture of **527** and **534** obtained in these reactions proved largely inseparable by regular purification techniques, it was recognised that a method for the separation of individual substrates had to be developed. Towards this aim, initial attempts surrounded the formation of the corresponding silyl ethers.

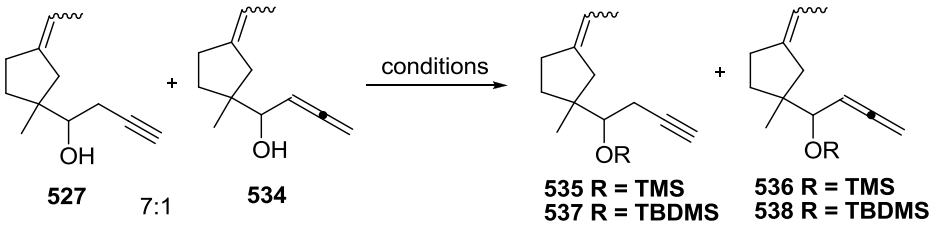


Table 51. Synthesis of silyl protected products 535-538

Entry	Conditions	Yield (%)	Combined yield (%)
1	TMSCl, Et_3N	**535** (85), **536** (12)	97
2	TBDMSOTf, Et_3N, DMAP	**537** (84), **538** (12)	96

To begin this process, the corresponding TMS ether analogues were synthesised under basic conditions to provide **535** and **536** in a combined yield of 97% (**Table 51**, Entry 1). Fortunately, separation of the two components proved successful by column chromatography, with a 7:1 ratio of products isolated by mass. The synthesis of the corresponding TBDMS derivative also proved successful under basic conditions, with **537** and **538** provided in a yield of 96% as a seperable 7:1 mixture of products (**Table 51**, Entry 2). Importantly, the successful formation of **537** confirmed that the removal of the *gem*-dimethyl group afforded an appreciable reduction in the steric environment around the heteroatom.

With the two substrates **535** and **537** synthesised in significant quantities, the two separate P-K precursors were examined under the standard screening protocols previously described (**Table 52**).

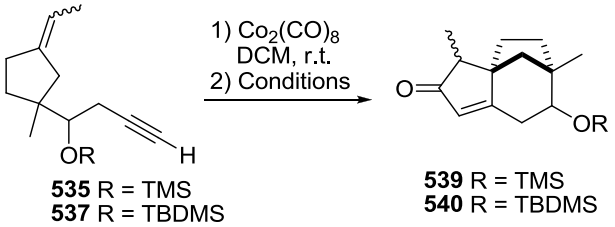


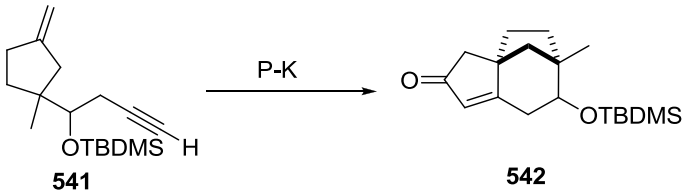
Table 52. Effect of steric bulk on the outcome of the P-K reaction

Entry	enyne	Additive	Temperature (°C)	Yield (%)
1	**535**	DodSMe	reflux	**539** (41)
2	**535**	TMANO·$2H_2O$	r.t.	**539** (32)
3	**535**	TMANO·$2H_2O$	0	**539** (31)
4	**537**	DodSMe	reflux	**540** (58)
5	**537**	TMANO·$2H_2O$	r.t.	**540** (49)
6	**537**	TMANO·$2H_2O$	0	**540** (48)

As the results in **Table 52** demonstrate, in all of the cases examined to date, the desired [5,6,5]-tricyclic core was successfully isolated. In terms of general reactivity profile, it would appear that the increased size of the TBDMS group had a positive effect on the isolated yields of **540**, comparative to the smaller TMS product **539** (**Table 52**, Entries 1-3 compared to Entries 4-6). Additionally, the higher temperature DodSMe promoted P-K reactions consistently provided higher yields of the tricyclic core comparative to the corresonding TMANO·$2H_2O$ reaction (**Table 52**, Entries 1 and 4). Critically, these results indicate that the presence of the *gem*-dimethyl group was the key structural characteristic preventing effective P-K cyclisation.

With regard to **535**, initial attempts to isolate **539** using DodSMe proved successful, with a yield of 41% isolated as a complex mixture of diastereomers (**Table 52**, Entry 1). Switching the reaction promoter to TMANO·$2H_2O$ also provided **539** in a yield of 32% at room temperature and 31% at 0 °C (**Table 52**, Entries 2 and 3). When the corresponding TBDMS derivative **537** was examined under DodSMe promotion, a significant increase in isolated yield was observed to 58% of **540** (**Table 52**, Entry 4). Importantly, just as with the previous attempts to form the tricyclic core with **535**, switching to TMANO·$2H_2O$ promotion afforded an appreciable reduction in the isolated yield of **540**, with 49% isolated upon reaction completion (**Table 52**, Entry 5). Importantly, in all cases, products **539** and **540** were isolated as a complex mixture of diastereoisomers largely inseparable by column chromatography. However, despite the mixture of compounds isolated upon reaction completion, positive identification of the desired product was still possible by ^{1}H NMR analyses and high resolution mass spectroscopy.

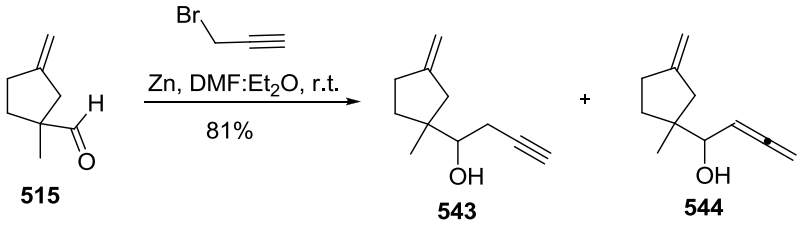
With the first successful implementation of the key P-K reaction towards the construction of the basic tricyclic core, the proposed strategy was recognised as a viable option. However, before proceeding any further, the synthesis of an additional variant of **527** was envisioned, incorporating the terminal methylene substrate **541** (**Scheme 209**). From this perspective, the synthesis of the corresponding tricyclic product **542** would provide the two key insights. Firstly, by removing the mixture of epimers at the methyl position, a significant simplification of the substrate would be achieved, allowing a clearer evaluation of the signals within the ^{1}H NMR spectrum of the resultant product. Secondly, the relative success of this transformation would provide insight as to whether the previous modifications to the alkene moiety were in fact beneficial to promoting the proposed reaction.



541 **542**

Scheme 209. Proposed P-K reaction of substrate 541

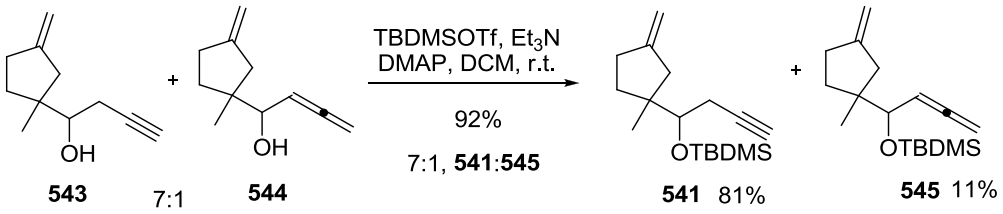
Accordingly, the formation of this additional structural variant was achieved following the previously identified zinc-mediated protocol, to provide the terminal methylene substrates as an inseparable 7:1 mixture of **543**:**544** in a yield of 81% (**Scheme 210**).



515 **543** **544**

Scheme 210. Synthesis of terminal methylene derivatives 543 and 544

With **543** and **544** now in hand, the corresponding silyl protected substrates were synthesised to allow separation of the mixture of compounds (**Scheme 211**).

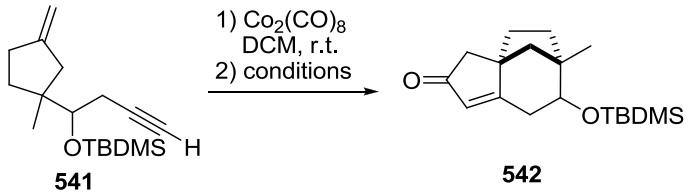


543 7:1 **544** **541** 81% **545** 11%

Scheme 211. Synthesis of silyl protected products 541 and 545

As the result in **Scheme 211** highlights, protection of **543** and **544** proved relatively facile under basic conditions, with a yield in excess of 90% achieved, as a 7:1 mixture of compounds. Importantly, just as with the more substituted variant **537** separation of the alkyne and allene products proved readily achievable using column chromatography.

Following the successful synthesis of **541**, the substrate was screened under the standard set of reaction conditions to determine whether the substitution pattern on the alkene had an effect on the rate of formation of the desired tricyclic core (**Table 53**).



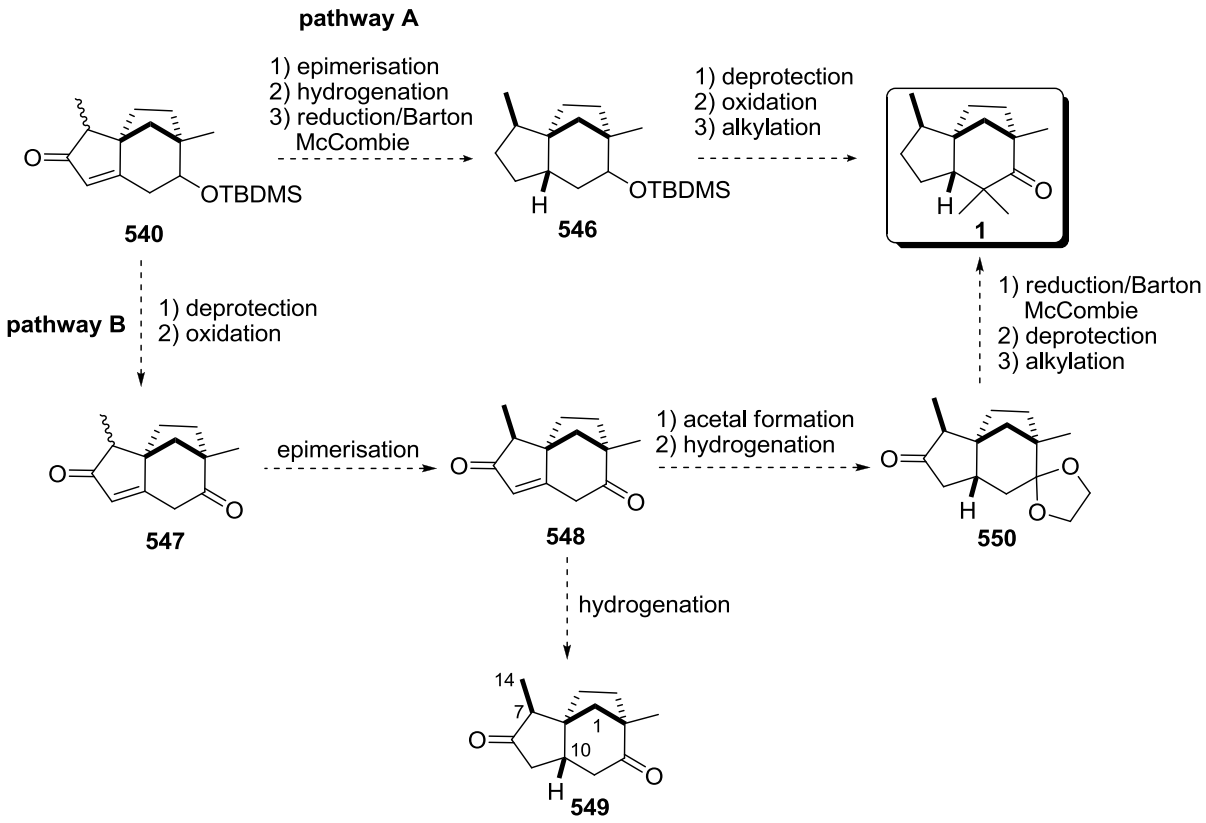
541 **542**

Table 53. Effect of alkene substitution on the P-K reaction

Entry	Additive	Temperature (°C)	Yield (%)
1	DodSMe	reflux	71
2	TMANO·$2H_2O$	r.t.	62
3	TMANO·$2H_2O$	0	59

As can be observed from the results presented in **Table 54**, substrate **541** not only proved successful towards the formation of the corresponding P-K product **542**, but also represented a slight increase in yield comparative to the more substituted equivalents **535** and **537** (**Table 52**). Importantly, **541** showed a similar reactivity profile to **535** and **537** under identical reaction conditions, with the DodSMe promoted P-K reaction again proving to be the most efficient form of promotion (**Table 53**, Entries 1-3). Crucially, these results clearly demonstrate that by reducing the substitution pattern on the alkene moiety within the enyne substrate, a notable increase in reactivity can be achieved with regard to the P-K reaction.

With the aim of completing the synthesis of sesquithuriferone substrate **540** was selected as the compound to take forward for subsequent manipulation. However, whilst the removal of the *gem*-dimethyl group had allowed the first successful synthesis of the tricyclic core to be achieved, it did result in a slightly more circuitous synthetic strategy to reach the natural target. From this perspective, two main options were identified (**Scheme 212**). Importantly, when deciding which strategy to follow it was recognised that the specific route chosen had to deliver answers to two key questions: (a) could an epimerisation process provide the required relative stereochemistry of the methyl at the C-7 position, to embed a *syn*-relationship between C-14 and C-1; and (b) was the hydrogenation facially selective, again embedding a *syn*-relationship between the C-14, C-1 and the hydrogen on the C-10 position.



Scheme 212. Two separate proposed pathways to access sesquithuriferone

The first route envisioned was pathway A, involving a three-step sequence to provide **546** *via* an initial epimerisation, followed by a sequential hydrogenation and reduction/Barton McCombie protocol (**Scheme 212**). This pathway initially appeared favourable as it allowed the selective removal of the enone moiety, before introducing the ketone functionality and *gem*-dimethyl group at an advanced stage in the sequence. Unfortunately, due to the complex mixtures of diastereomers present in **540**, determination of both the success of the epimerisation process and the facial selectivity of the hydrogenation was expected to be analytically challenging until almost the last step of the synthesis. Furthermore, by following this approach the removal of the ketone adjacent to the C-7 methyl meant there would be no further opportunities to affect the orientation of this group if the epimerisation was not completely successful.

Conversely, an alternative route was envisioned that allowed the removal of the protected alkanol stereogenic centre early in the synthetic sequence as shown in pathway B. This route appeared to be the more favoured approach, since it allowed the separate evaluation of first the epimerisation process resulting in **548**, before determining the facial selectivity of the subsequent hydrogenation in **549**. Providing these processes embedded the desired relative orientation, the synthesis of sesquithuriferone could be completed through compound **550**,

formed by chemoselective acetal formation and subsequent hydrogenation. From this point, removal of the ketone functionality could be attempted, before a final deprotection/alkylation process to provide sesquithuriferone, **1**. Additionally, from an asymmetric point of view, the early removal of the stereogenic centre containing the heteroatom should allow a more straightforward analysis of the key compounds obtained throughout the synthesis of sesquithuriferone.

From this perspective, it was decided to proceed *via* pathway B to determine whether the described processes could provide the necessary selectivity at the C-7 methyl and C-10 bridgehead hydrogen. Accordingly, the first synthetic target of interest was compound **551** (**Table 54**). To access **551**, an initial deprotection of the silyl group was attempted using various conditions to afford free alcohol.

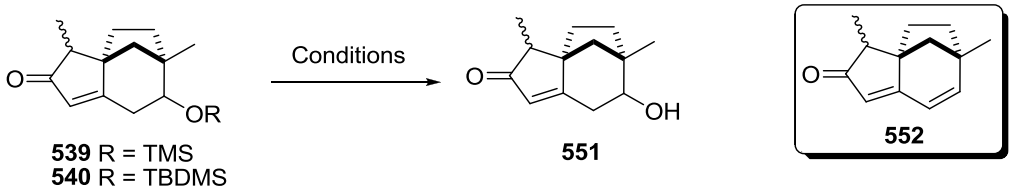


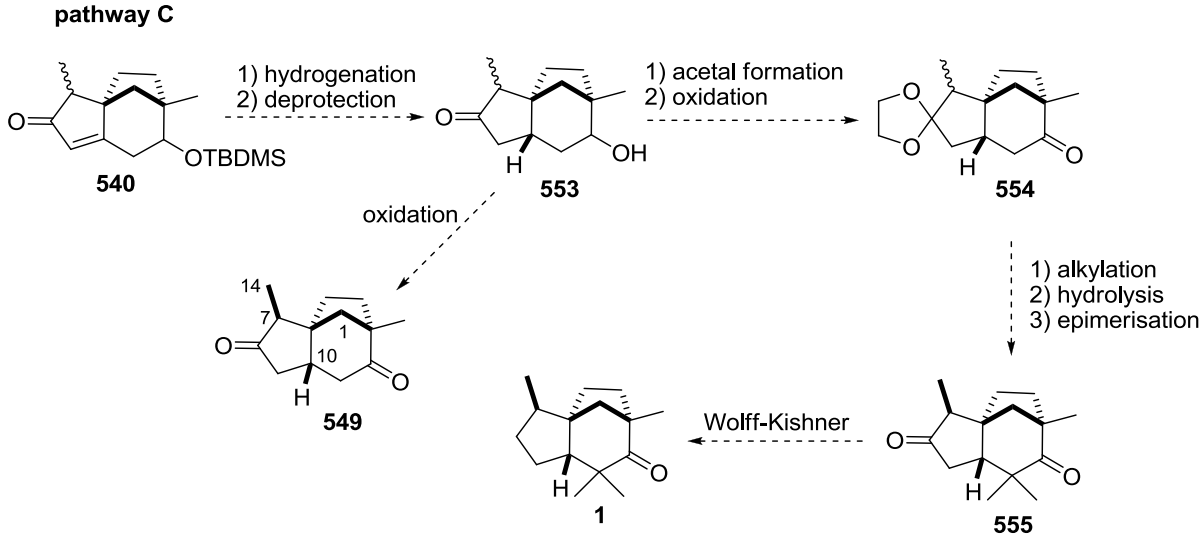
Table 54. Attempted deprotection of 540 to 551

Entry	Substrate	Conditions	Yield of **551** (%)	Yield of **552** (%)
1	**540**	TBAF, r.t.	0	0
2	**540**	TBAF, reflux	0	0
3	**540**	MeOH, TMSBr	0	81
4	**540**	MeOH, AcCl	0	84
5	**539**	TBAF, r.t.	91	0

As the results in **Table 54** demonstrate, removal of the TBDMS silyl group proved highly problematic. Initial attempts to form **551** using excess TBAF at room temperature and at reflux, proved ineffective, with a quantitative return of starting material **540** (**Table 55**, Entries 1 and 2). Following the failure of this initial approach, acidified conditions were investigated. Towards this aim, the formation of HBr *in situ* using a solution of TMSBr and methanol resulted in an 81% yield of the eliminated product **552** (**Table 54**, Entry 3). In one final attempt, **540** was added to a solution of methanol and acetyl chloride at room temperature. Unfortunately, **552** was again obtained as the major product in a yield of 84%.

Pleasingly, deprotection of the corresponding TMS derivative **539** in a solution of TBAF proved successful with a yield of 91% of **551** obtained (**Table 54**, Entry 5). This result

indicated that pathway B could be followed without any further modifications to the described protocols. However, due to the reduced yields afforded in the corresponding P-K reaction to form **539**, an alternative approach was required that would allow the use of the higher yielding TBDMS derivative **540**. Towards this aim, a slightly modified synthetic strategy was devised as shown in **Scheme 213**.



Scheme 213. Proposed pathway C to access sesquithuriferone

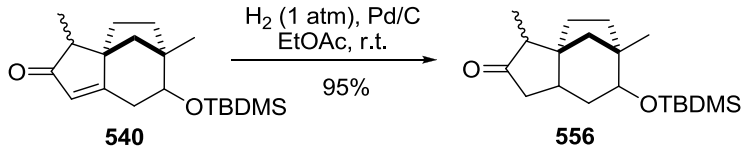
Pathway C involved an initial two-step protocol to access **553**, *via* sequential hydrogenation and deprotection. Crucially, it was compound **553** that was identified as key to the overall success of this strategy. In this regard, two possible directions could be taken. The first of these involved the removal of the alkanol sterreogenic centre through oxidation to provide **549**, an ideal substrate to attempt the epimerisation process. Providing the epimerisation step proved effective, the relative orientation of both the C-7 methyl and the C-10 bridgehead hydrogen could be determined, before attempting any further steps towards sesquithuriferone **1**.

Subsequent to this sequence, with a clearer understanding of the relative orientation of these two key positions, the synthesis of sesquithuriferone **1** could be attempted by converting **553** to **554** *via* acetal protection of the ketone functionality, followed by oxidation of the secondary alcohol. It was from this point that **555** could be accessed through alkylation of the α-position of the six-membered ring, before hydrolysis and epimerisation to install the the relative stereochemistry. Completion of the synthesis of the natural target **1** could then be attempted *via* a regioselective Wolff-Kishner reaction.

Importantly, by following this approach the ketone functionality in the five-membered ring would be present until the final step of the reaction sequence. This should provide an extra

opportunity to affect the relative orientation of the methyl at the C-7 position, if epimerisation is either not effective or installs the opposite orientation to that desired in sesquithuriferone **1**.

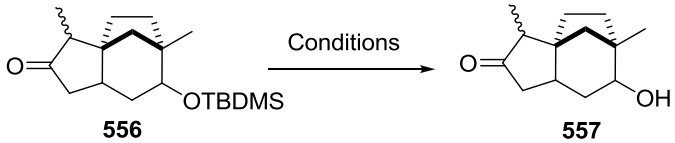
With a modified route devised, initial investigations towards the synthesis of key compound **549** were undertaken (**Scheme 214**). The first step in this process involved the hydrogenation of **540** to afford **556**. It was envisioned that by removing the enone functionality before attempting the subsequent deprotection of the silyl ether, the formation of any competitive elimination side-products would be reduced. Accordingly, a solution of **540** was stirred under an atmosphere of hydrogen, in the presence of Pd/C to provide **556** in an excellent 95% yield.



540 **556**

Scheme 214. Hydrogenation of 540 with Pd/C and H_2 to provide ketone 556

With significant quantities of **556** in hand, a re-evaluation of the deprotection process was undertaken. As the results in **Table 55** illustrate, the deprotection of **556** proved significantly more successful, with no elimination products isolated throughout. In this regard, initial attempts using TBAF remained unsuccessful, both at room temperature and at reflux (**Table 55**, Entries 1 and 2). However, through the use of acidified methanol, yields could be increased significantly, with TMSBr/MeOH providing **557** in a yield of 67% (**Table 55**, Entry 3). Optimised conditions involved the addition of **556** to a stirred solution of methanol and acetyl chloride, to provide **557** in an excellent yield of 91%. In all conditions examined, **557** was isolated as a complex mixture of diastereomers largely inseperable by column chromatography, with little detail of the relative orientations of the substituents possible.

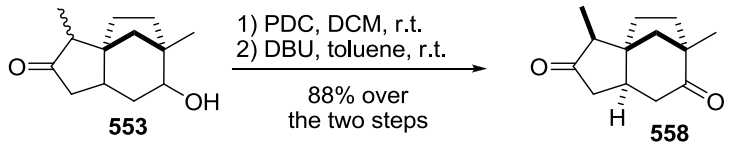


556 **557**

Table 55. Various conditions investigated towards the synthesis of 557

Entry	Conditions	Yield (%)
1	TBAF, r.t.	0
2	TBAF, reflux	0
3	MeOH, TMSBr	67
4	MeOH, AcCl	91

In order to simplify the isolated product, **557** was oxidised to the corresponding diketone **558** using PDC (**Scheme 215**). Following purification, a yield of 88% of **558** was isolated as a mixture of diastereoisomers. However, it was at this point that the proposed epimerisation process could be implemented. Accordingly, the diastereoisomeric mixture of **558** was stirred in a solution of DBU in toluene overnight. Following purification, a quantitative return of **558** was obtained as a single diastereoisomer.



Scheme 215. Sequential oxidation/epimerisation protocol to form 558 as a single diastereoisomer

In order to determine the relative stereochemistry a series of NOE experiments were carried out, the results of which conclusively identified two key points (**Firgure 25**). Firstly, the epimerisation process proved highly successful developing the correct relative methyl orientation at the C-7 position, with a *syn* relationship observed relative to the bridging methylene at the C-1 position of the fused ring system. Unfortunately, the NOE correlations also showed that the hydrogen at the C-10 bridgehead position of the fused tricyclic core was in the opposite orientation to the desired configuration in sesquithuriferone, maintaining a *syn*-relationship with the hydrogen present on the C-5 position of the bridging ethyl portion of the fused ring system.

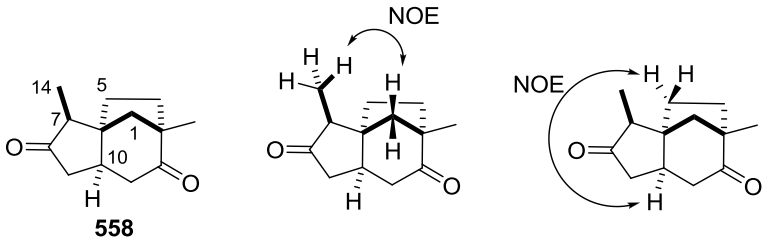
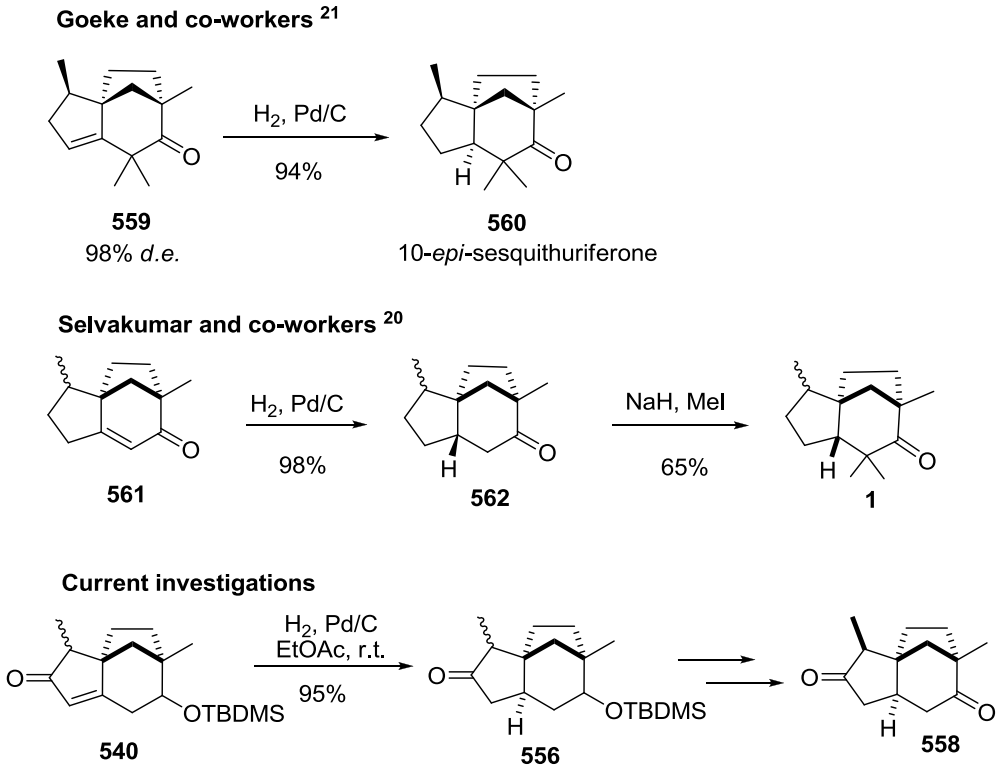


Figure 25. Key NOE correlations determining the relative stereochemistry in 558

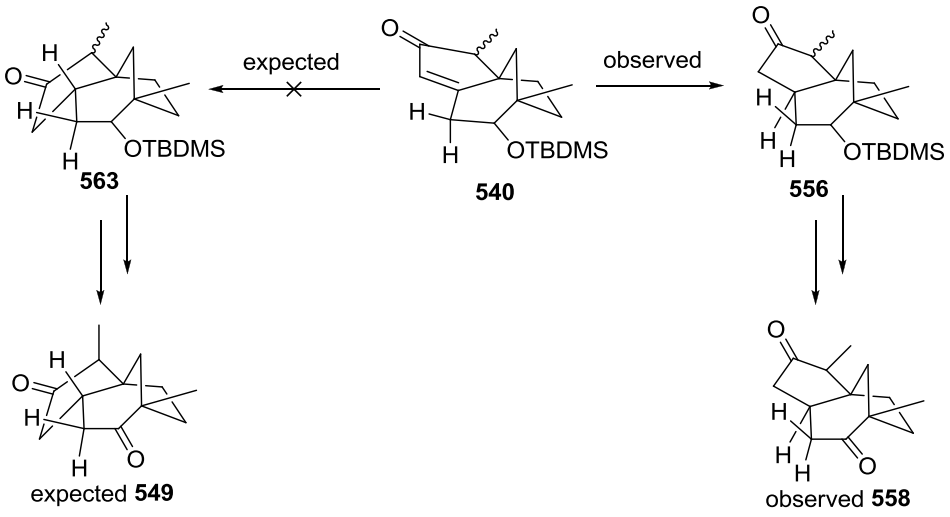
Whilst this result was disappointing, it was not without precedent (**Scheme 216**). In 2006, Geoke and co-workers observed a similar selectivity issue when attempting to reduce the double bond in the related fused ring system **559**.[21] Importantly, this indicated that hydrogenation using Pd/C occurred from what initially appeared to be the more hindered face of the molecule to afford **560**. It is important to note, that whilst the facial selectivity observed in **558** was supportive of the result reported by Geoke and co-workers, it was also contradictory to the facial selectivity reported by Selvakumar and co-workers.[20] Interestingly, in this case where the double bond is embedded within the six-membered ring of **561**, the

facial selectivity was completely reversed to provide a *syn*-relationship between the bridgehead hydrogen and the bridging methylene portion.



Scheme 216. Reported facial selectivity in the related fused ring systems

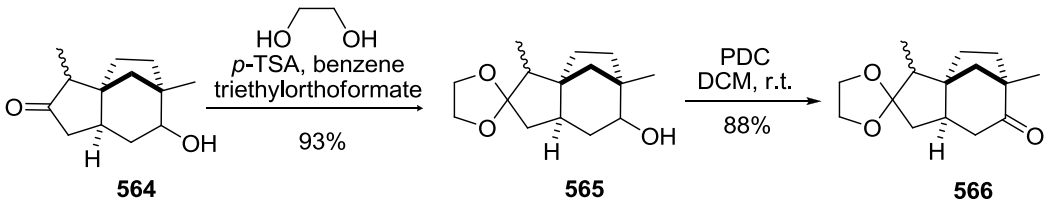
At present, it remains unclear why the facial selectivity does not occur as expected from the upper face. However, the subtle change in the position of the double bond embedded in the five-membered ring may be sufficient to distort the fused structure into a conformation that flattens the molecule and hence expose the lower face for preferential hydrogenation (**Scheme 217**).



Scheme 217. Facial selectivity of the hydrogenation process

Despite the obvious disappointments of this result it was recognised that the current route under investigation could still provide access to 10-*epi*-sesquithuriferone. Towards this aim, two key steps remained untested, involving the addition of the corresponding *gem*-dimethyl group and the regioselective removal of the ketone functionality within the five-membered ring.

The next step in the synthetic sequence involved the protection of the ketone in **564**, followed by oxidation of the secondary alcohol to provide **566** (**Scheme 218**).

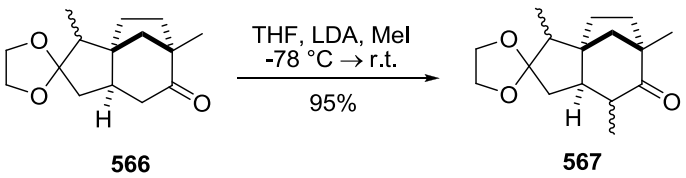


Scheme 218. Synthesis of acetal protected compounds 565 and 566

The formation of the corresponding acetal was carried out in an acidified solution of triethyl orthoformate and ethylene glycol in benzene, to provide **565** in an excellent yield of 93%. Subsequent oxidation using PDC provided **566** in a reproducible yield of 88%. Unfortunately, both **565** and **566** were isolated as an inseparable mixture of diastereoisomers of which little stereochemical information could be determined by ^{1}H NMR analyses.

With **566** now in hand an initial attempt at the insertion of the *gem*-dimethyl group could be attempted. Towards this aim, a two-step sequential alkylation protocol was envisioned involving the initial synthesis of monomethylated substrate **567**, before the subsequent development of conditions to facilitate the addition of the second methyl in **568**.

Initial investigations towards the isolation of **567** were carried out using LDA and MeI to provide **567** in an excellent yield of 95% (**Scheme 219**).



Scheme 219. Monomethylation of 566 using LDA and MeI

With a reliable process identified towards the synthesis of **567** established, a range of conditions were investigaed to access the corresponding *gem*-dimethyl variant **568** (**Table 56**).

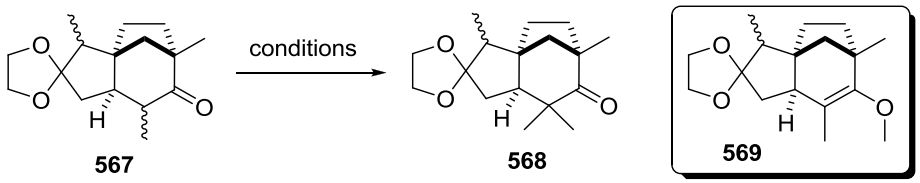
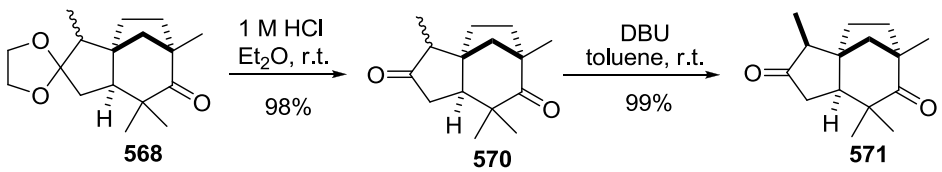


Table 56. Various conditions examined to insert the *gem*-dimethyl group in 568

Entry	Base	Electrophile	Yield of **568** or **569** (%)
1	KHMDS (1.5 eq.)	MeI (2.0 eq.)	0
2	LDA (1.5 eq.)	MeI (2.0 eq.)	0
3	LDA (1.5 eq.)	Dimethylsulfate (2.0 eq.)	**569** (65)
4	LDA (3.0 eq.)	MeI (4.0 eq.)	**568** (88)

As the results in **Table 56** demonstrate, insertion of the second methyl to form **568** proved problematic. An initial attempt using an excess of KHMDS and MeI proved completely ineffective, with a quantitative return of the starting material **567** isolated (**Table 56**, Entry 1). Switching the base to LDA was also ineffective with **567** returned exclusively (**Table 56**, Entry 2). However, through a subtle change in the electrophile to dimethyl sulfate, a yield of 65% of **569** was isolated (**Table 56**, Entry 3). Importantly, whilst *O*-methylation was not the desired outcome of the reaction, it did indicate that deprotonation was occurring under the conditions examined. Optimised conditions involved the addition of a large excess of LDA and MeI to provide the **568** in a yield of 88% (**Table 56**, Entry 4).

Unfortunately, due to the complex mixture of diastereoisomers still present in **568** little stereochemical information surrounding the resulting compound could be determined. With the aim of simplifying the molecule and determining the relative stereochemistry, a two-step protocol was initiated to provide **571** as a single diastereoisomer (**Scheme 220**). Accordingly, **568** was hydrolysed under aqueous acidic conditions to provide **570** in a yield of 98%, as a mixture of diastereomers. Following the previously developed epimerisation protocols **571** was successfully isolated as a single diastereomer in a yield of 99%.



Scheme 220. Synthesis of 571 as a single diastereoisomer

Subsequent analysis of the resultant product **571** by NOE provided a second confirmation of the initial findings regarding **558**, with the methyl at the C-7 position in the desired *syn*-configuration relative to the bridging methylene (**Figure 26**). However, once again the the bridgehead hydrogen was confirmed as having been embedded in the opposite orientation comparative to the desired configuration in sesquithuriferone.

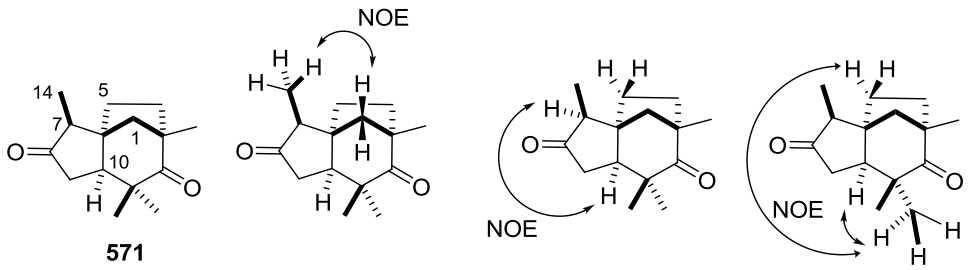
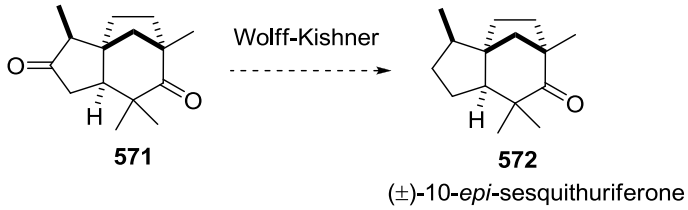


Figure 26. Key NOE correlations determining the relative stereochemistry in 571

Unfortunately, due to time constraints further progress through the synthetic sequence could not be attempted. However, a Wolff-Kishner-type process had been proposed to complete this key final transformation. In this regard, it was proposed that regioselectivity could be achieved through condensation of the hydrazine reagent at the least sterically hindered ketone on the five-membered ring.

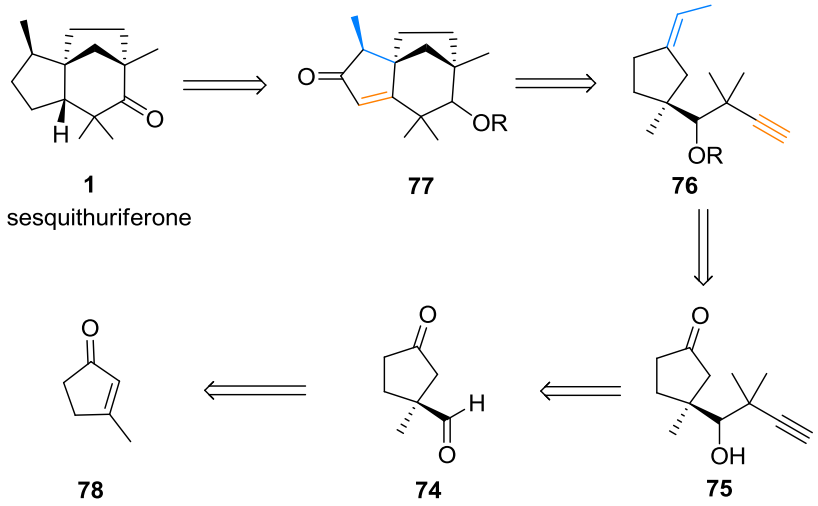


Scheme 221. Proposed final step to provide (±)-10-*epi*-sesquithuriferone 572 from 571

It was at this point in the synthetic sequence that the investigations towards the synthesis of sesquithuriferone concluded. The following section provides a summary of the work completed to date and outlines the future strategy to complete not just the synthesis of sesquithuriferone, but also the investigations planned to expand the identified strategy into additional targets within the same family of natural product compounds.

4.7 Summary

A novel synthetic strategy has been devised to access the natural product sesquithuriferone **1** from the commercially available starting material 3-methylcyclopentenone **78** (**Scheme 222**).

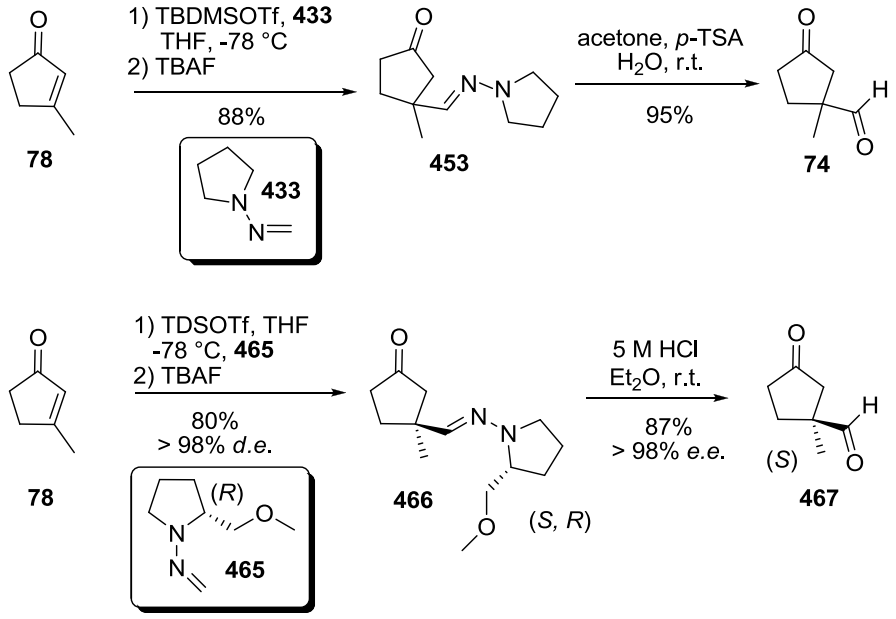


Scheme 222. Retrosynthetic strategy to access sesquithuriferone

It was envisioned that sesquithuriferone **1** could be constructed from the enone motif present in **77**, which in turn would be accessible *via* a P-K reaction from **76**. Preparation of **76** was proposed through a *Z*-selective olefination of ketone **75**, ultimately synthesised from the chemoselective addition of the alkynyl side-chain to **74**. Critical to the success of this proposed strategy were two key areas; firstly, embedding a *Z*-selective olefin in **76** and secondly, from an asymmetric point of view, embedding the correct chiral configuration in **74**, to promote a diastreoeselective P-K reaction.

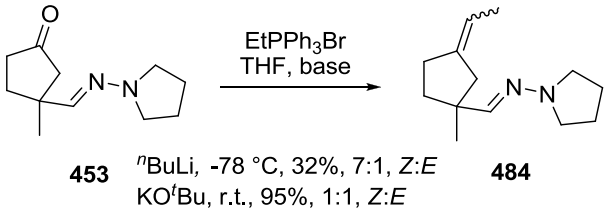
Towards this aim, a series of synthetic stratgeies were investigated to first provide a robust route through to the racemic variant of sesquithuriferone, before identifing key points within the preparative protocols to develop the high levels of selectivity required to attempt an asymmetric synthesis of the natural target **1**.

Following a series of optimisation programmes, a robust and scalable conjugate addition-based protocol was developed to provide both the racemic and asymmetric variants **74** and **447** respectively, with excellent yields and selectivity observed throughout (**Scheme 223**).



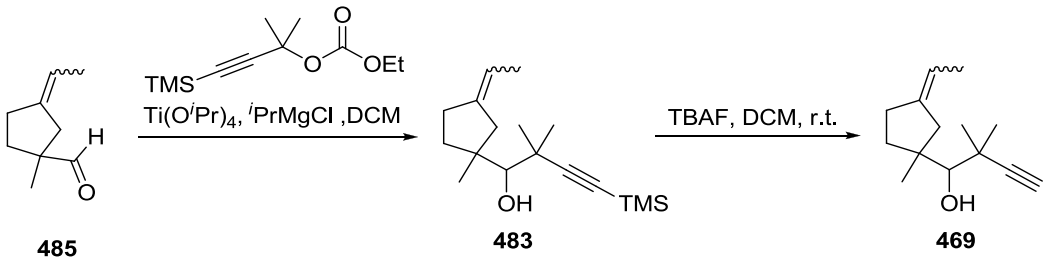
Scheme 223. Optimised conditions to provide the racemic and asymmetric variants 74 and 467

With significant quantities of **74** in hand, attention then turned towards the development of a *Z*-selective olefination. During these investigations, a temperature study involving the olefination of **453**, demonstrated that a significant level of selectivity could be achieved through the implementation of a low temperature protocol (**Scheme 224**). Unfortunately, under all of the conditions examined to date, poor levels of conversion to **484** were observed at reduced temperatures. As a result, an unselective olefination was employed with the aim of incorporating selectivity at a more advanced stage of the synthesis, through the incorporation of an epimerisation process.



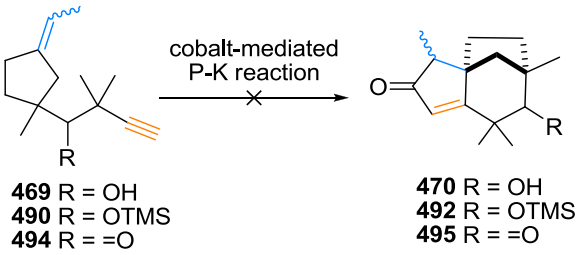
Scheme 224. Strategy towards the selective synthesis of 484

Following removal of the hydrazone in **484**, a titanium-mediated methodology was successfully employed to access the desired P-K precursor **469** (**Scheme 225**).



Scheme 225. Synthesis of 469 *via* a titanium-mediated alkynyl addition

Unfortunately, all attempts to promote the P-K reaction for the completion of the desired tricyclic scaffold using substrates **469** and derivatives **490** and **494** proved unsuccessful (**Scheme 226**).



Scheme 226. Attempted synthesis of the tricyclic scaffold *via* a P-K reaction

To circumvent this issue, a systematic study of the basic structural framework of **469** was initiated. Towards this aim, three points of diversity were investigated involving removal of the quaternary centre, reduced substitution on the alkene moiety, and finally, removal of the *gem*-dimethyl group (**Figure 27**). The synthesis of each of these derivatives was completed using an analogous strategy to the synthesis of **469**, providing evidence that this synthetic route was, in fact, robust and capable of delivering a wide variety of structural variants, with little modification of the established protocols required.

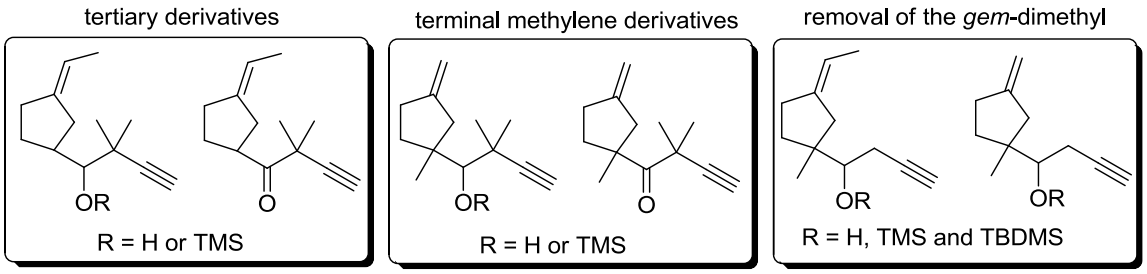
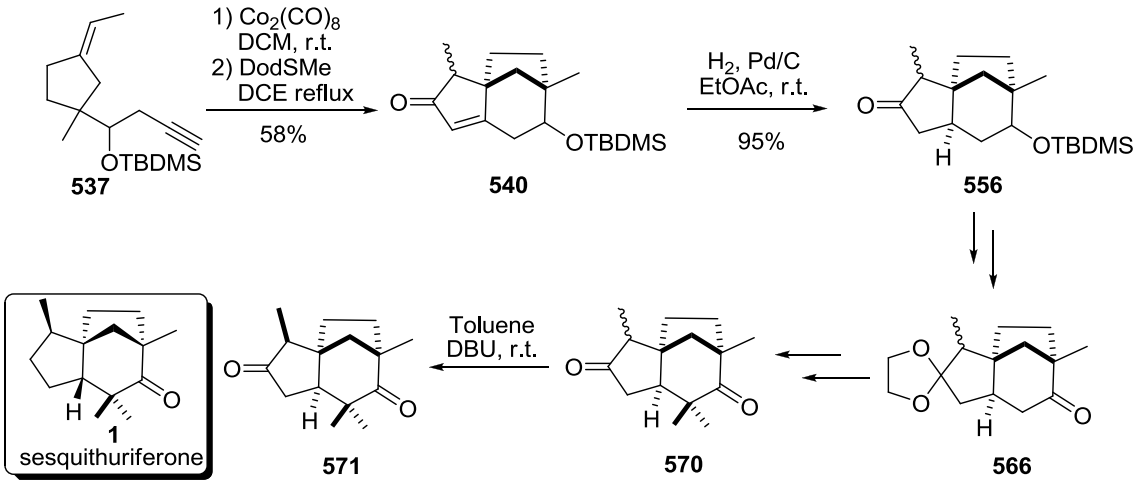


Figure 27. Structural variants synthesised using the current synthetic strategy

Following a systematic screening of the various structural derivatives in the P-K reaction, it was discovered that the key structural characteristic preventing the efficient transformation of the enyne substrate to the tricyclic core was the *gem*-dimethyl group.

With a suitable substrate identified to facilitate the desired P-K reaction, a number of synthetic routes were investigated to provide sesquithuriferone. At present, a robust route has been developed through to compound **571**, with one final step yet to be attempted, the regioselective removal of the ketone in the five-membered ring (**Scheme 227**). Importantly, despite the implementation of an unselective olefination protocol, the employment of an epimerisation process has proved highly successful, developing the correct relative orientation of the methyl on the five-membered ring in **571**. Unfortunately, NOE analyses of

571 also revealed that the bridgehead hydrogen was embedded in the opposite orientation to that required in sesquithuriferone. As a direct result of the observed configuration, the synthetic route under current development could only provide access to 10-*epi*-sesquithuriferone, rather than the desired natural target sesquithuriferone **1**.



Scheme 227. Product 571 formed by the current synthetic strategy

4.8 Future Work

Undoubtedly, the ground work has been established towards both the racemic and asymmetric synthesis of sesquithuriferone. However, two key issues have yet to be solved: the facial selectivity of the hydrogenation of the enone, and the regioselective removal of the ketone functionality within the five-membered ring as shown in **Figure 28**.

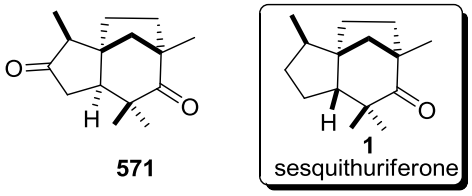


Figure 28. Relative structure of the current product 571 and sesquithuriferone

Of these two remaining steps requiring development, the most important transformation to establish a robust and selective set of conditions is the hydrogenation reaction. It is this step that is crucial to the completion of the synthesis of sesquithuriferone and possibly further members of the same family of natural products. In this regard, in order to provide the correct orientation of the hydrogen at the bridgehead position, a range of options are available. Firstly, a systematic study should be initiated involving alternative catalyst sources such as iridium- and rhodium-based systems, both from a racemic and asymmetric prespective.

Secondly, the rhodium-catalysed delivery of a hydride source should also be investigated. In relation to this, a range of compounds such as the P-K product **540**, have been synthesised to date and represent ideal candidates to begin these investigations.

With regard to the removal of the final ketone moiety, no clear outline has been established. Certainly, the Wolff-Kishner strategy could be a feasible approach, however, a range of alternative options could be utilised depending on the point at which a selective hydrogenation is incorporated into the synthesis. In this respect, addressing the removal of the ketone is much more flexible, once the selective hydrogenation has been completed.

At the outset of this project, one of key objectives was determining whether the general synthetic strategy could be expanded into other members of the same family of natural products. With this in mind, four additional candidates have been identified as potentially accessible using this synthetic approach: sesquithuriferol **9**, duprezianene **11**, prezizaene **32** and isozaene **31** (**Figure 29**).[16]

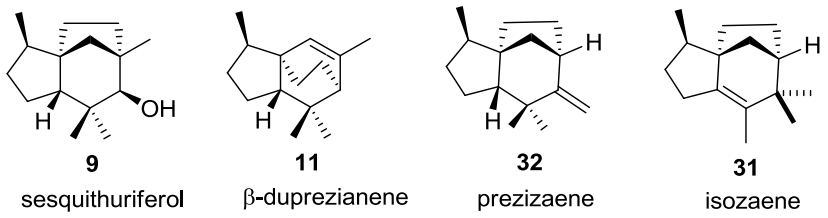
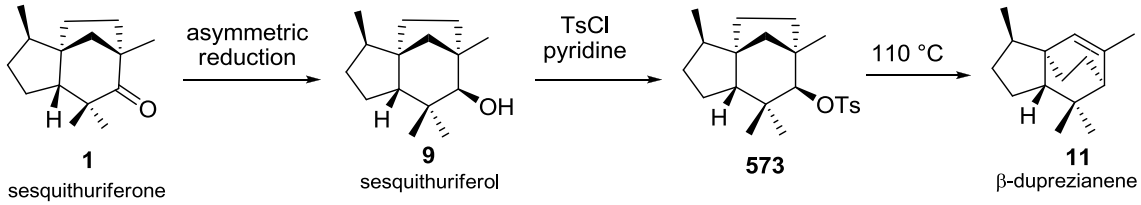


Figure 29. Structures of the four potential candidates for synthetic diversification

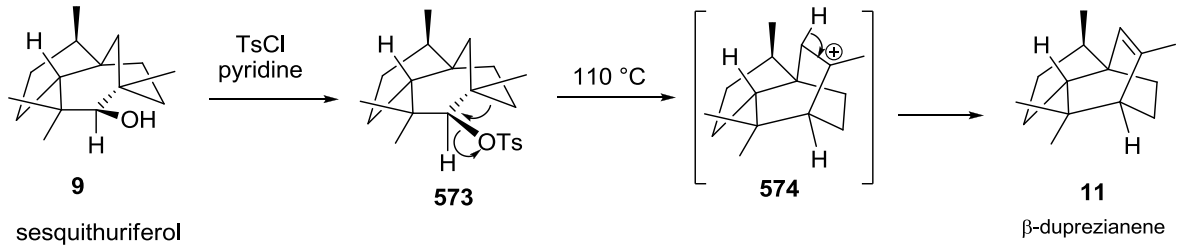
With regard to the first of these candidates sesquithuriferol **9**, the synthetic accessibility is clear from sesquithuriferone **1**, through the development of a stereoselective reduction process (**Scheme 228**).



Scheme 228. Synthetic strategy to access 9 and 11 from sesquithuriferone 1

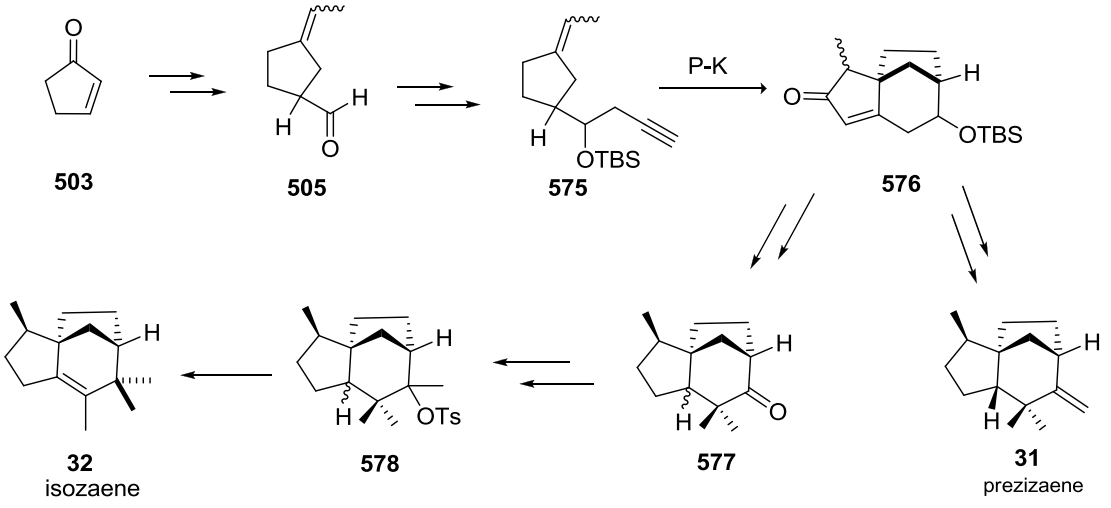
Remarkably, it is from sesquithuriferol **9** that a further diversification could be achieved through a step-wise, precedented alkyl shift from the activated alcohol functionality in **573** (**Scheme 229**).[11] In this regard, the synthesis of sesquithuriferone **1** would not only provide the basic structural scaffold of the closely realted sesquithuriferol **9**, but also provide a suitable substrate to diversify into further ring systems such as the [5,6,6]-fused system of β-duprezianene **11**. This strategy towards **11** is essentially a biomemitic approach, since an

analagous cationic rearrangement was thought to occur within the biosynthetic pathway (**Scheme 229**).[16]



Scheme 229. Conversion of sesquithuriferol to β-duprezianene

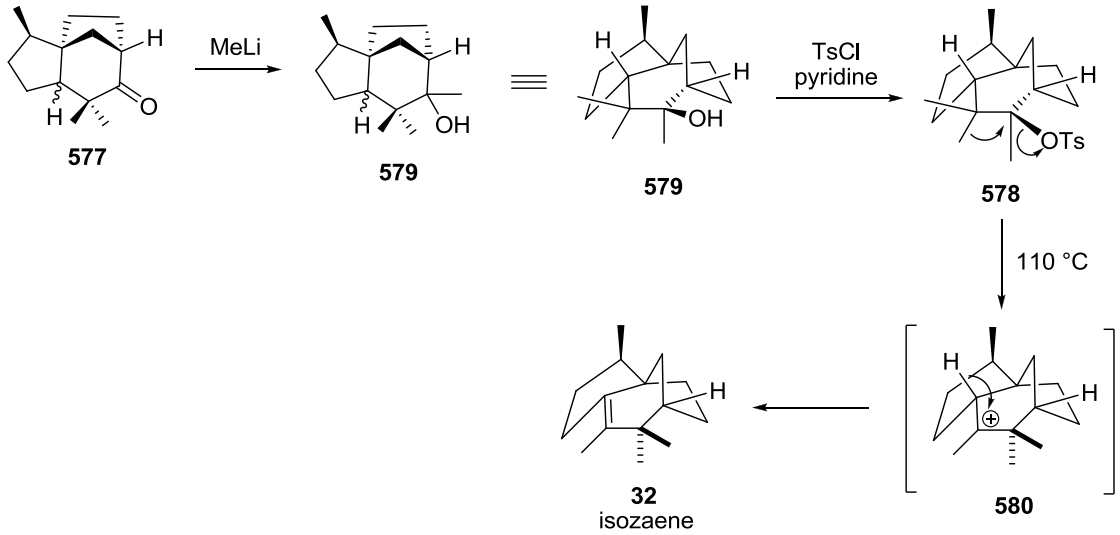
With regard to the final two substrates, prezizaene **31** and isozaene **32**, significantly more development work would be required (**Scheme 230**). However, following an analogous route to the current synthetic strategy, the tertiary derivative **575** could be rapidly built up from cyclopentenone **503** and investigated within the context of the P-K reaction to provide **576**. Whilst the tertiary derivative was unsuccessful in the current investigations towards the proposed P-K reaction in the presence of the *gem*-dimethyl, no equivalent studies were carried out using the corresponding equivalent **575**. Furthermore, it is now known that the *gem*-dimethyl was the limiting factor towards the P-K cyclisation and this approach could prove entirely accessible. However, just as with sesquithuriferone **1**, completion of the synthesis of the natural target **31** is reliant on the development of a selective hydrogenation reaction to embed the correct hydrogen orientation at the bridgehead position.



Scheme 230. Synthetic strategy to access prezizaene 31 and isozaene 32

In one final adaption of the synthetic route, conversion of **576** to the corresponding derivative **577** would allow the evaluation of a second proposed biomimetic process to form isozaene **32** (**Scheme 231**).[16] In this proposed transformation, the presence of the hydrogen at the bridgehead position could promote the formation of the more stabilised carbocation in **580**

through preferential migration of a methyl group in **578**. At present, there is no literature precedent for this transformation, however, just as with the synthesis of **11**, an analogous cationic shift is thought to occur in the biosynthetic pathway (**Scheme 2**).



Scheme 231. Proposed biomimetic synthesis of isozaene

As illustrated in the introduction (**Scheme 2**, **Section 2.3**), it is the close biosynthetic link of each of the identified compounds that could prove critical to the development of a generic strategy. Whilst each of these proposed routes are presented as a tentaive approach towards their individual syntheses, the synthetic strategy developed to date certainly appears to provide an excellent starting point to access a range of compounds from common intermediates.

5 Experimental

Reagents

All reagents were obtained from commercial suppliers and used without further purification, unless otherwise stated. All reactions were carried out under an inert, dry nitrogen atmosphere, unless otherwise stated. Purification was carried out according to standard laboratory methods.[258]

Tetrahydrofuran, toluene, benzene, and diethyl ether were dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under nitrogen. Dichloromethane, 1,2-dichloroethane, acetonitrile, dimethyl sulfoxides, and dimethoxy ethane were dried by heating to reflux over calcium hydride then distilled under nitrogen.

Petrol refers to petroleum ether in the boiling point range of 40-60 ºC. Low boiling point ether refers to petroleum ether in the boiling point range 30-40 ºC.

^{n}BuLi, ^{t}BuLi and ^{i}PrMgCl were obtain as solutions in hexanes, pentanes and THF or diethyl ether, respectively, and standardised using salicylaldehyde phenylhydrazone.[259]

Instrumentation and Data

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

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

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

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz, 100 MHz, 376 MHz, and 162 MHz respectively, unless otherwise stated. Chemical

shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions unless otherwise specified.

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

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

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

The experimental data will be presented in two separate sections. The first of these will described the experimental procedures followed to complete the synthesis of each of the individual molecules of interest. The second section contains the specific ^{1}H, ^{13}C NMR, IR and mass spectral data for each of the compounds successfully isolated. Additional pdf spectra have been provided in the appendix following these sections.

5.1 Experimental Procedures

General procedures:

General procedure (A): Preparation of Wittig salts under thermal conditions

To a flame dried round bottomed flask, fitted with a reflux condenser, was added PPh_3 and a solution of alkyl halide in toluene or MeCN. The resultant mixture was then heated to reflux for 12 h. The mixture was then cooled to r.t., concentrated to a minimum volume and triturated repeatedly with diethyl ether (10 mL). The trituration process was repeated until a fine white precipitate was observed. The resultant white solid was then filtered off and dried *in vacuo* to provide the corresponding phosphonium salt as a fine white solid.

General procedure (B): Preparation of Wittig salts by microwave promotion

To a flame dried 5 ml microwave tube was added alkyl halide, MeCN (2 mL) and PPh_3. The mixture was then sealed and heated in the microwave for the allotted time. Upon completion, the mixture was concentrated to a minimum volume and triturated repeatedly with diethyl ether (10 mL). The trituration process was repeated until a fine white precipitate was observed. The resultant white solid was then filtered off and dried *in vacuo* to provide the corresponding phosphonium salt as a fine white solid.

General procedure (C): Attempted synthesis of 79 by RCM at r.t.

A 3-necked round bottomed flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. To the vessel was charged DCM or toluene, a solution of Grubbs II catalyst, and $Ti(O^iPr)_4$. The mixture was stirred at r.t. for 15 min, before a solution of diene in DCM (2 mL) was added dropwise. The resulting solution was stirred at r.t. for a further 24 h. After this time, the mixture was opened to the air for 4 h, filtered through celite, concentrated under reduced pressure. The crude reaction mixture was analysed by GCMS prior to filtering, but before concentration, to determine if **79** was present. The crude products were purified by column chromatography (eluent: 0-20% diethyl ether in petrol).

General procedure (D): Attempted synthesis of 79 by RCM at reflux

A 3-necked, round bottomed flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. To the vessel was charged DCM or toluene, a solution of Grubbs II catalyst and $Ti(O^iPr)_4$, before heating the solution to reflux for 15 min. To the mixture was

added a solution of diene in DCM (2 mL) dropwise and the resulting solution refluxed for a further 24 h. The mixture was then cooled to r.t. and opened to the air for 4 h. The mixture was filtered through celite, concentrated under reduced pressure. The crude reaction mixture was analysed by GCMS prior to filtering, but before concentration, to determine if **79** was present. The crude products were purified by column chromatography (eluent: 0-20% diethyl ether in petrol).

General procedure (E): Attempted synthesis of 79 by RCM at reflux

A 3-necked, round bottomed flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. To the vessel was charged DCM or toluene and a solution of Grubbs II catalyst (5 mol%) in DCM (2 ml), before heating the solution to reflux for 15 min. To the mixture was added a solution of diene/triene in DCM (2 mL) dropwise and the resulting solution refluxed for a further 24 h. Additional portions of Grubbs II catalyst (5 mol%) in DCM (2 ml) were added after 6 h, 12 h and 18 h. The mixture was then cooled to r.t. and opened to the air for 4 h. The mixture was filtered through celite, concentrated under reduced pressure. The crude reaction mixture was analysed by GCMS prior to filtering, but before concentration, to determine if **79** was present. The crude products were purified by column chromatography (eluent: 0-20% diethyl ether in petrol).

General procedure (F): Studies towards the formation of 341

To a solution of diene in DCM or toluene (10 mL) at r.t. was added $Ti(O^{i}Pr)_4$ and the mixture heated to reflux for 6 h. The resultant mixture was then cooled to r.t., concentrated under reduced pressure and purified by column chromatography (eluent: 0-20% diethyl ether in petrol).

General procedure (G): Synthesis of trienes by Wittig olefination

To a stirred suspension of phosphonium salt in THF at r.t. was added $KO^{t}Bu$ in a single portion. The reaction mixture was stirred for 1 h at r.t., before of a solution of ketone in THF (2 mL) was added dropwise over 5 min. The reaction mixture was then stirred at r.t. for a further 12 h. Upon completion, the reaction mixture was diluted with diethyl ether (30 mL) and quenched with sat. aq. NH_4Cl solution (30 mL). The organic phase was separated off and washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-5% diethyl ether in petrol).

General procedure (H): Attempted synthesis of 79 by RCM at reflux

A 3-necked, round bottomed flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. To the vessel was charged DCM and Grubbs II catalyst (5 mol%), before heating the solution to reflux for 15 min. To the mixture was added a solution of triene in DCM (10 mL) dropwise over 36 h by syringe pump. Additional portions of Grubbs II catalyst (5 mol%) in DCM (2 ml) were added after 6 h, 12 h, 24 h and 36 h. The resulting solution was then refluxed for a further 12 h. The resultant mixture was then cooled to r.t. and opened to the air for 4 h. The mixture was filtered through celite, concentrated under reduced pressure and purified by column chromatography. The crude reaction mixture was analysed by GCMS prior to filtering, but before concentration, to determine if **79** was present.

General Procedure (I): Preparation of 420 by thermal promotion

To a flame dried microwave tube (5 mL) was added **419**, allyl alcohol, Et_3N, palladium catalyst and MeCN (2 mL). The tube was then sealed and heated to 100 °C in an oil bath for 24 h. Upon completion, the mixture was cooled to r.t. and added directly onto a column containing silica gel. The crude product was purified by column chromatography (eluent: 0-10% diethyl ether in petrol) to provide **420** as a colourless oil. Column fractions were concentrated at reduced pressure at 0˚C, 100 mbar, due to the volatility of **420**.

General Procedure (J): Preparation of 420 by microwave promotion

To a flame dried microwave tube (5 mL) was added **419**, allyl alcohol, Et_3N, palladium catalyst and MeCN (2 mL). The mixture was then heated to 110 °C in a sealed vessel in the microwave (6 x 30 min). Upon completion, the mixture was added directly onto a column containing silica gel. The crude product was purified by column chromatography (eluent: 0-10% diethyl ether in petrol) to provide **420** as a colourless oil. Column fractions were concentrated at reduced pressure at 0 ˚C, 100 mbar, due to volatility of **420**.

General procedure (K): Conjugate addition protocol

To a stirred solution of 3-methylcyclopentenone **78** in the appropriate solvent at the corresponding temperature was added TBDMSOTf dropwise. The cooled reaction mixture was stirred for 5 min before the addition of a solution of formyl hydrazone over 5 min. The mixture was stirred for the designated time period, before warming to r.t. and adding diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (10 mL). The organic phases were

combined, before adding a solution of TBAF dropwise at r.t.. The resulting mixture was stirred at r.t. for 6 h, before the addition of diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (20 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar. The crude product was purified by column chromatography (eluent: 0-50% ether in petrol) to provide the product as a colourless liquid.

General procedure (L): Conjugate addition protocol

To a stirred solution of 3-methylcyclopentenone **78** in THF (10 mL) at -78 °C was added TBDMSOTf dropwise. The cooled reaction mixture was stirred for the corresponding time period before the addition of a solution of **428** in THF over 5 min. The mixture was stirred for 30 min before warming to r.t. and adding diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase extracted with diethyl ether (10 mL). The organic phases were combined before adding a solution of TBAF dropwise at r.t. The resulting mixture was stirred at r.t. for 6 h, before the addition of diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar. The crude product was purified by column chromatography (eluent: 0-50% ether in petrol) to provide **429** as a colourless liquid.

General procedure (M): Conjugate addition protocol

To a stirred solution of 3-methylcyclopentenone **78** in THF (10 mL) at -78 °C was added silyl triflate dropwise. The reaction mixture was stirred at-78 °C for 30 min before the addition of a solution of **428** in THF over 5 min. The mixture was stirred at -78 °C for 30 min before warming to r.t. and adding diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase extracted with diethyl ether (10 mL). The organic phases were combined before adding a solution of TBAF dropwise at r.t. The resulting mixture was stirred at r.t. for 6 h, before the addition of diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure at 0 °C and 100 mbar. The crude

product was purified by column chromatography (eluent: 0-50% ether in petrol) to provide the product as a colourless liquid.

General procedure (N): Conjugate addition protocol

To a stirred solution of enone in THF at -78 °C was added TBDMSOTf dropwise. The reaction mixture was stirred at -78 °C for 30 min before the addition of a solution of formyl hydrazone (**428** or **443**) in THF over 5 min. The mixture was stirred at -78 °C for 30 min before warming to r.t. and adding diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase extracted with diethyl ether (10 mL). The organic phases were combined before adding a solution of TBAF dropwise at r.t. The resulting mixture was stirred at r.t. for 6 h, before the addition of diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar. The crude product was purified by column chromatography (eluent: 0-50% ether in petrol) to provide the product as a colourless liquid.

General procedure (O): Deprotection of hydrazones to the corresponding aldehyde

To a stirred solution of hydrazone in acetone (5 mL) at r.t. was added *p*-TSA·H_2O and water. The mixture was stirred at r.t. monitoring progress by TLC analysis, then dried over Na_2SO_4, filtered, and concentrated at reduced pressure at 0 °C and 100 mbar. The crude product was purified by column chromatography (eluent: 0-50%, ether in petrol) to provide the product as a colourless liquid.

General procedure (P): Preparation of 1-methyl-3-oxocyclopentanecarbaldehyde, 466

To a stirred solution of 3-methylcyclopentenone **78** in THF at -78 °C was added TBDMSOTf dropwise. The reaction mixture was stirred at -78 °C for 30 min before the addition of a cooled solution of **465** in THF at -78 °C *via* cannula over 5 min. The mixture was stirred at -78 °C for 30 min before warming to r.t. and adding diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase extracted with diethyl ether (10 mL). The organic phases were combined before adding a solution of TBAF dropwise at r.t. The resulting mixture was stirred at r.t. for 6 h, before the addition of diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were

combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar. The crude product was purified by column chromatography (eluent: 0-50% ether in petrol) to provide **466** as a colourless liquid.

General procedure (Q): Protocols towards the titanium-mediated alkynyl addition

To a stirred solution of $Ti(O^iPr)_4$ and the corresponding alkyne in the appropriate solvent at -50 °C was added ^{i}PrMgCl dropwise over 15 min. The resultant solution was stirred at -40 °C for the designated period of time, before cooling to -78 °C. To the cooled solution was added a solution of the aldehyde over 5 min. The mixture was warmed to -20 °C for the designated period of time, before warming to r.t. and quenching the reaction with aq. HCl (1 M). The organic layer was separated off and the aqueous phase further extracted with ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-25% ether in petrol) to provide the product as a colourless liquid.

General procedure (R): Wittig olefination protocol

To a stirred suspension of $EtPPh_3Br$ in THF (20 mL) at 0 °C was added the corresponding base. The mixture was then adjusted to the designated temperature before the addition of a solution of ketone in THF dropwise. The resultant reaction mixture was stirred at the specified temperature, monitoring reaction progress by TLC. Upon reaction completion, the mixture was warmed to r.t. and diluted with diethyl ether (20 mL) and sat. aq. NH_4Cl (20 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar. The crude product was purified by column chromatography (eluent: 0-20%, ether in petrol) to provide the product as a colourless oil.

General procedure (S): Preparation of alkyne cobalt complexes

A round bottomed flask was flame dried prior to cooling under a blanket of nitrogen. To this vessel was charged a solution of the corresponding enyne, followed by $Co_2(CO)_8$ in a single portion. The resulting mixture was stirred at r.t. monitoring reaction progress by TLC analysis. The mixture was then filtered through celite, eluting with petrol, and concentrated under reduced pressure. The crude product was purified by column chromatography (0-2% ether in petrol) to provide the complex as a deep red/brown oil.

General procedure (T): Thermal P-K reactions

A round bottomed flask was flame dried prior to cooling under a blanket of nitrogen. To this vessel was charged a solution of the corresponding enyne, followed by $Co_2(CO)_8$ as a single portion. The resulting mixture was stirred at r.t. monitoring reaction progress by TLC analysis. Upon complete complexation, the mixture was filtered through celite, eluting with petrol, and concentrated under reduced pressure. The crude product was then dissolved in DCE and heated to reflux, monitoring progress by TLC. The mixture was then cooled to r.t., filtered through celite, eluting with petrol, and concentrated under reduced pressure. The crude product was purified by column chromatography.

General procedure (U): DodSMe promoted P-K reactions

A round bottomed flask was flame dried prior to cooling under a blanket of nitrogen. To this vessel was charged a solution of the corresponding enyne, followed by $Co_2(CO)_8$ in a single portion. The resulting mixture was stirred at r.t. monitoring reaction progress by TLC analysis. Upon complete complexation, the mixture was filtered through celite, eluting with petrol ether, and concentrated under reduced pressure. The crude product was then dissolved in DCE and DodSMe was added in a single portion, before heating to reflux, monitoring progress by TLC analysis. The mixture was then cooled to r.t. filtered through celite, eluting with petrol and concentrated under reduced pressure. The crude product was purified by column chromatography.[a]

[a] If co-elution occurs between residual alkyne-cobalt complex and DodSMe, the mixed fractions are combined, concentrated under reduced pressure, and diluted with DCM (20 mL). To this was added TMANO·$2H_2O$ (20 eq.) and the resulting mixture stirred at r.t. until complete decomplexation is observed by TLC. The mixture was then filtered through celite, eluting with petrol and concentrated under reduced pressure. The enyne was purified by column chromatography.

General procedure (V): TMANO·$2H_2O$ promoted P-K reactions

A round bottomed flask was flame dried prior to cooling under a blanket of nitrogen. To this vessel was charged a solution of the corresponding enyne, followed by $Co_2(CO)_8$ as a single portion. The resulting mixture was stirred at r.t. monitoring reaction progress by TLC analysis. Upon complete complexation, the mixture was filtered through celite, eluting with

petrol, and concentrated under reduced pressure. The crude product was then dissolved in DCM and cooled to the specified reaction temperature. To the mixture was added TMANO·$2H_2O$ in a single portion and the resulting suspension was stirred at the specified reaction temperature, monitoring progress by TLC analysis. The mixture was then warmed to r.t. filtered through celite, eluting with petrol and concentrated under reduced pressure. The crude product was purified by column chromatography.

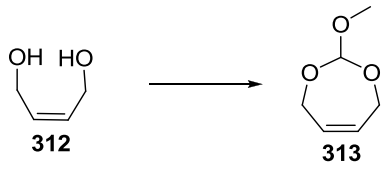
General procedure (W): microwave promoted P-K reactions

To a flame dried glass microwave tube (5 mL) was charged a solution of enyne in DCE or toluene, and $Co_2(CO)_8$. The mixture was stirred at r.t. for 1 h, before adding DodSMe in a single portion, sealing the tube and heating the mixture to 90 °C for 20 min. The reaction mixture was then heated to 90 °C for four more cycles of 20 min, before cooling back to r.t. To the resultant mixture was added silica gel (~2 g) and the mixture concentrated under reduced pressure. The crude product was purified by column chromatography.

General procedure (X): Organozinc addition of alkyne side-chain

To a stirred suspension of zinc powder in DMF (5 mL) and diethyl ether (5 mL) was added propargyl bromide **529** at r.t. and the mixture stirred for 15 min. To the mixture was added the corresponding aldehyde and the resulting suspension stirred at r.t. for 5 h. After the allotted time, the mixture was diluted with EtOAc (20 mL) and filtered. The filtrate was washed with sat. aq. NH_4Cl (2 x 10 mL) and brine (10 mL), the organic phases combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to afford an inseparable mixture of alkyne and allene products.

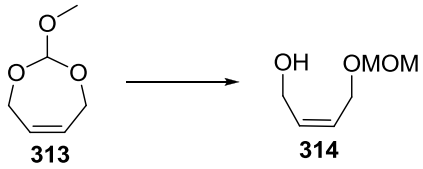
Preparation of 2-methoxy-4,7-dihydro-1,3-dioxepine, 313



Scheme 97:

To a solution of (*Z*)-but-2-ene-1,4-diol **312** (100.0 mmol, 8.8 g) in DCM (250 mL) was added *p*-TSA (1 mol%, 1.0 mmol, 172.0 mg) and trimethyl orthoformate (200.0 mmol, 21.2 g). The reaction mixture was stirred at r.t. for 1 h before the addition of Et_3N (300.0 mmol, 30.3 g). The resultant mixture was then diluted with diethyl ether and quenched with sat. aq. NH_4Cl (30 mL). The organic phase was separated off and washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to provide **313** as a colourless liquid (88%, 88.0 mmol, 11.44 g).

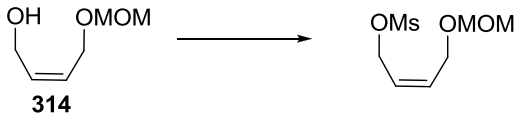
Preparation of (*Z*)-4-(methoxymethoxy)but-2-en-1-ol, 314



Scheme 97:

To a solution of **313** (50.0 mmol, 6.5 g) in toluene (100 mL) at –78 °C was added DIBAL-H (1 M in THF, 65.0 mmol, 65 mL) dropwise. Upon complete addition, the mixture was allowed to warm to r.t. and stirred for 16 h. The mixture was then cooled to 0 °C, carefully quenched with sat. aq. sodium tartrate solution (50 mL) and stirred for a further 1 h. The organic phase was separated off and washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-50% diethyl ether in petrol) to provide **314** as a colourless liquid (91%, 45.5 mmol, 6.01 g).

Preparation of (*Z*)-4-(methoxymethoxy)but-2-enyl methanesulfonate, (mesylate of 314)

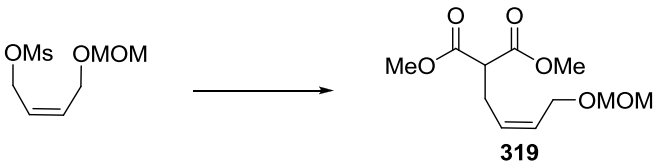


314

Scheme 98:

To a solution of **314** (40.0 mmol, 5.3 g) in DCM (50 mL) at 0 °C was added Et_3N (120.0 mmol, 12 mL). The reaction mixture was stirred at 0 °C for 15 min, before adding methanesulfonyl chloride (80.0 mmol, 9.2 g) dropwise. The mixture was stirred at 0 °C for 30 min, before adding 2 M aq. HCl (25 mL). The organic layer was separated off and further washed with 2 M aq. HCl (2 x 10 mL) and sat. aq. $NaHCO_3$ (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure, to provide the mesylate as an orange liquid (100%, 40.0 mmol, 8.40 g). The crude product was used without further purification in the next step.

Preparation of (*Z*)-dimethyl 2-(4-(methoxymethoxy)but-2-enyl)malonate, 319

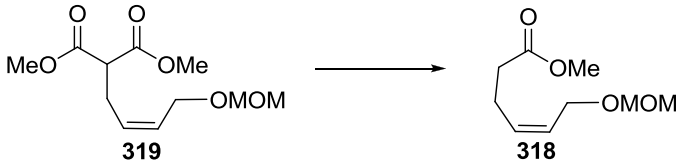


319

Scheme 98:

To a solution of dimethyl malonate (50.0 mmol, 6.6 g) in THF (100 mL) at 0 °C was added NaH (98% w/w, 50.0 mmol, 1.2 g) portionwise over 15 min. The reaction mixture was stirred at 0 °C for 15 min, before a solution of the mesylate (40.0 mmol, 8.4 g) in THF (5 mL) was added dropwise over 5 min. The reaction mixture was then stirred for an additional 8 h, allowing the temperature to rise to r.t. Upon completion, the mixture was diluted with diethyl ether and quenched with sat. aq. NH_4Cl (30 mL). The organic phase was separated off and washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-30% diethyl ether in petrol) to provide **319** as a colourless liquid (82%, 32.8 mmol, 8.08 g).

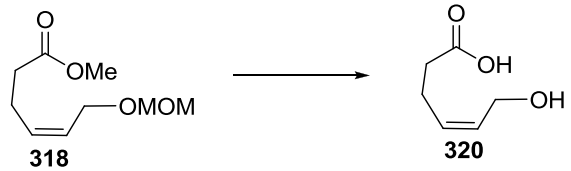
Preparation of (*Z*)-methyl 6-(methoxymethoxy)hex-4-enoate, 318



Scheme 99:

To a stirred solution of the **319** (30.0 mmol, 7.4 g) in DMF (100 mL) was added KI (90.0 mmol, 14.8 g). The mixture was heated to reflux and stirred for 12 h. The mixture was then cooled to r.t. and washed repeatedly with brine (5 x 10 mL). The aqueous layer was then extracted with diethyl ether (2 x 10 mL) and the organic layers combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-30% diethyl ether in petrol) to provide **318** as a colourless liquid (74%, 22.2 mmol, 4.18 g).

Preparation of (*Z*)-6-hydroxyhex-4-enoic acid, 320



Scheme 99:

To a stirred solution of **318** (10.1 mmol, 1.9 g) in THF (30 mL) was added 2 M aq. HCl (20 mL). The mixture was stirred at r.t. for 1 h, then partitioned between diethyl ether and H_2O. The organic layer was separated off and the aqueous layer further extracted with diethyl ether (3 x 20 mL), the organic layers combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide **320** (81%, 8.2 mmol, 1.07 g). Crude product **320** was used in the next step without further purification.

Preparation of 3,4-dihydrooxepin-2(7H)-one, 300

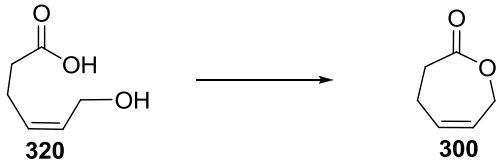


Table 6, Entry 1:

To a stirred solution of **320** (1.0 mmol, 130.0 mg) in toluene (10 mL) was added *p*-TSA (10 mol%, 0.1 mmol, 17.2 mg) and the resultant solution heated to reflux in a Dean Stark apparatus for 12 h. The mixture was then cooled to r.t., washed with sat. aq. $NaHCO_3$ (2 x 10

mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Trace amounts of product **300** were detected by ^1H NMR analysis of the crude product. The correct product mass was detected by GCMS analysis of the crude mixture, before and after concentration. A representative yield regarding the formation of **300** could not be achieved using this method, with the majority of the product lost upon concentration of the reaction mixture.

Table 6, Entry 2:

To a solution of **320** (1.0 mmol, 130.0 mg) in DCM (10 mL) at 0 °C was added DIC (1.2 mmol, 151.2 mg) portionwise and the mixture stirred for 1 h. To the mixture was added Et_3N (2.0 mmol, 202.0 mg) dropwise at 0 °C, before allowing the mixture to warm to r.t., stirring for a further 12 h. The mixture was then partitioned between H_2O (10 mL) and DCM (10 mL), the organic layer washed with sat. aq. NH_4Cl (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* at 0 ˚C, 100 mbar. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to provide **300** as a colourless liquid (81%, 0.81 mmol, 90.80 mg).

Table 6, Entry 3:

To a solution of **320** (1.0 mmol, 130.0 mg) in DCM (10 mL) at 0 °C was added DCC (1.2 mmol, 247.2 mg) portionwise and the mixture stirred for 1 h. To the mixture was added Et_3N (2.0 mmol, 202 mg) and DMAP (10 mol%, 0.1 mmol, 12.2 mg) portionwise at 0 °C, before allowing the mixture to warm to r.t., stirring for a further 12 h. The reaction mixture was then partitioned between H_2O (10 mL) and DCM (10 mL), the organic layer washed with sat. aq. NH_4Cl (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* at 0 ˚C, 100 mbar. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to provide **300** as a colourless liquid (45%, 0.45 mmol, 50.45 mg).

Table 6, Entry 4:

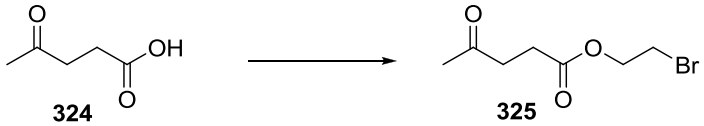
To a stirred solution of **320** (1.0 mmol, 130.0 mg) in benzene (10 mL) was added Aldrithiol (Py_2S_2) (1.5 mmol, 330.0 mg) and PPh_3 (1.5 mmol, 393.0 mg) and the resultant mixture stirred at r.t. for 2 h. The mixture was then diluted with benzene (50 mL) and added *via* syringe pump over 24 h to a 3-necked vessel containing refluxing benzene (100 mL). Upon complete addition of the solution, the reaction mixture was refluxed for a further 24 h, then cooled to r.t. The reaction mixture was then diluted with diethyl ether (30 mL) and quenched with sat. aq. $NaHCO_3$ (30 mL). The organic phase was separated off and washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* at 0 ˚C, 100 mbar. ^1H

NMR and GCMS analysis of the crude product revealed a complex mixture of compounds, amongst which product **300** was not observed.

Table 6, Entry 5:

To a solution of **320** (1.0 mmol, 130.0 mg) in DCM (10 mL) at 0 °C was added HATU (1.2 mmol, 456.0 mg) portionwise and the mixture stirred for 30 min. To the mixture was added Et_3N (2.0 mmol, 202.0 mg) dropwise at 0 °C, before allowing the mixture to rise to r.t., stirring for a further 12 h. The resultant mixture was then partitioned between H_2O (10 mL) and DCM (10 mL), the organic layer washed with sat. aq. NH_4Cl (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* at 0 ˚C, 100 mbar. The product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to provide **300** as a colourless liquid (83%, 0.83 mmol, 93.04 mg).

Preparation of 2-bromoethyl 4-oxopentanoate, 325



324 **325**

Scheme 103:

To a stirred solution of levulinic acid **324** (100.0 mmol, 11.6 g) in toluene (100 mL) was added 2-bromoethan-1-ol (200.0 mmol, 24.6 g) and *p*-TSA (5 mol%, 5.0 mmol, 860.0 mg). The resulting mixture was heated at reflux for 16 h in a Dean Stark apparatus. The mixture was then cooled to r.t. and partitioned with sat. aq. $NaHCO_3$ (2 x 10 mL). The organic phase was separated off and washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-30% diethyl ether in petrol) to provide **325** as a colourless liquid (85%, 85.0 mmol, 18.96 g).

Preparation of (2-(4-oxopentanoyloxy)ethyl)triphenylphosphonium bromide, 306

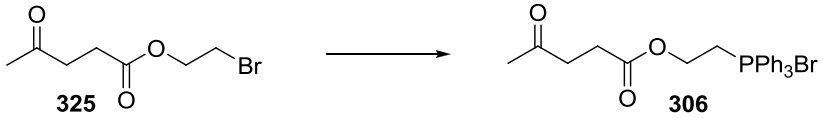


Table 7:

Following the **General Procedure (A)**, entries 1-3 are reported as (a) quantity of PPh_3, (b) quantity of **325**, (c) solvent, and (d) product yield.

Table 7, Entry 1:

(a) 1.2 mmol, 314.4 mg, (b) 1.0 mmol, 222.0 mg, (c) toluene (15 mL), and (d) **326** (15%, 0.15 mmol, 72.6 mg).

Table 7, Entry 2:

(a) 1.2 mmol, 314.4 mg, (b) 1.0 mmol, 222.0 mg, (c) MeCN (15 mL), and (d) **326** (33%, 0.33 mmol, 159.7 mg).

Table 7, Entry 3:

(a) 2.0 mmol, 524.0 mg, (b) 1.0 mmol, 222.0 mg, (c) MeCN (15 mL), and (d) **326** (81%, 0.81 mmol, 392.0 mg).

Following the **General Procedure (B)**, entries 4-6 are reported as (a) quantity of **325**, (b) quantity of PPh_3, (c) reaction temperature, (d) reaction length, and (e) yield of **326**.

Table 7, Entry 4:

(a) 1.0 mmol, 222.0 mg, (b) 2.0 mmol, 524.0 mg, (c) 80 °C, (d) 2 h, and (e) **326** (36%, 0.36 mmol, 174.2 mg).

Table 7, Entry 5:

(a) 1.0 mmol, 222.0 mg, (b) 2.0 mmol, 524.0 mg, (c) 100 °C, (d) 4 h, and (e) **326** (78%, 0.78 mmol, 377.5 mg).

Table 7, Entry 6:

(a) 1.0 mmol, 222.0 mg, (b) 2.0 mmol, 524.0 mg, (c) 110 °C, (d) 4 h, and (e) **326** (0%).

Attempted synthesis of 5-methyl-3,4-dihydrooxepin-2(7H)-one, 79

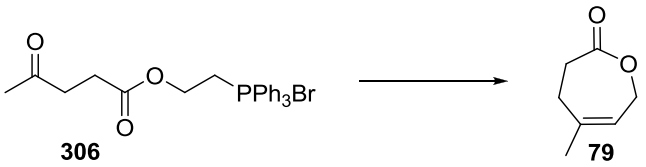


Table 8, Entry 1:

A 1 L, 2-neck, round bottomed flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. To the vessel was charged MeCN (500 mL) and Et_3N (30.0 mmol, 3.0 mL) and the resulting solution heated to reflux. To this was added a solution of **306** (0.5 mmol, 243.0 mg) in MeCN (50 mL) dropwise over 48 h *via* syringe pump. The resulting solution was refluxed for a further 168 h, before cooling to r.t. The mixture was then dried over Na_2SO_4, filtered, and concentrated *in vacuo* at 0 °C at 100 mbar, until a viscous oil. ^{1}H NMR and GCMS analysis of the crude product revealed a complex mixture of compounds amongst which product **79** was not observed.

Table 8, Entry 2:

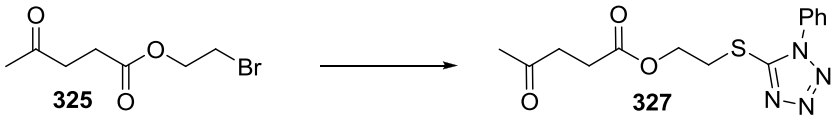
A 1 L, 2-necked, round bottomed flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. To the vessel was charged THF (500 mL) before stirring vigorously at r.t. To this was added separately and simultaneously: (a) **306** (0.5 mmol, 243.0 mg) in MeCN (20 mL) and (b) KO^{t}Bu (0.5 mmol, 56.0 mg) in THF (50 mL) dropwise *via* syringe pump over 48 h. Upon complete addition, the resultant solution was stirred at r.t. for a further 12 h, before quenching with a sat. aq. NH_4Cl (30 mL). The organic layer was separated off, the aqueous phase extracted with diethyl ether (2 x 15 mL), and the organic layers combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* at 0 °C at 100 mbar, until a viscous oil. ^{1}H NMR and GCMS analysis of the crude product revealed a complex mixture of compounds amongst which product **79** was not observed.

Table 8, Entry 3:

A 1 L, 2-necked, round bottomed flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. To the vessel was charged THF (500 mL) before cooling to 0 °C, stirring vigorously. To this was added separately and simultaneously (a) **306** (0.5 mmol, 243 mg) in THF (20 mL) and (b) ^{n}BuLi (1.43 M in hexanes, 0.55 mmol, 0.4 mL) dropwise *via* syringe pump over 36 h. Upon complete addition, the resultant solution was stirred at r.t. for a further 12 h, before quenching with a sat. aq. NH_4Cl (30 mL). The organic layer was separated off, the aqueous phase extracted with diethyl ether (2 x 15 mL), and the organic layers combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* at 0 °C at 100 mbar,

until a viscous oil. ^{1}H NMR and GCMS analysis of the crude product revealed a complex mixture of compounds amongst which product **79** was not observed.

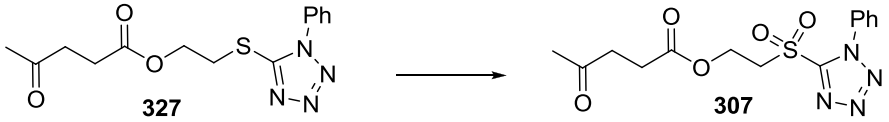
Preparation of 2-(1-phenyl-1*H*-tetrazol-5-ylthio)ethyl 4-oxopentanoate, 327



Scheme 104:

To a stirred solution of 1-phenyl-1H-tetrazole-5-thiol **326** (21.0 mmol, 3.7 g) and Et_3N (42.0 mmol, 4.2 mL) in MeCN (50 mL) at r.t., was added 2-bromoethyl 4-oxopentanoate **325** (14.0 mmol, 3.1 g) dropwise. The resulting mixture was heated to reflux for 8 h, before cooling back to r.t. The mixture was then diluted with diethyl ether (20 mL) and quenched with sat. aq. $NaHCO_3$ (30 mL). The organic phase was separated off and washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-50% diethyl ether in petrol) to provide **327** as a white solid (97%, 13.6 mmol, 4.35 g).

Preparation of 2-(1-phenyl-1H-tetrazol-5-ylsulfonyl)ethyl 4-oxopentanoate, 307



Scheme 104:

To a stirred solution of **327** (12.5 mmol, 4.0 g,) in DCM (100 mL) was added *m*CPBA (70 % w/w, 26.3 mmol, 6.5 g) and $NaHCO_3$ (37.5 mmol, 3.2 g) in a single portion. The resultant suspension was stirred at r.t. for 12 h. The mixture was then filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-50%, ethyl acetate in petrol) to provide **307** as a white solid (85%, 10.6 mmol, 3.73 g).

Attempted synthesis of 5-methyl-3,4-dihydrooxepin-2(7H)-one, 79

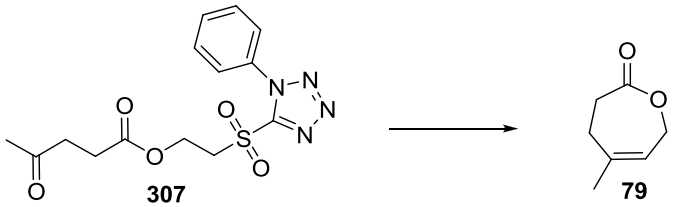
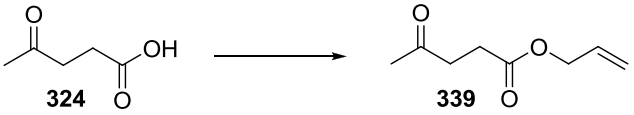


Table 9, Entry 1:
A solution of **307** (5.0 mmol, 1.8 g) in THF (12 mL) and DMF (3 mL) was added over 10 h *via* syringe pump to a suspension of Cs_2CO_3 (15.0 mmol, 4.9 g) in THF (366 mL), DMF (138 mL) and water (2.4 mL) at 70 ºC. The reaction mixture was then cooled to r.t., filtered through a pad of celite (eluting with DCM), and concentrated *in vacuo* at 0 °C at 100 mbar, until a minimum volume. ^{1}H NMR and GCMS analysis of the crude product revealed a complex mixture of compounds amongst which product **79** was not observed.

Table 9, Entry 2:
To a 1L, 3-necked, round bottomed vessel containing THF (500 mL) at -20 °C was added separately and simultaneously: (a) **307** (1.0 mmol, 352.0 mg) in THF (20 mL) and (b) ^{n}BuLi (1.43 M in hexanes, 1.0 mmol, 0.7 mL) dropwise *via* syringe pump over 10 h. Upon complete addition, the solution was warmed to r.t. and stirred for a further 12 h, before quenching with a sat. aq. NH_4Cl (30 mL). The organic layer was separated off, the aqueous phase extracted with diethyl ether (2 x 15 mL), and the organic layers combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* at 0 °C at 100 mbar, until a viscous oil. ^{1}H NMR and GCMS analysis of the crude product revealed a complex mixture of compounds amongst which product **79** was not observed.

Table 9, Entry 3:
To a 1L, 3-necked, round bottomed vessel containing THF (500 mL) at -20 °C was added separately and simultaneously: (a) **307** (1.0 mmol, 172.0 mg) in THF (50 mL) and (b) KHMDS (1 M in THF, 1.0 mmol, 1.0 mL) dropwise *via* syringe pump over 10 h. Upon complete addition, the solution was warmed to r.t. and stirred for a further 12 h, before quenching with a sat. aq. NH_4Cl (30 mL). The organic layer was separated off, the aqueous phase extracted with diethyl ether (2 x 15 mL), and the organic layers combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* at 0 °C at 100 mbar, until a viscous oil. ^{1}H NMR and GCMS analysis of the crude product revealed a complex mixture of compounds amongst which product **79** was not observed.

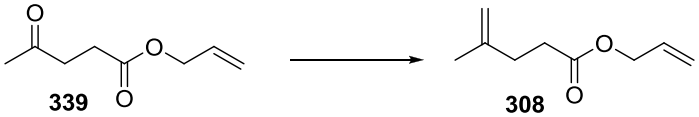
Preparation of allyl 4-oxopentanoate, 339



Scheme 110:

To a stirred solution of levulinic acid **324** (100.0 mmol, 11.6 g) in toluene (100 mL) was added allyl alcohol (200.0 mmol, 11.6 g) and *p*-TSA (5 mol%, 5.0 mmol, 860.0 mg). The resulting mixture was heated to reflux for 16 h in a Dean Stark apparatus. The mixture was then cooled to r.t., washed with sat. aq. $NaHCO_3$ (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to provide **339** as a colourless liquid (95%, 95.0 mmol, 14.82 g).

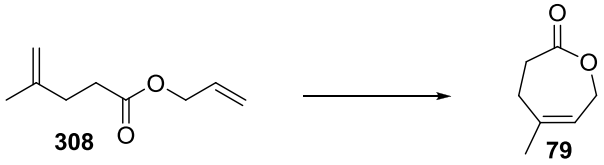
Preparation of allyl 4-methylpent-4-enoate, 308



Scheme 110:

To a stirred suspension of $MePPh_3Br$ (60.0 mmol, 21.3 g) in THF (150 mL) at r.t. was added KO^tBu (60.0 mmol, 6.7 g) in a single portion. The reaction mixture was stirred for 1 h at r.t., before the addition of **339** (50.0 mmol, 7.8 g) dropwise over 5 min. The reaction mixture was then stirred at r.t. for a further 12 h. Upon completion, the reaction mixture was diluted with diethyl ether (50 mL) and quenched with sat. aq. NH_4Cl (50 mL). The organic phase was separated off and washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-10% diethyl ether in petrol) to provide **308** as a colourless liquid (91%, 45.5 mmol, 7.01 g).

Attempted synthesis of 5-methyl-3,4-dihydrooxepin-2(7H)-one, 79



Following **General Procedure (C)**, entries 1-4 are reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of $Ti(O^iPr)_4$, (d) quantity of **308**, and (e) yield of product/s.

Table 10, Entry 1:

(a) DCM (10 mL), (b) 5 mol%, 0.05 mmol, 42.0 mg in DCM (2 mL), (c) 0 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%) and **340** (67%, 0.34 mmol, 93.8 mg).

Table 10, Entry 2:

(a) DCM (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%) and **340** (63%, 0.32 mmol, 88.2 mg).

Table 10, Entry 3:

(a) DCM (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0.3 mmol, 85.2 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%), **340** (62%, 0.31 mmol, 86.8 mg) and **341** (26%, 0.26 mmol, 40.6 mg).

Table 10, Entry 4:

(a) DCM (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 3.0 mmol, 852.0 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%), **340** (34%, 0.17 mmol, 47.6 mg) and **341** (57%, 0.57 mmol, 88.9 mg).

Following **General Procedure (D)**, entries 5-7 are reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of $Ti(O^iPr)_4$, (d) quantity of **308**, and (e) yield of product/s.

Table 10, Entry 5:

(a) DCM (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%) and **340** (62%, 0.31 mmol, 86.8 mg).

Table 10, Entry 6:

(a) DCM (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0.3 mmol, 85.2 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%), **340** (55%, 0.28 mmol, 77.0 mg) and **341** (28%, 0.28 mmol, 43.7 mg).

Table 10, Entry 7:

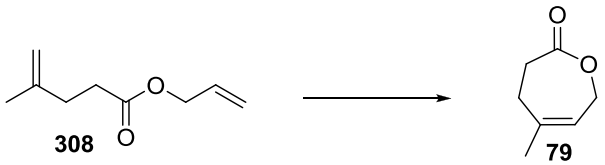
(a) DCM (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 3.0 mmol, 852.0 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%), **340** (21%, 0.11 mmol, 29.4 mg) and **341** (71%, 0.71 mmol, 110.8 mg).

Following **General Procedure (E)**, entry 8 is reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of **308**, and (d) yield of product/s.

Table 10, Entry 8:

(a) DCM (500 mL), (b) 4 x (5 mol%, 0.05 mmol, 42.0 mg in DCM (2 mL)), (c) 1.0 mmol, 154.0 mg, and (d) **79** (0%), **340** (58%, 0.29 mmol, 81.2 mg).

Attempted synthesis of 5-methyl-3,4-dihydrooxepin-2(7H)-one, 79



Following the **General Procedure (C)**, entries 1-4 are reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of $Ti(O^iPr)_4$, (d) quantity of **308**, and (e) yield of product/s.

Table 11, Entry 1:

(a) toluene (10 mL), (b) 5 mol%, 0.05 mmol, 42.0 mg in DCM (2 mL), (c) 0 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%) and **340** (58%, 0.29 mmol, 81.2 mg).

Table 11, Entry 2:

(a) toluene (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0.0 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%) and **340** (52%, 0.26 mmol, 77.0 mg).

Table 11, Entry 3:

(a) toluene (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0.3 mmol, 85.2 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%), **340** (57%, 0.29 mmol, 79.8 mg) and **341** (23%, 0.23 mmol, 35.9 mg).

Table 11, Entry 4:

(a) toluene (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 3.0 mmol, 852.0 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%), **340** (22%, 0.11 mmol, 30.8 mg) and **341** (56%, 0.56 mmol, 87.4 mg).

Following the **General Procedure (D)**, entries 5-7 are reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of $Ti(O^iPr)_4$, (d) quantity of **308**, and (e) yield of product/s.

Table 11, Entry 5:

(a) toluene (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%) and **340** (54%, 0.27 mmol, 75.6 mg).

Table 11, Entry 6:

(a) toluene (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0.3 mmol, 85.2 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%), **340** (56%, 0.28 mmol, 78.4 mg) and **341** (28%, 0.28 mmol, 43.7 mg).

Table 11, Entry 7:

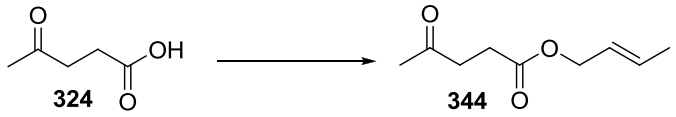
(a) toluene (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 3.0 mmol, 852.0 mg, (d) 1.0 mmol, 154.0 mg, and (e) **79** (0%), **340** (9%, 0.05 mmol, 12.6 mg) and **341** (88%, 0.88 mmol, 137.3 mg).

Following **General Procedure (E)**, entry 8 is reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of **308**, and (d) yield of product/s.

Table 11, Entry 8:

(a) toluene (500 mL), (b) 4 x (5 mol%, 0.05 mmol, 42.0 mg in DCM (2 mL)), (c) 1.0 mmol, 154.0 mg, and (d) **79** (0%), **340** (59%, 0.30 mmol, 82.6 mg).

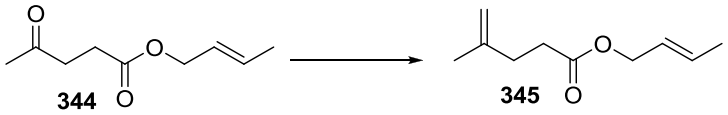
Preparation of (*E*)-but-2-enyl 4-oxopentanoate, 344



Scheme 112:

To a stirred solution of levulinic acid **324** (100.0 mmol, 11.6 g) in toluene (100 mL) was added crotyl alcohol (200.0 mmol, 14.4 g) and *p*-TSA (5 mol%, 5.0 mmol, 860.0 mg). The resulting mixture was heated to reflux for 16 h in a Dean Stark apparatus. The mixture was then cooled to r.t., washed with sat. aq. $NaHCO_3$ (2 x 10 mL), and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to provide **344** as a colourless liquid (91%, 91.0 mmol, 15.47 g).

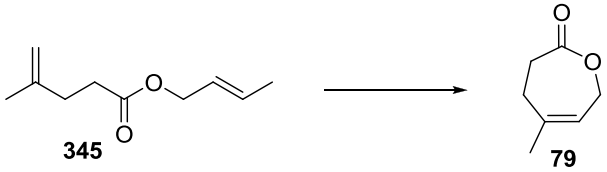
Preparation of (*E*)-but-2-enyl 4-methylpent-4-enoate, 345



Scheme 112:

To a stirred suspension of $MePPh_3Br$ (60.0 mmol, 21.3 g) in THF (150 mL) at r.t. was added KO^tBu (60.0 mmol, 6.7 g) in a single portion. The reaction mixture was stirred for 1 h at r.t., before the addition of **344** (50.0 mmol, 8.5 g) dropwise over 5 min. The mixture was then stirred at r.t. for a further 12 h. Upon completion, the reaction mixture was diluted with diethyl ether (50 mL) and quenched with sat. aq. NH_4Cl (50 mL). The organic phase was separated off and washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-10% diethyl ether in petrol) to provide **345** as a colourless liquid (86%, 43.0 mmol, 7.22 g).

Attempted synthesis of 5-methyl-3,4-dihydrooxepin-2(7H)-one, 79



Following the **General Procedure (C)**, entries 1-3 are reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of $Ti(O^iPr)_4$, (d) quantity of **345**, and (e) yield of product/s.

Table 12, Entry 1:

(a) DCM (10 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%) and **340** (59%, 0.30 mmol, 82.6 mg).

Table 12, Entry 2:

(a) DCM (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0.3 mmol, 85.2 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%), **340** (61%, 0.31 mmol, 85.4 mg) and **341** (27%, 0.27 mmol, 42.1 mg).

Table 12, Entry 3:

(a) DCM (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 3.0 mmol, 852.0 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%), **340** (32%, 0.16 mmol, 44.8 mg) and **341** (55%, 0.55 mmol, 85.8 mg).

Following the **General Procedure (D)**, entries 4-6 are reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of $Ti(O^iPr)_4$, (d) quantity of **345**, and (e) yield of product/s.

Table 12, Entry 4:

(a) DCM (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%) and **340** (63%, 0.32 mmol, 88.2 mg).

Table 12, Entry 5:

(a) DCM (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0.3 mmol, 85.2 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%), **340** (57%, 0.29 mmol, 79.8 mg) and **341** (28%, 0.28 mmol, 43.7 mg).

Table 12, Entry 6:

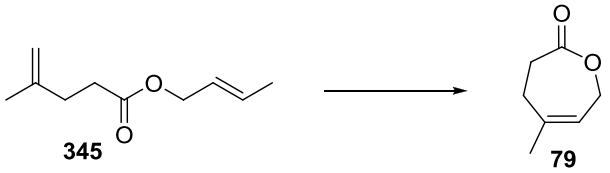
(a) DCM (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 3.0 mmol, 852.0 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%), **340** (21%, 0.11 mmol, 29.4 mg) and **341** (69%, 0.69 mmol, 107.6 mg).

Following **General Procedure (E)**, entry 8 is reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of **345**, and (d) yield of product/s.

Table 12, Entry 7:

(a) DCM (500 mL), (b) 4 x (5 mol%, 0.05 mmol, 42.0 mg in DCM (2 mL)), (c) 1.0 mmol, 168.0 mg, and (d) **79** (0%) and **340** (61%, 0.32 mmol, 85.4 mg).

Attempted synthesis of 5-methyl-3,4-dihydrooxepin-2(7H)-one, 79



Following the **General Procedure (C)**, entries 1-3 are reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of $Ti(O^iPr)_4$, (d) quantity of **345**, and (e) yield of product/s.

Table 13, Entry 1:

(a) toluene (10 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%) and **340** (54%, 0.27 mmol, 75.6 mg).

Table 13, Entry 2:

(a) toluene (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0.3 mmol, 85.2 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%), **340** (57%, 0.29 mmol, 79.8 mg) and **341** (25%, 0.25 mmol, 39.0 mg).

Table 13, Entry 3:

(a) toluene (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 3.0 mmol, 852.0 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%), **340** (26%, 0.13 mmol, 36.4 mg) and **341** (62%, 0.62 mmol, 96.7 mg).

Following the **General Procedure (D)**, entries 4-6 are reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of $Ti(O^iPr)_4$, (d) quantity of **345**, and (e) yield of product/s.

Table 13, Entry 4:

(a) toluene (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%) and **340** (57%, 0.29 mmol, 79.8 mg).

Table 13, Entry 5:

(a) toluene (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 0.3 mmol, 85.2 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%), **340** (53%, 0.27 mmol, 74.2 mg) and **341** (29%, 0.29 mmol, 45.2 mg).

Table 13, Entry 6:

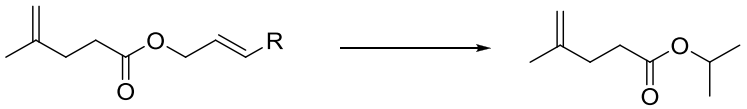
(a) toluene (50 mL), (b) 10 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL), (c) 3.0 mmol, 852.0 mg, (d) 1.0 mmol, 168.0 mg, and (e) **79** (0%), **340** (11%, 0.06 mmol, 15.4 mg) and **341** (86%, 0.86 mmol, 134.2 mg).

Following **General Procedure (E)**, entry 8 is reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of **345**, and (d) yield of product/s.

Table 13, Entry 7:

(a) toluene (500 mL), (b) 4 x (5 mol%, 0.05 mmol, 42.0 mg in DCM (2 mL)), (c) 1.0 mmol, 168.0 mg, and (d) **79** (0%) and **340** (61%, 0.31 mmol, 85.4 mg).

Preparation of isopropyl 4-methylpent-4-enoate, 341



308, R = H
345, R = CH_3

341

Following the **General Procedure (F)**, entries 1-3 are reported as (a) quantity of diene, (b) volume of solvent, (c) quantity of $Ti(O^iPr)_4$, and (d) product yield.

Table 14, Entry 1:

(a) **308** (1.0 mmol, 154.0 mg), (b) DCM (10 mL), (c) 3.0 mmol, 852.0 mg, and (d) **341** (28%, 0.28 mmol, 43.7 mg).

Table 14, Entry 2:

(a**) 308** (1.0 mmol, 154.0 mg), (b) toluene (10 mL), (c) 3.0 mmol, 852.0 mg, and (d) **341** (41%, 0.41 mmol, 64.0 mg).

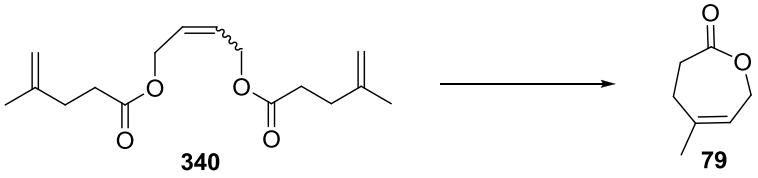
Table 14, Entry 3:

(a) **345** (1.0 mmol, 168.0 mg), (b) DCM (10 mL), (c) 3.0 mmol, 852.0 mg, and (d) **341** (27%, 0.27 mmol, 42.1 mg).

Table 14, Entry 4:

(a) 345 (1.0 mmol, 168.0 mg), (b) toluene (10 mL), (c) 3.0 mmol, 852.0 mg, and (d) **341** (45%, 0.45 mmol, 70.2 mg).

Attempted synthesis of 5-methyl-3,4-dihydrooxepin-2(7H)-one, 7



340 **79**

Following the **General Procedure (E)**, entries 1-4 are reported as (a) quantity of **340**, (b) volume of solvent, (c) quantity of Grubbs II, (d) reaction length, and (e) yield of product/s.

In the case of Entries 2 and 4, the reaction length described in the general procedure was extended to 48 h.

Table 15, Entry 1:

(a) **340** (1.0 mmol, 280.0 mg), (b) DCM (50 mL), (c) 4 x (5 mol%, 0.05 mmol, 42.0 mg in DCM (2 mL)), (d) 24 h, and (e) **79** (0%), **340** (100%, 1.0 mmol, 280.0 mg).

Table 15, Entry 2:

(a) **340** (1.0 mmol, 280.0 mg), (b) DCM (50 mL), (c) 4 x (5 mol%, 0.05 mmol, 42.0 mg in DCM (2 mL)), (d) 48 h, and (e) **79** (0%), **340** (100%, 1.0 mmol, 280.0 mg).

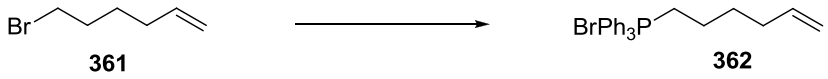
Table 15, Entry 3:

(a) **340** (1.0 mmol, 280.0 mg), (b) toluene (50 mL), (c) 4 x (5 mol%, 0.05 mmol, 42.0 mg in DCM (2 mL)), (d) 24 h, and (e) **79** (0%), **340** (100%, 1.0 mmol, 280.0 mg).

Table 15, Entry 4:

(a) **340** (1.0 mmol, 280.0 mg), (b) toluene (50 mL), (c) 4 x (5 mol%, 0.05 mmol, 42.0 mg in DCM (2 mL)), (d) 48 h, and (e) **79** (0%), **340** (100%, 1.0 mmol, 280.0 mg).

Preparation of 5-methyl-3,4-dihydrooxepin-2(7*H*)-one, 362



361 **362**

Following the **General Procedure (A)**, entries 1-3 are reported as (a) quantity of PPh_3, (b) quantity of **361**, (c) solvent, and (d) product yield.

Table 16, Entry 1:

(a) 11.0 mmol, 2.88 g, (b) 10.0 mmol, 1.62 g, (c) MeCN (25 mL), and (d) **362** (84%, 8.4 mmol, 3.57 g).

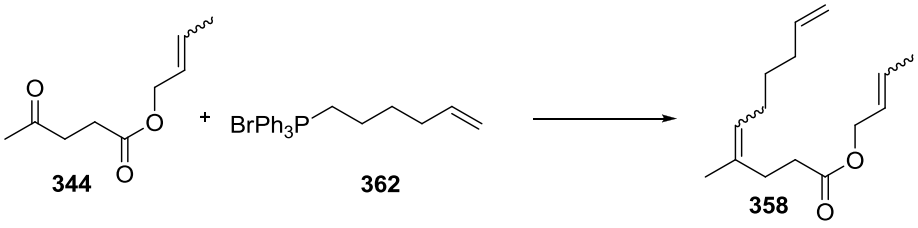
Table 16, Entry 2:

(a) 15.0 mmol, 3.93 g, (b) 10.0 mmol, 1.62 g, (c) MeCN (25 mL), and (d) **362** (93%, 9.3 mmol, 3.95 g).

Table 16, Entry 3:

(a) 20.0 mmol, 5.24 g, (b) 10.0 mmol, 1.62 g, (c) MeCN (25 mL), and (d) **262** (99%, 9.9 mmol, 4.21 g).

Preparation of but-2-enyl 4-methyldeca-4,9-dienoate, 358



344 **362** **358**

Following the **General Procedure (G)**, entries 1-3 are reported as (a) quantity of phosphonium salt **362**, (b) volume of solvent, (c) quantity of KO^tBu, (d) quantity of **344**, and (e) product yield.

Table 17, Entry 1:

(a) 11.0 mmol, 4.99 g, (b) THF (100 mL), (c) 11.0 mmol, 1.23 g, (d) 10.0 mmol, 1.70 g, and (e) **358** (43%, 4.3 mmol, 1.01 g).

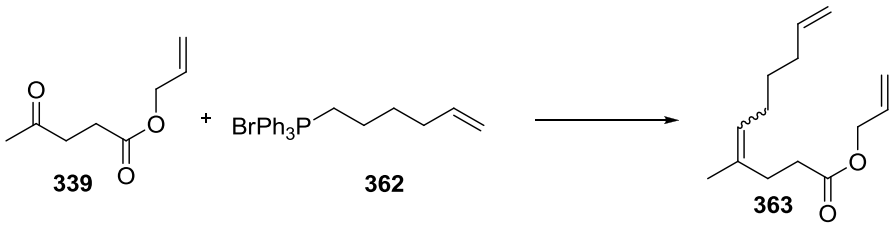
Table 17, Entry 2:

(a) 15.0 mmol, 6.81 g, (b) THF (100 mL), (c) 15.0 mmol, 1.68 g, (d) 10.0 mmol, 1.70 g, and (e) **358** (56%, 5.6 mmol, 1.32 g).

Table 17, Entry 3:

(a) 20.0 mmol, 8.48 g, (b) THF (100 mL), (c) 20.0 mmol, 2.25 g, (d) 10.0 mmol, 1.70 g, and (e) **358** (68%, 6.8 mmol, 1.60 g).

Preparation of allyl 4-methyldeca-4,9-dienoate, 363

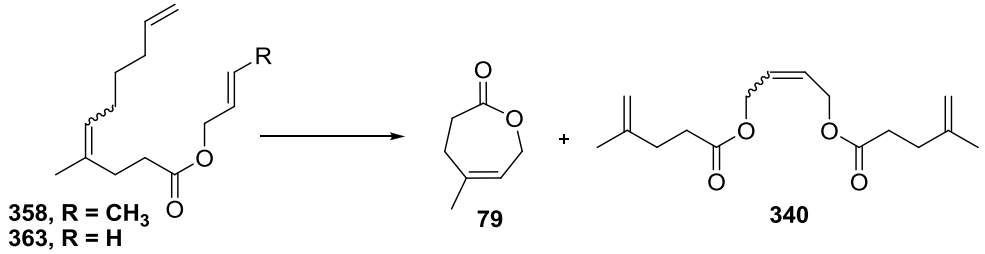


Following the **General Procedure (G)**, **Scheme 118** is reported as (a) quantity of phosphonium salt **362**, (b) volume of solvent, (c) quantity of KO^{t}Bu, (d) quantity of **339**, and (e) product yield.

Scheme 118:

(a) 20.0 mmol, 8.48 g, (b) THF (100 mL), (c) 20.0 mmol, 2.24 g, (d) 10.0 mmol, 1.56 g, and (e) **363** (63%, 6.3 mmol, 1.40 g).

Attempted synthesis of 5-methyl-3,4-dihydrooxepin-2(7H)-one, 79



Following the **General Procedure (E)**, entries 1 and 2 are reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of triene **358** or **363**, and (d) yield of product/s.

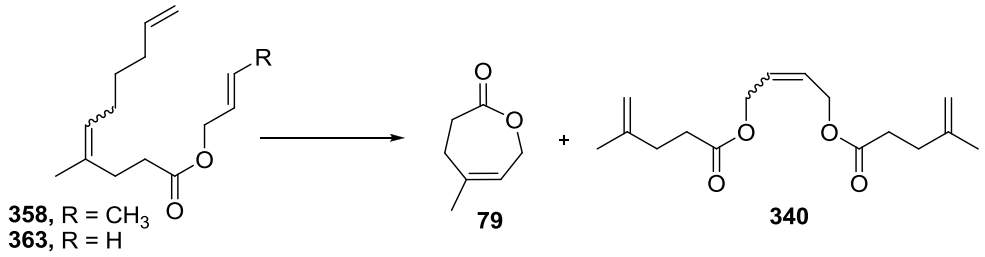
Table 18, Entry 1:

(a) DCM (100 mL), (b) 4 x (5 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL)), (c) **358** (1.0 mmol, 236.0 mg), and (d) **79** (0%) and **340** (58%, 0.29 mmol, 81.2 mg).

Table 18, Entry 2:

(a) DCM (100 mL), (b) 4 x (5 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL)), (c) 0 mg, (d) **363** (1.0 mmol, 222.0 mg), and (e) **79** (0%) and **340** (56%, 0.28 mmol, 78.4 mg).

Attempted synthesis of 5-methyl-3,4-dihydrooxepin-2(7H)-one, 79



Following the **General Procedure (H)**, entries 1 and 2 are reported as (a) volume of solvent, (b) quantity of Grubbs II catalyst, (c) quantity of triene **358** or **363**, and (d) yield of product/s.

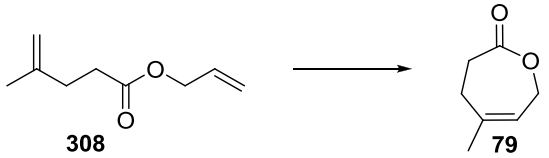
Table 19, Entry 1:

(a) DCM (100 mL), (b) 5 x (5 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL)), (c) **35**8 (1.0 mmol, 236.0 mg), and (d) **79** (0%) and **340** (41%, 0.21 mmol, 57.4 mg).

Table 19, Entry 2:

(a) DCM (100 mL), (b) 5 x (5 mol%, 0.1 mmol, 84.0 mg in DCM (2 mL)), (c) **363** (1.0 mmol, 222.0 mg), and (d) **79** (0%) and **340** (43%, 0.22 mmol, 60.2 mg).

Attempted synthesis of 5-methyl-3,4-dihydrooxepin-2(7H)-one, 79

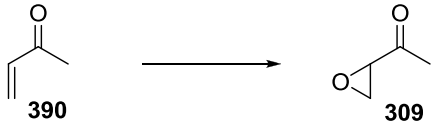


Scheme 121:

A 50 mL Schlenk tube was flame dried under vacuum prior to cooling under a blanket of nitrogen. To the vessel was charged a solution of 2,6-diphenylphenol (19.9 mmol, 4.9 g) in DCM (25 mL). To the stirred solution was added $AlMe_3$ (2 M solution in toluene, 6.6 mmol, 3.3 mL) dropwise over 15 min. Following complete addition, the reaction mixture was stirred at r.t. for 1 h, prior to removal of the solvent *in vacuo*, which afforded a yellow solid (ATPH) (95%, 6.27 mmol, 4.78g). The crude ATPH product was used without further purification in the next step.

ATPH (2.0 mmol, 1.53 g) was weighed out into a separate schlenk tube and dissolved in dry DCM (90 mL). To this was added **308** (1.9 mmol, 293.0 mg) and the resultant solution stirred at r.t. for 15 min. The vessel was then charged with a solution of Grubbs II catalyst (10 mol%, 0.2 mmol, 170.0 mg) in DCM (10 mL) and the reaction mixture heated to reflux for 24 h. The solution was then cooled to r.t., before adding silica gel (10.0 g) and diethyl ether (10 mL). The reaction mixture was then stirred for 30 min before opening the vessel to the air for 4 h. Following this, the mixture was filtered through celite, eluting with diethyl ether (3 x 10 mL) and the resulting solution concentrated under reduced pressure at 0 °C at 100 mbar. The crude product was purified by column chromatography (eluent: 0-10% diethyl ether in petrol) to provide acyclic dimer, **340** (47%, 0.45 mmol, 126.0 mg). ^{1}H NMR and GCMS analysis of the crude product indicated that product **79** was not present in the reaction mixture.

Preparation of 1-(oxiran-2-yl)ethanone, 309

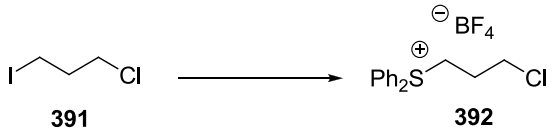


Scheme 127:

To a stirred solution of $NaHCO_3$ (400.0 mmol, 33.6 g) and H_2O_2 (30% w/w in H_2O, 600.0 mmol, 60 ml) in H_2O (500 mL) and MeCN (1 L) at 0 ^oC was added methyl vinyl ketone **390** (200.0 mmol, 14.0 g) dropwise. The resulting solution was then stirred for a further 24 h, allowing the temperature to rise to r.t. The mixture was then diluted with water (400 mL) and

$CHCl_3$ (300 mL), the organic phase separated off and the aqueous phase further extracted with $CHCl_3$ (5 x 100 mL). The organic phases were then combined, dried over Na_2SO_4, filtered, concentrated and purified by distillation (80 ^oC, 130 mbar) to isolate **309** as a colourless liquid (78%, 156.0 mmol, 13.42 g).

Preparation of (3-chloropropyl)diphenylsulfonium tetrafluoroborate, 392

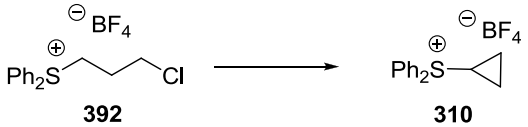


391 392

Scheme 128:

To a stirred solution of diphenyl sulfide (50.0 mmol, 11.2 g) in $MeNO_2$ (50 mL) was added 1-chloro-3-iodopropane **391** (150.0 mmol, 30.6 g) and the mixture shielded from light. To this was added $AgBF_4$ (40.0 mmol, 7.8 g) in a single portion and the mixture stirred at r.t. under nitrogen for 16 h. Initially, the temperature increased to ~40 ^oC, and then gradually fell to r.t., no external cooling required. The mixture was then diluted with DCM (50 mL) and filtered through celite. The solid residue was washed with DCM (3 x 10 mL), the organic phases combined and concentrated under reduced pressure until a solid appeared. To the suspension was added diethyl ether (100 mL) to precipitate the solid. The crude product was filtered, washed with diethyl ether (2 x 10 mL) and dried under reduced pressure. The resultant product was purified by recrystallisation with hot ethanol to provide **392** as a white solid (89%, 35.6 mmol, 12.48 g).

Preparation of cyclopropyldiphenylsulfonium tetrafluoroborate, 310

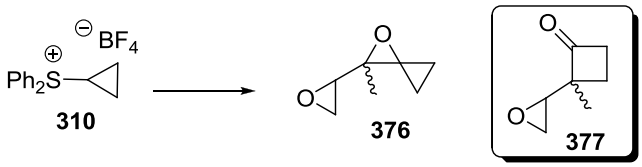


392 310

Scheme 128:

To a suspension of **392** (35.0 mmol, 12.3 g) in THF (50 mL) was added NaH (98% w/w, 36.0 mmol, 881.6 mg) at r.t., portion-wise. The resulting mixture was stirred at r.t. for 24 h. To this were added aq. HBF_4 (48% w/w, 10 mL), $NaBF_4$ (50.0 mmol, 5.5 g) and H_2O (40 mL) sequentially at r.t. To the mixture was added DCM (20 mL), the organic layer separated off and the aqueous layer further extracted with DCM (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by recrystallisation with hot ethanol to provide **310** as a white solid (88%, 30.8 mmol, 9.67 g).

Attempted synthesis of 2-methyl-2-(oxiran-2-yl)-1-oxaspiro[2.2]pentane, 376

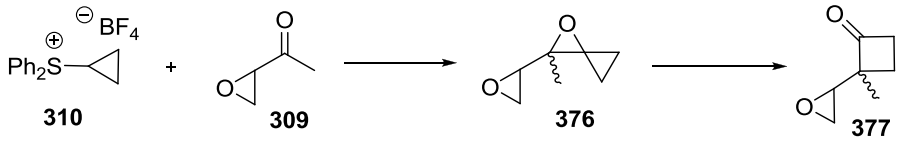


Scheme 129:

To a stirred suspension of **310** (5.0 mmol, 1.6 g) in DME (30 mL) at -40 °C was added dimsyl sodium (1 M in DMSO, 5.0 mmol, 5 mL) dropwise over 5 min. During the addition **310** dissolved, resulting in a bright yellow solution. After 5 min, **309** (5.0 mmol, 430.0 mg) was added dropwise, stirring at -40 °C for a further 15 min. The mixture was then warmed to r.t. over 60 min, before quenching with H_2O (30 mL). The reaction mixture was extracted with diethyl ether (50 mL) and the aqueous phase further extracted with diethyl ether (5 x 10 mL). The organic phases were combined and further washed with brine (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to provide **377** as a colourless liquid (3:2 mixture of diastereoisomers). In all cases no **376** was isolated. Representative yields proved variable with 5% (0.25 mmol, 31.6 mg) to 25% (1.25 mmol, 157.8 mg) of **377** isolated upon repeat experiments.

^{1}H NMR analysis of the crude product identified the correct formation of **376** as a 1:1 mixture of diastereoisomers.

Preparation of 2-methyl-2-(oxiran-2-yl)cyclobutanone, 377

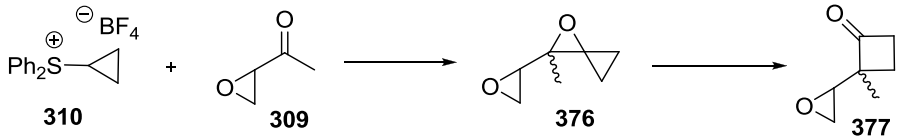


Preliminary attempts:

To a stirred suspension of **310** (5.0 mmol, 1.6 g) in DME (20 mL) at -40 °C was added dimsyl sodium (1 M in DMSO, 5.0 mmol, 5 mL) dropwise, by syringe over 5 min. During the addition **310** dissolved, becoming a bright yellow solution. After 5 min, **309** (5.0 mmol, 430.0 mg) was added dropwise, stirring at -40 °C for a further 15 min. The mixture was then warmed to r.t. over 60 min, before quenching with H_2O (30 mL). The reaction mixture was extracted with diethyl ether (50 mL) and the aqueous phase further extracted with diethyl ether (5 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure until approximately 5 mL. The mixture was then diluted with benzene (10 mL) and $LiBF_4$ (10.0 mmol, 940.0 mg) was added in a single portion. The resultant mixture was strirred at r.t. for 36-48 h (confirming complete conversion by ^{1}H

NMR). Upon completion, the mixture was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to provide **377** as a colourless liquid (3:2 mixture of diastereoisomers). Representative yields proved variable with 25% (1.25 mmol, 157.8 mg) to 45% (2.25 mmol, 283.5 mg) of **377** isolated upon repeat experiments.

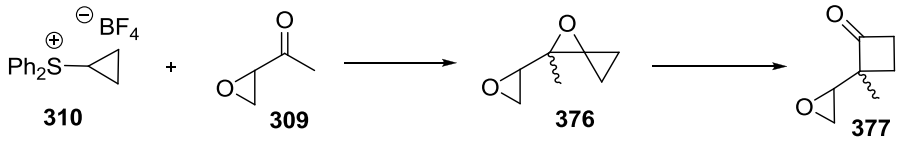
Preliminary investigations towards the preparation of 377



Scheme 131:

To a stirred suspension of **310** (5.0 mmol, 1.6 g) and **309** (5.0 mmol, 430.0 mg) in DMSO (10 mL) at r.t. was added powdered KOH (10.0 mmol, 560 mg) in a single portion. The mixture was stirred for 4 h at r.t., before partitioning the mixture between diethyl ether (20 mL) and H_2O (10 mL). The aqueous phase was further extracted with diethyl ether (3 x 10 mL), the organic phases combined and washed with brine (3 x 10 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure until approximately 5 mL. The mixture was then diluted with benzene (10 mL) and $LiBF_4$ (10.0 mmol, 940.0 mg) was added in a single portion. The resultant mixture was strirred at r.t. for 36-48 h (confirming complete conversion by ^1H NMR). Upon completion, the mixture was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to provide **377** as a colourless liquid (3:2 mixture of diastereoisomers). Representative yields proved variable with 30% (1.5 mmol, 189.6 mg) to 45% (2.25 mmol, 283.5 mg) of **377** isolated upon repeat experiments.

Preparation of 2-methyl-2-(oxiran-2-yl)cyclobutanone, 377

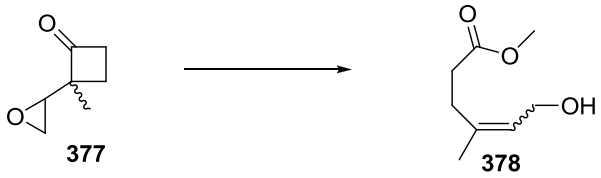


Scheme 131:

To a stirred suspension of **310** (5.0 mmol, 1.6 g) and **309** (5.0 mmol, 430.0 mg) in DMSO (10 mL) at r.t. was added powdered KOH (10.0 mmol, 560 mg) in a single portion. The mixture was stirred at r.t. for 4 h, before extracting with hexane (3 x 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure until approximately 5 mL. The mixture was then diluted with benzene (10 mL) and $LiBF_4$ (10.0

mmol, 940.0 mg) was added in a single portion. The resultant mixture was strirred at r.t. for 36-48 h (confirming complete conversion by ^{1}H NMR). Upon completion, the mixture was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to provide **377** (55%, 2.75 mmol, 346.5 mg) as a colourless liquid (3:2 mixture of diastereoisomers).

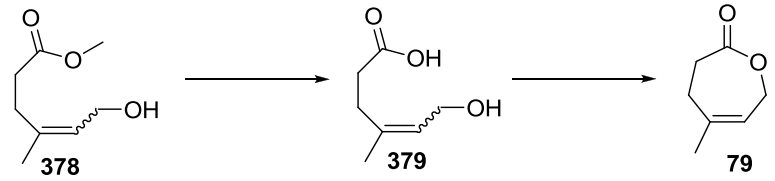
Preparation of methyl 6-hydroxy-4-methylhex-4-enoate, 378



Scheme 132:

To a stirred solution of **377** (2.0 mmol, 252 mg) in MeOH (15 mL) at r.t. was added a solution of sodium methoxide (1 M in MeOH, 4.0 mmol, 4 mL). The mixture was stirred at r.t. for 30 min, before diluting with H_2O (30 mL) and CCl_4 (25 mL). The organic layer was separated off and the aqueous layer further extracted with CCl_4 (2 x 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to provide **378** (88%, 1.76 mmol, 278.1 mg) as a colourless liquid (3:2, *Z*:*E* mixture of geometric isomers).

Preparation of 5-methyl-3,4-dihydrooxepin-2(7H)-one, 79



Preparation of crude 379:

To a stirred solution of **378** (2.0 mmol, 316.0 mg) in THF (10 mL) was added 1 M aq. LiOH (5 mL). The mixture was stirred at r.t. for 1 h, then partitioned between diethyl ether (20 mL) and H_2O (10 mL) and the aqueous layer acidified to pH 1 with 2 M aq. HCl (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide **379** as a colourless oil. The crude product was used without further purification in the next step.

Table 20, Entry 1:

A 250 mL round bottomed flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. To this was charged **379** (1.0 mmol, 144 mg) and PPh_3 (1.5 mmol, 393.0 mg) in THF (200 mL) at r.t. To the stirred mixture was added a solution of diethyl azodicarboxylate (1.5 mmol, 261.0 mg) in THF (25 mL) *via* syringe pump over 12 h at r.t. The resulting solution was then refluxed for a further 12 h, before cooling to r.t. and partitioning the mixture between sat. aq. NH_4Cl. The organic phase was further washed with brine (2 x 10 mL), the organic phases combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 ˚C, 100 mbar. ^1H NMR and GCMS analysis of the crude product revealed a complex mixture of compounds amongst which product **79** was not observed.

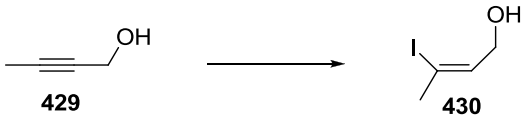
Table 20, Entry 2:

A 25 mL round bottomed flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. To the vessel was charged a solution of **379** (1.0 mmol, 144.0 mg) in DCM (10 mL), followed by DIC (1.1 mmol, 138.0 mg) dropwise over 5 min and the reaction mixture stirred at room temperature for 15 min. To this was added triethylamine (2.2 mmol, 222.0 mg) and the reaction stirred at r.t., for 12 h. The reaction mixture was then quenched with brine (10 mL) and the product extracted with DCM (2 x 10 mL). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 ˚C, 100 mbar. Product purification was achieved by column chromatography (eluent: 0-25% diethyl ether in petrol) to provide **79** (36%, 0.36 mmol, 45.3 mg) as a colourless oil.

Table 20, Entry 3:

A 25 mL round bottomed flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. To the vessel was charged a solution of **379** (1.0 mmol, 144.0 mg) in DCM (10 mL) followed by HATU (1.1 mmol, 418.0 mg) in a single portion and the reaction mixture stirred at r.t. for 15 min. To this was added triethylamine (2.2 mmol, 222.0 mg) and the reaction stirred at r.t. for 12 h. The reaction mixture was then quenched with brine (10 mL) and the product extracted with DCM (2 x 10 mL). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 ˚C, 100 mbar. Product purification was achieved by column chromatography (eluent: 0-25% diethyl ether in petrol) to provide **79** (43%, 0.43 mmol, 54.2 mg) as a colourless oil.

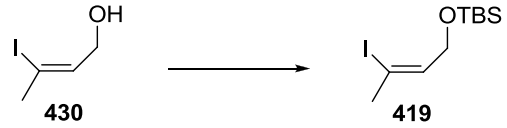
Preparation of (*Z*)-3-iodobut-2-en-1-ol, 430



Scheme 144:

To a stirred solution of 2-butyn-1-ol **429** (3.6 mmol, 250.0 mg) in dry ether (20 mL) at -78 °C, was added RED AL© (65 % w/w, 5.4 mmol, 1.7 mL) and the solution slowly allowed to rise to r.t. over 4 h. The mixture was then stirred at r.t. for a further 12 h, forming a white suspension. The suspension was then cooled to 0 °C before adding EtOAc (5 ml) and the mixture stirred at 0 °C for 30 min. The resultant solution was then cooled to -78 °C and quenched with iodine (11.1 mmol, 2.8 g). Following the addition of iodine the reaction mixture was heated to r.t. over 30 min, then stirred for a further 2 h. the reaction mixture was then diluted with diethyl ether (20 mL) and partitioned with H_2O (20 mL). The organic layer was separated off and washed with sat. aq. sodium thiosulfate (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to reveal a yellow oil. The crude product was purified by column chromatography (eluent: 0-25% diethyl ether in petrol), to isolate **430** as a colourless oil (95%, 3.42 mmol, 677.2 mg).

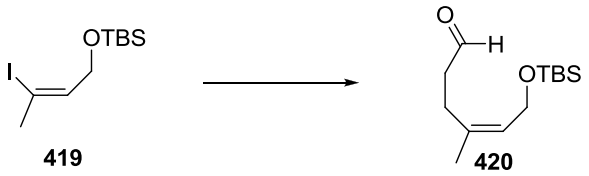
Preparation of (*Z*)-tert-butyl(3-iodobut-2-enyloxy)dimethylsilane, 419



Scheme 144:

To a stirred solution of (*Z*)-3-iodobut-2-en-1-ol **430** (5.0 mmol, 1.0 g) in dry DCM (30 mL) was added TBDMSCl (7.5 mmol, 1.13 g), DMAP (1.0 mmol, 122.0 mg) and Et_3N (15.0 mmol, 1.5 mL) and the reaction stirred at r.t. for 1 h. The reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL), the organic layer separated off and washed successively with sat. aq. NH_4Cl (3 x 10 mL) and brine (2 x 10 mL). The organic layers were then combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Product purification was achieved by column chromatography (eluent: 0-5% diethyl ether in petrol) to provide **419** as a colourless oil (96%, 4.8 mmol, 1.5 g).

Preparation of (*Z*)-6-(tert-butyldimethylsilyloxy)-4-methylhex-4-enal, 420



Following the **General Procedure (I)**, entries 1-4 are reported as (a) quantity of **419**, (b) quantity of allyl alcohol, (c) quantity of Et_3N, (d) quantity of palladium catalyst, and (e) yield of product.

Table 22, Entry 1:
(a) 2.0 mmol, 624.0 mg, (b) 2.5 mmol, 145.0 mg, (c) 2.5 mmol, 252.5 mg, and (d) $Pd(OAc)_2$ (5 mol%, 0.1 mmol, 22.4 mg), and (e) **420** (43%, 0.86 mmol, 208.1 mg).

Table 22, Entry 2:
(a) 2.0 mmol, 624.0 mg, (b) 2.5 mmol, 145.0 mg, (c) 2.5 mmol, 252.5 mg, and (d) $Pd(OAc)_2$ (2.5 mol%, 0.05 mmol, 11.2 mg), and (e) **420** (45%, 0.9 mmol, 217.8 mg).

Table 22, Entry 3:
(a) 2.0 mmol, 624.0 mg, (b) 2.5 mmol, 145.0 mg, (c) 2.5 mmol, 252.5 mg, and (d) $Pd_2(dba)_3$ (5 mol%, 0.1 mmol, 91.5 mg), and (e) **420** (31%, 0.62 mmol, 150.0 mg).

Table 22, Entry 4:
(a) 2.0 mmol, 624.0 mg, (b) 2.5 mmol, 145.0 mg, (c) 2.5 mmol, 252.5 mg, and (d) $Pd_2(dba)_3$ (2.5 mol%, 0.05 mmol, 45.8 mg), and (e) **420** (33%, 0.66 mmol, 159.7 mg).

Following the **General Procedure (J)**, entries 5-7 are reported as (a) quantity of **419**, (b) quantity of allyl alcohol, (c) quantity of Et_3N, (d) quantity of palladium catalyst, and (e) yield of product.

Table 22, Entry 5
(a) 2.0 mmol, 624.0 mg, (b) 2.5 mmol, 145.0 mg, (c) 2.5 mmol, 252.5 mg, and (d) $Pd(OAc)_2$ (5 mol%, 0.1 mmol, 22.4 mg), and (e) **420** (56%, 1.12 mmol, 271.0 mg).

Table 22, Entry 6
(a) 2.0 mmol, 624.0 mg, (b) 2.5 mmol, 145.0 mg, (c) 2.5 mmol, 252.5 mg, and (d) $Pd(OAc)_2$ (2.5 mol%, 0.05 mmol, 11.2 mg), and (e) **420** (57%, 1.14 mmol, 275.9 mg).

Table 22, Entry 7

(a) 2.0 mmol, 624.0 mg, (b) 2.5 mmol, 145.0 mg, (c) 2.5 mmol, 252.5 mg, and (d) $Pd_2(dba)_3$ (2.5 mol%, 0.05 mmol, 45.8 mg), and (e) **420** (39%, 0.78 mmol, 188.8 mg).

Attempted synthesis of (*Z*)-6-(tert-butyldimethylsilyloxy)-4-methylhex-4-enoic acid, 511

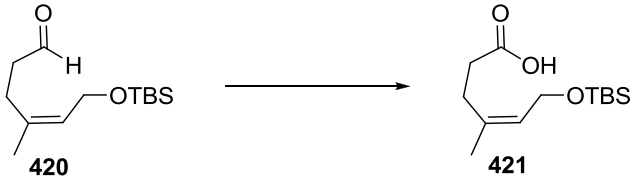


Table 23, Entry 1:

To a stirred solution of **420** (1.0 mmol, 242.0 mg) in ^{t}BuOH (10 mL) and water (5 mL) was added $NaClO_2$ (7.0 mmol, 623 mg), $KH_2PO_4 \cdot 2H_2O$ (7.5 mmol, 1.2 g) and 2-methyl-2-butene (15.0 mmol, 1.05 g) at r.t. The reaction was stirred at r.t. for 12 h, before diluting with DCM (20 mL). The organic phase was separated off and the aqueous phase further extracted with DCM (3 x 10 mL). The organic layers were then combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude mixture showed no residual aldehyde peak. All attempts to purify **421** by column chromatography (eluent: 0-100% diethyl ether in petrol) failed to isolate clean product for conclusive identification.

Table 23, Entry 2:

A solution of $NaClO_2$ (3.5 mmol, 315 mg), $KH_2PO_4 \cdot 2H_2O$ (2.5 mmol, 427.5 mg) in H_2O (1 mL) was added dropwise to a stirred solution of **420** (1.0 mmol, 242.0 mg) and 2-methyl-2-butene (15.0 mmol, 1.05 g) in ^{t}BuOH (10 mL), THF (20 mL) and water (5 mL) at 0 °C. After stirring for 1 h, the mixture was partitioned between diethyl ether (20 mL) and brine (10 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic layers were then combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude mixture showed no residual aldehyde peak. All attempts to purify **421** by column chromatography (eluent: 0-100% diethyl ether in petrol) failed to isolate clean product for conclusive identification.

Table 23, Entry 3:

To a stirred solution of **420** (1.0 mmol, 242.0 mg) in ^{t}BuOH (10 mL) and THF (10 mL) and 2-methyl-2-butene (10.0 mmol, 0.7 g) was added a solution of $NaClO_2$ (1.5 mmol, 134 mg), $KH_2PO_4 \cdot 2H_2O$ (2.0 mmol, 342 mg) in water (5 mL) dropwise at r.t. The mixture was then stirred at r.t. for 3 h, then acidified with 2 M HCl and extracted with DCM (3 x 10 mL). The

organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic layers were then combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^1H NMR analysis of the crude mixture showed no residual aldehyde peak. All attempts to purify **421** by column chromatography (eluent: 0-100% diethyl ether in petrol) failed to isolate clean product for conclusive identification.

Preparation of 1,1-dimethyl-2-methylenehydrazine, 428

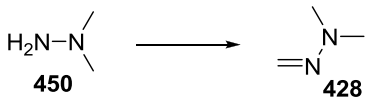


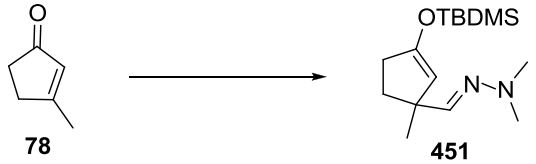
Table 23, Entry 1:

To a stirred solution of paraformaldehyde (37% w/w in H_2O, 120.0 mmol, 9.7 mL) at r.t. was added 1,1-dimethylhydrazine **450** (100.0 mmol, 6.0 g) dropwise over 15 min. The mixture was then stirred at r.t. for 24 h, before the addition of diethyl ether (30 mL) and sat. aq. NaOH (20 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar to approximately 20 mL. The crude product was purified by distillation (70-71 ºC, 760 mmHg) to provide **428** as a colourless liquid (58%, 58.0 mmol, 4.18 g).

Table 23, Entry 2:

To a stirred solution of paraformaldehyde (320.0 mmol, 9.6 g) in diethyl ether (100 mL) was added anhydrous Na_2SO_4 (10 g) and the resultant suspension cooled to 0 °C. To the reaction mixture was added 1,1-dimethylhydrazine **450** (160.0 mmol, 9.6 g) dropwise over 30 min, before allowing the mixture to warm to r.t. where it was stirred for a further 24 h. The mixture was diluted with sat. aq. $NaHCO_3$ (30 mL) and the organic phase separated off. The aqueous phase was further extracted with pentane (5 x 10 mL), the organic phases combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar to approximately 20 mL. The crude product was purified by distillation (70-71 ºC, 760 mmHg) to provide **428** as a colourless liquid (81%, 130.0 mmol, 9.36 g).

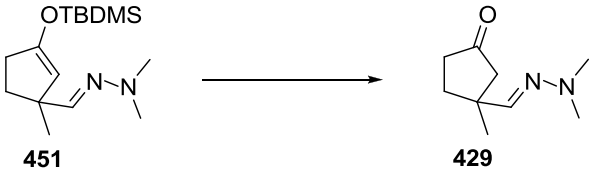
Preparation of (*E*)-2-((3-(*tert*-butyldimethylsilyloxy)-1-methylcyclopent-2-enyl)methylene)-1,1-dimethylhydrazine, 451



Scheme 164:

To a stirred solution of 3-methylcyclopentenone **78** (2.0 mmol, 192.0 mg) in diethyl ether (10 mL) at 0 °C was added TBDMSOTf (2.5 mmol, 660.0 mg) dropwise. The mixture was stirred for 5 min at 0 °C before the addition of a solution of **428** (4.0 mmol, 288.0 mg) in diethyl ether (4 mL) over 5 min. The mixture was stirred for 15 min, then quenched with sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar. The crude product was purified by column chromatography (eluent: 0-5% ether in petrol) to provide **451** as a colourless liquid (43%, 0.86 mmol, 242.5 mg). Also isolated: **78** (26%, 0.52 mmol, 49.9 mg) as a colourless liquid.

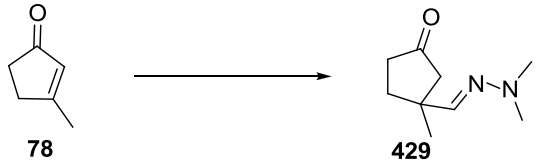
Preparation of (*E*)-3-((2,2-dimethylhydrazono)methyl)-3-methylcyclopentanone, 429



Scheme 165:

To a stirred solution of **451** (1.0 mmol, 282.0 mg) in THF (5 mL) at r.t. was added TBAF (1 M solution in THF, 1.2 mmol, 1.2 mL) dropwise. The resulting mixture was stirred at r.t. for 6 h, before the addition of diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar. The crude product was purified by column chromatography (eluent: 0-50% ether in petrol) to provide **429** as a colourless liquid (96%, 0.96 mmol, 161.3 mg).

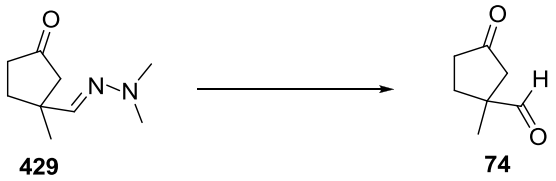
Preparation of (*E*)-3-((2,2-dimethylhydrazono)methyl)-3-methylcyclopentanone, 429



Scheme 166:

To a stirred solution of 3-methylcyclopentenone **78** (2.0 mmol, 192.0 mg) in diethyl ether (10 mL) at 0 °C was added TBDMSOTf (2.5 mmol, 660.0 mg) dropwise. The mixture was stirred for 5 min at 0 °C before the addition of a solution of **428** (4.0 mmol, 288.0 mg) in diethyl ether (4 mL) over 5 min. The mixture was stirred for 15 min, before adding TBAF (1 M solution in THF, 2.4 mmol, 2.4 mL) dropwise. The resulting mixture was stirred at r.t. for 6 h, before the addition of diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar. The crude product was purified by column chromatography (eluent: 0-50% ether in petrol) to provide **429** as a colourless liquid (49%, 0.98 mmol, 164.6 mg).

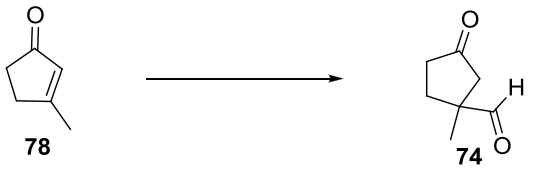
Preparation of 1-methyl-3-oxocyclopentanecarbaldehyde, 74



Scheme 167:

To a stirred solution of **429** (1.0 mmol, 126.0 mg) in diethyl ether (10 mL) at r.t. was added 5 M aq. HCl (5 mL). The resulting mixture was stirred at r.t. for 1 h, before the addition of diethyl ether (10 mL) and brine (10 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (5 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar. The crude product was purified by column chromatography (eluent: 0-50% ether in petrol) to provide **74** as a colourless liquid (88%, 0.88 mmol, 110.9 mg).

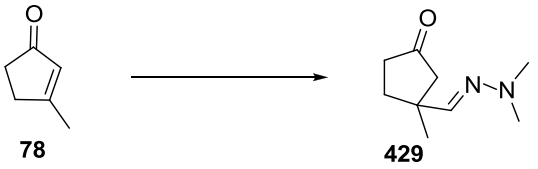
Preparation of 1-methyl-3-oxocyclopentanecarbaldehyde, 74



Scheme 168:

To a stirred solution of 3-methylcyclopentenone **78** (2.0 mmol, 192.0 mg) in diethyl ether (10 mL) at 0 °C was added TBDMSOTf (2.5 mmol, 660.0 mg) dropwise. The mixture was stirred for 5 min at 0 °C before the addition of a solution of **428** (4.0 mmol, 288.0 mg) in diethyl ether (4 mL) over 5 min. The mixture was stirred for 15 min, before adding 5 M aq. HCl (5 mL). The resulting mixture was stirred at r.t. for 1 h, before the addition of diethyl ether (10 mL) and brine (10 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (5 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C and 100 mbar. The crude product was purified by column chromatography (eluent: 0-50% ether in petrol) to provide **74** as a colourless liquid (48%, 0.96 mmol, 121.0 mg).

Preparation of (*E*)-3-((2,2-dimethylhydrazono)methyl)-3-methylcyclopentanone, 429



Following **General Procedure (K)**, entries 1-7 are reported as (a) quantity of 3-methylcyclopentenone **78**, (b) solvent, (c) reaction temperature, (d) quantity of TBDMSOTf, (e) quantity of **428**, (f) reaction length, (g) quantity of TBAF, and (h) yield of product.

Table 24, Entry 1:

(a) 2.0 mmol, 192.0 mg, (b) Et_2O (10 mL), (c) 0 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in Et_2O (4 mL), (f) 15 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (43%, 0.86 mmol, 144.5 mg).

Table 24, Entry 2:

(a) 2.0 mmol, 192.0 mg, (b) Et_2O (10 mL), (c) 0 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in Et_2O (4 mL), (f) 30 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (48%, 0.96 mmol, 161.3 mg).

Table 24, Entry 3:

(a) 2.0 mmol, 192.0 mg, (b) DCM (10 mL), (c) 0 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in DCM (4 mL), (f) 15 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (49%, 0.98 mmol, 164.6 mg).

Table 24, Entry 4:

(a) 2.0 mmol, 192.0 mg, (b) DCM (10 mL), (c) 0 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in DCM (4 mL), (f) 30 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (53%, 1.12 mmol, 178.1 mg).

Table 24, Entry 5:

(a) 2.0 mmol, 192.0 mg, (b) THF (10 mL), (c) 0 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in THF (4 mL), (f) 15 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (48%, 0.96 mmol, 161.3 mg).

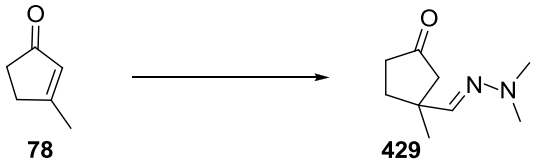
Table 24, Entry 6:

(a) 2.0 mmol, 192.0 mg, (b) THF (10 mL), (c) 0 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in THF (4 mL), (f) 30 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (58%, 1.16 mmol, 194.9 mg).

Table 24, Entry 7:

(a) 2.0 mmol, 192.0 mg, (b) THF (10 mL), (c) 0 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in THF (4 mL), (f) 60 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (56%, 1.12 mmol, 188.2 mg).

Preparation of (*E*)-3-((2,2-dimethylhydrazono)methyl)-3-methylcyclopentanone, 429



Following **General Procedure (K)**, entries 1-8 are reported as (a) quantity of 3-methylcyclopentenone **78**, (b) solvent, (c) reaction temperature, (d) quantity of TBDMSOTf, (e) quantity of **428**, (f) reaction length, (g) quantity of TBAF, and (h) yield of product.

Table 25, Entry 1:

(a) 2.0 mmol, 192.0 mg, (b) Et_2O (10 mL), (c) 0 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in Et_2O (4 mL), (f) 30 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (46%, 0.92 mmol, 154.6 mg).

Table 25, Entry 2:

(a) 2.0 mmol, 192.0 mg, (b) Et_2O (10 mL), (c) -78 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in Et_2O (4 mL), (f) 30 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (49%, 0.98 mmol, 164.6 mg).

Table 25, Entry 3:

(a) 2.0 mmol, 192.0 mg, (b) DCM (10 mL), (c) 0 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in DCM (4 mL), (f) 30 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (45%, 0.90 mmol, 151.2 mg).

Table 25, Entry 4:

(a) 2.0 mmol, 192.0 mg, (b) DCM (10 mL), (c) -78 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in DCM (4 mL), (f) 30 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (49%, 0.98 mmol, 164.6 mg).

Table 25, Entry 5:

(a) 2.0 mmol, 192.0 mg, (b) THF (10 mL), (c) 0 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in THF (4 mL), (f) 30 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (56%, 1.12 mmol, 188.2 mg).

Table 25, Entry 6:

(a) 2.0 mmol, 192.0 mg, (b) THF (10 mL), (c) -78 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in THF (4 mL), (f) 30 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (61%, 1.22 mmol, 205.0 mg).

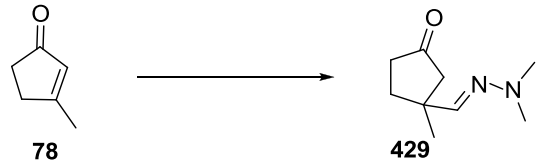
Table 25, Entry 7:

(a) 2.0 mmol, 192.0 mg, (b) THF (10 mL), (c) -78 °C, (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in THF (4 mL), (f) 60 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (60%, 1.20 mmol, 201.6 mg).

Table 25, Entry 8:

(a) 2.0 mmol, 192.0 mg, (b) Et_2O (10 mL), (c) r.t., (d) 2.5 mmol, 660.0 mg, (e) 4.0 mmol, 288.0 mg in THF (4 mL), (f) 30 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (32%, 0.64 mmol, 107.5 mg).

Preparation of (*E*)-3-((2,2-dimethylhydrazono)methyl)-3-methylcyclopentanone, 429



Following **General Procedure (L)**, entries 1-5 are reported as (a) quantity of 3-methylcyclopentenone **78**, (b) quantity of TBDMSOTf, (c) time period before addition of **428**, (d) quantity of **428**, (e) quantity of TBAF, and (f) yield of product.

Table 26, Entry 1:

(a) 2.0 mmol, 192.0 mg, (b) 2.5 mmol, 660.0 mg, (c) 5 min, (d) 4.0 mmol, 288.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **429** (52%, 1.04 mmol, 174.7 mg).

Table 26, Entry 2:

(a) 2.0 mmol, 192.0 mg, (b) 2.5 mmol, 660.0 mg, (c) 10 min, (d) 4.0 mmol, 288.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **429** (53%, 1.06 mmol, 178.1 mg).

Table 26, Entry 3:

(a) 2.0 mmol, 192.0 mg, (b) 2.5 mmol, 660.0 mg, (c) 20 min, (d) 4.0 mmol, 288.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **429** (54%, 1.08 mmol, 181.4 mg).

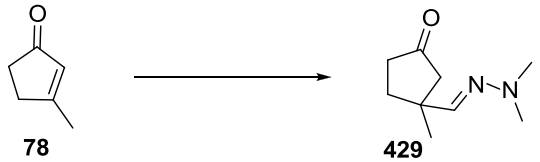
Table 26, Entry 4:

(a) 2.0 mmol, 192.0 mg, (b) 2.5 mmol, 660.0 mg, (c) 30 min, (d) 4.0 mmol, 288.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **429** (62%, 1.24 mmol, 208.3 mg).

Table 26, Entry 5:

(a) 2.0 mmol, 192.0 mg, (b) 2.5 mmol, 660.0 mg, (c) 60 min, (d) 4.0 mmol, 288.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **429** (62%, 1.24 mmol, 208.3 mg).

Preparation of (*E*)-3-((2,2-dimethylhydrazono)methyl)-3-methylcyclopentanone, 429



Following **General Procedure (M)**, entries 1-3 are reported as (a) quantity of 3-methylcyclopentenone **78**, (b) quantity of silyl triflate, (c) quantity of **428**, (d) quantity of TBAF, and (d) yield of product.

Table 27, Entry 1:

(a) 2.0 mmol, 192.0 mg, (b) TMSOTf (2.5 mmol, 555.0 mg), (c) 4.0 mmol, 288.0 mg in THF (4 mL), (d) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (e) **429** (28%, 0.56 mmol, 94.1 mg).

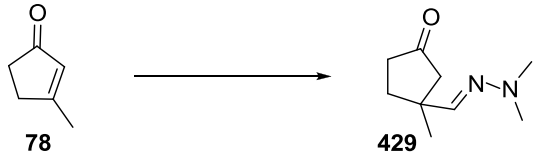
Table 27, Entry 2:

(a) 2.0 mmol, 192.0 mg, (b) TBDMSOTf (2.5 mmol, 660.0 mg), (c) 4.0 mmol, 288.0 mg in THF (4 mL), (d) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (e) **429** (60%, 1.2 mmol, 201.6 mg).

Table 27, Entry 3:

(a) 2.0 mmol, 192.0 mg, (b) TESOTf (2.5 mmol, 650.0 mg), (c) 4.0 mmol, 288.0 mg in THF (4 mL), (d) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (e) **429** (42%, 0.84 mmol, 141.1 mg).

Preparation of (*E*)-3-((2,2-dimethylhydrazono)methyl)-3-methylcyclopentanone, 429



Following **General Procedure (N)**, entries 1-7 are reported as (a) quantity of 3-methylcyclopentenone **78**, (b) volume of THF, (c) quantity of TBDMSOTf, (d) quantity of **428**, (e) quantity of TBAF, and (f) yield of product.

Table 28, Entry 1:

(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 2.5 mmol, 660.0 mg, (d) 4.0 mmol, 288.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **429** (59%, 1.18 mmol, 198.2 mg).

Table 28, Entry 2:

(a) 4.0 mmol, 384.0 mg, (b) 20 mL, (c) 5.0 mmol, 1.32 g, (d) 8.0 mmol, 576.0 mg in THF (4 mL), (e) (1 M solution in THF) 5.4 mmol, 5.4 mL, and (f) **429** (41%, 1.64 mmol, 275.5 mg).

Table 28, Entry 3:

(a) 4.0 mmol, 384.0 mg, (b) 40 mL, (c) 5.0 mmol, 1.32 g, (d) 8.0 mmol, 576.0 mg in THF (4 mL), (e) (1 M solution in THF) 5.4 mmol, 5.4 mL, and (f) **429** (40%, 1.60 mmol, 268.8 mg).

Table 28, Entry 4:

(a) 4.0 mmol, 384.0 mg, (b) 10 mL, (c) 5.0 mmol, 1.32 g, (d) 8.0 mmol, 576.0 mg in THF (4 mL), (e) (1 M solution in THF) 5.4 mmol, 5.4 mL, and (f) **429** (42%, 1.68 mmol, 282.2 mg).

Table 28, Entry 5:

(a) 6.0 mmol, 557.0 mg, (b) 30 mL, (c) 7.2 mmol, 1.90 g, (d) 12.0 mmol, 864.0 mg in THF (4 mL), (e) (1 M solution in THF) 8.0 mmol, 8.0 mL, and (f) **429** (37%, 2.22 mmol, 373.0 mg).

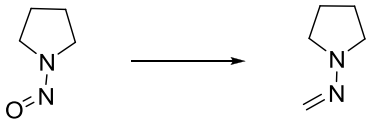
Table 28, Entry 6:

(a) 6.0 mmol, 557.0 mg, (b) 15 mL, (c) 7.2 mmol, 1.90 g, (d) 12.0 mmol, 864.0 mg in THF (4 mL), (e) (1 M solution in THF) 8.0 mmol, 8.0 mL, and (f) **429** (38%, 2.28 mmol, 383.0 mg).

Table 28, Entry 7:

(a) 6.0 mmol, 557.0 mg, (b) 60 mL, (c) 7.2 mmol, 1.90 g, (d) 12.0 mmol, 864.0 mg in THF (4 mL), (e) (1 M solution in THF) 8.0 mmol, 8.0 mL, and (f) **429** (37%, 2.22 mmol, 373.0 mg).

Preparation of *N*-methylenepyrrolidin-1-amine, 443

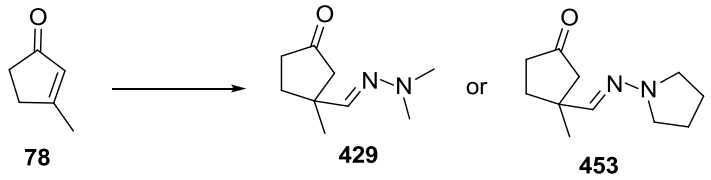


452 **443**

Scheme 169:

To a suspension of $LiAlH_4$ (200.0 mmol, 7.6 g) in diethyl ether (500 mL) at 0 °C was added 1-nitrosopyrrolidine **452** (100.0 mmol, 10.0 g) dropwise over 2 h. Following the complete addition of **452**, the reaction mixture was warmed to r.t. for 3 h. The mixture was then cooled to 0 °C and sat. aq. Na_2SO_4 (30 mL) was added dropwise over 2 h, before warming to r.t. where the mixture was stirred for 6 h, forming a fine white precipitate. To the resultant suspension was added paraformaldehyde (200.0 mmol, 6.0 g) at r.t., before stirring for a further 24 h. The suspension was then filtered, eluting with diethyl ether and the solid filtrate washed repeatedly with diethyl ether (4 x 100 mL). The solution was then concentrated under reduced pressure at 0 °C and 100 mbar to approximately 30 mL. The crude product was purified by distillation (50-55°C, 200 mmHg) to provide **443** as a colourless liquid (88%, 88.0 mmol, 8.62 g).

Preparation of (*E*)-3-((2,2-dimethylhydrazono)methyl)-3-methylcyclopentanone, 429 and (*E*)-3-methyl-3-((pyrrolidin-1-ylimino)methyl)cyclopentenone, 453.



78 **429** or **453**

Following **General Procedure (K)**, entries 1 and 3 are reported as (a) quantity of 3-methylcyclopentenone **78**, (b) solvent, (c) reaction temperature, (d) quantity of TBDMSOTf, (e) quantity of formyl hydrazone (**428** or **443**), (f) reaction length, (g) quantity of TBAF, and (h) yield of product.

Table 29, Entry 1:
(a) 2.0 mmol, 192.0 mg, (b) Et_2O (10 mL), (c) 0 °C, (d) 15 min, (d) 2.5 mmol, 660.0 mg, (e) **443** (4.0 mmol, 392.0 mg) in Et_2O (4 mL), (f) 15 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **453** (65%, 1.30 mmol, 252.2 mg).

Table 29, Entry 3:

(a) 2.0 mmol, 192.0 mg, (b) Et_2O (10 mL), (c) 0 °C, (d) 2.5 mmol, 660.0 mg, (e) **428** (4.0 mmol, 288.0 mg in Et_2O)) (4 mL), (f) 15 min, (g) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (h) **429** (48%, 0.96 mmol, 161.3 mg).

Following **General Procedure (N)**, entries 2 and 4 are reported as (a) quantity of 3-methylcyclopentenone **78**, (b) volume of THF, (c) quantity of TBDMSOTf, (d) quantity of hydrazone (**428** or **443**), (e) TBAF, and (f) yield of product.

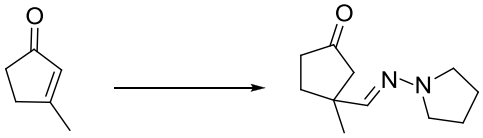
Table 29, Entry 2:

(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 2.5 mmol, 660.0 mg, (d) **443** (4.0 mmol, 392.0 mg in THF (4 mL)), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **453** (78%, 1.56 mmol, 302.6 mg).

Table 29, Entry 4:

(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 2.5 mmol, 660.0 mg, (d) **428** (4.0 mmol, 288.0 mg in THF (4 mL)), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **429** (59%, 1.18 mmol, 193.5 mg).

Preparation of (*E*)-3-((2,2-dimethylhydrazono)methyl)-3-methylcyclopentanone, 453



98 **453**

Following **General Procedure (N)**, entries 1-8 are reported as (a) quantity of 3-methylcyclopentenone **78**, (b) volume of THF, (c) quantity of TBDMSOTf, (d) quantity of **443**, (e) TBAF, and (f) yield of product.

Table 30, Entry 1:

(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 2.0 mmol, 528.0 mg, (d) 2.0 mmol, 196.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.2 mmol, 2.2 mL, and (f) **453** (58%, 1.16 mmol, 225.0 mg).

Table 30, Entry 2:
(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 2.0 mmol, 528.0 mg, (d) 3.0 mmol, 294.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.2 mmol, 2.2 mL, and (f) **543** (77%, 1.54 mmol, 298.8 mg).

Table 30, Entry 3:
(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 2.0 mmol, 528.0 mg, (d) 4.0 mmol, 392.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **453** (78%, 1.56 mmol, 302.6 mg).

Table 30, Entry 4:
(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 2.4 mmol, 633.6 mg, (d) 2.0 mmol, 196.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **453** (53%, 1.06 mmol, 205.6 mg).

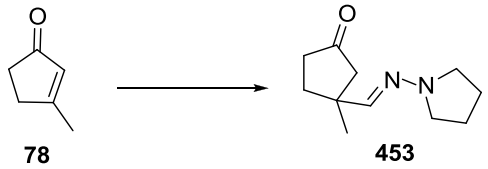
Table 30, Entry 5:
(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 2.4 mmol, 633.6 mg, (d) 3.0 mmol, 294.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **453** (81%, 1.62 mmol, 314.3 mg).

Table 30, Entry 6:
(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 2.4 mmol, 633.6 mg, (d) 4.0 mmol, 392.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.8 mmol, 2.8 mL, and (f) **453** (84%, 1.68 mmol, 325.9 mg).

Table 30, Entry 7:
(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 3.0 mmol, 792.0 mg, (d) 4.0 mmol, 392.0 mg in THF (4 mL), (e) (1 M solution in THF) 3.2 mmol, 3.2 mL, and (f) **453** (88%, 1.76 mmol, 341.4 mg).

Table 30, Entry 8:
(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 1.8 mmol, 475.2 mg, (d) 2.4 mmol, 235.2.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.0 mmol, 2.0 mL, and (f) **453** (88%, 1.58 mmol, 306.5 mg).

Preparation of (*E*)-3-((2,2-dimethylhydrazono)methyl)-3-methylcyclopentanone, 453



Following **General Procedure (N)**, entries 1-4 are reported as (a) quantity of 3-methylcyclopentenone **78**, (b) volume of THF, (c) quantity of TBDMSOTf, (d) quantity of **443**, (e) TBAF, and (f) yield of product.

Table 31, Entry 1:

(a) 2.2 mmol, 211.2 mg, (b) 10 mL, (c) 2.0 mmol, 528.0 mg, (d) 2.7 mmol, 261.7 mg in THF (4 mL), (e) (1 M solution in THF) 2.2 mmol, 2.2 mL, and (f) **453** (88%, 1.76 mmol, 341.4 mg).

Table 31, Entry 2:

(a) 5.6 mmol, 533.3 mg, (b) 25 mL, (c) 5.0 mmol, 1.32 g, (d) 6.7 mmol, 653.3 mg in THF (4 mL), (e) (1 M solution in THF) 5.5 mmol, 5.5 mL, and (f) **453** (84%, 4.2 mmol, 814.8 mg).

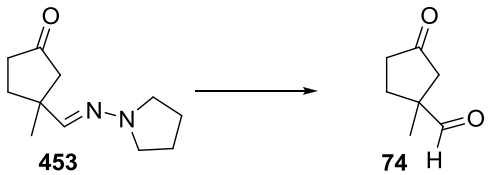
Table 31, Entry 3:

(a) 11.1 mmol, 1.07 g, (b) 50 mL, (c) 10.0 mmol, 2.64 g, (d) 13.3 mmol, 1.31 g in THF (4 mL), (e) (1 M solution in THF) 11.0 mmol, 11.0 mL, and (f) **453** (78%, 7.02 mmol, 1.51 g).

Table 31, Entry 4:

(a) 33.3 mmol, 3.2 g, (b) 150 mL, (c) 30.0 mmol, 7.13 g, (d) 40.0 mmol, 3.92 g in THF (4 mL), (e) (1 M solution in THF) 33.0 mmol, 33.0 mL, and (f) **453** (76%, 22.8 mmol, 4.42 g).

Preparation of 1-methyl-3-oxocyclopentanecarbaldehyde, 74



Following **General Procedure (O)**, entries 1-4 are reported as (a) quantity of **453**, (b) quantity of *p*-TSA·H_2O, (c) volume of water, and (d) yield of product.

Table 32, Entry 1:

(a) 2.0 mmol, 388.0 mg, (b) 2.0 mmol, 380.0 mg, (c) 0 mg, and (d) **74** (56%, 1.12 mmol, 141.1 mg).

Table 32, Entry 2:

(a) 2.0 mmol, 388.0 mg, (b) 3.0 mmol, 570.0 mg, (c) 0 mg, and (d) **74** (78%, 1.56 mmol, 196.6 mg).

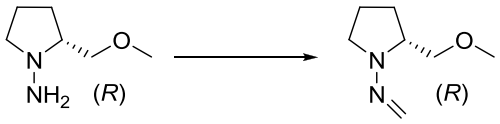
Table 32, Entry 3:

(a) 2.0 mmol, 388.0 mg, (b) 4.0 mmol, 760.0 mg, (c) 0 mg, and (d) **74** (86%, 1.72 mmol, 216.7 mg).

Table 32, Entry 4:

(a) 2.0 mmol, 388.0 mg, (b) 4.0 mmol, 760.0 mg, (c) 2.0 mmol, 36 mg, and (d) **74** (94%, 1.88 mmol, 236.9 mg).

Preparation of (*R*)-2-(methoxymethyl)-*N*-methylenepyrrolidin-1-amine, 465

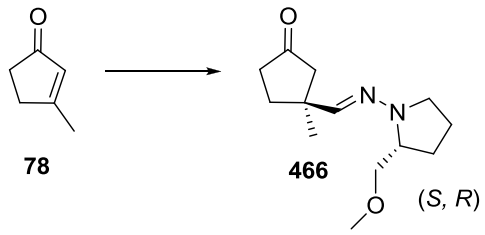


464 **465**

Scheme 173:

To a stirred solution of paraformaldehyde (10.0 mmol, 300.0 mg) in diethyl ether (10 mL) was added anhydrous Na_2SO_4 (1.0 g) and the resultant suspension cooled to 0 °C. To the reaction mixture was added a solution of **464** (5.0 mmol, 650.0 mg) in Et_2O (2 mL) dropwise, before allowing the mixture to warm to r.t. where it was stirred for a further 24 h. The mixture was then diluted with diethyl ether (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20% ether in petrol) to provide **465** as a colourless liquid (85%, 4.25 mmol, 603.5 mg). $[\alpha]_D$ (c = 1.0, $CHCl_3$) = + 89.3.

Preparation of (*S*)-3-((*E*)-((*R*)-2-(methoxymethyl)pyrrolidin-1-ylimino)methyl)-3-methylcyclopentanone, 466



Following **General Procedure (P)**, entries 1-3 are reported as (a) quantity of 3-methylcyclopentenone **78**, (b) volume of THF, (c) quantity of TBDMSOTf, (d) quantity of **465**, (e) TBAF, and (f) yield of product.

Table 33, Entry 1:

(a) 2.0 mmol, 192.0 mg, (b) 10 mL, (c) 2.2 mmol, 580.8 mg, (d) 2.5 mmol, 355.0 mg in THF (4 mL), (e) (1 M solution in THF) 2.5 mmol, 2.5 mL, and (f) **466** (78%, 1.56 mmol, 371.3 mg, >98% *d.e.*). $[\alpha]_D$ (c = 1.0, $CHCl_3$) = +218.1

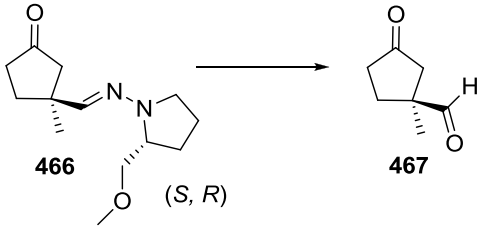
Table 33, Entry 2:

(a) 6.0 mmol, 576.0 mg, (b) 60 mL, (c) 6.6 mmol, 1.74 g, (d) 7.5 mmol, 1.07 g in THF (4 mL), (e) (1 M solution in THF) 7.0 mmol, 7.0 mL, and (f) **466** (76%, 4.56 mmol, 1.09 g, >98% *d.e.*). $[\alpha]_D$ (c = 1.0, $CHCl_3$) = +218.0

Table 33, Entry 3:

(a) 10.0 mmol, 960.0 mg, (b) 100 mL, (c) 11.0 mmol, 2.90 g, (d) 12.5 mmol, 1.78 g in THF (4 mL), (e) (1 M solution in THF) 12.0 mmol, 12.0 mL, and (f) **466** (77%, 7.70 mmol, 1.83 g, >98% *d.e.*). $[\alpha]_D$ (c = 1.0, $CHCl_3$) = +218.2

Preparation of (*S*)-1-methyl-3-oxocyclopentanecarbaldehyde, 467



Following **General Procedure (O)**, entries 1-3 are reported as (a) quantity of **466**, (b) quantity of *p*-TSA·H_2O, (c) volume of water, (d) yield of product.

Table 33, Entry 1:

(a) 1.56 mmol, 371.3 mg, (b) 3.0 mmol, 570.0 mg, (c) 28.0 mg, (d) **466** (90%, 1.40 mmol, 176.9 mg, >98% *e.e.*). $[\alpha]_D$ (c = 1.0, $CHCl_3$) = +21.8

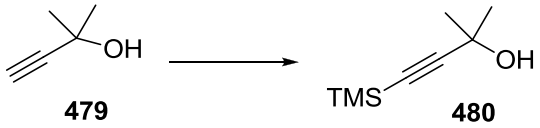
Table 33, Entry 2:

(a) 4.56 mmol, 1.09 g, (b) 9.0 mmol, 1.71 g, (c) 81.0 mg, (d) **466** (92%, 4.20 mmol, 528.5 mg, >98% *e.e.*). $[\alpha]_D$ (c = 1.0, $CHCl_3$) = +21.6

Table 33, Entry 3:

(a) 7.70 mmol, 1.83 g, (b) 15.4 mmol, 1.46 g, (c) 138.6 mg, (d) **466** (92%, 7.08 mmol, 892.6 mg, >98% *e.e.*). $[\alpha]_D$ (c = 1.0, $CHCl_3$) = +21.7

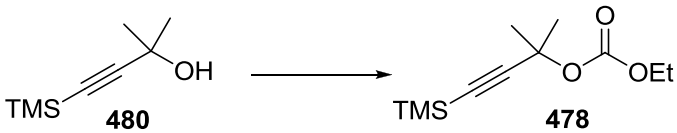
Preparation of 2-methyl-4-(trimethylsilyl)but-3-yn-2-ol, 480



479 **480**

To a stirred solution of 2-methylbut-3-yn-2-ol **479** (100.0 mmol, 8.4 g) in THF (500 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexanes, 205.0 mmol, 82 mL) dropwise over 30 min. The mixture was then stirred at 0 °C for 30 min, before TMSCl (210.0 mmol, 22.68 g) was added dropwise over 1 h. The mixture was warmed to r.t. over 2 h, before the addition of diethyl ether (200 mL) and aq. HCl (1 M, 100 mL). The resultant solution was stirred at r.t. for 1 h, the organic phase separated off and the aqueous phase was further extracted with diethyl ether (2 x 100 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide **480** as a yellow oil (100%, 100.0 mmol, 15.6 g). The crude product was used in the next step without further purification.

Preparation of ethyl 2-methyl-4-(trimethylsilyl)but-3-yn-2-yl carbonate, 478

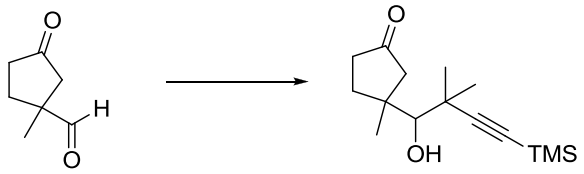


480 **478**

To a stirred solution of **480** (100.0 mmol, 15.6 g) in THF (300 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexanes, 105.0 mmol, 39.2 mL) dropwise over 30 min. The mixture was then

stirred at 0 °C for 30 min, before the addition of ethyl chloroformate (110.0 mmol, 11.88 g) dropwise over 15 min. The mixture was warmed to r.t. and stirred for a further 12 h, before the addition of diethyl ether (200 mL) and sat. aq. NH_4Cl (100 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (2 x 100 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20%, ether in petrol) to provide **478** as a colourless oil (98%, 98.0 mmol, 22.34 g).

Preparation of 3-(1-hydroxy-2,2-dimethyl-4-(trimethylsilyl)but-3-ynyl)-3-methylcyclopentanone, 482



74 **482**

Following **General Procedure (Q)**, entries 1-3 are reported as (a) quantity of $Ti(O^iPr)_4$, (b) quantity of **478**, (c) volume of solvent, (d) quantity of ^{i}PrMgCl, (e) reaction length at -40 °C, (f) quantity of **74**, (g) reaction length at -20 °C, and (h) yield of product.

Table 34, Entry 1:

(a) 2.0 mmol, 568.0 mg, (b) 2.0 mmol, 456.0 mg, (c) Et_2O (20 mL), (d) (1 M solution in THF) 4.0 mmol, 4 mL, (e) 60 min, (f) 1.5 mmol, 189.0 mg in Et_2O (2 mL), (g) 30 min, and (h) **482** (43%, 0.65 mmol, 171.6 mg).

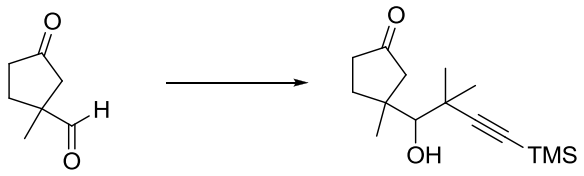
Table 34, Entry 2:

(a) 2.0 mmol, 568.0 mg, (b) 2.0 mmol, 456.0 mg, (c) Et_2O (20 mL), (d) (1 M solution in THF) 4.0 mmol, 4 mL, (e) 90 min, (f) 1.5 mmol, 189.0 mg in Et_2O (2 mL), (g) 30 min, and (h) **482** (48%, 0.72 mmol, 191.5 mg).

Table 34, Entry 3:

(a) 2.0 mmol, 568.0 mg, (b) 2.0 mmol, 456.0 mg, (c) Et_2O (20 mL), (d) (1 M solution in THF) 4.0 mmol, 4 mL, (e) 90 min, (f) 1.5 mmol, 189.0 mg in Et_2O (2 mL), (g) 60 min, and (h) **482** (58%, 0.87 mmol, 231.4 mg).

Preparation of 3-(1-hydroxy-2,2-dimethyl-4-(trimethylsilyl)but-3-ynyl)-3-methylcyclopentanone, 482



Following **General Procedure (Q)**, entries 1-3 are reported as (a) quantity of $Ti(O^iPr)_4$, (b) quantity of **478**, (c) volume of solvent, (d) quantity of ^{i}PrMgCl, (e) reaction length at -40 °C, (f) quantity of **74**, (g) reaction length at -20 °C, and (h) yield of **482**.

Table 35, Entry 1:

(a) 2.0 mmol, 568.0 mg, (b) 2.0 mmol, 456.0 mg, (c) Et_2O (20 mL), (d) (1 M solution in THF) 4.0 mmol, 4 mL, (e) 90 min, (f) 1.5 mmol, 189.0 mg in Et_2O (2 mL), (g) 60 min, and (h) **482** (58%, 0.87 mmol, 231.4 mg).

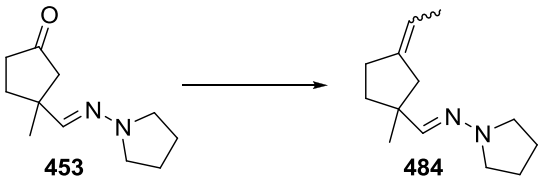
Table 35, Entry 2:

(a) 2.0 mmol, 568.0 mg, (b) 2.0 mmol, 456.0 mg, (c) DCM (20 mL), (d) 1 M solution in THF, 4.0 mmol, 4 mL, (e) 90 min, (f) 1.5 mmol, 189.0 mg in DCM (2 mL), (g) 60 min, and (h) **482** (63%, 0.95 mmol, 251.4 mg).

Table 35, Entry 3:

(a) 2.0 mmol, 568.0 mg, (b) 2.0 mmol, 456.0 mg, (c) THF (20 mL), (d) 1 M solution in THF, 4.0 mmol, 4 mL, (e) 90 min, (f) 1.5 mmol, 189.0 mg in THF (2 mL), (g) 60 min, and (h) **482** (45%, 0.68 mmol, 180.0 mg).

Preparation of (*NE*)-*N*-((3-ethylidene-1-methylcyclopentyl)methylene)pyrrolidin-1-amine, 484



Following **General Procedure (R)**, entries 1-4 was reported as (a) quantity of $EtPPh_3Br$, (b) quantity of base, (c) reaction temperature, (d) quantity of **453**, (e) reaction length, and (f) yield of product.

Table 37, Entry 1:

(a) 5.0 mmol, 1.85 g, (b) KO^{t}Bu (5.0 mmol, 560.0 mg), (c) r.t., (d) 1.0 mmol, 194.0 mg in THF (2 mL), (e) 12 h, and (f) **484** (94%, 0.94 mmol, 193.6 mg) as a 1:1, *Z*:*E* mixture of geometric isomers.

Table 37, Entry 2:

(a) 5.0 mmol, 1.85 g, (b) KO^{t}Bu (5.0 mmol, 560.0 mg), (c) 0 °C, (d) 1.0 mmol, 194.0 mg in THF (2 mL), (e) 36 h, (f) **484** (54%, 0.54 mmol, 111.2 mg) as a 5:2, *Z*:*E* mixture of geometric isomers.

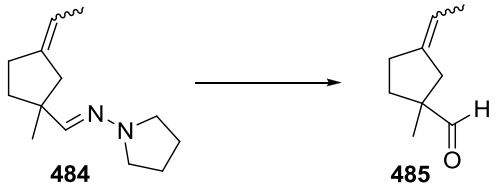
Table 37, Entry 3:

(a) 5.0 mmol, 1.85 g, (b) ^{n}BuLi (2.5 M in hexanes, 5.0 mmol, 2.0 mL), (c) -30 °C, (d) 1.0 mmol, 194.0 mg in THF (2 mL), (e) 72 h, (f) **484** (42%, 0.42 mmol, 86.5 mg) as a 4:1, *Z*:*E* mixture of geometric isomers.

Table 37, Entry 4:

(a) 5.0 mmol, 1.85 g, (b) ^{n}BuLi (2.5 M in hexanes, 5.0 mmol, 2.0 mL), (c) -78 °C, (d) 1.0 mmol, 194.0 mg in THF (2 mL), (e) 120 h, (f) **484** (32%, 0.32 mmol, 65.9 mg) as a 7:1, *Z*:*E* mixture of geometric isomers.

Preparation of 3-ethylidene-1-methylcyclopentanecarbaldehyde, 485



484 **485**

Following **General Procedure (O)**, entries 1-3 are reported as (a) quantity of **484**, (b) quantity of *p*-TSA·H_2O, (c) volume of water, (d) yield of **485**.

Table 37, Entry 1:

(a) 0.94 mmol, 193.6 mg, (b) 2.0 mmol, 380.0 mg, (c) 1.0 mmol, 18.0 mg, (d) **485** (95%, 0.89 mmol, 122.8 mg) as a 1:1, *Z*:*E* mixture of geometric isomers.

Table 37, Entry 2:

(a) 0.54 mmol, 111.2 mg, (b) 1.1 mmol, 209.0 mg, (c) 0.5 mmol, 9.0 mg, (d) **485** (94%, 0.51 mmol, 70.4 mg) as a 5:2, *Z*:*E* mixture of geometric isomers.

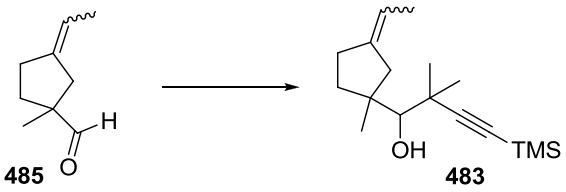
Table 37, Entry 3:

(a) 0.42 mmol, 86.5 mg, (b) 0.9 mmol, 171.0 mg, (c) 0.5 mmol, 9.0 mg, (d) **485** (94%, 0.39 mmol, 54.5 mg) as a 4:1, *Z*:*E* mixture of geometric isomers.

Table 37, Entry 3:

(a) 0.32 mmol, 65.9 mg, (b) 0.7 mmol, 133.0 mg, (c) 0.3 mmol, 6.0 mg, (d) **485** (95%, 0.30 mmol, 41.9 mg) as a 7:1, *Z*:*E* mixture of geometric isomers.

Preparation of 1-(3-ethylidene-1-methylcyclopentyl)-2,2-dimethyl-4-(trimethylsilyl)but-3-yn-1-ol, 483

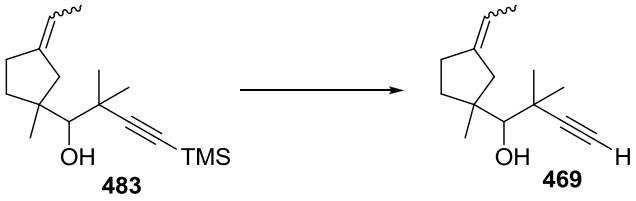


Following **General Procedure (Q)**, **Scheme 186** was reported as (a) quantity of $Ti(O^iPr)_4$, (b) quantity of **478**, (c) volume of solvent, (d) quantity of ^{i}PrMgCl, (e) reaction length at -40 °C, (f) quantity of **485**, (g) reaction length at -20 °C, and (h) yield of product.

Scheme 186:

(a) 2.0 mmol, 568.0 mg, (b) 2.0 mmol, 456.0 mg, (c) DCM (20 mL), (d) (1 M solution in THF) 4.0 mmol, 4 mL, (e) 90 min, (f) 1.5 mmol, 207.0 mg in DCM (2 mL), (g) 60 min, and (h) **483** (73%, 1.10 mmol, 304.4 mg).

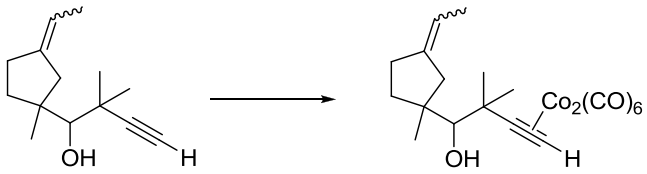
Preparation of 1-(3-ethylidene-1-methylcyclopentyl)-2,2-dimethylbut-3-yn-1-ol, 469



To a stirred solution of **483** (2.0 mmol, 532.0 mg) in DCM (10 mL) at r.t. was added TBAF (1 M solution in THF, 2.2 mmol, 2.2 mL) dropwise. The mixture was then stirred at r.t. for 6 h before the addition of diethyl ether (10 mL) and H_2O (10 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced

pressure. The crude product was purified by column chromatography (eluent: 0-25%, ether in petrol) to provide **469** as a colourless oil (94%, 1.88 mmol, 387.3 mg).

Preparation of cobalt-alkyne complex 484



469 **484**

Following **General Procedure (S)**, entries 1-4 are reported as (a) quantity of **469**, (b) quantity of $Co_2(CO)_8$, (c) reaction length, and (d) yield of product.

Table 38, Entry 1:

(a) 1.0 mmol, 206.0 mg in petrol ether (5 mL), (b) 1.1 mmol, 376.0 mg, (c) 12 h, and (d) **484** (57%, 0.57 mmol, 279.9 mg).

Table 38, Entry 2:

(a) 1.0 mmol, 206.0 mg in petrol ether (5 mL), (b) 1.1 mmol, 376.0 mg, (c) 24 h, and (d) **484** (72%, 0.72 mmol, 353.5 mg).

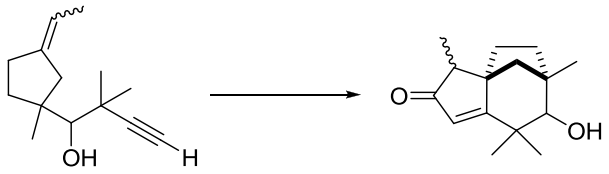
Table 38, Entry 3:

(a) 1.0 mmol, 206.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) 6 h, and (d) **484** (95%, 0.95 mmol, 466.5 mg).

Table 38, Entry 4:

(a) 1.0 mmol, 206.0 mg in DCE (5 mL), (b) 1.1 mmol, 376.2 mg, (c) 6 h, and (d) **484** (94%, 0.94 mmol, 461.4 mg).

Attempted synthesis of 470



469 **470**

Following **General Procedure (T)**, entry 1 was reported as (a) quantity of **469**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) reaction length, and (e) yield of product.

Table 39, Entry 1:

(a) 1.0 mmol, 206.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, and (c) DCE (10 mL), (d) 72 h, and (e) **470** (0%), **484** (86%, 0.85 mmol, 422.3 mg), and **469** (10%, 0.1 mmol, 20.6 mg).

Following **General Procedure (U)**, entry 2 was reported as (a) quantity of **469**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

Table 39, Entry 2:

(a) 1.0 mmol, 206.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 72 h, and (f) **470** (0%), **484** (73%, 0.73 mmol, 362.8 mg), and **469** (19%, 0.19 mmol, 39.1 mg).

Following **General Procedure (V)**, entries 3 and 4 were reported as (a) quantity of **469**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) reaction temperature, (e) quantity of $TMANO{\cdot}2H_2O$, (f) reaction length, and (g) yield of product.

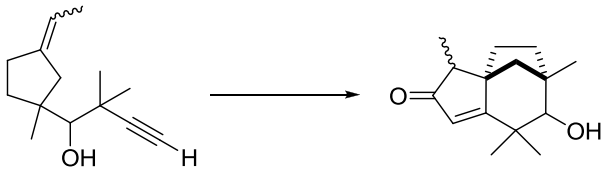
Table 39, Entry 3:

(a) 1.0 mmol, 206.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **470** (0%), **469** (100%, 1.0 mmol, 206.0 mg).

Table 39, Entry 4:

(a) 1.0 mmol, 206.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **470** (0%), **469** (100%, 1.0 mmol, 206.0 mg).

Attempted synthesis of 470



469 **470**

Following **General Procedure (W)**, entries 1-3 were reported as (a) quantity of **469**, (b) quantity of $Co_2(CO)_8$, (c) quantity of DodSMe, and (d) yield of product/s.

Table 40, Entry 1:

(a) 1.0 mmol, 206.0 mg in toluene (4 mL), (b) 1.05 mmol, 358.1 mg, (c) 0 mg, and (d) **470** (0%), **484** (92%, 0.92 mmol, 451.7 mg).

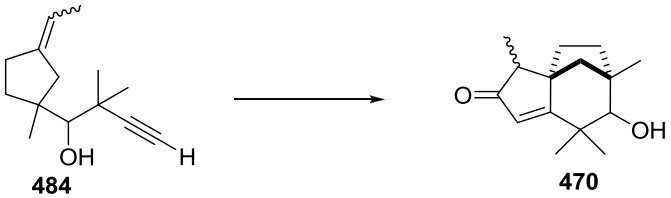
Table 40, Entry 2:

(a) 1.0 mmol, 206.0 mg in DCE (4 mL), (b) 1.05 mmol, 358.1 mg, (c) 0 mg, and (d) **470** (0%), **484** (89%, 0.89 mmol, 437.0 mg).

Table 40, Entry 3:

(a) 1.0 mmol, 206.0 mg in DCE (3 mL), (b) 1.05 mmol, 358.1 mg, (c) 4.5 mmol, 972.0 mg, and (d) **470** (0%), **484** (95%, 0.95 mmol, 466.5 mg).

Attempted synthesis of 470



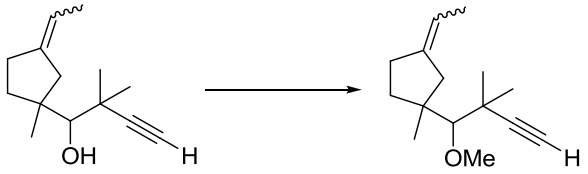
484 **470**

Scheme 190:

A 15 mL round bottomed flask was flame dried prior to cooling under a blanket of nitrogen. To this vessel was charged **469** (1.0 mmol, 206.0 mg) in a solution of DCM (5 mL), followed by $Co_2(CO)_8$ (1.1 mmol, 376.0 mg) in a single portion. The resulting mixture was stirred at r.t. monitoring progress by TLC analysis. Upon complete complexation, the mixture was filtered through celite, eluting with petrol, and concentrated under reduced pressure until approximately 5 mL. To the mixture was added silca gel (~1 g) and the resultant mixture concentrated under reduced pressure until a fine flowing solid. The solid was then warmed to 40 °C in a sealed vessel for 30 min. The crude product was purified by column

chromatography (eluent: 0-20% ether in petrol) to provide **469** as a colourless oil (94%, 0.94 mmol, 193.6 mg).

Attempted preparation of 3-ethylidene-1-(1-methoxy-2,2-dimethylbut-3-ynyl)-1-methyl cyclopentane, 489



469 **489**

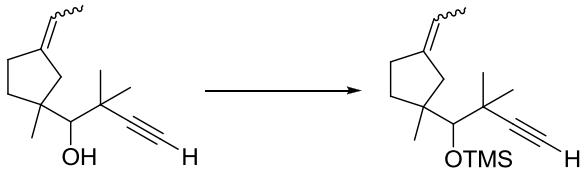
Table 41, Entry 1:

To a stirred solution of **469** (3.5 mmol, 721.0 mg) and MeI (10.0 mmol, 1.42 g) in DCM (10 mL) at 0 °C was added K_2CO_3 (14.0 mmol, 1.93 g) in a single portion. The mixture was then stirred at 0 °C for 3 h, before warming the mixture to r.t. and stirring for a further 48 h. TLC analysis of the reaction mixture indicated only starting material. The mixture was then diluted with diethyl ether (20 mL) and water (20 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude product analysis indicated a quantitative return of the starting material **469**.

Table 41, Entry 2:

To a stirred suspension of NaH (98% w/w, 4.1 mmol, 98.0 mg) in THF (20 mL) at 0 °C was added a solution of **469** (4.0 mmol, 824.0 mg) in THF (2 mL) dropwise. The mixture was stirred at 0 °C for a further 30 min, before the addition of MeI (12.0 mmol, 1.7 g). The mixture was slowly warmed to r.t. over 12 h, before warming further to 40 °C, where the mixture was stirred for 48 h. The mixture was then cooled to r.t. and diluted with diethyl ether (20 mL) and water (20 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude product analysis indicated a quantitative return of the starting material **469**.

Preparation of (1-(3-ethylidene-1-methylcyclopentyl)-2,2-dimethylbut-3-ynyloxy) trimethylsilane, 490

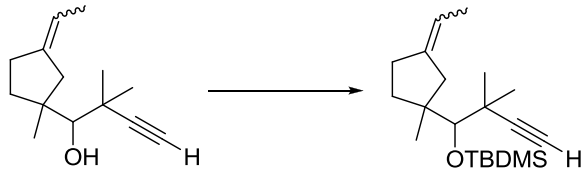


469 **490**

Table 41, Entry 3:

To a stirred solution of **469** (3.5 mmol, 721.0 mg) in DCM at 0 °C was added Et_3N (10.0 mmol, 1.0 g) and TMSCl (4.0 mmol, 432.0 mg). The mixture was then slowly warmed to r.t. where the mixture was stirred until complete consumption of the starting material had been observed by TLC analysis. Complete conversion of **469** to **490** required 48 h. The mixture was then diluted with diethyl ether (20 mL) and sat. aq. NH_4Cl (20 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-5% ether in petrol) to provide **490** as a colourless liquid (94%, 3.29 mmol, 914.6 mg).

Attempted preparation of tert-butyl(1-(3-ethylidene-1-methylcyclopentyl)-2,2-dimethyl but-3-ynyloxy)dimethylsilane, 491



469 **491**

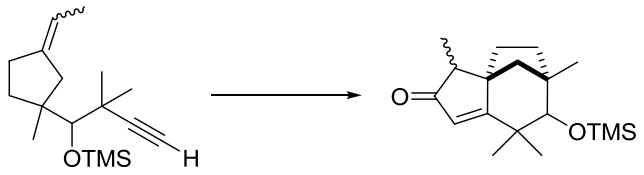
Table 41, Entry 4:

To a stirred solution of **469** (3.5 mmol, 721.0 mg) in DCM at r.t. was added imidazole (10.0 mmol, 680.0 mg) and TBDMSCl (4.0 mmol, 600.0 mg). The mixture was then stirred at r.t. for 24 h. TLC analysis showed only **469** to be present. To the mixture was added a further portion of imidazole (10.0 mmol, 680.0 mg) and TBDMSCl (4.0 mmol, 600.0 mg) and the reaction mixture stirred for a further 48 h at r.t. The mixture was then diluted with diethyl ether (20 mL) and sat. aq. NH_4Cl (20 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude product analysis indicated a quantitative return of the starting material **469**.

Table 41, Entry 5:

To a stirred solution of **469** (3.5 mmol, 721.0 mg) in DCM at 0 °C was added Et_3N (20.0 mmol, 2.0 g), DMAP (1.0 mmol, 122.0 mg) and TBDMSOTf (5.0 mmol, 1.32 g). The mixture was then stirred at 0 °C for 6 h, before slowly warming to r.t. The mixture was then stirred at r.t. for 24 h before adding diethyl ether (20 mL) and sat. aq. NH_4Cl (20 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude product analysis indicated a quantitative return of the starting material **469**.

Attempted synthesis of 490



490 **492**

Following **General Procedure (T)**, entry 1 was reported as (a) quantity of **490**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) reaction length, and (e) yield of product.

Table 42, Entry 1:

(a) 1.0 mmol, 278.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, and (c) DCE (10 mL), (d) 72 h, and (e) **492** (0%) and **490** (96%, 0.96 mmol, 272.4 mg).[a]

[a] Starting material **490** was recovered by stirring the crude complex in DCM (10 mL) at r.t. in the presence of $TMANO{\cdot}2H_2O$ (20.0 mmol, 1.5 g) for 24 h. The crude product was purified by column chromatography (eluent: 0-10% ether in petrol) to afford **490** (96%, 0.96 mmol, 272.4 mg) as a colourless oil.

Following **General Procedure (U)**, entry 2 was reported as (a) quantity of **469**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

Table 42, Entry 2:

(a) 1.0 mmol, 278.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 72 h, and (f) **492** (0%) and **490** (95%, 0.95 mmol, 264.1 mg).[a]

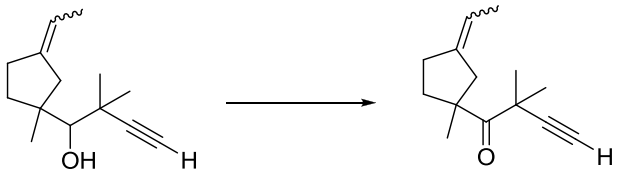
[a]The crude complex/DodSMe mixture recovered from column chromatography, was first concentrated under reduced pressure, then dissolved in DCM (10 mL) and stirred at r.t. To the mixture was added TMANO·$2H_2O$ (20.0 mmol, 1.5 g) and the mixture stirred at r.t. for 24 h. The crude product was then filtered through celite, concentrated under reduced pressure and purified by column chromatography (eluent: 0-10% ether in petrol) to afford **490** (95%, 0.95 mmol, 264.1 mg) as a colourless oil.

Following **General Procedure (V)**, entries 3 and 4 were reported as (a) quantity of **490**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) reaction temperature, (e) quantity of TMANO·$2H_2O$, (f) reaction length, and (g) yield of product.

Table 42, Entry 3:
(a) 1.0 mmol, 278.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **492** (0%), **490** (96%, 0.96 mmol, 266.9 mg).

Table 42, Entry 4:
(a) 1.0 mmol, 278.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **492** (0%), **490** (91%, 0.91 mmol, 253.0 mg).

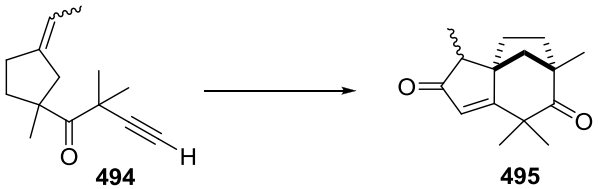
Preparation of 1-(3-ethylidene-1-methylcyclopentyl)-2,2-dimethylbut-3-yn-1-one, 494



469 **494**

Scheme 192:
To a stirred solution of **469** (5.0 mmol, 1.03 g) in DCM (15 mL) at r.t. was added celite (~2 g) and the resultant suspension stirred for 10 min. To the mixture was added PDC (7.0 mmol, 2.63 g) as a single portion. The resultant suspension was stirred at r.t. for 24 h, after which the mixture was then filtered through celite, eluting with DCM, and the mixture concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20% ether in petrol) to afford **494** as a colourless liquid (87%, 4.35 mmol, 887.4 mg).

Attempted synthesis of 495



494 **495**

Following **General Procedure (U)**, entry 1 was reported as (a) quantity of **494**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

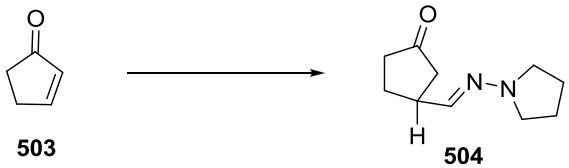
Table 43, Entry 1:
(a) 1.0 mmol, 204.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 72 h, and (f) **495** (0%), **494** (0%).

Following **General Procedure (V)**, entries 2 and 3 were reported as (a) quantity of **494**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) reaction temperature, (e) quantity of $TMANO{\cdot}2H_2O$, (f) reaction length, and (g) yield of product.

Table 43, Entry 2:
(a) 1.0 mmol, 204.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **495** (0%), **494** (91%, 0.91 mmol, 185.6 mg).

Table 43, Entry 3:
(a) 1.0 mmol, 204.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **495** (0%), **494** (89%, 0.89 mmol, 181.6 mg).

Preparation of (*E*)-3-((pyrrolidin-1-ylimino)methyl)cyclopentenone, 504



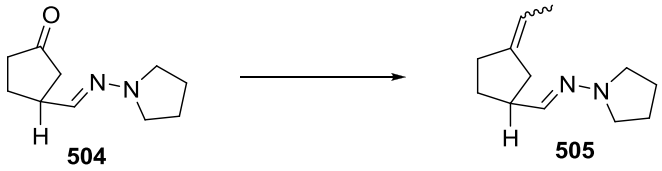
503 **504**

Following **General Procedure (N)**, the above reaction (**Scheme 196**) was reported as (a) quantity of cycolpentenone **503**, (b) volume of THF, (c) quantity of TBDMSOTf, (d) quantity of **443**, (e) TBAF, and (f) yield of product.

Scheme 196:

(a) 2.2 mmol, 182.2 mg, (b) 10 mL, (c) 2.0 mmol, 528.0 mg, (d) 2.7 mmol, 261.7 mg in THF (4 mL), (e) (1 M solution in THF) 2.2 mmol, 2.2 mL, and (f) **504** (78%, 1.56 mmol, 280.8 mg).

Preparation of (*NE*)-*N*-((3-ethylidenecyclopentyl)methylene)pyrrolidin-1-amine, 505

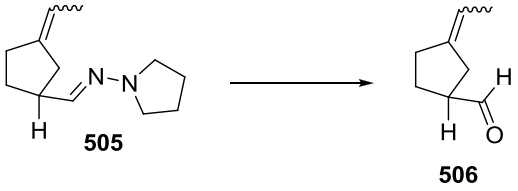


Following **General Procedure (R)**, the above reaction (**Scheme 196**) was reported as (a) quantity of $EtPPh_3Br$, (b) quantity of base, (c) reaction temperature, (d) quantity of **504**, (e) reaction length, and (f) yield of product.

Scheme 196:

(a) 1.5 mmol, 555.0 mg, (b) KO^tBu (1.5 mmol, 168.0 mg), (c) r.t., (d) 1.0 mmol, 180.0 mg in THF (2 mL), (e) 12 h, and (f) **505** (95%, 0.95 mmol, 182.4 mg).

Preparation of 3-ethylidenecyclopentanecarbaldehyde, 506

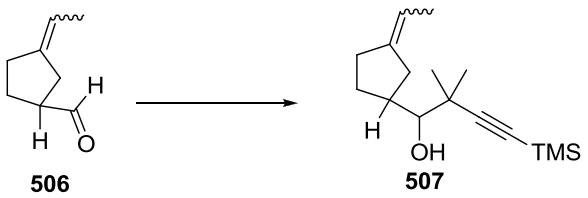


Following **General Procedure (O)**, the above reaction (**Scheme 196**) was reported as (a) quantity of **505**, (b) quantity of *p*-TSA·H_2O, (c) volume of water, and (d) yield of product.

Scheme 196:

(a) 2.0 mmol, 384.0 mg, (b) 4.0 mmol, 760.0 mg, (c) 2.0 mmol, 36 mg, and (d) **506** (87%, 1.74 mmol, 215.8 mg).

Preparation of 1-(3-ethylidenecyclopentyl)-2,2-dimethyl-4-(trimethylsilyl)but-3-yn-1-ol, 507



506 **507**

Following **General Procedure (Q)**, the above reaction (**Scheme 196**) was reported as (a) quantity of $Ti(O^iPr)_4$, (b) quantity of **478**, (c) volume of solvent, (d) quantity of ^iPrMgCl, (e) reaction length at -40 °C, (f) quantity of **506**, (g) reaction length at -20 °C, and (h) yield of product.

Scheme 196:

(a) 2.0 mmol, 568.0 mg, (b) 2.0 mmol, 456.0 mg, (c) DCM (20 mL), (d) (1 M solution in THF) 4.0 mmol, 4 mL, (e) 90 min, (f) 1.5 mmol, 186.0 mg, (g) 60 min, and (h) **507** (69%, 1.04 mmol, 273.2 mg).

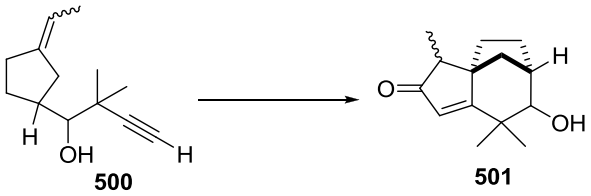
Preparation of 1-(3-ethylidenecyclopentyl)-2,2-dimethylbut-3-yn-1-ol, 500

507 **500**

Scheme 196:

To a stirred solution of **507** (2.0 mmol, 528.0 mg) in DCM (10 mL) at r.t. was added TBAF (1 M solution in THF, 2.2 mmol, 2.2 mL) dropwise. The mixture was then stirred at r.t. for 6 h before the addition of diethyl ether (10 mL) and H_2O (10 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-25%, ether in petrol) to provide **500** as a colourless oil (93%, 1.86 mmol, 357.1 mg).

Attempted synthesis of 501



500 **501**

Following **General Procedure (U)**, entry 1 was reported as (a) quantity of **500**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

Table 44, Entry 1:

(a) 1.0 mmol, 192.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 72 h, and (f) **501** (0%), **500** (45%, 0.45 mmol, 86.4 mg).

Following **General Procedure (V)**, entries 2 and 3 were reported as (a) quantity of **500**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) reaction temperature, (e) quantity of $TMANO{\cdot}2H_2O$, (f) reaction length, and (g) yield of product.

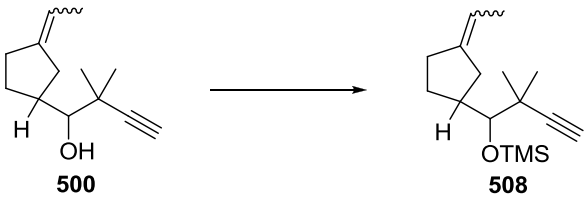
Table 44, Entry 2:

(a) 1.0 mmol, 192.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **501** (0%), **500** (55%, 0.55 mmol, 105.6 mg).

Table 44, Entry 3:

(a) 1.0 mmol, 192.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **501** (0%), **500** (59%, 0.59 mmol, 113.3 mg).

Preparation of (1-(3-ethylidenecyclopentyl)-2,2-dimethylbut-3-ynyloxy)trimethylsilane, 508



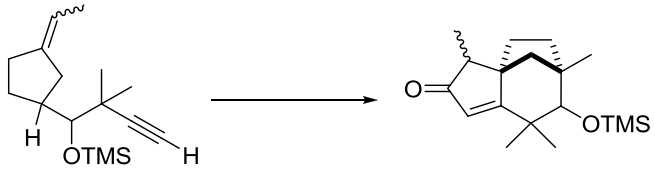
500 **508**

Scheme 197:

To a stirred solution of **500** (5.5 mmol, 1.06 g) in DCM (30 mL) at r.t. was added Et_3N (15.0 mmol, 1.5 g) and TMSCl (7.0 mmol, 756.0 mg). The mixture was then stirred at r.t.

monitoring progress by TLC analysis. Complete conversion of **500** to **508** observed within 30 min. The mixture was then diluted with diethyl ether (20 mL) and sat. aq. NH_4Cl (20 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-5% ether in petrol) to provide **508** as a colourless liquid (91%, 5.0 mmol, 1.32 g).

Attempted synthesis of 509



508 **509**

Following **General Procedure (U)**, entry 1 was reported as (a) quantity of **508**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

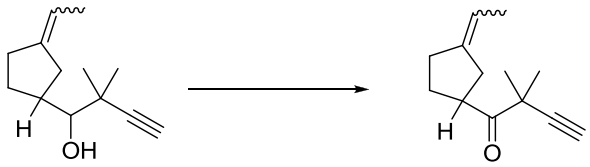
Table 45, Entry 1:
(a) 1.0 mmol, 264.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 72 h, and (f) **509** (0%), **508** (52%, 0.52 mmol, 137.3 mg).

Following **General Procedure (V)**, entries 2 and 3 were reported as (a) quantity of **508**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) reaction temperature, (e) quantity of $TMANO{\cdot}2H_2O$, (f) reaction length, and (g) yield of product.

Table 45, Entry 2:
(a) 1.0 mmol, 264.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **509** (0%), **508** (63%, 0.63 mmol, 166.3 mg).

Table 45, Entry 3:
(a) 1.0 mmol, 264.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **509** (0%), **508** (68%, 0.68 mmol, 179.5 mg).

Preparation of 1-(3-ethylidenecyclopentyl)-2,2-dimethylbut-3-yn-1-one, 510

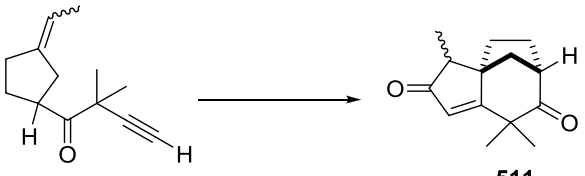


500 **510**

Scheme 198:

To a stirred solution of **500** (4.0 mmol, 760.0 mg) in DCM (10 mL) at r.t. was added celite (~2 g) and the resultant suspension stirred for 10 min. To the mixture was added PDC (6.0 mmol, 2.26 g) as a single portion. The resultant suspension was stirred at r.t. for 24 h. The mixture was then filtered through celite, eluting with DCM, and the crude product concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20% ether in petrol) to afford **510** as a colourless liquid (90%, 3.6 mmol, 684.0 mg).

Attempted synthesis of 511



510 **511**

Following **General Procedure (U)**, entry 1 was reported as (a) quantity of **510**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

Table 46, Entry 1:

(a) 1.0 mmol, 190.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 72 h, and (f) **511** (0%), **510** (60%, 0.6 mmol, 114.0 mg).

Following **General Procedure (V)**, entries 2 and 3 were reported as (a) quantity of **510**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) reaction temperature, (e) quantity of $TMANO{\cdot}2H_2O$, (f) reaction length, and (g) yield of product.

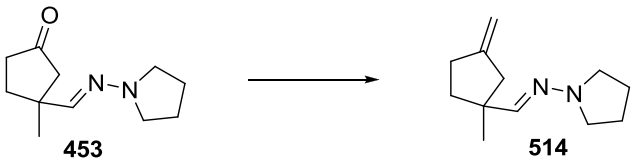
Table 46, Entry 2:

(a) 1.0 mmol, 190.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **511** (0%), **510** (64%, 0.64 mmol, 121.6 mg).

Table 46, Entry 3:

(a) 1.0 mmol, 190.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **511** (0%), **510** (65%, 0.65 mmol, 123.5 mg).

Preparation of (*E*)-*N*-((1-methyl-3-methylenecyclopentyl)methylene)pyrrolidin-1-amine, 514

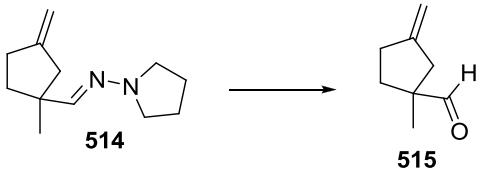


Following **General Procedure (R)**, the above reaction (**Scheme 200**) was reported as (a) quantity of $MePPh_3Br$, (b) quantity of base, (c) reaction temperature, (d) quantity of **453**, (e) reaction length, and (f) yield of product.

Scheme 200:

(a) 1.5 mmol, 535.0 mg, (b) KO^tBu (1.5 mmol, 168.0 mg), (c) r.t., (d) 1.0 mmol, 194.0 mg in THF (2 mL), (e) 12 h, and (f) **514** (86%, 0.86 mmol, 165.1 mg).

Preparation of 1-methyl-3-methylenecyclopentanecarbaldehyde, 515

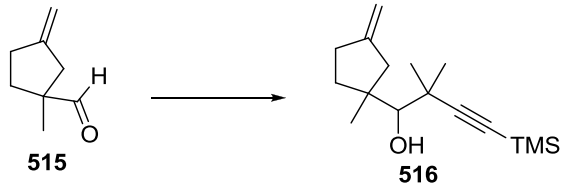


Following **General Procedure (O)**, the above reaction (**Scheme 200**) was reported as (a) quantity of **514**, (b) quantity of *p*-TSA·H_2O, (c) volume of water, and (d) yield of product.

Scheme 200:

(a) 2.0 mmol, 384.0 mg, (b) 4.0 mmol, 760.0 mg, (c) 2.0 mmol, 36 mg, and (d) **515** (87%, 1.74 mmol, 215.8 mg).

Preparation of 2,2-dimethyl-1-(1-methyl-3-methylenecyclopentyl)-4-(trimethylsilyl)but-3-yn-1-ol, 526



515 516

Following **General Procedure (Q)**, the above reaction (**Scheme 200**) was reported as (a) quantity of $Ti(O^iPr)_4$, (b) quantity of **478**, (c) volume of solvent, (d) quantity of ^iPrMgCl, (e) reaction length at -40 °C, (f) quantity of **515**, (g) reaction length at -20 °C, and (h) yield of product.

Scheme 200:

(a) 2.0 mmol, 568.0 mg, (b) 2.0 mmol, 456.0 mg, (c) DCM (20 mL), (d) (1 M solution in THF) 4.0 mmol, 4 mL, (e) 90 min, (f) 1.5 mmol, 186.0 mg, (g) 60 min, and (h) **516** (65%, 0.98 mmol, 257.4 mg).

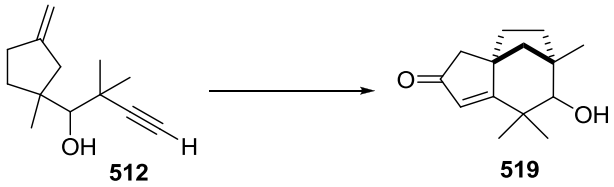
Preparation of 2,2-dimethyl-1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-ol, 512

516 512

Scheme 200:

To a stirred solution of **516** (3.0 mmol, 792.0 mg) in DCM (10 mL) at r.t. was added TBAF (1 M solution in THF, 3.3 mmol, 3.3 mL) dropwise. The mixture was then stirred at r.t. for 6 h before the addition of diethyl ether (10 mL) and H_2O (10 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-25%, ether in petrol) to provide **512** as a colourless oil (96%, 2.88 mmol, 553.0 mg).

Attempted synthesis of 519



Following **General Procedure (U)**, entry 1 was reported as (a) quantity of **512**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

Table 47, Entry 1:

(a) 1.0 mmol, 192.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 72 h, and (f) **519** (0%), **512** (96%, 0.96 mmol, 184.3 mg).[a]

[a]The crude complex/DodSMe mixture recovered from column chromatography was first concentrated under reduced pressure, then dissolved in DCM (10 mL) and stirred at r.t. To the mixture was added $TMANO{\cdot}2H_2O$ (20.0 mmol, 1.5 g) and the mixture stirred at r.t. for 24 h. The crude product was then filtered through celite, concentrated under reduced pressure and purified by column chromatography (eluent: 0-10% ether in petrol) to afford **512** (96%, 0.96 mmol, 184.3 mg) as a colourless oil.

Following **General Procedure (V)**, entries 2 and 3 were reported as (a) quantity of **512**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) reaction temperature, (e) quantity of $TMANO{\cdot}2H_2O$, (f) reaction length, and (g) yield of product.

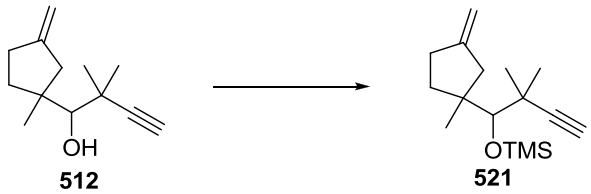
Table 47, Entry 2:

(a) 1.0 mmol, 192.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **519** (0%), **512** (89%, 0.89 mmol, 170.9 mg).

Table 47, Entry 3:

(a) 1.0 mmol, 192.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **519** (0%), **512** (94%, 0.94 mmol, 180.5 mg).

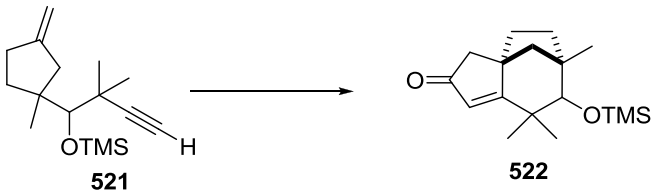
Preparation of (2,2-dimethyl-1-(1-methyl-3-methylenecyclopentyl)but-3-ynyloxy) trimethylsilane, 521



Scheme 202:

To a stirred solution of **512** (4.0 mmol, 768.0 mg) in DCM (15 mL) at r.t. was added Et_3N (12.0 mmol, 1.2 g) and TMSCl (6.0 mmol, 648.0 mg). The mixture was then stirred at r.t. monitoring progress by TLC analysis. Complete conversion of **512** to **521** required 48 h. The mixture was then diluted with diethyl ether (20 mL) and sat. aq. NH_4Cl (20 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent:0-5% ether in petrol) to provide **521** as a colourless liquid (86%, 3.44 mmol, 908.2 mg).

Attempted synthesis of 522



Following **General Procedure (U)**, entry 1 was reported as (a) quantity of **521**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

Table 48, Entry 1:

(a) 1.0 mmol, 192.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 72 h, and (f) **522** (0%), **521** (91%, 0.91 mmol, 240.2 mg).[a]

[a]The crude complex/DodSMe mixture recovered from column chromatography was first concentrated under reduced pressure, then dissolved in DCM (10 mL) and stirred at r.t. To the mixture was added $TMANO{\cdot}2H_2O$ (20.0 mmol, 1.5 g) and the mixture stirred at r.t. for 24 h. The crude product was then filtered through celite, concentrated under reduced pressure and purified by column chromatography (eluent: 0-10% ether in petrol) to afford **521** (91%, 0.91 mmol, 240.2 mg) as a colourless oil.

Following **General Procedure (V)**, entries 2 and 3 were reported as (a) quantity of **521**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) reaction temperature, (e) quantity of $TMANO{\cdot}2H_2O$, (f) reaction length, and (g) yield of product.

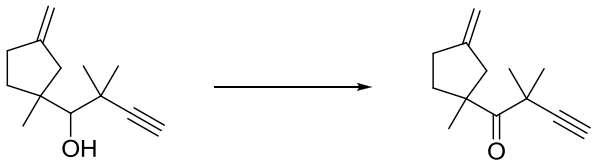
Table 48, Entry 2:

(a) 1.0 mmol, 192.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **522** (0%), **521** (93%, 0.93 mmol, 245.5 mg).

Table 48, Entry 3:

(a) 1.0 mmol, 192.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 24 h, and (g) **522** (0%), **521** (88%, 0.88 mmol, 232.3 mg).

Preparation of 2,2-dimethyl-1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-one, 524

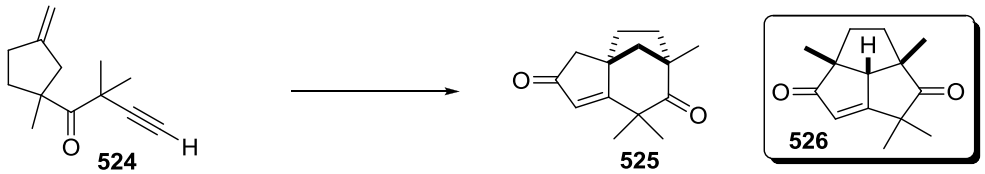


512 **524**

Scheme 203:

To a stirred solution of **512** (6.0 mmol, 1.15 g) in DCM (20 mL) at r.t. was added celite (~2 g) and the resultant suspension stirred for 10 min. To the mixture was added PDC (10.0 mmol, 3.76 g) as a single portion. The resultant suspension was stirred at r.t. for 24 h. The mixture was then filtered through celite, eluting with DCM, and the crude product concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20% ether in petrol) to afford **524** as a colourless liquid (85%, 5.1 mmol, 969.0 mg).

Attempted preparation of 525



524 **525** **526**

Following **General Procedure (U)**, entry 1 was reported as (a) quantity of **524**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

Table 49, Entry 1:

(a) 1.0 mmol, 190.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 12 h, and (f) **525** (0%), **526** (58%, 0.58 mmol, 126.4 mg).

Following **General Procedure (V)**, entries 2 and 3 were reported as (a) quantity of **524**, (b) quantity of $Co_2(CO)_8$, (c) quantity of solvent, (d) reaction temperature, (e) quantity of $TMANO{\cdot}2H_2O$, (f) reaction length, and (g) yield of product.

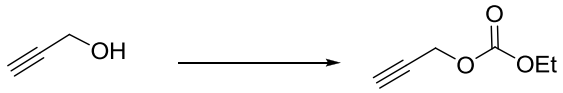
Table 49, Entry 2:

(a) 1.0 mmol, 190.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 5 h, and (g) **525** (0%), **526** (75%, 0.75 mmol, 163.5 mg).

Table 49, Entry 3:

(a) 1.0 mmol, 190.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 8 h, and (g) **525** (0%), **526** (78%, 0.78 mmol, 170.0 mg).

Preparation of ethyl prop-2-ynyl carbonate, 530

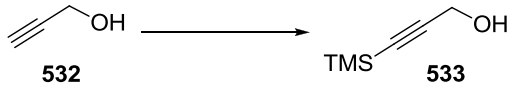


532 **530**

Scheme 206:

To a stirred solution of **532** (10.0 mmol, 560.3 mg) in THF (50 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexanes, 10.5 mmol, 4.2 mL) dropwise over 30 min. The mixture was then stirred at 0 °C for 30 min, before the addition of ethyl chloroformate (11.0 mmol, 1.19 g) dropwise over 15 min. The mixture was warmed to r.t. and stirred for a further 12 h, before the addition of diethyl ether (200 mL) and sat. aq. NH_4Cl (100 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (2 x 100 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20%, ether in petrol) to provide **530** as a colourless oil (97%, 9.7 mmol, 1.24 g).

Preparation of 3-(trimethylsilyl)prop-2-yn-1-ol, 533

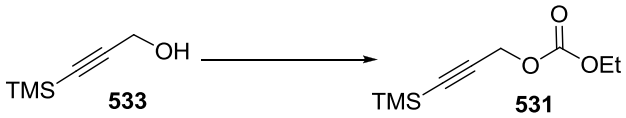


532 **533**

Scheme 207:

To a stirred solution of **532** (10.0 mmol, 560.3 mg) in THF (100 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexanes, 20.5 mmol, 8.2 mL) dropwise over 30 min. The mixture was then stirred at 0 °C for 30 min, before TMSCl (21.0 mmol, 2.27 g) was added dropwise over 1 h. The mixture was warmed to r.t. over 2 h, before the addition of diethyl ether (200 mL) and aq. HCl (1 M, 100 mL). The resultant solution was stirred at r.t. for 1 h, the organic phase separated off and the aqueous phase was further extracted with diethyl ether (2 x 100 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide **533** as a yellow oil (100%, 10.0 mmol, 1.28 g). The crude product was used in the next step without further purification.

Preparation of ethyl 3-(trimethylsilyl)prop-2-ynyl carbonate, 531

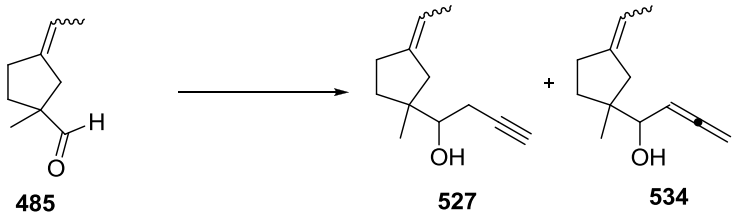


533 **531**

Scheme 207:

To a stirred solution of **533** (10.0 mmol, 1.28 g) in THF (50 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexanes, 10.5 mmol, 4.2 mL) dropwise over 30 min. The mixture was then stirred at 0 °C for 30 min, before the addition of ethyl chloroformate (11.0 mmol, 1.19 g) dropwise over 15 min. The mixture was warmed to r.t. and stirred for a further 12 h, before the addition of diethyl ether (200 mL) and sat. aq. NH_4Cl (100 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (2 x 100 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-20%, ether in petrol) to provide **531** as a colourless oil (95%, 9.5 mmol, 1.90 g).

Preparation of 1-(3-ethylidene-1-methylcyclopentyl)but-3-yn-1-ol, 527 and 1-(3-ethylidene-1-methylcyclopentyl)buta-2,3-dien-1-ol, 534



485 527 534

Following **General Procedure (Q)**, entries 1-2 was reported as (a) quantity of $Ti(O^iPr)_4$, (b) quantity of alkyne, (c) volume of solvent, (d) quantity of ^{i}PrMgCl, (e) reaction length at -40 °C, (f) quantity of **485**, (g) reaction length at -20 °C, and (h) yield of product.

Table 50, Entry 1:

(a) 2.0 mmol, 568.0 mg, (b) **529** (80% w/w in toluene, 2.0 mmol, 297.5 mg), (c) DCM (20 mL), (d) (1 M solution in THF) 4.0 mmol, 4 mL, (e) 90 min, (f) 1.5 mmol, 207.0 mg, (g) 60 min, and (h) inseparable 2:1 mixture of **527** and **534** (44%, 0.66 mmol, 117.5 mg).

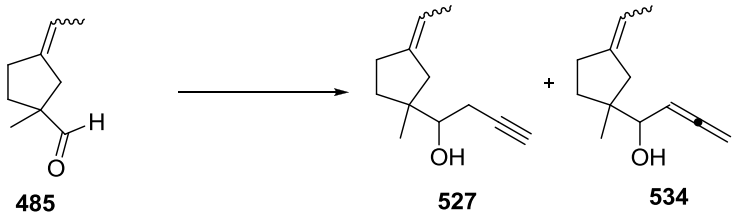
Table 50, Entry 2:

(a) 2.0 mmol, 568.0 mg, (b) **530** (2.0 mmol, 256.0 mg, (c) DCM (20 mL), (d) (1 M solution in THF) 4.0 mmol, 4 mL, (e) 90 min, (f) 1.5 mmol, 207.0 mg, (g) 60 min, and (h) inseparable 2:1 mixture of **527** and **534** (41%, 0.62 mmol, 109.5 mg).

Table 50, Entry 3:

To a stirred solution of $Ti(O^iPr)_4$ (2.0 mmol, 568.0 mg) and **531** (2.0 mmol, 400.0 mg) in DCM (20 mL) at -50 °C was added ^{i}PrMgCl (1 M solution in THF, 4.0 mmol, 4 mL) dropwise over 15 min. The resultant solution was stirred at -40 °C for 90 min, before cooling back to -78 °C. To the cooled solution was added a solution of **485** (1.5 mmol, 207.0 mg) in DCM (2 mL) over 5 min. The mixture was warmed to -20 °C for 60 min, before warming to r.t. and quenching the reaction with aq. HCl (1 M, 20 mL). The organic layer was separated off and the aqueous phase further extracted with ether (3 x 10 mL). The organic phases were combined and TBAF (1 M in THF, 2.5 mmol, 2.5 mL) was added. The mixture was then stirred at r.t. for 12 h, before the addition of diethyl ether (20 mL) and H_2O (20 mL). The organic phase was separated off and the aqueous phase further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-25% ether in petrol) to afford an inseparable 2:5 mixture of **527** and **534** (42%, 0.63 mmol, 112.1 mg) as a colourless liquid.

Preparation of 1-(3-ethylidene-1-methylcyclopentyl)but-3-yn-1-ol, 527 and 1-(3-ethylidene-1-methylcyclopentyl)buta-2,3-dien-1-ol, 534



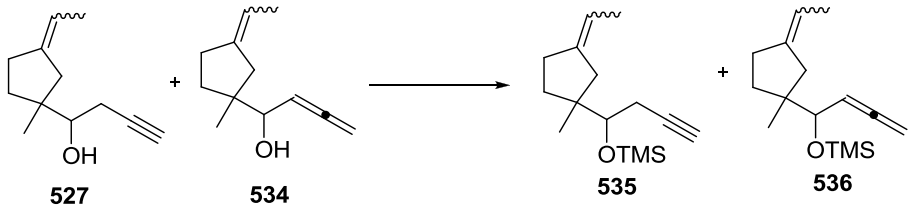
485 527 534

Following **General Procedure (X)**, the above reaction (**Scheme 208**) was reported as (a) quantity of zinc powder, (b) quantity of alkyne, (c) quantity of **485**, and (d) yield of product.

Scheme 208:

(a) 4 mmol, 260 mg, (b) propargyl bromide **529** (80% w/w in toluene, 3.0 mmol, 446.3 mg), (c) 1.0 mmol, 138.0 mg, and (d) inseparable 7:1 mixture of **527** and **534** (88%, 0.88 mmol, 156.6 mg).

Preparation of (1-(3-ethylidene-1-methylcyclopentyl)but-3-ynyloxy)trimethylsilane, 535 and (1-(3-ethylidene-1-methylcyclopentyl)buta-2,3-dienyloxy)trimethylsilane, 536

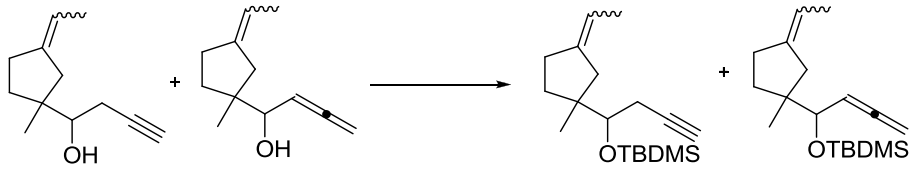


527 534 535 536

Table 51, Entry 1:

To a stirred solution of **527** and **234** (7:1 mixture, 3.0 mmol, 534.0 mg) in DCM (15 mL) at r.t. was added Et_3N (9.0 mmol, 0.9 g) and TMSCl (4.5 mmol, 486.0 mg). The mixture was then stirred at r.t. monitoring progress by TLC analysis. The mixture was then diluted with diethyl ether (20 mL) and sat. aq. NH_4Cl (20 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-5% ether in petrol) to provide **535** (85%, 2.55 mmol, 636.6 mg) and **536** (12%, 0.36 mmol, 90.0 mg) as colourless liquids. Combined yield of **535** and **536** (97%, 2.91 mmol, 727.5 mg) isolated as a 7:1 mixture.

Preparation of *tert*-butyl(1-(3-ethylidene-1-methylcyclopentyl)but-3-ynyloxy)dimethyl silane, 537 and *tert*-butyl(1-(3-ethylidene-1-methylcyclopentyl)buta-2,3-dienyloxy) dimethylsilane, 538

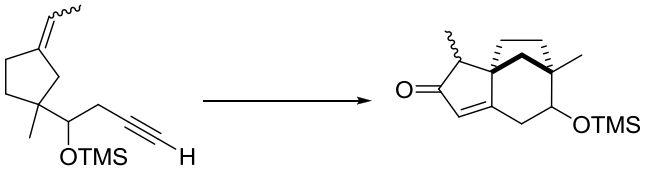


527 **534** **537** **538**

Table 51, Entry 2:

To a stirred solution of **527** and **234** (7:1 mixture, 3.0 mmol, 534.0 mg) in DCM at 0 °C was added Et_3N (6.0 mmol, 0.6 g), DMAP (1.0 mmol, 122.0 mg) and TBDMSOTf (4.0 mmol, 1.06 g). The mixture was then stirred at 0 °C for 6 h, before slowly warming to r.t. The mixture was then stirred at r.t. for 6 h before adding diethyl ether (20 mL) and sat. aq. NH_4Cl (20 mL). The organic phase was separated off and the aqueous phase was further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-5% ether in petrol) to provide **537** (84%, 2.52 mmol, 735.8 mg) and **536** (12%, 0.36 mmol, 105.1 mg) as colourless liquids. Combined yield of **537** and **538** (96%, 2.88 mmol, 841.0 mg) isolated as a 7:1 mixture.

Preparation of 539



535 **539**

Following **General Procedure (U)**, entry 1 was reported as (a) quantity of **535**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

Table 52, Entry 1:

(a) 1.0 mmol, 250.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 12 h, and (f) **539** (41%, 0.41 mmol, 114.0 mg).

Following **General Procedure (V)**, entries 2 and 3 were reported as (a) quantity of **535**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) reaction temperature, (e) quantity of $TMANO{\cdot}2H_2O$, (f) reaction length, and (g) yield of product.

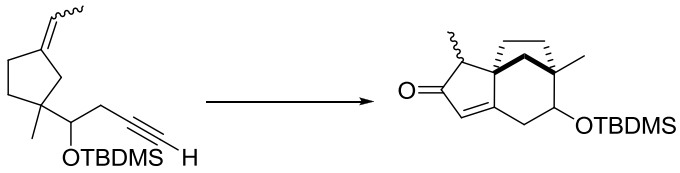
Table 52, Entry 2:

(a) 1.0 mmol, 250.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 8 h, and (g) **539** (32%, 0.32 mmol, 89.0 mg).

Table 52, Entry 3:

(a) 1.0 mmol, 250.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 8 h, and (g) **539** (31%, 0.31 mmol, 86.2 mg).

Preparation of 540



537 **540**

Following **General Procedure (U)**, entry 4 was reported as (a) quantity of **537**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

Table 52, Entry 4:

(a) 1.0 mmol, 292.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 12 h, and (f) **540** (58%, 0.58 mmol, 185.6 mg).

Following **General Procedure (V)**, entries 5 and 6 were reported as (a) quantity of **537**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) reaction temperature, (e) quantity of $TMANO{\cdot}2H_2O$, (f) reaction length, and (g) yield of product.

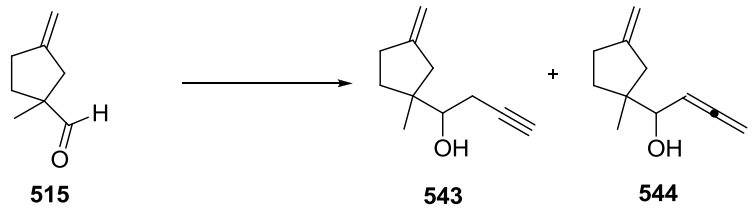
Table 52, Entry 5:

(a) 1.0 mmol, 292.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 8 h, and (g) **540** (49%, 0.49 mmol, 156.8 mg).

Table 52, Entry 6:

(a) 1.0 mmol, 292.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 8 h, and (g) **540** (48%, 0.48 mmol, 153.6 mg).

Preparation of 1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-ol, 543 and 1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-ol, 544



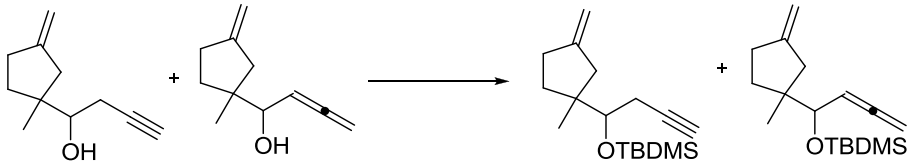
515 543 544

Following **General Procedure (X)**, the above reaction (**Scheme 210**) was reported as (a) quantity of zinc powder, (b) quantity of alkyne, (c) quantity of **515**, and (d) yield of product.

Scheme 210:

(a) 4 mmol, 260 mg, (b) propargyl bromide **529** (80% w/w in toluene, 3.0 mmol, 446.3 mg), (c) 1.0 mmol, 124.0 mg, and (d) inseparable 7:1 mixture of **543** and **544** (81%, 0.81 mmol, 132.8 mg).

Preparation of *tert*-butyldimethyl(1-(1-methyl-3-methylenecyclopentyl)but-3-ynyloxy) silane, 541 and *tert*-butyldimethyl(1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dienyl oxy)silane, 545

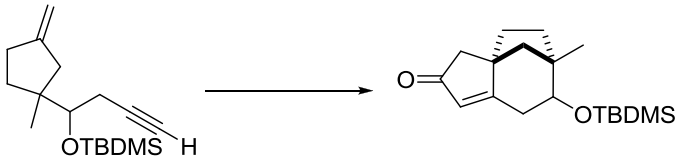


543 544 541 545

Scheme 211:

To a stirred solution of **543** and **544** (4.0 mmol, 656.0 mg) in DCM at 0 °C was added Et_3N (10.0 mmol, 1.0 g), DMAP (1.0 mmol, 122.0 mg) and TBDMSOTf (5.0 mmol, 1.32 g). The mixture was then stirred at 0 °C for 6 h, before slowly warming to r.t. The mixture was stirred at r.t. for 6 h before adding diethyl ether (20 mL) and sat. aq. NH_4Cl (20 mL). The organic phase was separated and the aqueous phase was further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-5% ether in petrol) to provide **541** (81%, 3.22 mmol, 895.2 mg) and **545** (11%, 0.46 mmol, 127.9 mg) as colourless liquids. Combined yield of **541** and **545** (92%, 3.68 mmol, 1.02 g) isolated as a 7:1 mixture.

Preparation of 542



541 **542**

Following **General Procedure (U)**, entry 1 was reported as (a) quantity of **541**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) quantity of DodSMe, (e) reaction length, and (f) yield of product.

Table 53, Entry 1:

(a) 1.0 mmol, 278.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCE (10 mL), (d) 4.5 mmol, 972.0 mg, (e) 12 h, and (f) **542** (71%, 0.71 mmol, 217.3.6 mg).

Following **General Procedure (V)**, entries 2 and 3 were reported as (a) quantity of **541**, (b) quantity of $Co_2(CO)_8$, (c) volume of solvent, (d) reaction temperature, (e) quantity of $TMANO{\cdot}2H_2O$, (f) reaction length, and (g) yield of product.

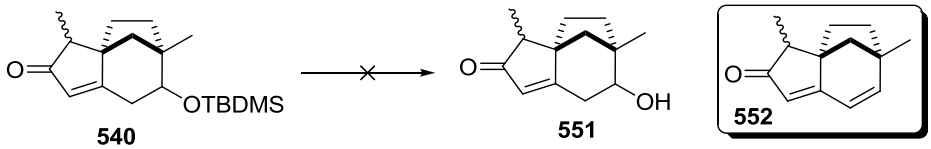
Table 53, Entry 2:

(a) 1.0 mmol, 278.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) r.t., (e) 4.5 mmol, 499.5 mg, (f) 8 h, and (g) **542** (62%, 0.62 mmol, 189.7 mg).

Table 53, Entry 3:

(a) 1.0 mmol, 278.0 mg in DCM (5 mL), (b) 1.1 mmol, 376.2 mg, (c) DCM (10 mL), (d) 0 °C, (e) 4.5 mmol, 499.5 mg, (f) 8 h, and (g) **542** (59%, 0.59 mmol, 180.5 mg).

Attempted preparation of 551



540 **551** **552**

Table 54, Entry 1:

To a stirred solution of **540** (2.0 mmol, 640.0 mg) in DCM (10 mL) at r.t. was added TBAF (1 M solution in THF, 3.0 mmol, 3 mL). The mixture was stirred at r.t. for 72 h, monitoring progress by TLC analysis. Following the alotted time, only the starting material **540** was

detected. To the mixture was added diethyl ether (10 mL) and H_2O (20 mL), the organic layer separated off and the aqueous phase further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude product indicated only **540** present.

Table 54, Entry 2:

To a stirred solution of **540** (2.0 mmol, 640.0 mg) in DCM (10 mL) at r.t. was added TBAF (1 M solution in THF, 6.0 mmol, 6 mL). The mixture was warmed to reflux and stirred for 72 h, monitoring progress by TLC analysis. Following the alotted time, only the starting material **540** was detected. To the mixture was added diethyl ether (10 mL) and H_2O (20 mL), the organic layer separated off and the aqueous phase further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude product indicated only **540** present.

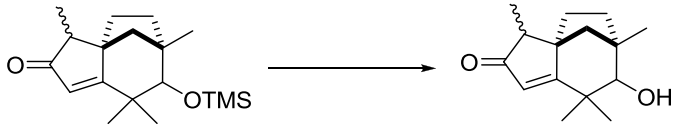
Table 54, Entry 3:

To a stirred solution of **540** (2.0 mmol, 640.0 mg) in MeOH (10 mL) at r.t. was added TMSBr (0.3 mmol, 45.9 mg) dropwise. The mixture was was stirred at r.t. for 24 h, monitoring progress by TLC analysis. To the mixture were added diethyl ether (10 mL) and brine (20 mL), the organic layer separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-30% diethyl ether in petrol) to afford **552** (81%, 1.62 mmol, 304.6 mg) as a colourless oil.

Table 54, Entry 4:

To a stirred solution of **540** (2.0 mmol, 640.0 mg) in MeOH (10 mL) at r.t. was added AcCl (0.3 mmol, 23.6 mg) dropwise. The mixture was was stirred at r.t. for 24 h, monitoring progress by TLC analysis. To the mixture were added diethyl ether (10 mL) and brine (20 mL), the organic layer separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-30% diethyl ether in petrol) to afford **552** (84%, 1.68 mmol, 315.8 mg) as a colourless oil.

Preparation of 551

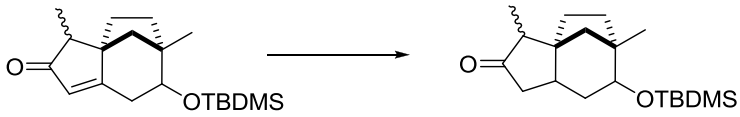


539 **551**

Table 54, Entry 5:

To a stirred solution of **539** (1.0 mmol, 306.0 mg) in DCM (10 mL) at r.t. was added TBAF (1 M solution in THF, 2.0 mmol, 2 mL). The mixture was stirred at r.t. for 24 h, monitoring progress by TLC analysis. To the mixture was added diethyl ether (10 mL) and H_2O (20 mL), the organic layer separated off and the aqueous phase further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-100% ether in petrol) to afford **551** (91%, 0.91 mmol, 187.5 mg) as a colourless oil.

Preparation of 556

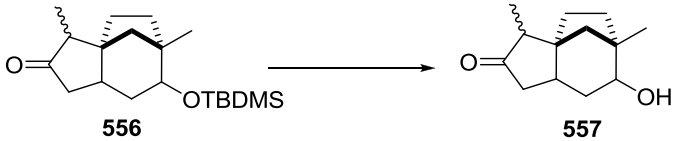


540 **556**

Scheme 214:

To a stirred solution of **540** (2.0 mmol, 320.0 mg) in EtOAc (10 mL) at r.t. was added Pd/C (10% w/w on carbon, 10 mol%, 0.2 mmol, 1.06 g). The reaction vessel was sealed, the air evacuated and the reaction mixture flushed with an atmosphere of hydrogen. The mixture was stirred at r.t. for 24 h, before filtering the mixture through a plug of silica, and eluting with EtOAc. The crude product was then concentrated under reduced pressure and purified by column chromatography (eluent 0-50% ether in petrol) to provide **556** (95%, 1.9 mmol, 611.8 mg) as a colourless oil.

Preparation of 557



556 **557**

Table 55, Entry 1:

To a stirred solution of **556** (1.0 mmol, 322.0 mg) in DCM (10 mL) at r.t. was added TBAF (1 M solution in THF, 3.0 mmol, 3 mL). The mixture was stirred at r.t. for 72 h, monitoring progress by TLC analysis. Following the alotted time, only the starting material **556** was

detected. To the mixture was added diethyl ether (10 mL) and H_2O (20 mL), the organic layer separated off and the aqueous phase further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude product indicated only **556** present.

Table 55, Entry 2:

To a stirred solution of **556** (1.0 mmol, 322.0 mg) in DCM (10 mL) at r.t. was added TBAF (1 M solution in THF, 6.0 mmol, 6 mL). The mixture was warmed to reflux and stirred for 72 h, monitoring progress by TLC analysis. Following the alotted time, only the starting material **556** was detected. To the mixture was added diethyl ether (10 mL) and H_2O (20 mL), the organic layer separated off and the aqueous phase further extracted with diethyl ether (2 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude product indicated only **556** present.

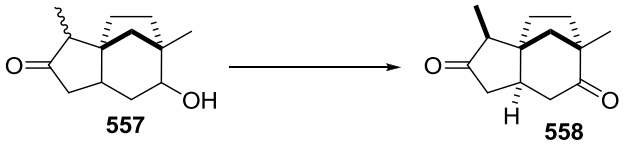
Table 55, Entry 3:

To a stirred solution of **556** (1.0 mmol, 322.0 mg) in MeOH (10 mL) at r.t. was added TMSBr (0.3 mmol, 23.0 mg) dropwise. The mixture was was stirred at r.t. for 24 h, monitoring progress by TLC analysis. To the mixture were added diethyl ether (10 mL) and brine (20 mL), the organic layer separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to afford **557** (67%, 0.67 mmol, 139.4 mg) as a colourless oil.

Table 55, Entry 4:

To a stirred solution of **556** (1.0 mmol, 322.0 mg) in MeOH (10 mL) at r.t. was added AcCl (0.3 mmol, 12.0 mg) dropwise. The mixture was was stirred at r.t. for 24 h, monitoring progress by TLC analysis. To the mixture were added diethyl ether (10 mL) and brine (20 mL), the organic layer separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to afford **557** (91%, 0.91 mmol, 189.3 mg) as a colourless oil.

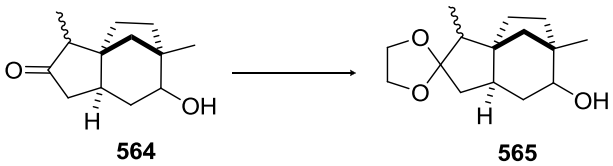
Preparation of 558



Scheme 215:

To a stirred solution of **557** (1.0 mmol, 208.0 mg) in DCM (15 mL) at r.t. was added celite (~2 g) and the resultant suspension stirred for 10 min. To the mixture was added PDC (2.0 mmol, 750.0 mg) in a single portion. The resultant suspension was stirred at r.t. for 24 h, after which the mixture was then filtered through celite, eluting with DCM, and the mixture concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-50% ether in petrol) to afford **558** as a colourless oil (88%, 0.88 mmol, 181.3 mg). Following purification **558** (0.88 mol, 181.3 mg) was dissolved in toluene (5 mL) at r.t. before adding DBU (2.0 mmol, 304.0 mg) as a single portion. The mixture was then stirred at r.t. for 24 h before adding the reaction mixture directly onto a silica column. The cude product was purified by column chromatography (eluent: 0-80% ether in petrol) to afford 558 (100%, 0.88 mmol, 181.3 mg) as a colourless oil.

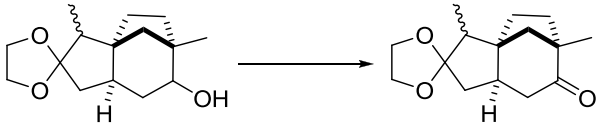
Preparation of 565



Scheme 218:

To a stirred solution of **564** (2.0 mmol, 208.0 mmol) in benzene (10 mL) was added triethyl orthoformate (4.0 mmol, 396.0 mg), ethylene glycol (4.0 mmol, 248.0 mg) and *p*-TSA·H_2O (0.1 mmol, 17 mg) at r.t. and the resultant mixture was stirred for 48 h. The mixture was then diluted with diethyl ether (20 mL) and brine (20 mL), the organic layer separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to afford **565** (93%, 1.86 mmol, 468.7 mg) as a colourless oil.

Preparation of 566

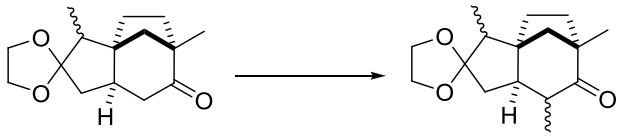


565 **566**

Scheme 218:

To a stirred solution of **565** (1.0 mmol, 252.0 mg) in DCM (15 mL) at r.t. was added celite (~2 g) and the resultant suspension stirred for 10 min. To the mixture was added PDC (2.0 mmol, 750.0 mg) in a single portion. The resultant suspension was stirred at r.t. for 24 h, after which the mixture was then filtered through celite, eluting with DCM, and the mixture concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-100% ether in petrol) to afford **566** as a colourless oil (88%, 0.88 mmol, 220.0 mg).

Preparation of 567



566 **567**

Scheme 219:

To a stirred solution of diisopropylamine (1.6 mmol, 161.6 mg) in THF (20 mL) at -20 °C was added ^{n}BuLi (2.5 M in hexanes, 1.5 mmol, 0.6 mL) dropwise over 5 min. The mixture was then warmed to r.t. over 1 h, before cooling to -78 °C. To the mixture was added a solution of **566** (1.0 mmol, 250.0 mg) in THF (1 mL) dropwise over 10 min, before warming the solution to r.t. over 1 h. The mixture was then cooled to -78 °C where MeI (1.6 mmol, 227.2 mg) was added dropwise. Upon complete addition, the mixture was slowly warmed to r.t., where it was stirred for 6 h. The mixture was then diluted with diethyl ether (10 mL) and sat. aq. NH_4Cl (20 mL), the organic phase separated off and the aqueous phase further extracted with diethyl ether (10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to afford **567** (95%, 0.95 mmol, 250.8 mg) as a colourless oil.

Preparation of 568 or 569

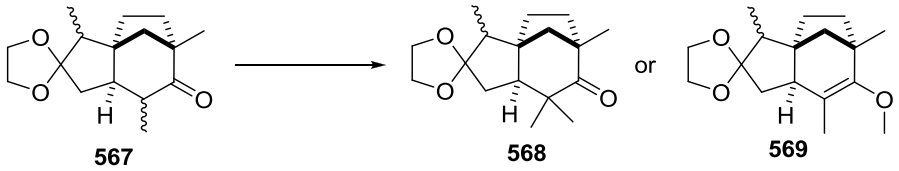


Table 56, Entry 1:

To a stirred solution of **567** (1.0 mmol, 264 .0 mg) in THF (10 mL) at -20 °C was added KHMDS (1 M solution in THF, 1.5 mmol, 1.5 mL). The mixture was stirred at -20 °C for 1 h before adding MeI (2.0 mmol, 284.0 mg) dropwise. The resultant solution was stirred at -20 °C for 1 h, then warmed to r.t. where it was stirred for 3 h. The mixture was then diluted with diethyl ether (10 mL) and sat. aq. NH_4Cl (20 mL), the organic phase was separated off and the aqueous phase further extracted with diethyl ether (10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to afford starting material **567** (99%, 0.99 mmol, 261.4 mg) as a colourless oil.

Table 56, Entry 2:

To a stirred solution of diisopropylamine (1.6 mmol, 161.6 mg) in THF (20 mL) at -20 °C was added ^{n}BuLi (2.5 M in hexanes, 1.5 mmol, 0.6 mL) dropwise over 5 min. The mixture was then warmed to r.t. over 1 h, before cooling to -78 °C. To the mixture was added a solution of **567** (1.0 mmol, 264.0 mg) in THF (1 mL) dropwise over 10 min, before warming the solution to r.t. over 1 h. The mixture was then cooled to -78 °C where MeI (2.0 mmol, 284.0 mg) was added dropwise. The mixture was then slowly warmed to r.t., where it was stirred for 3 h. The mixture was then diluted with diethyl ether (10 mL) and sat. aq. NH_4Cl (20 mL), the organic phase was separated off and the aqueous phase further extracted with diethyl ether (10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to afford starting material **567** (98%, 0.98 mmol, 258.7 mg) as a colourless oil.

Table 56, Entry 3:

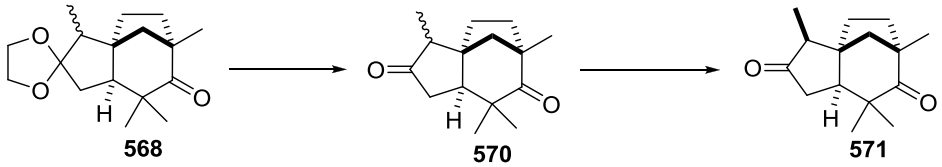
To a stirred solution of diisopropylamine (1.6 mmol, 161.6 mg) in THF (20 mL) at -20 °C was added ^{n}BuLi (2.5 M in hexanes, 1.5 mmol, 0.6 mL) dropwise over 5 min. The mixture was then warmed to r.t. over 1 h, before cooling to -78 °C. To the mixture was added a solution of **567** (1.0 mmol, 264.0 mg) in THF (1 mL) dropwise over 10 min, before warming

the solution to r.t. over 1 h. The mixture was then cooled to -78 °C where dimethylsulfate (2.0 mmol, 252.0 mg) was added dropwise. The mixture was then slowly warmed to r.t., where it was stirred for 3 h. The mixture was then diluted with diethyl ether (10 mL) and sat. aq. NH_4Cl (20 mL), the organic phase was separated off and the aqueous phase further extracted with diethyl ether (10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-50% diethyl ether in petrol) to afford **569** (65%, 0.65 mmol, 180.7 mg) as a colourless oil.

Table 56, Entry 4:

To a stirred solution of diisopropylamine (3.5 mmol, 353.5 mg) in THF (20 mL) at -20 °C was added ^{n}BuLi (2.5 M in hexanes, 3.0 mmol, 1.2 mL) dropwise over 5 min. The mixture was then warmed to r.t. over 2 h, before cooling to -78 °C. To the mixture was added a solution of **567** (1.0 mmol, 264.0 mg) in THF (1 mL) dropwise over 10 min, before warming the solution to r.t. over 2 h. The mixture was then cooled to -78 °C where MeI (4.0 mmol, 568.0 mg) was added dropwise. The mixture was then slowly warmed to r.t., where it was stirred for 12 h. The mixture was then diluted with diethyl ether (10 mL) and sat. aq. NH_4Cl (20 mL), the organic phase was separated off and the aqueous phase further extracted with diethyl ether (10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to afford **568** (88%, 0.88 mmol, 244.6 mg) as a colourless oil.

Preparation of 571



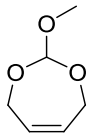
Scheme 220:

To a stirred solution of **568** (1.0 mmol, 278.0 mg) in diethyl ether (5 mL) was added aq. HCl (1 M, 5 mL) at r.t. and the resultant mixture stirred for 6 h. The mixture was then diluted with diethyl ether (10 mL) and sat. aq. $NaHCO_3$ (20 mL), the organic phase was separated off and the aqueous phase further extracted with diethyl ether (3 x 10 mL). The organic phases were combined dried over Na_2SO_4, filtered, and concentrated under reduced pressure, to provide

crude product **570** (98%, 0.98 mmol, 229.3 mg). The crude product was then diluted with toluene (5 mL), before adding DBU (2.0 mmol, 304.0 mg) and the mixture stirred at r.t. for 12 h. Following the allotted time, the mixture was added directly on a column containing silica. The crude product was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to afford **571** (97%, 0.97 mmol, 227.0 mg) as a colourless oil.

5.2 Spectral Data

2-methoxy-4,7-dihydro-1,3-dioxepine, 313[260]



Chemical Formula: $C_6H_{10}O_3$
Molecular Weight: 130.14

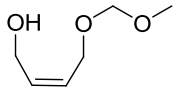
FTIR ($CDCl_3$): 2941, 2852, 1448, 1390 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 3.43 (s, 3H, OCH_3), 4.15 (d, ^2J = 14.8 Hz, 2H, OCH_2), 4.50 (d, ^2J = 14.8 Hz, 2H, OCH_2), 5.42 (s, 1H, OCH), 5.73 (s, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 53.0, 61.0, 113.3, 128.7 ppm.

HRMS m/z (ESI) Calc. for $C_6H_{11}O_3$ (M^++H): 131.0703. Found 131.0704.

(*Z*)-4-(methoxymethoxy)but-2-en-1-ol, 314[260]



Chemical Formula: $C_6H_{12}O_3$
Molecular Weight: 132.16

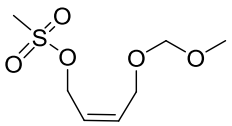
FTIR ($CDCl_3$): 3412, 2937, 1450, 1400 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 3.42 (s, 3H, OCH_3), 4.19 (d, J = 6.7 Hz, 2H, OCH_2), 4.24 (d, J = 6.6 Hz, 2H, CH_2OH), 4.67 (s, 2H, OCH_2O), 5.69-5.76 (m, 1H, olefinic CH), 5.85-5.92 (m, 1H, olefinic CH) ppm. No OH observed.

^{13}C NMR δ (100 MHz, $CDCl_3$): 54.9, 57.9, 62.0, 94.9, 127.4, 132.2 ppm.

HRMS m/z (ESI) Calc. for $C_6H_{13}O_3$ (M^++H): 133.0859. Found: 133.0856.

(*Z*)-4-(methoxymethoxy)but-2-enyl methanesulfonate, (mesylate of 314)[182]



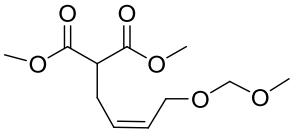
Chemical Formula: $C_7H_{14}O_5S$
Molecular Weight: 210.25

FTIR ($CDCl_3$): 2987, 2889, 1444, 1396, 1326, 1304 cm^{-1}

^1H NMR δ (400 MHz, $CDCl_3$): 3.05 (s, 3H, SCH_3), 3.41 (s, 3H, OCH_3), 4.20 (d, J = 6.4 Hz, 2H, OCH_2), 4.67 (s, 2H, OCH_2O), 4.88 (d, J = 6.4 Hz, 2H, CH_2OS), 5.76-5.84 (m, 1H, olefinic CH), 5.89-5.97 (m, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 38.3, 55.4, 62.9, 65.3, 96.0, 125.1, 132.5 ppm.

(*Z*)-dimethyl 2-(4-(methoxymethoxy)but-2-enyl)malonate, 319



Chemical Formula: $C_{11}H_{18}O_6$
Molecular Weight: 246.26

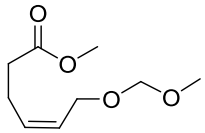
FTIR ($CDCl_3$): 2953, 2891, 1732, 1435, 1336 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 2.72 (apparent t, *J* = 7.7 Hz, 2H, CH_2), 3.40 (s, 3H, OCH_3), 3.45, (t, *J* = 7.7 Hz, 1H, CH), 3.76 (s, 6H, OCH_3), 4.17 (d, *J* = 6.6 Hz, 2H, OCH_2), 4.65 (s, 2H, OCH_2O), 5.51-5.59 (m, 1H, olefinic CH), 5.66-5.73 (m, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 27.1, 51.3, 52.8, 55.5, 63.0, 95.9, 128.1, 128.4, 169.4 ppm.

HRMS m/z (ESI): Calc. for $C_{11}H_{19}O_6$ (M^++H): 247.1176. Found 247.1177.

(*Z*)-methyl 6-(methoxymethoxy)hex-4-enoate, 318



Chemical Formula: $C_9H_{16}O_4$
Molecular Weight: 188.22

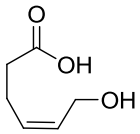
FTIR ($CDCl_3$): 2951, 2926, 1735, 1436, 1359 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 2.38-2.49 (m, 4H, CH_2-CH_2), 3.41 (s, 3H, OCH_3), 3.71(s, 3H, OCH_3), 4.17 (d, *J* = 6.2 Hz, 2H, OCH_2), 4.66 (s, 2H, OCH_2O), 5.56-5.68 (m, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 22.9, 34.0, 51.7, 55.5, 62.8, 95.7, 127.4, 131.6, 173.6 ppm.

HRMS m/z (ESI) Calc. for $C_9H_{17}O_4$ (M^++H):189.1121. Found 189.1121.

(*Z*)-6-hydroxyhex-4-enoic acid, 320



Chemical Formula: $C_6H_{10}O_3$
Molecular Weight: 130.14

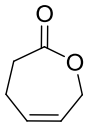
FTIR ($CDCl_3$): 3512, 2948, 2886, 1718, 1442 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 2.37-2.43 (m, 4H, CH_2-CH_2), 4.34 (d, *J* = 6.1 Hz, 2H, OCH_2), 5.37-5.44 (m, 1H, olefinic CH), 5.58-5.65 (m, 1H, olefinic CH) ppm. No OH detected.

^{13}C NMR δ (100 MHz, $CDCl_3$): 23.4, 34.8, 63.1, 126.2, 131.7, 176.2 ppm.

HRMS m/z (ESI) Calc. for $C_6H_{14}N_1O_3$ (M^++NH_4): 148.0968. Found 148.0965.

3,4-dihydrooxepin-2(7H)-one, 300



Chemical Formula: $C_6H_8O_2$
Molecular Weight: 112.13

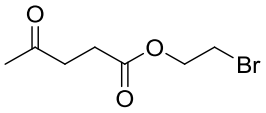
FTIR ($CDCl_3$): 2983, 2899, 1724, 1444, 1402, 1386 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 2.49-2.57 (m, 2H, CH_2), 2.90-2.97 (dd, J = 6.5 and 6.8 Hz, 2H, CH_2), 4.69-4.73 (m, 2H, OCH_2), 5.80-5.90 (m, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 25.3, 31.5, 63.9, 124.1, 132.1, 174.7 ppm.

HRMS m/z (ESI) Calc. for $C_6H_9O_2$ (M^++H): 113.0597. Found 113.0954.

2-bromoethyl 4-oxopentanoate, 325



Chemical Formula: $C_7H_{11}BrO_3$
Molecular Weight: 223.06

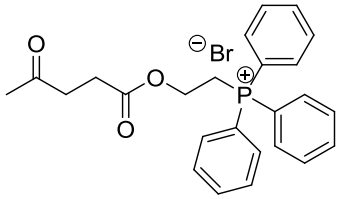
FTIR ($CDCl_3$): 2987, 1739, 1720, 1408, 1357 1158 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 2.20 (s, 3H, CH_3), 2.62 (t, J = 6.6 Hz, 2H, CH_2), 2.78 (t, J = 6.6 Hz, 2H, CH_2), 3.50 (t, J = 6.0 Hz, 2H, CH_2Br), 4.39 (t, J = 6.0 Hz, 2H, OCH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 26.9, 28.1, 29.3, 37.2, 62.3, 171.7, 205.9 ppm.

HRMS m/z (ESI) Calc. for $C_7H_{11}BrO_3$ (M^+): 222.9964. Found 222.9967.

(2-(4-oxopentanoyloxy)ethyl)triphenylphosphonium bromide, 306



Chemical Formula: $C_{25}H_{26}BrO_3P$
Molecular Weight: 485.35

FTIR ($CDCl_3$): 3055, 3016, 2927, 2875, 1735, 1710, 1436, 1367 cm^{-1}.

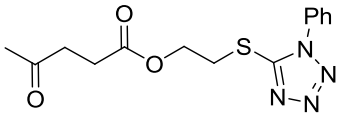
^1H NMR δ (400 MHz, $CDCl_3$): 2.14 (apparent t, J = 6.2 Hz, 2H, CH_2), 2.16 (s, 3H, CH_3), 2.65 (apparent t, J = 6.2 Hz, 2H, CH_2), 4.40-4.58 (m, 4H, OCH_2 and PCH_2), 7.69-7.75 (m, 6H, ArH), 7.78-7.84 (m, 3H, ArH), 7.87-7.94 (m, 6H, ArH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 23.3 (d, $^1J_{P\text{-}C}$ = 57.9 Hz), 26.8, 29.4, 37.1, 57.4 117.5 (d, $^1J_{P\text{-}C}$ = 86.6 Hz), 129.9, 133.4, 134.6, 171.3, 206.1 ppm.

^{31}P NMR δ (162 MHz): 23.09 ppm.

HRMS m/z (ESI) Calc. for $C_{25}H_{26}O_3P$ (M^+): 405.1614. Found 405.1613.

2-(1-phenyl-1H-tetrazol-5-ylthio)ethyl 4-oxopentanoate, 327



Chemical Formula: $C_{14}H_{16}N_4O_3S$
Molecular Weight: 320.37

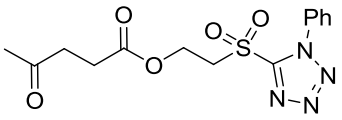
FTIR ($CDCl_3$): 2958, 2922, 1735, 1714, 1597, 1498 1406, 1384, 1354 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 2.18 (s, 3H, CH_3), 2.58 (t, *J* = 6.5 Hz, 2H, CH_2), 2.75 (t, *J* = 6.5 Hz, 2H, CH_2), 3.65 (t, *J* = 6.1 Hz, 2H, CH_2S), 4.49 (t, *J* = 6.1 Hz, 2H, OCH_2), 7.53-7.62 (m, 5H, ArH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 27.6, 30.1, 31.7, 37.9, 62.2, 123.8, 129.8, 130.3, 133.5, 153.7, 172.4, 206.5 ppm.

HRMS m/z (ESI) Calc. for $C_{14}H_{17}N_4O_3S$ (M^++H): 321.1014. Found 321.1016.

2-(1-phenyl-1H-tetrazol-5-ylsulfonyl)ethyl 4-oxopentanoate, 307



Chemical Formula: $C_{14}H_{16}N_4O_5S$
Molecular Weight: 352.37

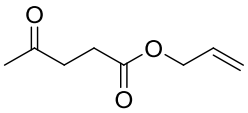
FTIR ($CDCl_3$): 2970, 2927, 1751, 1712, 1496, 1400, 1357, 1340, 1305 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 2.15 (s, 3H, CH_3), 2.43 (t, *J* = 6.1 Hz, 2H, CH_2), 2.70 (t, *J* = 6.1 Hz, 2H, CH_2), 4.03 (t, *J* = 5.7 Hz, 2H, CH_2S), 4.60 (t, *J* = 5.7 Hz, 2H, OCH_2), 7.56-7.69 (m, 5H, ArH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 27.7, 29.7, 37.5, 55.1, 56.2, 125.1, 129.8, 131.6, 133.1, 153.7, 171.7, 206.5 ppm.

HRMS m/z (ESI) Calc. for $C_{14}H_{20}N_5O_5S$ (M^++NH_4): 370.1182. Found 370.1181.

allyl 4-oxopentanoate, 339



Chemical Formula: $C_8H_{12}O_3$
Molecular Weight: 156.18

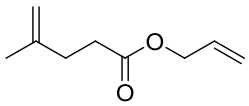
FTIR ($CDCl_3$): 2994, 2936, 1739, 1717, 1412, 1365 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 2.23 (s, 3H, CH_3), 2.64 (t, *J* = 6.2 Hz, 2H, CH_2), 2.79 (t, *J* = 6.2 Hz, 2H, CH_2), 4.61 (dt, ^4J = 1.4 and *J* = 5.7 Hz, 2H, OCH_2), 5.26 (dt, ^4J = 1.4 and *J* = 10.3 Hz, 1H, olefinic CH_2), 5.34 (dt, ^4J = 1.4 and *J* = 17.3 Hz, 1H, olefinic CH_2), 5.93 (ddt, *J* = 5.7, 10.3 and 17.3 Hz, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 27.4, 29.4, 37.4, 64.8, 117.8, 131.6, 171.9, 206.0 ppm.

HRMS m/z (ESI) Calc. for $C_8H_{13}O_3$ (M^++H): 157.0859. Found 157.0858.

allyl 4-methylpent-4-enoate, 308



Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154.21

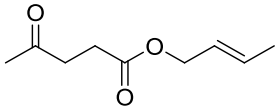
FTIR ($CDCl_3$): 2977, 1732, 1592, 1438 cm^{-1}.

^1H NMR δ (400MHz, $CDCl_3$): 1.77 (s, 3H, CH_3), 2.37 (t, *J* = 7.3 Hz, 2H, CH_2), 2.49-2.52 (m, 2H, CH_2), 4.61 (dt, ^4J = 1.3 and *J* = 5.7 Hz, 2H, OCH_2), 4.72 (s, 1H, olefinic CH_2), 4.78 (s, 1H, olefinic CH_2), 5.26 (dt, ^4J = 1.5 and *J* = 10.6 Hz, 1H, olefinic CH_2), 5.34 (dt, ^4J = 1.5 and *J* = 17.3 Hz, 1H, olefinic CH_2), 5.94 (ddt, *J* = 5.7, 10.6 and 17.3 Hz, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 22.6, 31.1, 32.7, 65.1, 110.6, 118.5, 134.0, 144.4, 173.0 ppm.

HRMS m/z (ESI) Calc. for $C_9H_{15}O_2$ (M^++H): 155.1067. Found 155.1069.

(*E*)-but-2-enyl 4-oxopentanoate, 344



Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170.21

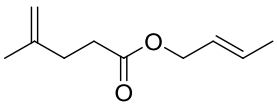
FTIR ($CDCl_3$): 2969, 2920, 1731, 1719, 1410, 1354 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.75 (d, *J* = 6.5 Hz, 3H, olefinic CH_3), 2.21 (s, 3H, CH_3), 2.61 (t, *J* = 6.5 Hz, 2H, CH_2), 2.77 (t, *J* = 6.5 Hz, 2H, CH_2), 4.53 (dd, ^4J = 1.2 and *J* = 6.5 Hz, 2H, OCH_2), 5.60 (dtq, ^4J = 1.2 and *J* = 6.5 and 15.3 Hz, 1H, olefinic CH), 5.81 (dqt, ^4J = 1.2 and *J* = 6.5 and 15.3 Hz, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 17.3, 27.5, 29.4, 37.4, 64.9, 124.5, 131.0, 172.0, 206.1 ppm.

HRMS m/z (ESI) Calc. for $C_9H_{18}NO_3$ (M^++NH_4): 188.1281. Found 188.1282.

(*E*)-but-2-enyl 4-methylpent-4-enoate, 345



Chemical Formula: $C_{10}H_{16}O_2$
Molecular Weight: 168.23

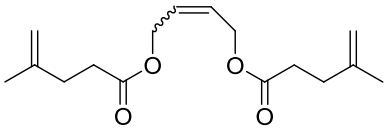
FTIR ($CDCl_3$): 2972, 2920, 1731, 1448, 1377 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.73 (dd, ^4J = 1.5 and *J* = 6.6 Hz, 3H, olefinic CH_3), 1.74 (s, 3H, CH_3), 2.34 (t, *J* = 6.7 Hz, 2H, CH_2), 2.47-2.51 (m, 2H, CH_2), 4.51 (dd, ^4J = 1.2 and *J* = 6.6 Hz, 2H, OCH_2), 4.69 (s, 1H, olefinic CH_2), 4.75 (s, 1H, olefinic CH_2), 5.59 (dtq,^4J = 1.5 and *J* = 6.6 and 15.4 Hz, 1H, olefinic CH), 5.80 (dqt, ^4J = 1.5 and ^3J = 6.6 and 15.4 Hz, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 17.7, 22.5, 32.6, 32.7, 65.1, 110.4, 125.1, 131.3, 144.1, 173.1 ppm.

HRMS m/z (ESI) Calc. for $C_{10}H_{16}O_2$ (M^+): 168.1145. Found 168.1146

but-2-ene-1,4-diyl bis(4-methylpent-4-enoate), 340



Chemical Formula: $C_{16}H_{24}O_4$
Molecular Weight: 280.36

See **Appendix 1** for a copy of the ^{1}H NMR spectrum.

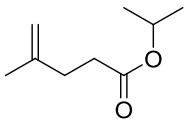
FTIR ($CDCl_3$): 2972, 2937, 1732, 1649, 1442, 1375 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 1.77 (s, 6H, CH_3), 2.37 (t, *J* = 7.3 Hz, 4H, CH_2), 2.48-2.52 (m, 4H, CH_2), 4.57-4.63 (m, 4H, OCH_2), 4.71 (s, 2H, olefinic CH_2), 4.77 (s, 2H, olefinic CH_2), 5.85-5.90 (m, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 22.5, 32.6, 60.0, 63.8, 110.5, 128.1, 144.0, 172.9 ppm.

HRMS m/z (ESI) Calc. for $C_{16}H_{28}NO_4$ (M^++NH_4): 298.2013. Found 298.2014.

isopropyl 4-methylpent-4-enoate, 341



Chemical Formula: $C_9H_{16}O_2$
Molecular Weight: 156.22

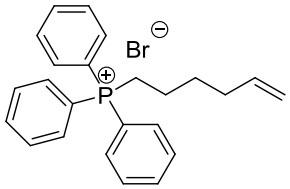
FTIR ($CDCl_3$): 2982, 2938, 1724, 1454, 1375 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 1.25 (d, *J* = 6.2 Hz, 6H, CH_3), 1.77 (s, 3H, CH_3), 2.35 (t, *J* = 7.3 Hz, 2H, CH_2), 2.44 (t, *J* = 7.3 Hz, 2H, CH_2), 4.71 (s, 1H, olefinic CH_2), 4.76 (s, 1H, olefinic CH_2), 5.04 (sept, *J* = 6.2 Hz, 1H, OCH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 21.3, 22.0, 32.2, 32.5, 67.0, 109.8, 143.7, 172.3 ppm.

HRMS m/z (ESI) Calc. for $C_9H_{16}O_2$ (M^+): 156.1145. Found 156.1148.

hex-5-enyltriphenylphosphonium bromide, 362



Chemical Formula: $C_{24}H_{26}BrP$
Molecular Weight: 425.34

FTIR ($CDCl_3$): 3076, 3001, 2883, 1485, 1436 cm^{-1}.

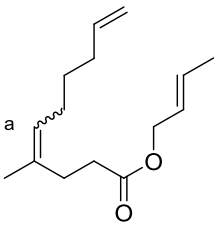
^1H NMR δ (400 MHz, $CDCl_3$): 1.58-1.70 (m, 2H, CH_2), 1.73-1.83 (m, 2H, CH_2), 2.04-2.14 (m, 2H, CH_2), 3.80-3.91 (m, 2H, CH_2P), 4.89 (d, J = 10.3 Hz, 1H, olefinic CH_2), 4.93 (d, J = 17.2 Hz, 1H, olefinic CH_2), 5.68 (ddt, J = 6.6, 10.3 and 17.2 Hz, 1H, olefinic CH), 7.68-7.75 (m, 6H, ArH), 7.78-7.83 (m, 3H, ArH), 7.86-7.92 (m, 6H, ArH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 21.9, 22.7 (d, $^1J_{P-C}$ = 54.0 Hz), 29.1, 33.0, 115.3, 118.4 (d, $^1J_{P-C}$ = 86.1 Hz), 130.4, 133.8, 135.0, 137.7 ppm.

^{31}P NMR δ (64 MHz): 24.7 ppm.

HRMS m/z (ESI) Calc. for $C_{24}H_{26}P$ (M^+): 345.1758. Found 345.1760.

but-2-enyl 4-methyldeca-4,9-dienoate, 358



Chemical Formula: $C_{15}H_{24}O_2$
Molecular Weight: 236.35

[a] Isolated as a suspected 1:2 *E*:*Z* mixture of geometric isomers

The mixture of geometric isomers was inseparable by column chromatography.

See **Appendix 1** for a copy of the ^1H NMR spectrum.

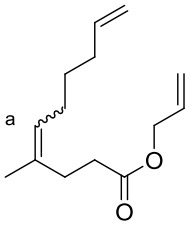
FTIR ($CDCl_3$): 2960, 2927, 2858, 1735, 1442, 1377 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.37-1.46 (m, 2H, CH_2), 1.61 and 1.69 (s, 3H in total, CH_3, ratio 1:2), 1.73 (d, J = 6.5 = Hz, 3H, CH_3), 1.97-2.07 (m, 4H, CH_2-CH_2), 2.30-2.43 (m, 4H, CH_2-CH_2), 4.45-4.56 (d, J = 6.4 Hz, 2H, OCH_2), 4.95 (d, J = 10.1 Hz, 1H, olefinic CH_2), 5.00 (d, J = 17.2 Hz, 1H, olefinic CH_2), 5.14-5.20 (m, 1H, olefinic CH), 5.47-5.63 (m, 1H, olefinic CH), 5.74-5.87 (m, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 17.8, 23.0, 27.2, 27.3, 29.0, 29.2, 33.0, 33.3, 33.4, 34.7, 65.1, 65.2 114.4, 125.2, 126.5, 131.1, 131.2, 133.4, 138.9, 173.2 ppm.

HRMS m/z (ESI) Calc. for $C_{15}H_{25}O_2$ (M^++H): 237.1849. Found 237.1851.

allyl 4-methyldeca-4,9-dienoate, 363



Chemical Formula: $C_{14}H_{22}O_2$
Molecular Weight: 222.32

[a] Isolated as a suspected 1:2 *E*:*Z* mixture of geometric isomers

The mixture of geometric isomers was inseparable by column chromatography.

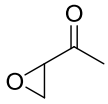
FTIR ($CDCl_3$): 2960, 2927, 2858, 1735, 1442 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.39-1.45 (m, 2H, CH_2), 1.61 and 1.69 (s, 3H in total, CH_3, ratio 1:2), 1.98-2.07 (m, 4H, CH_2-CH_2), 2.32-2.42 (m, 4H, CH_2-CH_2), 4.51-4.63 (m, 2H, OCH_2), 4.94 (d, *J* = 10.4 Hz, 1H, olefinic CH_2), 5.00 (d, *J* = 17.4 Hz, 1H, olefinic CH_2), 5.15-5.19 (m, 1H, olefinic CH), 5.23 (d, *J* = 10.4 Hz, 1H, olefinic CH_2), 5.31 (d, *J* = 17.4 Hz, 1H, olefinic CH_2), 5.80 (ddt, *J* = 5.8, 10.4 and 17.4 Hz, 1H, olefinic CH), 5.91 (ddt, *J* = 5.8, 10.4 and 17.4 Hz, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 22.9, 27.2, 27.3, 28.9, 29.2, 32.8, 33.3, 33.4, 34.6, 65.0, 65.2, 114.4, 118.0, 118.1, 125.1, 125.3, 126.4, 126.6, 132.3, 133.3, 133.4, 138.8, 173.0, 173.5 ppm.

HRMS m/z (ESI) Calc. for $C_{14}H_{23}O_2$ (M^++H): 223.1693. Found 223.1694.

1-(oxiran-2-yl)ethanone, 309[261]



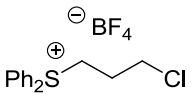
Chemical Formula: $C_4H_6O_2$
Molecular Weight: 86.09

FTIR ($CDCl_3$): 3064, 3002, 1711, 1359 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 2.06 (s, 3H, CH_3), 2.90 (dd, *J* = 2.4 and ^2J = 5.4 Hz, 1H, CH_2), 3.01 (dd, *J* = 4.7 and ^2J = 5.4 Hz, 1H, CH_2), 3.40 (dd, *J* = 2.4 and 4.7 Hz, 1H, CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 23.8, 45.9, 53.7, 205.8 ppm.

(3-chloropropyl)diphenylsulfonium tetrafluoroborate, 392[218]



Chemical Formula: $C_{15}H_{16}BClF_4S$
Molecular Weight: 350.61

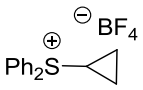
FTIR ($CDCl_3$): 3097, 3049, 1579, 1477, 1444 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 2.28-2.36 (m, 2H, CH_2), 3.80 (apparent t, *J* = 5.9 Hz, 2H, CH_2Cl), 4.36 (apparent t, *J* = 7.3 Hz, 2H, CH_2S), 7.70-7.82 (m, 6H, ArH), 7.94-8.01 (m, 4H, ArH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 27.4, 42.0, 42.2, 123.9, 130.5, 131.6, 134.8 ppm.

^{19}F NMR δ (376 MHz): 150.5 ppm.

cyclopropyldiphenylsulfonium tetrafluoroborate, 310[218]



Chemical Formula: $C_{15}H_{15}BF_4S$
Molecular Weight: 314.15

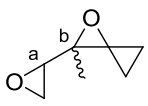
FTIR ($CDCl_3$): 3070, 1581, 1479, 1448 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.43-1.48 (m, 2H, CH_2), 1.64-170 (m, 2H, CH_2), 3.75-3.80 (m, 1H, CHS), 7.65-7.75 (m, 8H, ArH), 7.94-7.98 (m, 2H, ArH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 8.3, 22.5, 126.5, 129.8, 131.6, 134.7 ppm.

^{19}F NMR δ (376 MHz): 151.7 ppm.

2-methyl-2-(oxiran-2-yl)-1-oxaspiro[2.2]pentane, 376[216]



Chemical Formula: $C_7H_{10}O_2$
Molecular Weight: 126.15

[a,b] Isolated as a 1:1 mixture of diastereisomers

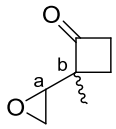
The mixture of diastereoisomers was inseparable by column chromatography.

See **Appendix 1** for a copy of the ^1H NMR spectrum.

FTIR ($CDCl_3$): 3068, 2998, 2956, 1221, 905 cm^{-1}

^1H NMR δ (400 MHz, $CDCl_3$): 0.88-1.24 (m, 4H, CH_2-CH_2), 1.39 and 1.41 (s, 3H in total, CH_3, ratio 1:1), 2.71 (dd, *J* = 2.7 and 5.0 Hz, 0.5H, CH), 2.81-2.84 (m, 1H, CH_2), 2.84-2.86 (dd, *J* = 2.7 and 5.0 Hz, 0.5H, CH), 3.05-3.08 (m, 1H, CH_2) ppm.

2-methyl-2-(oxiran-2-yl)cyclobutanone 377[216]



Chemical Formula: $C_7H_{10}O_2$
Molecular Weight: 126.15

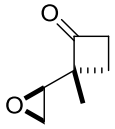
[a,b] Isolated as a 3:2 (**377a**:**377b**) mixture of diastereisomers

The mixture of diastereoisomers was separable by column chromatography.

Isolated as 3:2 (**377a**:**377b**) by mass.

See **Appendix 1** for a copy of the ^{1}H NMR spectra of **377a** and **377b**.

2-methyl-2-(oxiran-2-yl)cyclobutanone, 377a



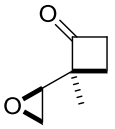
Chemical Formula: $C_7H_{10}O_2$
Molecular Weight: 126.15

FTIR ($CDCl_3$): 3079, 2934, 2875, 2254, 1777, 1476, 1381 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 1.30 (s, 3H, CH_3), 1.84 (ddd, J = 7.3 and 10.1 Hz and ^2J = 11.4 Hz, 1H, CH_2), 2.31 (ddd, J = 6.1 and 11.1 Hz and ^2J = 11.4 Hz, 1H, CH_2), 2.76 (dd, J = 4.1 and ^2J = 4.8 Hz, 1H, CH_2), 2.80 (dd, J = 2.8 and ^2J = 4.8 Hz, 1H, CH_2), 2.93 (ddd, J = 6.1 and 10.1 Hz and ^2J = 18.2 Hz, 1H, CH_2), 2.99 (dd, J = 2.8 and 4.1 Hz, 1H, CH), 3.04 (ddd, J = 7.3 and 11.1 Hz and ^2J = 18.2 Hz, 1H, CH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 18.5, 23.0, 43.6, 46.0, 54.8, 64.0, 211.4 ppm.

2-methyl-2-(oxiran-2-yl)cyclobutanone, 377b



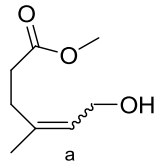
Chemical Formula: $C_7H_{10}O_2$
Molecular Weight: 126.15

FTIR ($CDCl_3$): 3083, 2945, 2879, 2251, 1781, 1469, 1384 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 1.29 (s, 3H, CH_3), 1.58 (ddd, J = 7.3 and 9.9 Hz, ^2J = 11.3 Hz, 1H, CH_2), 1.93 (ddd, J = 7.0 and 10.2 Hz, ^2J = 11.3 Hz, 1H, CH_2), 2.53 (dd, J = 2.7 and ^2J = 4.7 Hz, 1H, CH_2), 2.80 (dd, J = 4.2 and ^2J = 4.7 Hz, 1H, CH_2), 2.98 (ddd, J = 7.0 and 9.9 Hz, ^2J = 18.0 Hz, 1H, CH_2), 3.02 (ddd, J = 7.3 and 10.2 Hz, ^2J = 18.0 Hz, 1H, CH_2), 3.09 (dd, J = 4.2 and 2.78 Hz, 1H, CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 18.1, 18.6, 43.3, 43.6, 52.3, 64.1, 212.1 ppm.

methyl 6-hydroxy-4-methylhex-4-enoate, 378[216]



Chemical Formula: $C_8H_{14}O_3$
Molecular Weight: 158.19

[a] Isolated as a 3:2 *Z*:*E* mixture of geometric isomers

The mixture of geometric isomers was inseparable by column chromatography.

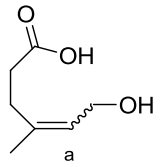
FTIR ($CDCl_3$): 3643, 2992, 2958, 1741, 1445, 1386 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.71 and 1.76 (s, 3H in total, CH_3, 3:2 ratio), 2.34-2.52 (m, 4H, CH_2-CH_2), 3.69 (s, 3H, CH_3), 4.13-4.19 (m, 2H, OCH_2), 5.45 and 5.55 (tq and t, 1H in total, olefinic CH, 2:3 ratio)* ppm. No OH observed.

*5.45 (tq, J = 6.9 Hz and ^4J = 1.3 Hz) and 5.55 (t, J = 7.6 Hz) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 22.8, 23.8, 30.5, 32.5, 51.6, 58.6, 59.4, 123.7, 124.5, 140.8, 141.4, 174.3 ppm.

6-hydroxy-4-methylhex-4-enoic acid, 379



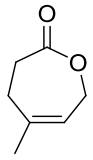
Chemical Formula: $C_7H_{12}O_3$
Molecular Weight: 144.17

[a] Isolated as a suspected 3:2 *Z*:*E* mixture of geometric isomers

The crude product was used without further purification.

^1H NMR δ (400 MHz, $CDCl_3$): 1.73-1.77 (m, 3H, CH_3), 2.43-2.52 (m, 4H, CH_2-CH_2), 4.13-4.20 and 4.58-4.64 (m, 2H in total, OCH_2, ratio 3:2), 5.36-5.51 and 5.53-5.57 (m, 1H in total, CH, ratio 3:2) ppm. No OH observed.

5-methyl-3,4-dihydrooxepin-2(7H)-one, 79



Chemical Formula: $C_7H_{10}O_2$
Molecular Weight: 126.15

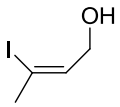
FTIR ($CDCl_3$): 2974, 2921, 1735, 1444, 1398, 1336 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.75 (s, 3H, CH_3), 2.42 (apparent t, J = 6.3 Hz, 2H, CH_2), 2.90 (apparent, J = 6.3 Hz, 2H, CH_2), 6.64 (d, J = 5.6 Hz, 2H, OCH_2), 5.59 (t, J = 5.6 Hz, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 23.2, 26.8, 31.2, 63.8, 133.0, 134.1, 174.4 ppm.

HRMS m/z (ESI) Calc. for $C_7H_{11}O_2$ (M^++H): 127.0752. Found 127.0752.

(*Z*)-3-iodobut-2-en-1-ol, 520[262]



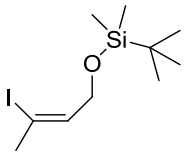
Chemical Formula: C_4H_7IO
Molecular Weight: 198.00

FTIR ($CDCl_3$): 3545, 2954, 2930, 2857, 1471, 1464, 1268, 1251 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.64 (s, 1H, OH), 2.56 (d, ^4J = 1.2 Hz, 3H, CH_3), 4.19 (d, J = 6.1 Hz, 2H, OCH_2), 5.80 (tq, J = 6.1 Hz and ^4J = 1.2 Hz, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 33.1, 66.9, 101.3, 133.6 ppm.

(*Z*)-*tert*-butyl(3-iodobut-2-enyloxy)dimethylsilane, 509



Chemical Formula: $C_{10}H_{21}IOSi$
Molecular Weight: 312.26

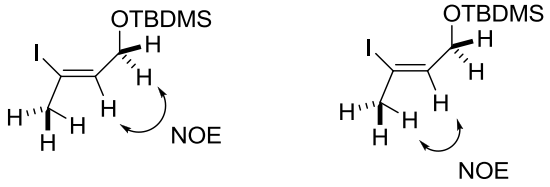
FTIR ($CDCl_3$): 2951, 2927, 2856, 1471, 1462, 1249 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.13 (s, 6H, CH_3), 0.93 (s, 9H, CH_3), 2.54 (d, ^4J = 1.5 Hz, 3H, CH_3), 4.20 (d, J = 5.5 Hz, 2H, OCH_2), 5.71 (tq, J = 5.5 Hz and ^4J = 1.5 Hz, 1H, olefinic CH) ppm.

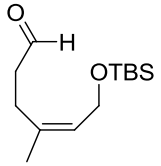
^{13}C NMR δ (100 MHz, $CDCl_3$): -5.6, 22.3, 25.4, 32.7, 68.2, 98.8, 135.1 ppm.

HRMS m/z (ESI) Calc. for $C_{10}H_{22}IOSi$ (M^++H): 313.0482. Found 313.0482.

NOE correlations confirm *Z*-selective olefin.



(*Z*)-6-(tert-butyldimethylsilyloxy)-4-methylhex-4-enal, 510



Chemical Formula: $C_{13}H_{26}O_2Si$
Molecular Weight: 242.43

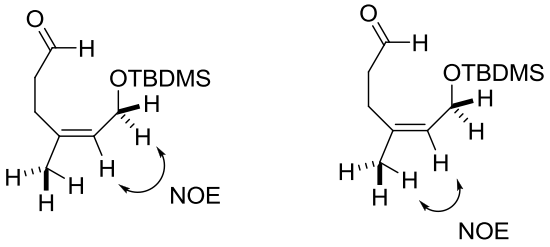
FTIR ($CDCl_3$): 2954, 2927, 2856, 1726, 1463, 1446 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.11 (s, 6H, CH_3), 0.89 (s, 9H, CH_3), 1.75 (d, ^4J = 1.4 Hz, 3H, CH_3), 2.39 (apparent t, J = 7.5 Hz, 2H, CH_2), 2.55 (apparent t, J = 7.5 Hz, 2H, CH_2), 4.19 (d, J = 6.3 Hz, 2H, OCH_2), 5.41 (t, J = 6.3 Hz, 1H, olefinic CH), 9.81 (t, J = 1.5 Hz, 1H, CHO) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): -5.4, 18.8, 23.0, 24.6, 26.2, 42.0, 59.6, 126.6, 135.7, 202.0 ppm.

HRMS m/z (ESI) Calc. for $C_{13}H_{27}O_2Si$ (M^++H): 243.1775. Found 243.1773.

NOE correlations confirm *Z*-selective olefin.



1,1-dimethyl-2-methylenehydrazine, 428[239]

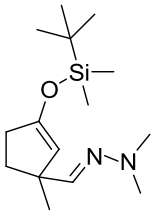
Chemical Formula: $C_3H_8N_2$
Molecular Weight: 72.11

FTIR ($CDCl_3$): 2962, 1682 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 2.85 (s, 6H, CH_3), 6.13 (d, ^2J = 11.2 Hz, 1H, CH_2), 6.19 (d, ^2J = 11.2 Hz, 1H, CH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 42.1, 122.2 ppm.

(*E*)-2-((3-((*tert*-butyldimethylsilyl)oxy)-1-methylcyclopent-2-en-1-yl)methylene)-1,1-dimethylhydrazine, 451[233]



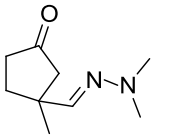
Chemical Formula: $C_{15}H_{30}N_2OSi$
Molecular Weight: 282.50

FTIR ($CDCl_3$): 2964, 2895, 1654, 1467, 1389 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 0.18 (s, 6H, CH_3), 0.95 (s, 9H, CH_3), 1.22 (s, 3H, CH_3), 1.70 (ddd, *J* = 6.3 and 8.0 Hz, and ^2J = 14.5 Hz, 1H, CH_2), 2.08 (ddd, *J* = 8.3 and 12.5 Hz and ^2J = 14.5 Hz, 1H, CH_2), 2.32-2.38 (m, 2H, CH_2), 2.71 (s, 6H, CH_3), 4.57 (t, ^4J = 1.6 Hz, 1H, olefinic CH), 6.65 (s, 1H, CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): -4.1, 18.5, 26.6, 26.9, 32.6, 33.3, 43.0, 45.7, 104.3, 142.3, 152.1 ppm.

(*E*)-3-((2,2-dimethylhydrazono)methyl)-3-methylcyclopentanone, 429[233]



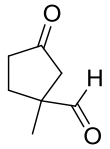
Chemical Formula: $C_9H_{16}N_2O$
Molecular Weight: 168.24

FTIR ($CDCl_3$): 2859, 1738, 1651 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.24 (s, 3H, CH_3), 1.78 (ddd, J = 8.5 and 12.7 Hz, and ^2J = 16.9 Hz, 1H, CH_2), 2.04 (d, ^2J = 17.8 Hz, 1H, CH_2), 2.16 (ddd, J = 5.5 and 8.8 Hz, and ^2J = 17.8 Hz, 1H, CH_2), 2.25-2.36 (m, 2H, CH_2), 2.65 (d, ^2J = 17.8 Hz, 1H, CH_2), 2.74 (s, 6H, CH_3), 6.51 (s, 1H, CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 25.4, 29.7, 34.8, 36.7, 43.9, 49.9, 141.3, 210.5 ppm.

1-methyl-3-oxocyclopentanecarbaldehyde, 74[233]



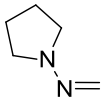
Chemical Formula: $C_7H_{10}O_2$
Molecular Weight: 126.15

FTIR ($CDCl_3$): 2724, 1742, 1711 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.34 (s, 3H, CH_3), 1.77-1.86 (m, 1H, CH_2), 2.06 (d, ^2J = 18.2 Hz, 1H, CH_2), 2.26-2.51 (m, 3H, CH_2), 2.69 (d, ^2J = 18.2 Hz, 1H, CH_2), 9.60 (s, 1H, CHO) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 20.0, 30.3, 36.2, 45.5, 50.7, 202.3, 215.5 ppm.

***N*-methylenepyrrolidin-1-amine, 443**[237]



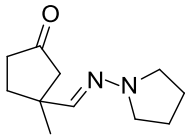
Chemical Formula: $C_5H_{10}N_2$
Molecular Weight: 98.15

FTIR ($CDCl_3$): 1569, 1541 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.86-1.89 (m, 4H, CH_2), 3.16-3.18 (m, 4H, CH_2), 5.99 (d, ^2J = 11.5 Hz, 1H, CH_2), 6.04 (d, ^2J = 11.5 Hz, 1H, CH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 23.3, 50.6, 121.2 ppm.

(*E*)-3-methyl-3-((pyrrolidin-1-ylimino)methyl)cyclopentanone, 453



Chemical Formula: $C_{11}H_{18}N_2O$
Molecular Weight: 194.27

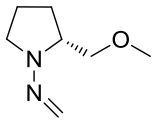
FTIR ($CDCl_3$): 2954, 2929, 2870, 1738, 1597, 1458, 1402 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.25 (s, 3H, CH_3), 1.80 (ddd, J = 8.2 and 12.5 Hz, and ^2J = 17.2 Hz, 1H, CH_2), 1.83-1.89 (m, 4H, CH_2), 2.01 (d, ^2J = 17.9 Hz, 1H, CH_2), 2.14 (ddd, J = 5.5 and 8.3 Hz, and ^2J = 17.2 Hz, 1H, CH_2), 2.20-2.35 (m, 2H, CH_2), 2.61 (d, ^2J = 17.9 Hz, 1H, CH_2), 3.04-3.12 (m, 4H, CH_2), 6.47 (s, 1H, CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 22.7, 25.2, 34.1, 36.6, 42.3, 49.4, 51.0, 140.9, 209.4 ppm.

HRMS m/z (ESI) Calc. for $C_{11}H_{19}N_2O$ (M^++H): 195.1492. Found 195.1491.

(*R*)-2-(methoxymethyl)-N-methylenepyrrolidin-1-amine, 465[236]



Chemical Formula: $C_7H_{14}N_2O$
Molecular Weight: 142.20

FTIR ($CDCl_3$): 3065, 2998, 2986, 2874, 1568, 1452, 1436, 1356 cm^{-1}.

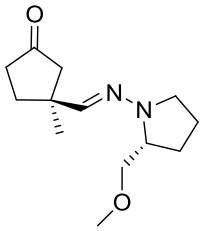
^1H NMR δ (400 MHz, $CDCl_3$): 1.79-2.05 (m, 4H, CH_2), 2.82-2.89 (m, 1H, CH_2), 3.32-3.38 (m, 1H, CH), 3.40 (s, 3H, OCH_3), 3.46-3.50 (m, 1H, CH), 3.54-3.65 (m, 2H, CH_2), 6.05 (d, ^2J = 11.6 Hz, 1H, olefinic CH), 6.16 (d, ^2J = 11.6 Hz, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 22.1, 26.8, 48.5, 59.2, 62.9, 74.7, 121.9 ppm.

HRMS m/z (ESI) Calc. for $C_7H_{15}N_2O$ (M^++H): 143.1179. Found 143.1177.

Literature: $[\alpha]_D$ (c = 1.0, $CHCl_3$) = - 89. Found: $[\alpha]_D$ (c = 1.0, $CHCl_3$) = + 89.3.

(*S*)-3-((*E*)-((*R*)-2-(methoxymethyl)pyrrolidin-1-ylimino)methyl)-3-methylcyclopentanone, 466[233]



Chemical Formula: $C_{13}H_{22}N_2O_2$
Molecular Weight: 238.33

FTIR ($CDCl_3$): 3063, 2996, 2983, 2875, 1742, 1594, 1448 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.29 (s, 3H, CH_3), 1.78-1.98 (m, 5H, CH_2), 2.00 (d, ^2J = 17.5 Hz, 1H, CH_2), 2.14 (ddd, J = 4.4, 8.7 and 13.1 Hz, 1H, CH_2), 2.22 (ddd, J = 4.4 and 8.7 Hz,

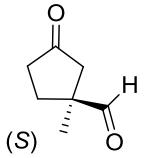
and ^{2}J = 18.7 Hz, 1H, CH_2), 2.24-2.36 (m, 1H, CH_2), 2.65 (d, ^{2}J = 17.5 Hz, 1H, CH_2), 2.68-2.76 (m, 1H, CH), 3.30-3.37 (m, 2H, CH_2), 3.38 (s, 3H, OCH_3), 3.47 (dd, J = 6.0 and 9.3 Hz, 1H, CH_2), 3.54 (dd, J = 3.5 and 9.3 Hz, 1H, CH_2), 6.55 (s, 1H, CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 21.8, 25.5, 26.0, 34.6, 36.7, 42.0, 49.2, 49.6, 58.8, 63.1, 73.9, 141.2, 219.1 ppm.

HRMS m/z (ESI) Calc. for $C_{13}H_{23}N_2O_2$ (M^++H): 239.1754. Found 239.1755.

Literature: $[\alpha]_D$ (c = 1.0, $CHCl_3$) = - 210.4. Found: $[\alpha]_D$ (c = 1.0, $CHCl_3$) = +218.1

(*S*)-1-methyl-3-oxocyclopentanecarbaldehyde, 467[233]



Chemical Formula: $C_7H_{10}O_2$
Molecular Weight: 126.15

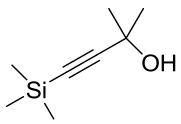
FTIR ($CDCl_3$): 2724, 1742, 1711 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 1.34 (s, 3H, CH_3), 1.77-1.86 (m, 1H, CH_2), 2.06 (d, ^{2}J = 18.2 Hz, 1H, CH_2), 2.26-2.51 (m, 3H, CH_2), 2.69 (d, ^{2}J = 18.2 Hz, 1H, CH_2), 9.60 (s, 1H, CHO) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 20.0, 30.3, 36.2, 45.5, 50.7, 202.3, 215.5 ppm.

Literature: $[\alpha]_D$ (c = 1.0, $CHCl_3$) = - 22.0. Found: $[\alpha]_D$ (c = 1.0, $CHCl_3$) = +21.8

2-methyl-4-(trimethylsilyl)but-3-yn-2-ol, 480[263]



Chemical Formula: $C_8H_{16}OSi$
Molecular Weight: 156.30

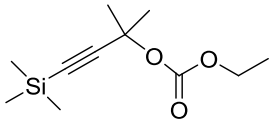
FTIR ($CDCl_3$): 3565, 2983, 2961 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 0.18 (s, 9H, CH_3), 1.53 (s, 6H, CH_3) ppm. No OH observed.

^{13}C NMR δ (100 MHz, $CDCl_3$): -0.1, 31.4, 68.0, 86.0, 110.5 ppm.

HRMS m/z (ESI) Calc. for $C_8H_{20}NO_1Si$ (M^++NH_4): 174.1309. Found 174.1304.

ethyl (2-methyl-4-(trimethylsilyl)but-3-yn-2-yl) carbonate, 478



Chemical Formula: $C_{11}H_{20}O_3Si$
Molecular Weight: 228.36

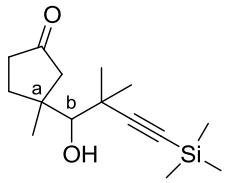
FTIR ($CDCl_3$): 2989, 2963, 1755, 1368 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.19 (s, 9H, CH_3), 1.34 (t, *J* = 6.8 Hz, 3H, CH_3), 1.73 (s, 6H, CH_3), 4.20 (q, *J* = 6.8 Hz, 2H, CH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): -0.2, 14.3, 29.0, 63.5, 74.4, 88.9, 105.6, 152.7 ppm.

HRMS m/z (ESI) Calc. for $C_{11}H_{24}NO_3Si$ (M^++ NH_4): 246.1336. Found 246.1332.

3-(1-hydroxy-2,2-dimethyl-4-(trimethylsilyl)but-3-yn-1-yl)-3-methylcyclopentanone, 482



Chemical Formula: $C_{15}H_{26}O_2Si$
Molecular Weight: 266.45

[a] ±
[b] 3:2

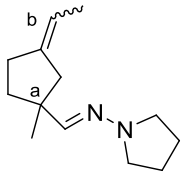
FTIR ($CDCl_3$): 3455, 2960, 2873, 1737, 1455, 1403 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.17 (s, 9H, CH_3), 1.19 and 1.22 (s, 3H in total, CH_3, ratio 2:3), 1.28 and 1.34 (s, 3H in total, CH_3, ratio 2:3), 1.37 and 1.39 (s, 3H in total, CH_3, ratio 3:2), 1.88-2.36 (m, 6H, CH_2), 3.18 and 3.28 (s, 1H in total, CH, ratio 3:2) ppm. No OH observed.

^{13}C NMR δ (100 MHz, $CDCl_3$): -0.6, 19.3, 20.7, 26.3, 26.5, 28.1, 29.3, 34.1, 34.5, 35.6, 50.8, 51.7, 82.7, 83.7, 96.3, 95.5, 104.2, 105.1, 139.7, 138.5 ppm.

HRMS m/z (ESI) Calc. for $C_{15}H_{30}NO_2Si$ (M^++NH_4): 284.2040. Found 284.2044.

(*NE*)-*N*-((3-ethylidene-1-methylcyclopentyl)methylene)pyrrolidin-1-amine, 484



Chemical Formula: $C_{13}H_{22}N_2$
Molecular Weight: 206.33

[a] ±
[b] *Z*:*E* ratio

From the ^{1}H NMR analysis, the ratio of the quaternary methyl peaks at 1.11 and 1.14 ppm, and olefinic hydrazone hydrogen at 6.59 and 6.61 ppm allowed the relative determination of the *Z*:*E* ratios.

Reaction at r.t.: **Table 37**, Entry 1. Isolated as a 1:1 ratio of *Z*:*E*

FTIR ($CDCl_3$): 2949, 2927, 2860, 1598 1458 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 1.11 and 1.14 (s, 3H in total, CH_3, ratio 1:1), 1.47-1.66 (m, 4H, CH_2), 1.76-1.93 (m, 5H, olefinic CH_3 and CH_2), 2.10 (d, ^2J = 16.1 Hz, 1H, CH_2), 2.26-2.38 (m, 2H, CH_2), 2.44 (d, ^2J = 16.1 Hz, 1H, CH_2), 3.04-3.14 (m, 4H, CH_2), 5.25-5.35 (m, 1H, olefinic CH), 6.59 and 6.61 (s, 1H in total, CH, ratio 1:1) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 14.4, 14.7, 22.6, 22.9, 24.1, 24.3, 27.4, 31.8, 31.9, 41.2, 46.3, 51.9, 115.6, 142.7, 145.7 ppm.

HRMS m/z (ESI) Calc. for $C_{13}H_{23}N_2$ (M^++H): 207.1856. Found 207.1853.

Reaction at 0 °C: **Table 37**, Entry 2.

1.11 and 1.14 (s, 3H in total, CH_3, ratio of 5:2) ppm, and 6.59 and 6.61 (s, 1H in total, CH, ratio 5:2) ppm corresponding to a 5:2, *Z*:*E* selectivity.

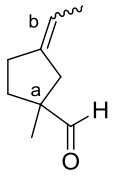
Reaction at -30 °C: **Table 37**, Entry 3.

1.11 and 1.14 (s, 3H in total, CH_3, ratio of 4:1) ppm, and 6.59 and 6.61 (s, 1H in total, CH, ratio 4:1) ppm corresponding to a 4:1, *Z*:*E* selectivity.

Reaction at -78 °C: **Table 37**, Entry 4.

1.11 and 1.14 (s, 3H in total, CH_3, ratio of 7:1) ppm, and 6.59 and 6.61 (s, 1H in total, CH, ratio 7:1) ppm corresponding to a 7:1, *Z*:*E* selectivity.

3-ethylidene-1-methylcyclopentanecarbaldehyde, 485



Chemical Formula: $C_9H_{14}O$
Molecular Weight: 138.21

[a] ±

[b] *Z*:*E* ratio

From the ^{1}H NMR analysis, the ratio of the quaternary methyl peaks at 1.10 and 1.15 ppm, and the aldehyde hydrogen peaks at 9.49 and 9.52 ppm allowed the relative determination of the *Z*:*E* ratios.

Reaction at r.t.: **Table 37**, Entry 1. 1:1 ratio of *E*:*Z*.

See **Appendix 1** for a copy of the 1H NMR spectrum.

FTIR ($CDCl_3$): 2927, 2858, 1708, 1452, 1433 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 1.10 and 1.15 (s, 3H in total, CH_3, ratio of 1:1), 1.42-1.55 (m, 1H, CH_2), 1.55-1.61 (m, 3H, olefinic CH_3), 1.92-2.11 (m, 2H, CH_2), 2.45-2.47 (m, 2H, CH_2), 2.56-2.66 (m, 1H, CH_2), 5.29-5.41 (m, 1H, olefinic CH), 9.49 and 9.52 (s, 1H in total, CHO, ratio 1:1) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 14.3, 18.4, 19.9, 26.8, 31.2, 33.2, 36.6, 40.9, 52.9, 115.8, 140.0, 204.7 ppm.

HRMS m/z (ESI) Calc. for $C_9H_{15}O$ (M^++H): 139.1117. Found 139.1117.

Reaction at 0 °C: **Table 37**, Entry 2

1.10 and 1.15 (s, 3H in total, CH_3, ratio of 5:2) ppm, and 9.49 and 9.52 (s, 1H in total, CHO, ratio 5:2) ppm, corresponding to a 5:2 *Z*:*E* selectivity.

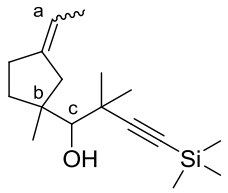
Reaction at -30 °C: **Table 37**, Entry 3

1.10 and 1.15 (s, 3H in total, CH_3, ratio of 4:1) ppm, and 9.49 and 9.52 (s, 1H in total, CHO, ratio 4:1) ppm, corresponding to a 4:1 *Z*:*E* selectivity.

Reaction at -78 °C: **Table 37**, Entry 4

1.10 and 1.15 (s, 3H in total, CH_3, ratio of 7:1) ppm, and 9.49 and 9.52 (s, 1H in total, CHO, ratio 7:1) ppm, corresponding to a 7:1 *Z*:*E* selectivity.

1-(3-ethylidene-1-methylcyclopentyl)-2,2-dimethyl-4-(trimethylsilyl)but-3-yn-1-ol, 483



Chemical Formula: $C_{17}H_{30}OSi$
Molecular Weight: 278.51

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 3:2

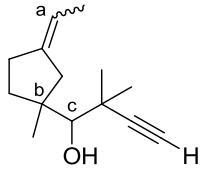
FTIR ($CDCl_3$): 3565, 2958, 2869, 1460, 1436 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.16 (s, 9H, CH_3), 1.03 and 1.08 (s, 3H in total, CH_3, ratio 3:2), 1.28-1.39 (m, 6H, CH_3), 1.56-1.61 (m, 3H, olefinic CH_3), 1.61-1.72 (m, 2H, CH_2), 2.10-2.43 (m, 4H, CH_2), 3.05-3.13 (m, 1H, OCH), 5.26-5.37 (m, 1H, olefinic CH) ppm. No OH observed.

^{13}C NMR δ (100 MHz, $CDCl_3$): -0.6, 14.2, 14.5, 18.3, 20.9, 28.1, 29.3, 32.5, 32.8, 34.1, 34.5, 36.3, 37.1, 46.2, 82.5, 83.7, 96.5, 95.8, 104.6, 112.1, 113.2, 205.1 ppm.

HRMS m/z (ESI) Calc. for $C_{17}H_{31}OSi$ (M^++H): 279.2139. Found 279.2136.

1-(3-ethylidene-1-methylcyclopentyl)-2,2-dimethylbut-3-yn-1-ol, 469



Chemical Formula: $C_{14}H_{22}O$
Molecular Weight: 206.32

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 3:2

See **Appendix 1** for a copy of the NMR spectrum.

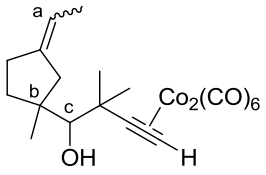
FTIR ($CDCl_3$): 3520, 3304, 2966, 2927, 1454, 1382 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.05 and 1.09 (s, 3H in total, CH_3, ratio 3:2), 1.29-1.36 (m, 3H, CH_3), 1.37-1.42 (m, 3H, CH_3), 1.54-1.60 (m, 3H, olefinic CH_3), 1.61-1.81 (m, 2H, CH_2), 2.06-2.12 (m, 1H, CH_2), 2.16-2.35 (m, 5H, CH_2, OH and CH) 3.07-3.17 (m, 1H, OCH), 5.24-5.37 (m, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 14.7, 18.7, 19.7, 25.0, 27.1, 30.2, 31.3, 37.4, 39.5, 41.9, 43.7, 46.7, 48.2, 71.8, 84.9, 90.1, 115.8, 141.5, 143.6 ppm.

HRMS m/z (ESI) Calc. for $C_{14}H_{23}O$ (M^++H): 207.1743. Found 207.1743.

Cobalt complex 484



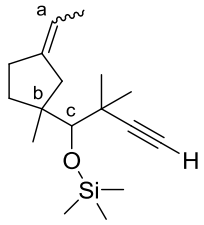
Chemical Formula: $C_{20}H_{22}Co_2O_7$
Molecular Weight: 492.26

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 3:2

See **Appendix 1** for a copy of the NMR spectrum.

FTIR ($CDCl_3$): 2967, 2906, 2876, 2089, 2043, 1991, 1511, 1505, 1462 cm^{-1}.
^1H NMR δ (400 MHz, $CDCl_3$): 1.05 and 1.09 (s, 3H in total, CH_3, ratio 3:2), 1.33-1.39 (m, 6H, CH_3), 1.50-1.66 (m, 3H, olefinic CH_3), 1.67-1.77 (m, 1H, CH_2), 1.79-1.87 (m, 1H, CH_2), 2.06-2.44 (m, 4H, CH_2), 3.28-3.34 (m, 1H, OCH), 5.25-5.41 (m, 1H, olefinic CH), 6.17 and 6.18 (s, 1H in total, CH, ratio 3:2) ppm. No OH observed.
^{13}C NMR δ (100 MHz, $CDCl_3$): 14.2, 18.7, 19.7, 24.4, 26.0, 27.0, 28.5, 39.8, 31.1, 37.5, 39.2, 42.2, 44.4, 46.3, 48.1, 74.4, 86.2, 115.8, 140.3, 142.7, 199.9 ppm.

((1-(3-ethylidene-1-methylcyclopentyl)-2,2-dimethylbut-3-yn-1-yl)oxy)trimethylsilane, 490

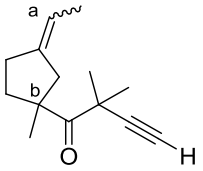


Chemical Formula: $C_{17}H_{30}OSi$
Molecular Weight: 278.51

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 3:2

FTIR ($CDCl_3$): 3310, 2966, 2862, 1456, 1380 cm^{-1}.
^1H NMR δ (400 MHz, $CDCl_3$): 0.16-0.20 (m, 9H, CH_3), 1.03 and 1.07 (s, 3H in total, CH_3, ratio of 3:2), 1.26-1.32 (m, 6H, CH_3), 1.46-1.61 (m, 4H, olefinic CH_3 and CH_2), 1.64-1.79 (m, 1H, CH_2), 2.05-2.39 (m, 5H, CH_2 and CH), 3.39-3.46 (m, 1H, OCH), 5.25-5.35 (m, 1H, olefinic CH) ppm.
^{13}C NMR δ (100 MHz, $CDCl_3$): 1.1, 14.8, 20.1, 20.2, 26.6, 26.8, 30.2, 30.4, 37.4, 37.6, 39.8, 42.5, 44.5, 46.7, 48.9, 70.2, 86.5, 86.6, 92.6, 115.6, 142.0, 143.8 ppm.
HRMS m/z (ESI) Calc. for $C_{17}H_{31}OSi$ (M^++H): 279.2139. Found 279.2136.

1-(3-ethylidene-1-methylcyclopentyl)-2,2-dimethylbut-3-yn-1-one, 494



Chemical Formula: $C_{14}H_{20}O$
Molecular Weight: 204.31

[a] 1:1 (*E*:*Z*)
[b] ±

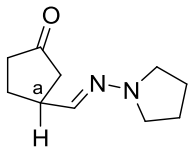
FTIR ($CDCl_3$): 3304, 2974, 2933, 2922, 1703, 1463, 1435, 1377 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.40-1.47 (m, 9H, CH_3 and *gem*-CH_3), 1.55-1.62 (m, 3H, olefinic CH_3), 1.68-1.80 (m, 1H, CH_2), 2.24-2.42 (m, 4H, CH_2), 2.49 and 2.50 (s, 1H in total, CH, ratio 1:1), 3.03 (apparent t, ^2J = 16.5 Hz, 1H, CH_2), 5.27-5.40 (m, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 14.7, 23.1, 23.9, 26.9, 29.3, 31.0, 39.6, 44.0, 56.4, 73.5, 88.4, 115.9, 141.2, 212.8 ppm.

HRMS m/z (ESI) Calc. for $C_{14}H_{21}O$ (M^++H): 205.1587. Found 205.1584.

(*E*)-3-((pyrrolidin-1-ylimino)methyl)cyclopentanone, 504



Chemical Formula: $C_{10}H_{16}N_2O$
Molecular Weight: 180.25

[a] ±

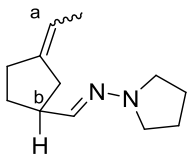
FTIR ($CDCl_3$): 2960, 2935, 2873, 2814, 1748, 1573, 1458, 1405 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.81-1.92 (m, 5H, CH_2), 2.10-2.44 (m, 5H, CH_2 and CH), 2.96-3.01 (m, 1H, CH_2), 3.08-3.11 (m, 4H, CH_2), 6.48 (d, J = 5.9 Hz, 1H, CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 22.5, 27.9, 37.4, 39.47, 42.8, 50.8, 137.0, 208.6 ppm.

HRMS m/z (ESI) Calc. for $C_{10}H_{17}N_2O$ (M^++H): 181.1335. Found 181.1334.

(*NE*)-*N*-((3-ethylidenecyclopentyl)methylene)pyrrolidin-1-amine, 505



Chemical Formula: $C_{12}H_{20}N_2$
Molecular Weight: 192.30

[a] 1:1 (*E*:*Z*)
[b] ±

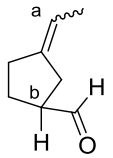
FTIR ($CDCl_3$): 2941, 2933, 2856, 2818, 1602, 1458, 1433 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.48-1.62 (m, 4H, CH_3 and CH_2), 1.83-1.99 (m, 5H, CH_2), 2.06-2.39 (m, 3H, CH_2 and CH), 2.43-2.56 (m, 1H, CH_2), 2.64-2.81 (m, 1H, CH_2), 3.07-3.16 (m, 4H, CH_2), 5.26-5.36 (m, 1H, olefinic CH), 6.50 and 6.53 (d, J = 6.4 Hz, 1H in total, CH, ratio 1:1) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 14.1, 22.3, 27.7, 31.4, 31.7, 32.1, 32.7, 33.4, 33.7, 38.6, 43.0, 51.0, 114.7, 129.8, 142.0 ppm.

HRMS m/z (ESI) Calc. for $C_{12}H_{21}N_2$ (M^++H): 193.1699. Found 193.1696.

3-ethylidenecyclopentanecarbaldehyde, 506



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

[a] 1:1 (*E*:*Z*)
[b] ±

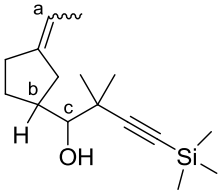
FTIR ($CDCl_3$): 2941, 2887, 2808, 1708, 1433 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 1.59 (m, 3H, CH_3), 1.83-1.91 (m, 2H, CH_2), 2.21-2.36 (m, 2H, CH_2), 2.42-2.59 (m, 2H, CH_2), 2.72-2.88 (m, 1H, CH), 5.31-5.40 (m, 1H, olefinic CH), 9.63 and 9.66 (d, *J* = 2.4 Hz, 1H in total, CHO, ratio 1:1) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 14.7, 14.8, 26.1, 26.3, 27.0, 28.0, 31.9, 33.1, 51.1, 65.3, 115.5, 115.7, 139.9, 140.0, 203.0 ppm.

HRMS m/z (ESI) Calc. for $C_8H_{13}O$ (M^++H): 125.0961. Found 125.0959.

1-(3-ethylidenecyclopentyl)-2,2-dimethyl-4-(trimethylsilyl)but-3-yn-1-ol, 507



Chemical Formula: $C_{16}H_{28}OSi$
Molecular Weight: 264.48

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 2:1

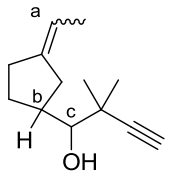
FTIR ($CDCl_3$): 3508, 2962, 2899, 1444, 1433, 1247 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 0.14-0.17 (m, 9H, CH_3), 1.21, 1.22, 1.23 and 1.24 (s, 3H in total, CH_3, ratio 2:1:2:1), 1.26, 1.27, 1.28 and 1.29 (s, 3H in total, CH_3, ratio 1:2:1:2), 1.55-1.69 (m, 4H, olefinic CH_3 and CH_2), 1.83-1.92 (m, 1H, CH), 2.06-2.25 (m, 3H, CH_2), 2.29-2.35 (m, 2H, CH_2), 3.25-3.36 (m, 1H, OCH), 5.25-5.34 (m, 1H, olefinic CH) ppm. No OH observed

^{13}C NMR δ (100 MHz, $CDCl_3$): 0.2, 14.7, 25.6, 27.3, 27.5, 28.1, 30.0, 31.3, 31.5, 33.0, 35.1, 39.3, 39.4, 42.6, 79.5, 87.0, 112.0, 114.6, 143.4 ppm.

HRMS m/z (ESI) Calc. for $C_{16}H_{29}OSi$ (M^++H): 265.1982. Found 265.1977.

1-(3-ethylidenecyclopentyl)-2,2-dimethylbut-3-yn-1-ol, 500



Chemical Formula: $C_{13}H_{20}O$
Molecular Weight: 192.30

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 2:1

See **Appendix 1** for a copy of the ^{1}H NMR spectrum.

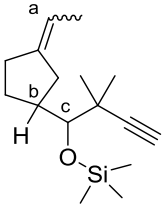
FTIR ($CDCl_3$): 3483, 3288, 2970, 2845, 1460, 1381 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 1.25 and 1.27 (s, 3H, CH_3, ratio 2:1), 1.30 and 1.31 (s, 3H, CH_3, ratio 2:1), 1.54-1.65 (m, 4H, olefinic CH_3 and CH_2), 1.79-1.86 (m, 1H, CH), 2.06-2.28 (m, 4H, CH_2 and terminal CH), 2.29-2.42 (m, 2H, CH_2), 3.28-3.40 (m, 1H, OCH), 5.24-5.32 (m, 1H, olefinic CH) ppm. No OH observed.

^{13}C NMR δ (100 MHz, $CDCl_3$): 15.0, 25.7, 27.1, 28.1, 31.1, 33.2, 34.4, 35.6, 37.2, 39.3, 42.6, 70.6, 79.5, 90.0, 114.8, 143.2 ppm.

HRMS m/z (ESI) Calc. for $C_{13}H_{21}O$ (M^{+}+H): 193.1587. Found 193.1583.

((1-(3-ethylidenecyclopentyl)-2,2-dimethylbut-3-yn-1-yl)oxy)trimethylsilane, 508



Chemical Formula: $C_{16}H_{28}OSi$
Molecular Weight: 264.48

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 2:1

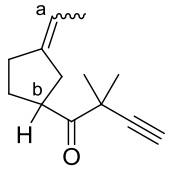
FTIR ($CDCl_3$): 3309, 2956, 2872, 1460, 1433 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 0.11-0.15 (m, 9H, CH_3), 0.79-0.92 (m, 6H, CH_3), 1.13-1.36 (m, 2H, CH_2), 1.54-1.67 (m, 3H, olefinic CH_3), 1.71-1.85 (m, 1H, CH_2), 1.86-2.36 (m, 5H, CH_2), 3.26-3.78 (m, 1H, OCH), 5.22-5.33 (m, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 0.9, 14.5, 16.4, 20.8, 27.6, 28.1, 30.2, 30.6, 31.1, 31.5, 32.0, 32.2, 34.9, 37.9, 44.2, 46.1, 73.7, 82.1, 114.6, 143.4 ppm.

HRMS m/z (ESI) Calc. for $C_{16}H_{29}OSi$ (M^{+}+H): 265.1982. Found 265.1980.

1-(3-ethylidenecyclopentyl)-2,2-dimethylbut-3-yn-1-one, 510



Chemical Formula: $C_{13}H_{18}O$
Molecular Weight: 190.28

[a] 1:1 (*E*:*Z*)
[b] ±

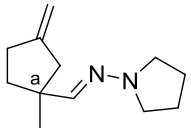
FTIR ($CDCl_3$): 3282, 2980, 2935, 2870, 1709, 1462, 1435 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.36-1.42 (m, 6H, CH_3), 1.55-1.61 (m, 3H, olefinic CH_3), 1.73-1.90 (m, 1H, CH_2), 1.93-2.07 (m, 1H, CH_2), 2.16-2.56 (m, 5H, CH_2 and terminal CH), 3.53-3.70 (m, 1H, CH), 5.26-5.38 (m, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 15.2, 26.0, 28.3, 31.6, 33.2, 34.4, 39.3, 44.0, 47.7, 71.3, 87.2, 115.5, 141.5, 212.4 ppm.

HRMS m/z (ESI) Calc. for $C_{13}H_{19}O$ (M^++H): 191.1430. Found 191.1429.

(*E*)-*N*-((1-methyl-3-methylenecyclopentyl)methylene)pyrrolidin-1-amine, 514



Chemical Formula: $C_{12}H_{20}N_2$
Molecular Weight: 192.30

[a] ±

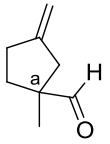
FTIR ($CDCl_3$): 2947, 2926, 2866, 2816, 1656, 1598, 1454, 1427, 1338 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.14 (s, 3H, CH_3), 1.57 (ddd, *J* = 7.0 and 13.1 Hz, and ^2J = 18.5 Hz, 1H, CH_2), 1.85-193 (m, 5H, CH_2), 2.15 (d, ^2J = 17.3 Hz, 1H, CH_2), 2.40 (dd, *J* = 7.0 and 8.1 Hz, 2H, CH_2), 2.53 (d, ^2J = 17.3 Hz, 1H, CH_2), 3.07-3.14 (m, 4H, CH_2), 4.85 (s, 1H, olefinic CH), 4.89 (s, 1H, olefinic CH), 6.59 (s, 1H, CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 23.1, 24.3, 31.1, 38.1, 44.9, 45.8, 51.9, 105.7, 145.5, 152.2 ppm.

HRMS m/z (ESI) Calc. for $C_{12}H_{21}N_2$ (M^++H): 193.1699. Found 193.1696.

1-methyl-3-methylenecyclopentanecarbaldehyde, 515



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

[a] ±

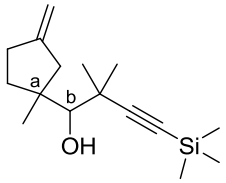
FTIR ($CDCl_3$): 2949, 2933, 2872, 2812, 1722, 1660, 1454, 1429 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.16 (s, 3H, CH_3), 1.54 (ddd, *J* = 7.3 and 13.4 Hz and ^2J = 18.3 Hz, 1H, CH_2), 2.06 (ddd, *J* = 4.8 and 8.3 Hz, and ^2J = 18.3 Hz, 1H, CH_2), 2.13 (d, ^2J = 17.3 Hz, 1H, CH_2), 2.36-2.52 (m, 2H, CH_2), 2.71 (d, ^2J = 17.1 Hz, 1H, CH_2), 4.92-4.96 (m, 2H, olefinic CH), 9.53 (s, 1H, CHO) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 19.7, 31.1, 34.4, 41.6, 66.2, 107.6, 149.9, 205.1 ppm.

HRMS m/z (ESI) Calc. for $C_8H_{13}O$ (M^++H): 125.0961. Found 125.0960.

2,2-dimethyl-1-(1-methyl-3-methylenecyclopentyl)-4-(trimethylsilyl)but-3-yn-1-ol, 516



Chemical Formula: $C_{16}H_{28}OSi$
Molecular Weight: 264.48

[a] ±
[b] 3:2

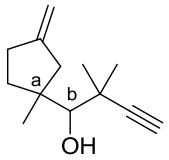
FTIR ($CDCl_3$): 3566, 2958, 2934, 2900, 2870, 1656, 1452, 1381 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 0.15 (s, 9H, CH_3), 1.05 (s, 3H, CH_3), 1.29, (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.65-1.77 (m, 1H, CH_2), 2.10 and 2.21 (d, *J* = 8.9 Hz, 1H in total, OH, ratio 3:2), 2.20-2.34 (m, 4H, CH_2), 2.37-2.46 (m, 1H, CH_2), 3.07 and 3.10 (d, *J* = 8.9 Hz, 1H in total, ratio 3:2, OCH), 4.82-4.90 (m, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 0.5, 19.2, 19.3, 26.9, 29.7, 29.9, 37.9, 38.4, 39.5, 46.8, 48.7, 84.9, 88.2, 105.9, 112.2, 153.2 ppm.

HRMS m/z (ESI) Calc. for $C_{16}H_{29}OSi$ (M^++H): 265.1982. Found 265.1979.

2,2-dimethyl-1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-ol, 512



Chemical Formula: $C_{13}H_{20}O$
Molecular Weight: 192.30

[a] ±
[b] 3:2

See **Appendix 1** for a copy of the ^{1}H NMR spectrum.

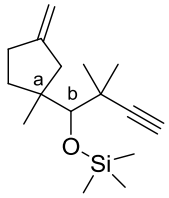
FTIR ($CDCl_3$): 3508, 3304, 2970, 2931, 1654, 1454, 1384 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 1.08 (s, 3H, CH_3), 1.31 and 1.32 (s, 3H in total, CH_3, ratio 2:3), 1.38 and 1.39 (s, 3H in total, CH_3, ratio 3:2), 1.65-1.75 (m, 2H, CH_2), 2.05 and 2.06 (d, *J* = 8.4 Hz, 1H in total, OH, ratio 2:3), 2.24 and 2.25 (d, *J* = 8.4 Hz, 1H, CH, ratio 2:3), 2.27-2.33 (m, 2H, CH_2), 2.37-2.44 (m, 2H, CH_2), 3.11 and 3.14 (d, *J* = 8.4 Hz, 1H, OCH, ratio 3:2), 4.82-4.90 (m, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 19.4, 27.4, 29.8, 30.0, 31.3, 37.8, 37.9, 39.8, 46.8, 48.2, 71.8, 84.7, 90.0, 106.7, 151.1, 153.2 ppm.

HRMS m/z (ESI) Calc. for $C_{13}H_{21}O$ (M^++H): 193.1587. Found 193.1586.

((2,2-dimethyl-1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-yl)oxy)trimethylsilane, 521



Chemical Formula: $C_{16}H_{28}OSi$
Molecular Weight: 264.48

[a] ±
[b] 3:2

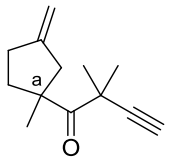
FTIR ($CDCl_3$): 3307, 2964, 2885, 1654, 1456, 1429, 1381 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.18 and 0.19 (s, 9H in total, CH_3, ratio 3:2), 1.07 and 1.09 (s, 3H in total, CH_3, ratio 3:2), 1.28 and 1.29 (s, 3H in total, CH_3, ratio 2:3), 1.30 (s, 3H, CH_3), 1.58-1.86 (m, 2H, CH_2), 2.16 and 2.17 (s, 1H in total, terminal CH, ratio 3:2), 2.27-2.45 (m, 4H, CH_2), 3.42 and 3.46 (s, 1H in total, OCH, ratio 3:2), 4.82-4.90 (m, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 20.0, 20.6, 26.1, 26.6, 29.2, 30.0, 32.2, 32.4, 30.8, 36.6, 37.8, 39.9, 46.4, 48.2, 49.1, 49.3, 70.1, 85.7, 86.4, 92.1, 105.8, 151.7, 153.1 ppm.

HRMS m/z (ESI) Calc. for $C_{16}H_{29}OSi$ (M^++H): 265.1982. Found 265.1977.

1-(3-ethylidenecyclopentyl)-2,2-dimethylbut-3-yn-1-one, 524



Chemical Formula: $C_{13}H_{18}O$
Molecular Weight: 190.28

[a] ±

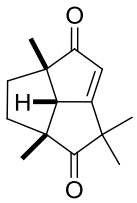
FTIR ($CDCl_3$): 3288, 2980, 2935, 2872, 1736, 1658, 1463, 1431, 1377 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.43 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.72-1.79 (m, 1H, CH_2), 2.34-2.41 (m, 4H, CH_2), 2.49 (s, 1H, CH), 3.11 (d, ^2J = 17.3 Hz, 1H, CH_2), 4.87 (s, 1H, olefinic CH), 4.90 (s, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 23.3, 28.9, 30.0, 35.5, 41.1, 43.5, 56.5, 72.8, 87.8, 105.8, 150.3, 203.8 ppm.

HRMS m/z (ESI) Calc. for $C_{13}H_{19}O$ (M^++H): 191.1430. Found 191.1427.

2,2,4a,6a-tetramethyl-4a,5,6,6a-tetrahydrocyclopenta[cd]pentalene-1,4(2H,2a1H)-dione, 526



Chemical Formula: $C_{14}H_{18}O_2$
Molecular Weight: 218.29

See **Appendix 1** for a copy of the ^{1}H NMR spectrum.

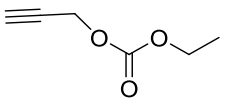
FTIR ($CDCl_3$): 2960, 2929, 2868, 1745, 1702, 1625, 1450, 1375, 1311 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 1.30 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.40 (dd, J = 7.3 and 13.2 Hz, 1H, CH_2), 1.52 (dd, J = 7.6 and 13.2 Hz, 1H, CH_2), 1.85 (dd, J = 7.3 and 13.5 Hz, 1H, CH_2), 1.99 (dd, J = 7.6 and 13.5 Hz, 1H, CH_2), 3.04 (s, 1H, CH), 6.12 (s, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 19.3, 21.5, 22.0, 23.5, 35.0, 38.1, 49.9, 58.2, 65.9, 127.0, 188.0, 212.1, 217.8 ppm

HRMS m/z (ESI) Calc. for $C_{14}H_{19}O_2$ (M^++H): 219.1380. Found 219.1381.

ethyl prop-2-ynyl carbonate, 530



Chemical Formula: $C_6H_8O_3$
Molecular Weight: 128.13

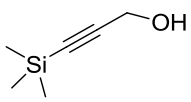
FTIR ($CDCl_3$): 2962, 1747, 1371 cm^{-1}.

^{1}H NMR δ (400MHz, $CDCl_3$): 1.35 (t, J = 6.9 Hz, 3H, CH_3), 2.54 (t, ^4J = 2.4 Hz, 1H, CH), 4.27 (q, J = 6.9 Hz, 2H, OCH_2), 4.77 (d, ^4J = 2.4 Hz, 2H, OCH_2).

^{13}C NMR δ (100 MHz, $CDCl_3$): 14.2, 54.9, 64.3, 75.4, 77.3, 154.4 ppm.

HRMS m/z (ESI) Calc. for $C_6H_9O_3$ (M^++ H): 129.0546. Found 129.0543.

3-(trimethylsilyl)prop-2-yn-1-ol, 533[264]



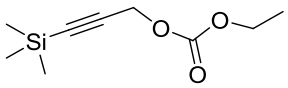
Chemical Formula: $C_6H_{12}OSi$
Molecular Weight: 128.24

FTIR ($CDCl_3$): 3559, 2983, 2953 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 0.20 (s, 9H, CH_3), 1.79 (s, 1H, OH), 4.25 (s, 2H, CH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): -0.2, 51.4, 90.9, 103.6 ppm.

ethyl 3-(trimethylsilyl)prop-2-ynyl carbonate, 531



Chemical Formula: $C_9H_{16}O_3Si$
Molecular Weight: 200.31

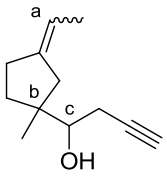
FTIR ($CDCl_3$): 2962, 1747, 1371 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.22 (s, 9H, CH_3), 1.34 (t, J = 6.7 Hz, 3H, CH_3), 4.28 (q, J = 6.7 Hz, 2H, OCH_2), 4.77 (s, 2H, OCH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): -.0.4, 14.5, 56.0, 64.3, 93.0, 98.4, 154.4 ppm.

HRMS m/z (ESI) Calc. for $C_9H_{17}O_3Si$ (M^++ H): 201.0941. Found 201.0938.

1-(3-ethylidene-1-methylcyclopentyl)but-3-yn-1-ol, 527



Chemical Formula: $C_{12}H_{18}O$
Molecular Weight: 178.27

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 4:3

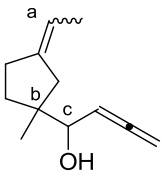
FTIR ($CDCl_3$): 3476, 3304, 2958, 2914, 1451, 1431, 1377 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.89 and 0.93 (s, 3H, CH_3 in total, ratio 4:3), 1.32-1.76 (m, 5H, CH_2 and olefinic CH_3), 2.08 (m, 1H, CH), 2.10-2.24 (m, 2H, CH_2), 2.26-2.46 (m, 4H, CH_2), 3.56-3.64 (m, 1H, OCH), 5.25-5.36 (m, 1H, olefinic CH) ppm. No OH observed.

^{13}C NMR δ (100 MHz, $CDCl_3$): 15.0, 18.7, 20.1, 20.2, 23.6, 26.9, 31.1, 35.8, 40.0, 40.1, 44.4, 46.6, 70.6, 82.3, 116.3, 142.2 ppm.

HRMS m/z (ESI) Calc. for $C_{12}H_{19}O$ (M^++H): 179.1352. Found 179.1352.

1-(3-ethylidene-1-methylcyclopentyl)buta-2,3-dien-1-ol, 534



Chemical Formula: $C_{12}H_{18}O$
Molecular Weight: 178.27

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 4:3

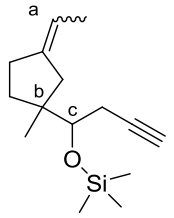
FTIR ($CDCl_3$): 3489, 2956, 2867, 1955, 1450, 1433 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.95 and 0.99 (s, 3H in total, CH_3, ratio 4:3), 1.34-1.56 (m, 1H, CH_2), 1.57-1.62 (m, 3H, olefinic CH_3), 1.64-1.76 (m, 2H, CH_2), 1.92-2.15 (m, 1H, CH_2), 2.16-2.43 (m, 3H, CH_2 and OH), 3.97-4.02 (m, 1H, OCH), 4.86-4.92 (m, 2H, olefinic CH), 5.26-5.36 (m, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 14.5, 15.9, 19.7, 21.1, 27.4, 31.3, 35.6, 39.3, 44.2, 47.0, 66.0, 92.4, 116.0, 142.7, 207.5 ppm.

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

((1-(3-ethylidene-1-methylcyclopentyl)but-3-yn-1-yl)oxy)trimethylsilane, 535



Chemical Formula: $C_{15}H_{26}OSi$
Molecular Weight: 250.45

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 4:3

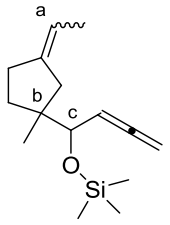
FTIR ($CDCl_3$): 3309, 2956, 2935, 2918, 1452, 1433, 1419 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 0.15-0.17 (m, 9H, CH_3), 0.85 and 0.89 (s, 3H in total, CH_3, ratio 4:3), 1.27-1.59 (m, 5H, olefinic CH_3 and CH_2), 1.85-2.07 (m, 2H, CH_2 and CH), 2.21-2.41 (m, 5H, CH_2), 3.60-3.66 (m, 1H, OCH), 5.25-5.32 (m, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 1.7, 15.0, 19.2, 20.1, 20.9, 24.1, 26.9, 31.1, 36.3, 36.7, 39.8, 41.2, 41.8, 44.2, 45.8, 47.5, 70.0, 79.3, 84.2, 115.6, 142.4 ppm.

HRMS m/z (ESI) Calc. for $C_{15}H_{27}OSi$ (M^++H): 251.1325. Found 251.1321.

(1-(3-ethylidene-1-methylcyclopentyl)buta-2,3-dienyloxy)trimethylsilane, 536



Chemical Formula: $C_{15}H_{26}OSi$
Molecular Weight: 250.45

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 4:3

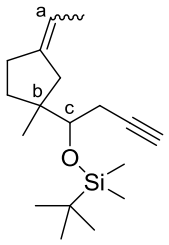
FTIR ($CDCl_3$): 2954, 2927, 2883, 2856, 1955, 1462, 1433, 1249 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 0.11-0.15 (m, 9H, CH_3), 0.92 and 0.96 (s, 3H in total, CH_3, ratio 4:3), 1.36-1.52 (m, 1H, CH_2), 1.55-1.62 (m, 3H, olefinic CH_3), 1.63-1.75 (m, 1H, CH_2), 1.83-2.01 (m, 1H, CH_2), 2.14-2.44 (m, 3H, CH_2), 3.90-3.98 (m, 1H, OCH), 4.68-4.78 (m, 2H, olefinic CH_2), 5.09-5.18 (m, 1H, olefinic CH), 5.25-5.34 (m, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 0.5, 15.0, 20.3, 20.4, 21.8, 26.9, 31.1, 35.6, 39.1, 43.7, 43.8, 47.8, 75.1, 91.0, 115.6, 142.9, 208.6 ppm.

HRMS m/z (ESI) Calc. for $C_{15}H_{27}OSi$ (M^++H): 251.1826. Found 251.1821.

***tert*-butyl((1-(3-ethylidene-1-methylcyclopentyl)but-3-yn-1-yl)oxy)dimethylsilane, 537**



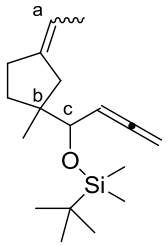
Chemical Formula: $C_{18}H_{32}OSi$
Molecular Weight: 292.53

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 4:3

See **Appendix 1** for a copy of the ^{1}H NMR spectrum.

FTIR ($CDCl_3$): 3311, 2954, 2929, 2856, 1462, 1377 cm^{-1}.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.10-0.13 (m, 3H, CH_3), 0.16-0.19 (m, 3H, CH_3), 0.92-0.95 (m, 12H, CH_3), 1.30-1.44 (m, 1H, CH_2), 1.52-1.61 (m, 5H, CH_2 and olefinic CH_3), 1.90-2.10 (m, 2H, CH_2 and CH), 2.17-2.37 (m, 3H, CH_2), 2.38-2.46 (m, 1H, CH_2), 3.60-3.65 (m, 1H, OCH), 5.25-5.32 (m, 1H, olefinic CH) ppm.
^{13}C NMR δ (100 MHz, $CDCl_3$): -5.1, -4.0, 14.0, 14.3, 14.5, 15.0, 17.8, 18.1, 19.0, 23.9, 25.4, 26.1, 30.4, 35.3, 36.5, 39.4, 40.9, 44.1, 45.4, 47.1, 65.3, 69.4, 78.4, 80.0, 115.0, 142.1 ppm.
HRMS m/z (ESI) Calc. for $C_{18}H_{33}OSi$ (M^{+}+H): 293.2295. Found 293.2294.

***tert*-butyl(1-(3-ethylidene-1-methylcyclopentyl)buta-2,3-dienyloxy)dimethylsilane, 538**

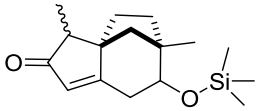


Chemical Formula: $C_{18}H_{32}OSi$
Molecular Weight: 292.53

[a] 1:1 (*E*:*Z*)
[b] ±
[c] 4:3

FTIR ($CDCl_3$): 2954, 2927, 2883, 2856, 1955, 1462, 1433, 1377 cm^{-1}.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.05-0.07 (m, 6H, CH_3), 0.88 and 0.93 (m, 12H, CH_3 and $(CH_3)_3$), 1.26-1.40 (m, 1H, CH_2), 1.56-1.62 (m, 3H, olefinic CH_3), 1.62-1.74 (m, 1H, CH_2), 1.83-2.01 (m, 1H, CH_2), 2.14-2.44 (m, 3H, CH_2), 3.90-3.98 (m, 1H, OCH), 4.68-4.78 (m, 2H, olefinic CH_2), 5.09-5.18 (m, 1H, olefinic CH), 5.25-5.34 (m, 1H, olefinic CH) ppm.
^{13}C NMR δ (100 MHz, $CDCl_3$): -5.1, -4.0, 14.3, 14.4, 17.8, 17.9, 19.6, 19.8, 20.1, 20.7, 22.6, 25.3, 26.4, 29.1, 30.7, 34.7, 38.5, 41.1, 43.9, 47.3, 74.7, 78.1, 91.7, 115.0, 142.1, 206.0 ppm.
HRMS m/z (ESI) Calc. for $C_{18}H_{33}OSi$ (M^{+}+H): 293.2295. Found 293.2294.

Compound 539



Chemical Formula: $C_{16}H_{26}O_2Si$
Molecular Weight: 278.46

Isolated as a complex mixture of diastereoisomers, partially separable by column chromatography, 2 spots by TLC analysis.

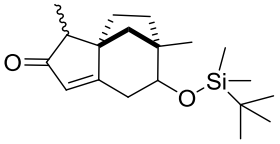
Spot 1, a complex mixture of diastereoisomers: **539a**
See **Appendix 1** for a copy of the ^{1}H NMR spectrum.

FTIR ($CDCl_3$): 2951, 2910, 2870, 1697, 1625, 1450, 1371 cm^{-1}.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.10 (s, 9H, CH_3), 1.01-1.05 (m, 6H, CH_3), 1.14-1.43 (m, 2H, CH_2), 1.52-1.61 (m, 1H, CH_2), 1.65 and 1.77 (d, J = 11.8 Hz, 1H in total, CH_2, ratio 2:1), 1.83-1.92 (m, 1H, CH_2), 2.02-2.10 (m, 1H, CH_2), 2.21 (q, J = 7.8 Hz, 1H, CH), 2.29-2.38 (m, 1H, CH_2), 2.85-2.93 (m, 1H, CH_2), 3.49 and 3.55 (dd, J = 6.4 and 9.3 Hz, 1H in total, OCH, ratio 2:1), 5.65 (s, 1H, olefinic CH) ppm.
^{13}C NMR δ (100 MHz, $CDCl_3$): 0.1, 10.5, 12.6, 12.8, 23.5, 23.8, 23.9, 29.0, 29.1, 29.6, 30.7, 33.5, 33.5, 34.9, 35.0, 36.1, 36.3, 44.6, 44.9, 45.4, 46.8, 46.9, 49.0, 54.7, 55.0, 76.2, 122.9, 123.1, 124.3, 183.7, 184.2, 184.8, 211.0, 211.5, 211.7 ppm.
HRMS m/z (ESI) Calc. for $C_{27}H_{33}O_2Si$ (M^++H): 279.1778. Found 279.1775.

Spot 2, a single diastereomer: **539b**
See **Appendix 1** for a copy of the ^{1}H NMR spectrum.

FTIR ($CDCl_3$): 2951, 2902, 2868, 1697, 1625, 1450, 1371 cm^{-1}.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.10 (s, 9H, CH_3), 1.05 (s, 3H, CH_3), 1.07 (d, J = 7.5 Hz, 3H, CH_3), 1.31 (d, ^2J = 11.3 Hz, 1H, CH_2), 1.53-1.63 (m, 3H, CH_2), 1.72 (d, ^2J = 11.3 Hz, 1H, CH_2), 1.83-1.91 (m, 1H, CH_2), 2.24 (q, J = 7.5 Hz, 1H, CH), 2.56 (d, ^2J = 15.7 Hz, 1H, CH_2), 2.67 (ddd, ^4J = 1.9 Hz, J = 5.0 Hz and ^2J = 15.7 Hz, 1H, CH_2), 3.66 (d, J = 5.0 Hz, 1H, OCH), 5.71 (d, ^4J = 1.9 Hz, 1H, olefinic CH) ppm.
^{13}C NMR δ (100 MHz, $CDCl_3$): 0.2, 10.2, 24.6, 33.6, 33.7, 35.1, 41.0, 45.3, 47.2, 55.8, 76.6, 124.6, 184.6, 211.0 ppm.
HRMS m/z (ESI) Calc. for $C_{27}H_{33}O_2Si$ (M^++H): 279.1778. Found 279.1775.

Compound 540



Chemical Formula: $C_{19}H_{32}O_2Si$
Molecular Weight: 320.54

Isolated as a complex mixture of diastereoisomers, partially separable by column chromatography. 2 spots by TLC analysis.

Spot 1, a mixture of diastereoisomers: **540a**

FTIR ($CDCl_3$): 2954, 2927, 2856, 1689, 1624, 1462, 1361 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.04-0.07 (m, 3H, CH_3), 0.07-0.10 (m, 3H, CH_3), 0.91 (s, 9H, CH_3), 1.06 (s, 3H, CH_3), 1.07 (d, *J* = 7.7 Hz, 3H, CH_3), 1.17-1.22 (m, 1H, CH_2), 1.31-1.46 (m, 2H, CH_2), 1.66 and 1.79 (d, *J* = 12.2 Hz, 1H in total, CH_2, ratio 1:2), 1.85-1.96 (m, 1H, CH_2), 2.05-2.14 (m, 1H, CH_2), 2.24 (q, *J* = 7.7 Hz, 1H, CH), 2.27-2.37 (m, 1H, CH_2), 2.89-2.97 (m, 1H, CH_2), 3.52 and 3.58 (dd, *J* = 6.5 and 9.7 Hz, 1H in total, CH, ratio 1:2), 5.66 and 5.70 (s, 1H in total, olefinic CH, ratio 2:1) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): -4.8, -4.4, -4.1, 10.1, 10.5, 12.6, 18.0, 23.7, 24.0, 24.2, 25.7, 25.8, 26.2, 28.9, 29.0, 30.6, 33.5, 33.7, 34.8, 35.1, 36.2, 36.3, 41.3, 44.6, 46.8, 46.9, 47.2, 49.0, 76.3, 122.9, 123.1, 124.5, 183.9, 184.7, 211.1, 211.3, 211.6 ppm.

HRMS m/z (ESI) Calc. for $C_{19}H_{33}O_2Si$ (M^++H): 321.2244. Found 321.2244.

Spot 2, a single diastereomer: **540b**

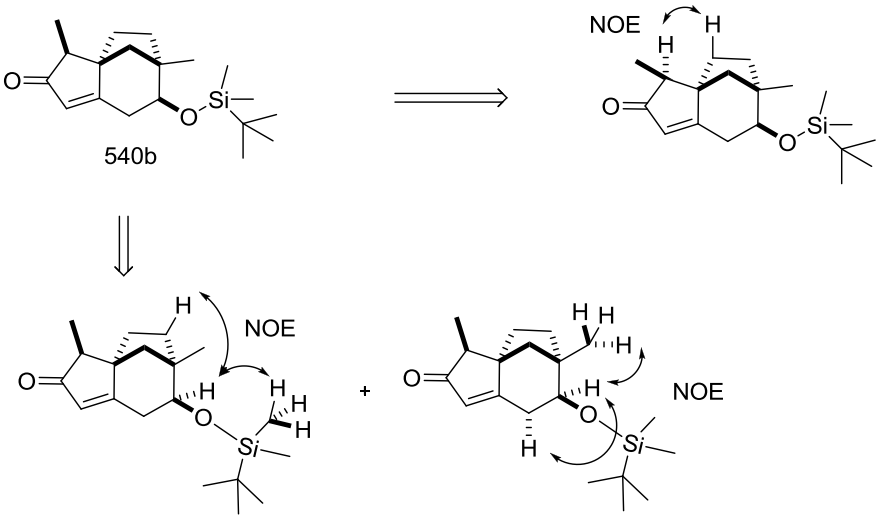
FTIR ($CDCl_3$): 2950, 2913, 2871, 1697, 1624, 1451, 1372 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.04 (s, 3H, CH_3), 0.07 (s, 3H, CH_3), 0.86 (s, 9H, CH_3), 1.08 (s, 3H, CH_3), 1.09 (d, *J* = 7.5 Hz, 3H, CH_3), 1.34 (d, *J* = 12.0 Hz, 1H, CH_2), 1.52-1.65 (m, 3H, CH_2), 1.72 (d, *J* = 12.0 Hz, 1H, CH_2), 1.84-1.93 (m, 1H, CH_2), 2.25 (q, *J* = 7.5 Hz, 1H, CH), 2.60 (d, ^2J = 15.5 Hz, 1H, CH_2), 2.67 (dd, *J* = 3.8 Hz and ^2J = 15.5 Hz, 1H, CH), 3.68 (d, *J* = 3.8 Hz, 1H, OCH), 5.72 (s, 1H, olefinic CH) ppm.

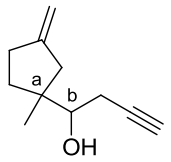
^{13}C NMR δ (100 MHz, $CDCl_3$): -4.8, -4.4, 10.1, 22.6, 24.7, 25.8, 33.6, 33.7, 35.1, 41.3, 45.6, 47.2, 55.8, 76.7, 124.6, 184.7, 210.9 ppm.

HRMS m/z (ESI) Calc. for $C_{19}H_{33}O_2Si$ (M^++H): 321.2244. Found 321.2244.

Assignment



1-(3-ethylidene-1-methylcyclopentyl)but-3-yn-1-ol, 543



Chemical Formula: $C_{11}H_{16}O$
Molecular Weight: 164.24

a ±
b 4:3

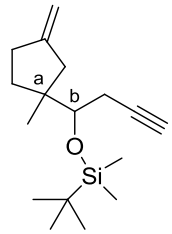
FTIR ($CDCl_3$): 3489, 3300, 2951, 2872, 1656, 1427, 1377 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.92 (s, 3H in total, CH_3), 1.38 and 1.56 (ddd, J = 5.8 and 12.2 Hz, and ^2J = 18.4 Hz, 1H in total, CH_2, ratio 3:4), 1.65 and 1.73 (ddd, J = 9.8 and 12.4 Hz, and ^2J = 18.4 Hz, 1H in total, CH_2, ratio 3:4), 1.96 and 2.14 (d, ^2J = 16.1 Hz, 1H in total, CH_2, ratio 3:4), 2.07 (t, ^4J = 2.6 Hz, 1H, CH), 2.19-2.23 (s, 1H, OH), 2.26-2.44 (m, 5H, CH_2), 3.56-3.61 (m, 1H, OCH), 4.82-4.88 (m, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 19.4, 19.6, 23.4, 23.5, 30.6, 30.7, 35.7, 44.0, 44.3, 46.3, 70.5, 76.7, 82.2, 92.4, 106.3, 151.5 ppm.

HRMS m/z (ESI) Calc. for $C_{11}H_{17}O$ (M^++H): 165.1274. Found 165.1273.

1-(3-ethylidene-1-methylcyclopentyl)but-3-yn-1-ol, 541



Chemical Formula: $C_{17}H_{30}OSi$
Molecular Weight: 278.51

[a] ±
[b] 4:3

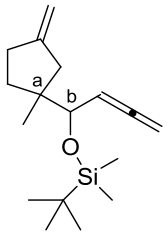
FTIR ($CDCl_3$): 3317, 2953, 2929, 2856, 1658, 1462, 1251 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.09 and 0.15 (s, 6H in total, CH_3, ratio 3:4), 0.91-0.92 (m, 9H, CH_3), 0.93-0.94 (m, 3H, CH_3), 1.56-1.70 (m, 2H CH_2), 1.98 and 1.99 (t, ^4J = 3.0 Hz, 1H in total, CH, ratio 4:3), 1.98 and 2.10 (d, ^2J = 15.8 Hz, 1H in total, CH_2, ratio 4:3), 2.23-2.32 (m, 2H, CH_2), 2.33-2.46 (m, 3H, CH_2), 3.63 (t, J = 5.4 Hz, 1H, OCH), 4.82-4.88 (m, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): -4.5, -3.4, 18.8, 19.7, 24.2, 24.4, 26.0, 26.2, 30.2, 30.4, 36.0, 37.4, 44.5, 45.9, 48.4, 70.5, 78.4, 78.8, 83.5, 106.1, 152.0 ppm.

HRMS m/z (ESI) Calc. for $C_{17}H_{31}OSi$ (M^++H): 279.2139. Found 279.2134.

***tert*-butyldimethyl(1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dienyloxy)silane, 545**



Chemical Formula: $C_{17}H_{30}OSi$
Molecular Weight: 278.51

[a] ±
[b] 4:3

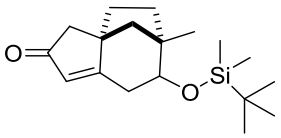
FTIR ($CDCl_3$): 2954, 2927, 2856, 1955, 1462 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.06 (s, 6H, CH_3), 0.90 (s, 9H, CH_3), 0.95 (s, 3H, CH_3), 1.33 and 1.46 (ddd, J = 5.8 and 12.2 Hz and ^2J = 18.4 Hz, 1H in total, CH_2, ratio 3:4), 1.72 (ddd, J = 9.7 and 12.2 Hz, and ^2J = 18.5 Hz, 1H, CH_2), 1.91 and 2.02 (d, ^2J = 15.8 Hz, 1H in total, CH_2, ratio 4:3), 2.29-2.39 (m, 3H, CH_2), 3.92 (d, J = 8.7 Hz, 1H, CH), 4.67-4.75 (m, 2H, olefinic CH), 4.81-4.87 (m, 2H, olefinic CH), 5.08 (ddd, J = 8.7 Hz and ^4J = 6.8 and 13.2 Hz, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): -5.1, -4.1, -2.9, 18.2, 20.4, 20.7, 25.7, 30.0, 30.6, 30.9, 35.1, 35.5, 43.4, 43.9, 48.2, 75.0, 78.0, 78.2, 92.0, 105.7, 152.4, 208.3 ppm.

HRMS m/z (ESI) Calc. for $C_{17}H_{31}OSi$ (M^++H): 279.2139. Found 279.2138.

compound 542



Chemical Formula: $C_{18}H_{30}O_2Si$
Molecular Weight: 306.52

Isolated as a complex mixture of diastereoisomers, separable by column chromatography. 2 spots by TLC analysis.

Spot 1, a single diastereoisomer: **542a**

See **Appendix 1** for a copy of the ^{1}H NMR spectrum.

FTIR ($CDCl_3$): 2956, 2932, 2858, 1689, 1622, 1464, 1363 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 0.05 (s, 3H, CH_3), 0.08 (s, 3H, CH_3), 0.87 (s, 9H, CH_3), 1.08 (s, 3H, CH_3), 1.26 (d, ^2J = 13.1 Hz, 1H, CH_2), 1.41 (ddd, J = 4.1 and 12.8 Hz, and ^2J = 17.6 Hz, 1H, CH_2), 1.66 (ddd, J = 4.1 and 9.5 Hz, and ^2J = 17.6 Hz, 1H, CH_2), 1.80 (d, ^2J = 13.1 Hz, 1H, CH_2), 1.93 (ddd, J = 5.9 and 12.8 Hz, and ^2J = 18.6 Hz, 1H, CH_2), 2.11 (ddd, J = 5.9 and 9.5 Hz, and ^2J = 18.6 Hz, 1H, CH_2), 2.35 (dd, J = 9.5 Hz, and ^2J = 15.5 Hz, 1H, CH_2), 2.94 (dd, J = 6.3 Hz and ^2J = 15.5 Hz, 1H, CH_2), 2.38 (s, 2H, CH_2), 3.57 (dd, J = 6.3 and 9.5 Hz, 1H, OCH), 5.67 (d, ^4J = 2.0 Hz, 1H, CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): -4.8, -4.0, 15.4, 18.2, 24.0, 26.0, 35.5, 36.2, 44.5, 46.1, 51.3, 65.8, 76.3, 124.6, 185.3, 208.9 ppm.

HRMS m/z (ESI) Calc. for $C_{18}H_{31}O_2Si$ (M^++H): 307.2088. Found 307.2089.

Spot 2, a single diastereoisomer: **542b**

See **Appendix 1** for a copy of the ^{1}H NMR spectrum

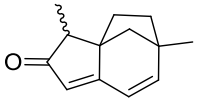
FTIR ($CDCl_3$): 2952, 2929, 2855, 1690, 1621, 1464, 1363 cm^{-1}.

^{1}H NMR δ (400 MHz, $CDCl_3$): 0.05 (s, 3H, CH_3), 0.08 (s, s, 3H, CH_3), 0.87 (s, 9H, CH_3), 1.08 (s, 3H, CH_3), 1.47 (d, ^2J = 12.7 Hz, 1H, CH_2), 1.58-1.71 (m, 3H, CH_2), 1.92 (ddd, J = 6.9 and 11.4 Hz and ^2J = 17.2 Hz, 1H, CH_2), 1.96 (d, ^2J = 12.7 Hz, 1H, CH_2), 2.36 (d, ^2J = 18.4 Hz, 1H, CH_2), 2.42 (d, ^2J = 18.4 Hz, 1H, CH_2), 2.61 (dd, J = 2.0 Hz and ^2J = 16.2 Hz, 1H, CH_2), 2.66 (ddd, ^4J =1.7 Hz, J = 4.3 Hz and ^2J = 16.2 Hz, 1H, CH_2), 3.68 (dd, J = 2.0 and 4.3 Hz, 1H, OCH), 5.72 (d, ^4J = 1.7 Hz, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): -4.8, -4.1, 15.3, 17.9, 24.1, 25.7, 34.2, 34.9, 45.2, 46.0, 52.0, 66.0, 76.3, 125.6, 185.9, 208.7 ppm.

HRMS m/z (ESI) Calc. for $C_{18}H_{31}O_2Si$ (M^++H): 307.2088. Found 307.2089.

compound 552



Chemical Formula: $C_{13}H_{16}O$
Molecular Weight: 188.27

Isolated as an inseparable 1:1 mixture of diastereoisomers.

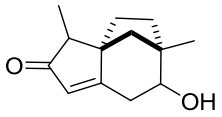
FTIR ($CDCl_3$): 2949, 2933, 2868, 1691, 1610, 1571, 1454, 1373 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.10 and 1.11 (d, *J* = 7.5 Hz, 3H in total, CH_3, ratio 1:1), 1.14-1.24 (m, 1H, CH_2), 1.27 (s, 3H, CH_3), 1.59 and 1.62 (d, ^2J = 12.5 Hz, 1H in total, CH_2, ratio 1:1), 1.64-1.76 (m, 2H, CH_2), 1.77-1.89 (m, 1H, CH_2), 2.02 and 2.09 (ddd, *J* = 4.0 and 11.4 Hz, and ^2J = 15.2 Hz, 1H in total, CH_2, ratio 1:1), 2.33 and 2.44 (q, *J* = 7.5 Hz, 1H in total, CH, ratio 1:1), 5.58 and 5.67 (s, 1H in total, olefinic CH, ratio 1:1), 6.35-6.44 (m, 2H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 11.3, 13.2, 24.4, 29.8, 37.1, 38.7, 40.2, 43.8, 46.0, 48.9, 54.4, 55.3, 65.8, 119.2, 120.0, 120.8, 121.1, 153.6, 179.0, 179.6, 210.5, 212.3 ppm.

HRMS m/z (ESI) Calc. for $C_{13}H_{17}O$ (M^++H): 189.1274. Found 189.1274.

Compound 551



Chemical Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.28

Isolated from **551b**

Isolated as a single diastereoisomer.

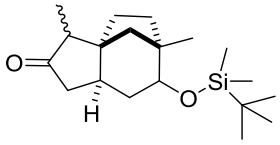
FTIR ($CDCl_3$): 3445, 2953, 2912, 2864, 1697, 1625, 1450, 1371 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 1.09 (d, *J* = 7.6 Hz, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.42 (d, ^2J = 12.4 Hz, 1H, CH_2), 1.61-1.69 (m, 5H, CH_2 and OH), 1,91 (ddd, *J* = 9.3 and 13.4 Hz and ^2J = 16.9 Hz, 1H, CH_2), 2.27 (q, *J* = 7.6 Hz, 1H, CH), 2.73 (d, ^2J = 15.3 Hz, 1H, CH_2), 2.77 (dd, *J* = 4.2 Hz and ^2J = 15.3 Hz, 1H, CH_2), 3.76 (d, *J* = 4.2 Hz, 1H, OCH), 5.8 (s, 1H, olefinic CH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 10.8, 23.2, 28.3, 30.9, 34.9, 44.8, 46.9, 49.4, 55.3, 76.9, 123.7, 184.0, 211.6 ppm.

HRMS m/z (ESI) Calc. for $C_{13}H_{19}O_2$ (M^++H): 207.1380. Found 207.1380.

Compound, 556



Chemical Formula: $C_{19}H_{34}O_2Si$
Molecular Weight: 322.56

Isolated as a complex mixture of diastereoisomers, separable by column chromatography. 2 spots by TLC analysis.

Spot 1, isolated as a complex mixture of diastereoisomers, **556a**.

FTIR ($CDCl_3$): 2951, 2927, 2856, 1739, 1471, 1462, 1454, 1359 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.02-0.06 (m, 6H, CH_3), 0.87-0.91 (m, 9H, CH_3), 0.92-0.96 (m, 3H, CH_3), 1.01-1.04 (m, 3H, CH_3), 1.13-1.21 (m, 2H, CH_2), 1.27-1.36 (m, 1H, CH_2), 1.40-1.48 (m, 1H, CH_2), 1.49-1.58 (m, 1H, CH_2), 1.65-1.73 (m, 1H, CH_2), 1.82-1.92 (m, 2H, CH and CH_2), 1.98-2.07 (m, 2H, CH_2), 2.10-2.20 (m, 1H, CH), 2.23-2.32 (m, 1H, CH_2), 3.48-3.56 (m, 1H, OCH) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): -4.8, -4.0, 7.4, 7.9, 18.1, 22.6, 23.5, 24.0, 25.0, 25.9, 28.7, 30.0, 32.3, 33.4, 35.8, 39.4, 40.0, 41.0, 41.7, 42.7, 44.6, 45.9, 48.1, 51.1, 51.6, 75.1, 221.1 ppm.

HRMS m/z (ESI) Calc. for $C_{19}H_{35}O_2Si$ (M^++H): 323.2401. Found 323.2402.

556b from **540b**. Isolated as a single diastereomer.

See **Appendix 1** for copy of the ^1H NMR spectra.

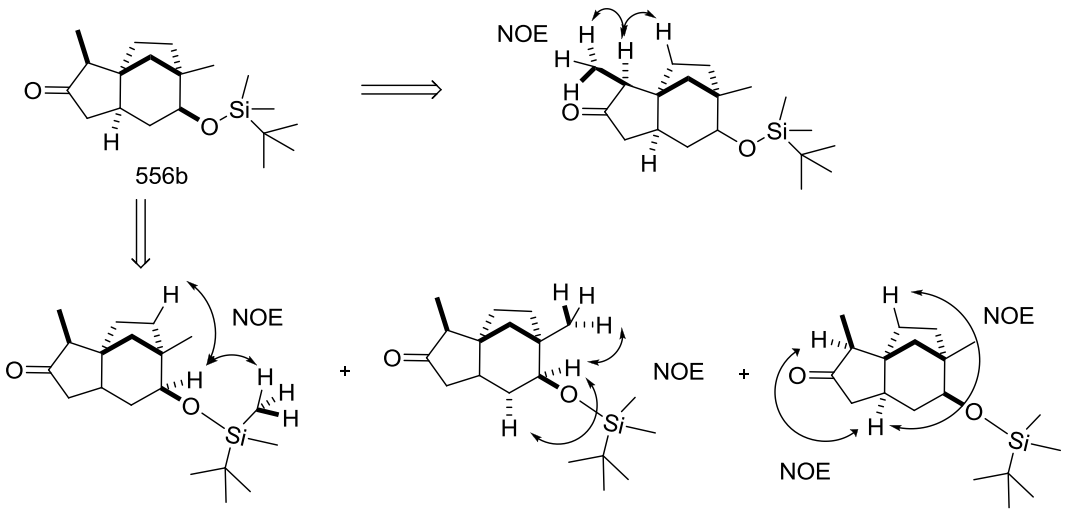
FTIR ($CDCl_3$): 2949, 2928, 2855, 1740, 1472, 1462, 1452, 1357 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.02 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.88 (m, 9H, CH_3), 0.96 (d, J = 6.9 Hz, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.34-1.64 (m, 5H, CH_2), 1.68 (d, ^2J = 15.4 Hz, 1H, CH_2), 1.81-1.91 (m, 2H, CH and CH_2), 1.97-2.02 (ddd, J = 5.2, 7.9 and 13.1 Hz, 1H, CH_2), 2.09 (q, J = 6.9 Hz, 1H, CH), 2.27 (dd, J = 7.9 Hz and ^2J = 18.3 Hz, 1H, CH_2), 2.46 (dd, J = 13.1 Hz and ^2J = 18.3 Hz, 1H, CH_2), 3.51 (d, J = 4.8 Hz, 1H, OCH) ppm.

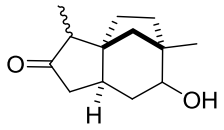
^{13}C NMR δ (100 MHz, $CDCl_3$): -4.9, -4.3, 7.0, 18.0, 25.5, 26.2, 29.9, 32.5, 33.0, 34.5, 40.9, 42.7, 44.2, 51.8, 51.9, 76.2, 221.2 ppm.

HRMS m/z (ESI) Calc. for $C_{19}H_{35}O_2Si$ (M^++H): 323.2401. Found 323.2402.

Assignment



Compound 557



Chemical Formula: $C_{13}H_{20}O_2$
Molecular Weight: 208.30

Isolated as a complex mixture of diastereoisomers, separable by column chromatography. 2 spots by TLC analysis. See **Appendix 1** for a copy of the NMR spectra.

Spot 1. Isolated as a single diastereomer **557a**
See **Appendix 1** for copy of the ^{1}H NMR spectra.

FTIR ($CDCl_3$): 3454, 2929, 2866, 1733, 1452, 1409, 1373 cm^{-1}.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.98 (d, J = 7.5 Hz, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.43-1.55 (m, 3H, CH_2), 1.58-1.65 (m, 2H, CH_2), 1.77 (d, ^2J = 15.4 Hz, 1H, CH_2), 1.84-1.96 (m, 2H, CH_2), 2.03-2.16 (m, 2H, CH_2 and CH), 2.30-2.38 (m, 1H, CH_2), 2.39-2.48 (m, 1H, CH), 3.58-3.64 (m, 1H, OCH) ppm. No OH observed.
^{13}C NMR δ (100 MHz, $CDCl_3$): 7.1, 7.4, 22.9, 23.9, 24.6, 27.9, 29.5, 29.9, 30.7, 31.0, 32.3, 33.3, 34.4, 39.5, 40.7, 41.8, 42.9, 51.3, 52.0, 76.3, 216.1 ppm.
HRMS m/z (ESI) Calc. for $C_{13}H_{21}O_2$ (M^++H): 209.1536. Found 209.1536.

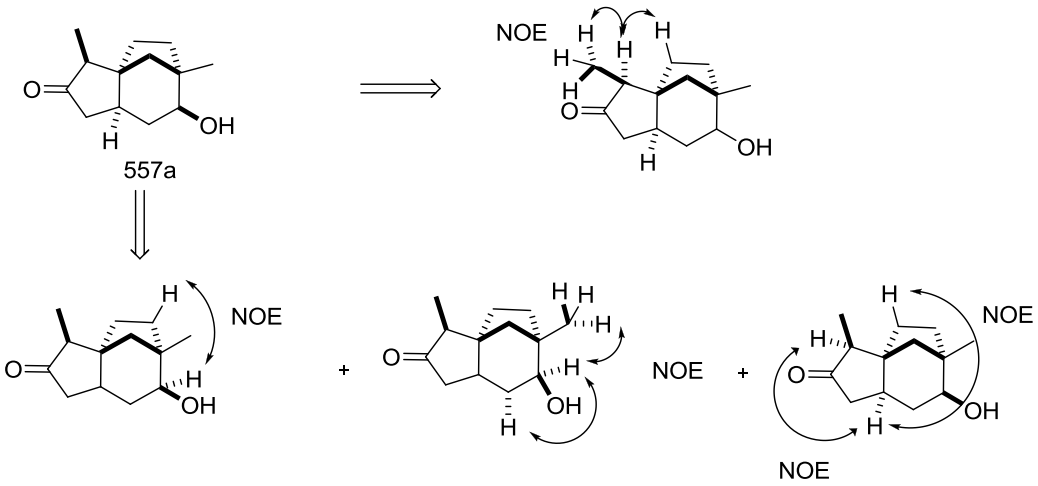
Spot 2. Isolated as a complex mixture of diastereomers **557b**
FTIR ($CDCl_3$): 3450, 2926, 2858, 1734, 1451, 1419, 1369 cm^{-1}.
^{1}H NMR δ (400 MHz, $CDCl_3$): 0.94-0.99 (m, 3H, CH_3), 1.11-1.14 (m, 3H, CH_3), 1.23-1.34 (m, 2H, CH_2), 1.44-1.54 (m, 1H, CH_2), 1.60-1.67 (m, 1H, CH_2), 1.70-1.83 (m, 1H, CH_2),

1.85-1.98 (m, 2H, CH_2), 2.01-2.11 (m, 2H, CH), 2.12-2.21 (m, 1H, CH_2), 2.27-2.37 (m, 2H, CH_2), 3.55-3.65 (m, 1H, OCH) ppm. No OH observed.

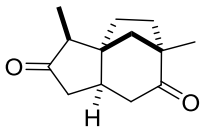
^{13}C NMR δ (100 MHz, $CDCl_3$): 7.2, 7.4, 22.8, 24.0, 24.6, 28.0, 29.5, 30.0, 30.7, 31.1, 32.4, 33.3, 34.6, 39.5, 40.7, 41.8, 42.6, 51.3, 52.2, 76.2, 216.2 ppm.

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

Assignment



Compound, 558



Chemical Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.28

Isolated as a single diastereoisomer.

See **Appendix 1** for copy of the ^1H NMR spectra.

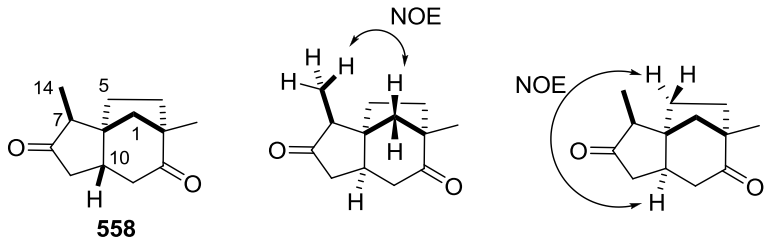
FTIR ($CDCl_3$): 2964, 2933, 2868, 1736, 1711, 1452, 1413 cm^{-1}.

^1H NMR δ (600 MHz, $CDCl_3$): 1.00 (d, J = 7.1 Hz, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.38 (d, ^2J = 12.7 Hz, 1H, CH_2), 1.50 (d, ^2J = 12.7 Hz, 1H, CH_2), 1.68-1.74 (m, 2H, CH_2), 1.94 (ddd, J = 5.0 and 12.5 Hz, ^2J = 17.6 Hz, 1H, CH_2), 1.99 (dd, J = 11.9 Hz and ^2J = 18.6 Hz, 1H, CH_2), 2.10-2.16 (m, 1H, CH_2), 2.29 (q, J = 7.1 Hz, 1H, CH), 2.31 (dd, J = 2.5 Hz and ^2J = 18.1 Hz, 1H, CH_2), 2.40 (dddd, J = 1.8, 2.5, 9.5 and 11.9 Hz, 1H, CH), 2.56 (ddd, J = 1.8 and 8.5 Hz and ^2J = 18.6 Hz, 1H, CH_2), 2.79 (dd, J = 9.5 Hz and ^2J = 18.1 Hz, 1H, CH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 7.6, 20.4, 34.2, 34.8, 38.5, 41.1, 43.6, 50.9, 51.5, 65.8, 52.1, 213.7, 217.3 ppm.

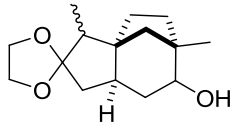
HRMS m/z (ESI) Calc. for $C_{13}H_{19}O_2$ (M^++H): 207.1380. Found: 207.1377.

Key NOE correlations:



558

Compound 565



Chemical Formula: $C_{15}H_{24}O_3$
Molecular Weight: 252.35

Isolated as a complex mixture of diastereoisomers. 2 spots by TLC, separable by column chromatography.

Spot 1 a complex mixture of diastereoisomers **565a**.

FTIR ($CDCl_3$): 3456, 2933, 2865, 1456 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.80 and 0.86 (d, J = 7.5 Hz, 3H in total, CH_3, ratio 2:3), 1.09 and 1.28 (s, 3H in total, CH_3, ratio 3:2), 1.35-1.48 (m, 3H, CH_2), 1.50-1.56 (m, 1H, CH_2), 1.57-1.62 (m, 1H, CH_2), 1.64-1.73 (m, 2H, CH_2 and CH), 1.74-1.78 (m, 1H, CH_2), 1.84-1.92 (m, 1H, CH_2), 1.93-2.01 (m, 2H, CH_2 and CH), 2.05-2.27 (m, 1H, CH_2), 3.38-3.41 and 3.49-3.55 (m, 1H, OCH, ratio 2:3), 3.73-3.84 and 3.87-3.98 (m, 4H in total, CH_2, ratio 2:3) ppm. No OH observed.

^{13}C NMR δ (100 MHz, $CDCl_3$): 14.7, 24.1, 29.4, 31.9, 32.2, 33.7, 41.8, 42.8, 43.1, 47.3, 50.8, 51.4, 52.2, 63.3, 64.4, 65.4, 75.4, 75.9, 116.8, 117.7 ppm.

HRMS m/z (ESI) Calc. for $C_{15}H_{25}O_3$ (M^++H): 253.1798. Found 253.1797.

Spot 2 a complex mixture of diastereoisomers **565b**.

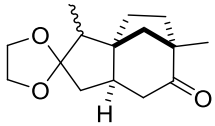
FTIR ($CDCl_3$): 3454, 2935, 2871, 1444 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.83 and 0.85 (d, J = 7.5 Hz, 3H in total, CH_3, ratio 5:4), 1.09 and 1.18 (s, 3H in total, CH_3, ratio 3:2), 1.22-1.31 (m, 1H, CH_2), 1.37-1.44 (m, 1H, CH_2), 1.47-1.56 (m, 2H, CH_2), 1.57-1.64 (m, 1H, CH_2), 1.68-1.80 (m, 2H, CH_2 and CH), 1.81-2.01 (m, 5H, CH_2 and CH), 3.47-3.58 (m, 1H, OCH), 3.71-3.83 and 3.85-3.98 (m, 4H in total, CH_2, ratio 4:5) ppm. No OH observed.

^{13}C NMR δ (100 MHz, $CDCl_3$): 14.6, 24.3, 29.4, 32.2, 32.5, 33.7, 41.8, 42.6, 43.1, 47.4, 50.8, 51.5, 52.2, 63.6, 64.4, 65.5, 75.4, 75.9, 116.9, 117.6 ppm.

HRMS m/z (ESI) Calc. for $C_{15}H_{25}O_3$ (M^++H): 253.1798. Found 253.1797.

Compound 566



Chemical Formula: $C_{15}H_{22}O_3$
Molecular Weight: 250.33

Isolated as a complex mixture of diastereomers.

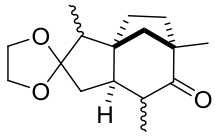
FTIR ($CDCl_3$): 2956, 2929, 2872, 1717, 1473, 1452 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.88 and 0.91 (d, *J* = 7.4 Hz, 3H, CH_3, ratio 4:3), 1.11 and 1.15 (s, 3H in total, CH_3, ratio 4:3), 1.37-1.42 (m, 1H, CH_2), 1.43-1.50 (m, 1H, CH_2), 1.55-1.71 (m, 3H, CH_2), 1.72-1.85 (m, 2H, CH_2 and CH), 1.91-1.98 (m, 1H, CH_2), 2.09-2.14 (m, 2H, CH_2 and CH), 2.19-2.27 (m, 1H, CH_2), 2.38-2.42 and 2.53-2.59 (m, 1H in total, CH_2, ratio 3:4), 3.75-3.86 (m, 2H, CH_2), 3.88-3.97 (m, 2H, CH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 6.9, 7.1, 19.8, 20.7, 23.3, 34.6, 35.3, 35.8, 38.7, 40.2, 41.4, 41.6, 43.7, 46.8, 47.0, 48.4, 52.4, 52.5, 52.6, 64.7, 64.9, 117.6, 117.8, 213.9, 219.3 ppm.

HRMS m/z (ESI) Calc. for $C_{15}H_{23}O_3$ (M^++H): 251.1642. Found 251.1642.

Compound 567



Chemical Formula: $C_{16}H_{24}O_3$
Molecular Weight: 264.36

Isolated as a complex mixture of diastereomers, 1 spot by TLC analysis.

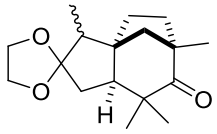
FTIR ($CDCl_3$): 2960, 2929, 2873, 1713, 1458, 1371 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.86, 0.88 and 0.90 (d, *J* = 7.5 Hz, 3H in total, CH_3, ratio 1:3:1), 0.97, 0.99 and 1.04 (d, *J* = 7.4 Hz, 3H in total, CH_3, ratio 1:1:3), 1.12 and 1.18 (s, 3H in total, CH_3, ratio 2:3), 1.28-1.35 (m, 1H, CH_2), 1.46-1.57 (m, 2H, CH_2), 1.58-1.72 (m, 3H, CH_2 and CH), 1.78-1.88 (m, 1H, CH_2), 1.99-2.11 (m, 2H, CH_2 and CH), 2.13-2.26 (m, 2H, CH), 3.73-97 (m, 4H, CH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 7.2, 14.0, 21.0, 24.1, 35.7, 37.6, 38.1, 40.7, 42.3, 44.3, 45.6, 46.4, 46.8, 47.2, 50.9, 51.8, 64.9, 65.0, 117.3, 117.4, 209.01 ppm.

HRMS m/z (ESI) Calc. for $C_{16}H_{25}O_3$ (M^++H): 265.1798. Found 265.1802.

Compound 568



Chemical Formula: $C_{17}H_{26}O_3$
Molecular Weight: 278.39

Isolated as a complex mixture of diastereomers, 1 spot by TLC analysis.

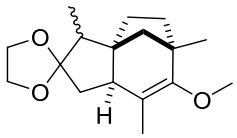
FTIR ($CDCl_3$): 2960, 2929, 2870, 1709, 1475, 1454, 1375 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.88 (d, J = 7.2 Hz, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.20-1.22 (m, 3H, CH_3), 1.38 (d, ^2J = 12.7 Hz, 1H, CH_2), 1.52-1.64 (m, 3H, CH_2), 1.70 (d, ^2J = 12.7 Hz, 1H, CH_2), 1.78-1.88 (m, 2H, CH_2 and CH), 1.93-2.01 (m, 2H, CH_2), 2.10 (q, J = 7.2 Hz, 1H, CH), 3.76-3.87 and 3.93-3.98 (m, 4H, CH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 7.8, 21.9, 25.3, 32.2, 35.0, 35.3, 35.8, 38.4, 40.0, 47.4, 52.3, 52.8, 54.2, 64.2, 65.0, 65.1, 115.9, 209.9 ppm.

HRMS m/z (ESI) Calc. for $C_{17}H_{27}O_3$ (M^++H): 279.1955. Found 279.1956.

Compound 569



Chemical Formula: $C_{17}H_{26}O_3$
Molecular Weight: 278.39

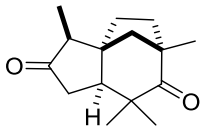
FTIR ($CDCl_3$): 2954, 2929, 2858, 2829, 1664, 1448, 1373 cm^{-1}.

^1H NMR δ (400 MHz, $CDCl_3$): 0.85 (d, J = 7.4 Hz, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.36-1.42 (m, 3H, CH_2), 1.50 (ddd, J = 5.5 and 11.9 Hz, and ^2J = 17.7 Hz, 1H, CH_2), 1.54 (s, 3H, CH_3), 1.62 (dd, J = 11.2 Hz and ^2J = 13.7 Hz, 1H, CH_2), 1.82 (ddd, J = 3.8 and 12.1 Hz, and ^2J = 15.6 Hz, 1H, CH_2), 1.93 (ddd, J = 3.3 and 12.1 Hz, and ^2J = 15.6 Hz, 1H, CH_2), 2.04 (m, 2H, CH and CH_2), 2.21 (dd, J = 8.8 and ^2J = 13.7 Hz, 1H, CH_2), 3.54 (s, 3H, OCH_3), 3.74-3.84 (m, 2H, CH_2), 3.88-3.95 (m, 2H, CH_2) ppm.

^{13}C NMR δ (100 MHz, $CDCl_3$): 6.8, 14.2, 20.9, 34.9, 41.6, 41.8, 43.5, 44.2, 47.8, 51.8, 52.6, 60.7, 64.2, 64.9, 116.8, 117.0, 157.5 ppm.

HRMS m/z (ESI) Calc. for $C_{17}H_{27}O_3$ (M^++H): 209.1955. Found 209.1958.

Compound 571



Chemical Formula: $C_{15}H_{22}O_2$
Molecular Weight: 234.33

See **Appendix 1** for copy of the ^{1}H NMR spectra.

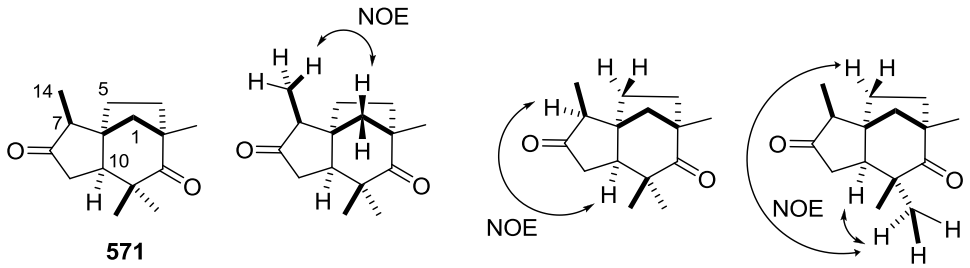
FTIR ($CDCl_3$): 2964, 2936, 2888, 1735, 1704, 1449, 1432 cm^{-1}.

^{1}H NMR δ (600 MHz, $CDCl_3$): 1.02 (d, *J* = 7.0 Hz, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.44 (d, ^2J = 16.9 Hz, 1H, CH_2), 1.46 (d, ^2J = 16.9 Hz, 1H, CH_2), 1.73 (ddd, *J* = 4.9 and 13.4 Hz, ^2J = 17.3 Hz, 1H, CH_2), 1.78-1.86 (ddd, *J* = 4.9 and 9.0 Hz, and ^2J =17.9 Hz, 1H, CH_2), 2.00 (ddd, *J* = 4.9 and 9.0 Hz, and ^2J =17.9 Hz, 1H, CH_2), 2.14 (ddd, *J* = 4.9 and 13.4 Hz, and ^2J = 17.3 Hz, 1H, CH_2), 2.17 (dd, *J* = 12.4 Hz and ^2J = 17.8 Hz, 1H, CH_2), 2.28 (dd, *J* = 7.3 and 12.4 Hz, 1H, CH), 2.31 (q, *J* = 7.0 Hz, 1H, CH), 2.46 (dd, *J* = 7.3 and ^2J = 17.8 Hz, 1H, CH_2) ppm.

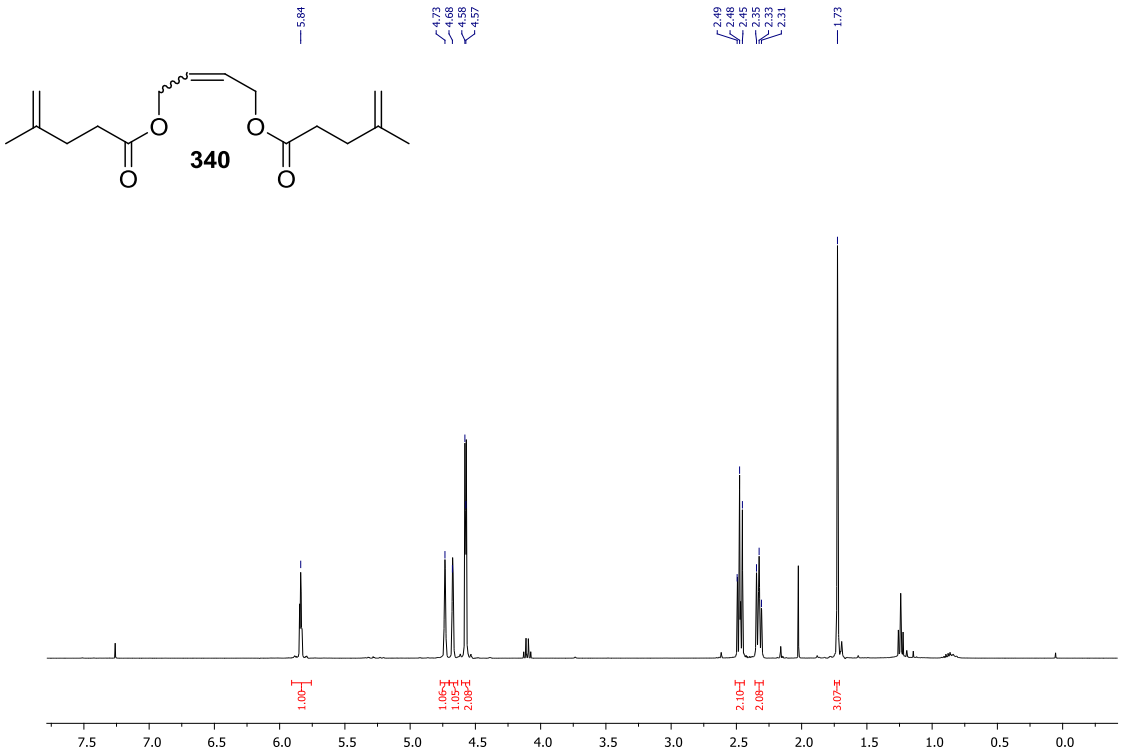
^{13}C NMR δ (100 MHz, $CDCl_3$): 7.2, 21.1, 25.3, 32.8, 33.1, 35.0, 37.5, 40.2, 43.2, 51.1, 51.7, 52.2, 53.1 ppm. Carbonyls not observed.

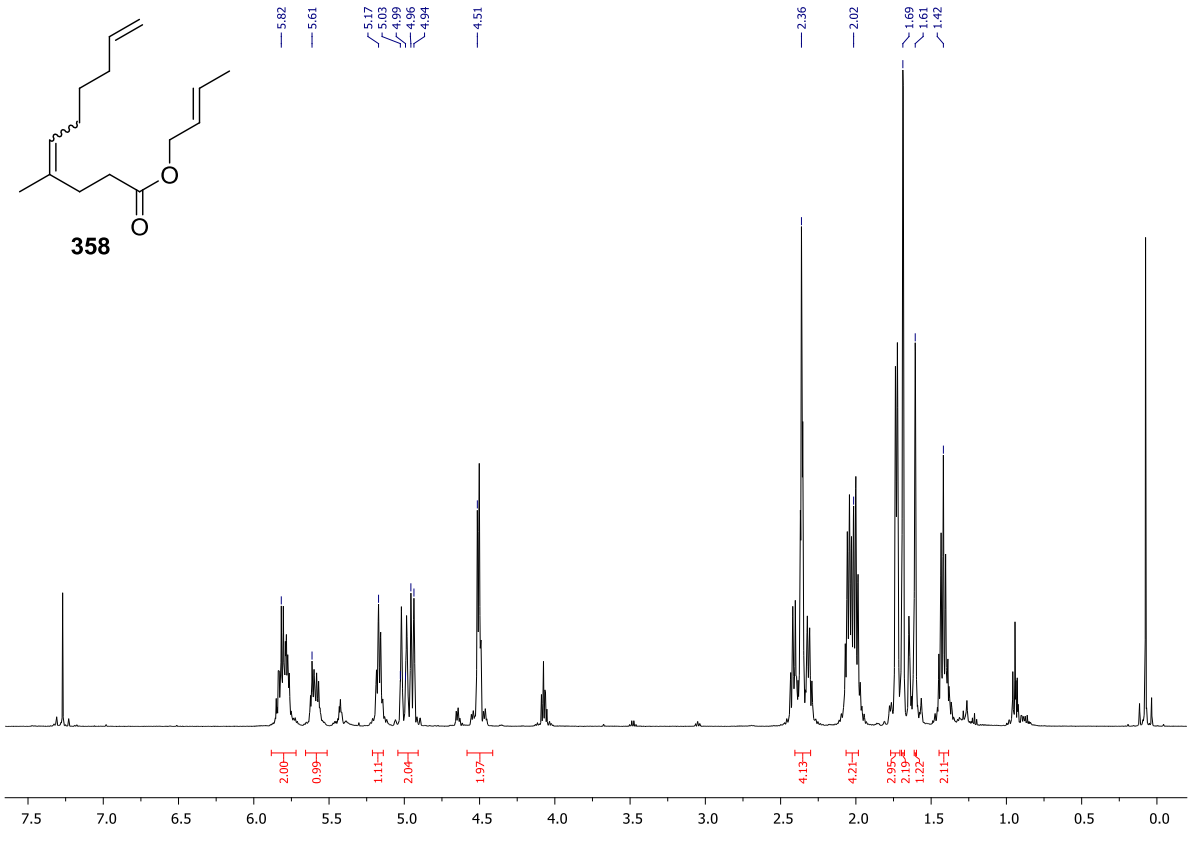
HRMS m/z (ESI) Calc. for $C_{15}H_{23}O_2$ (M^++H): 235.1693. Found: 235.1694.

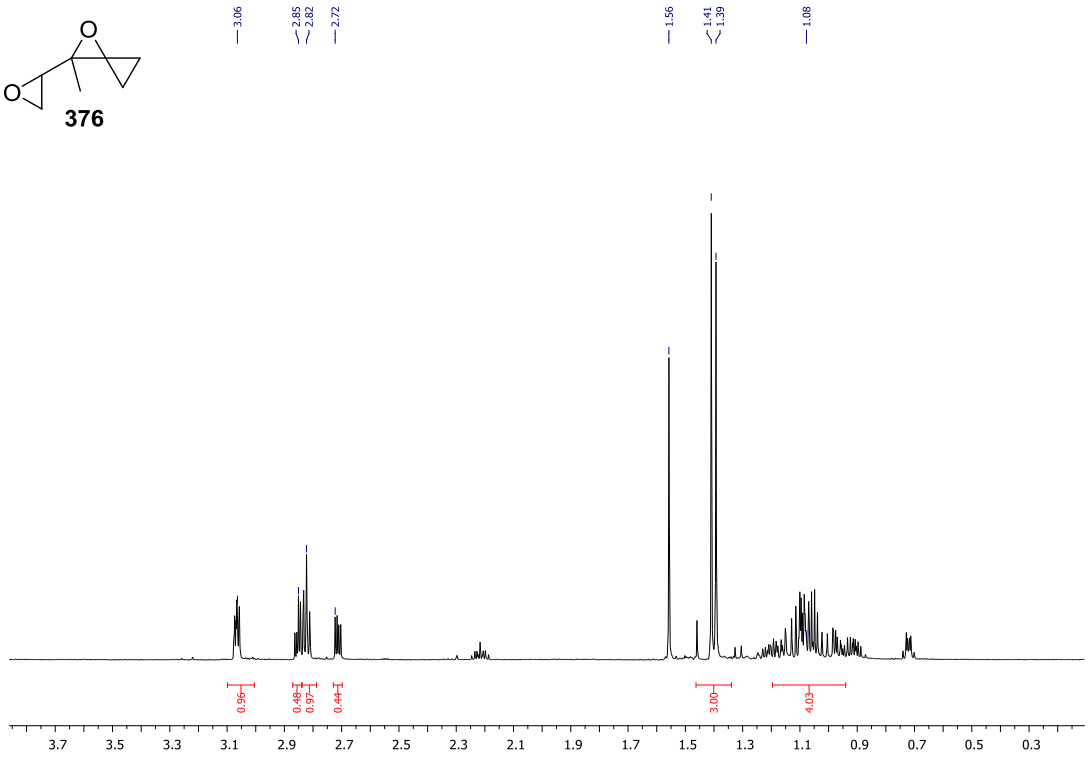
Key NOE correlations

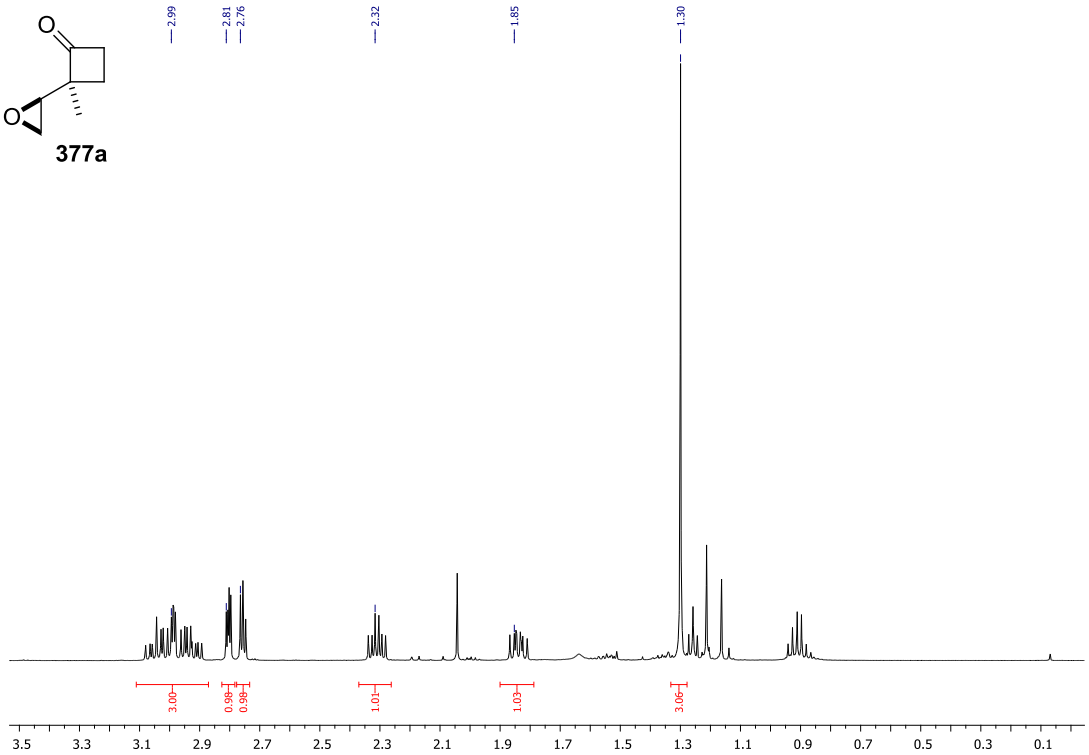


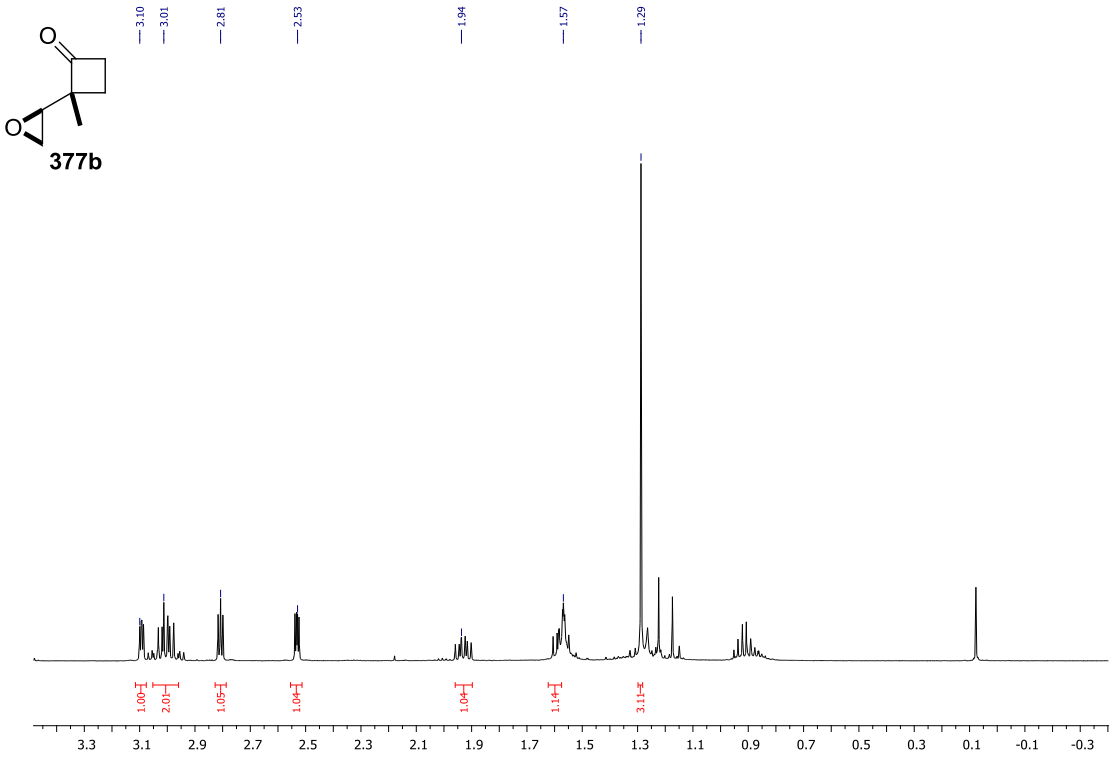
5.3 Appendix 1



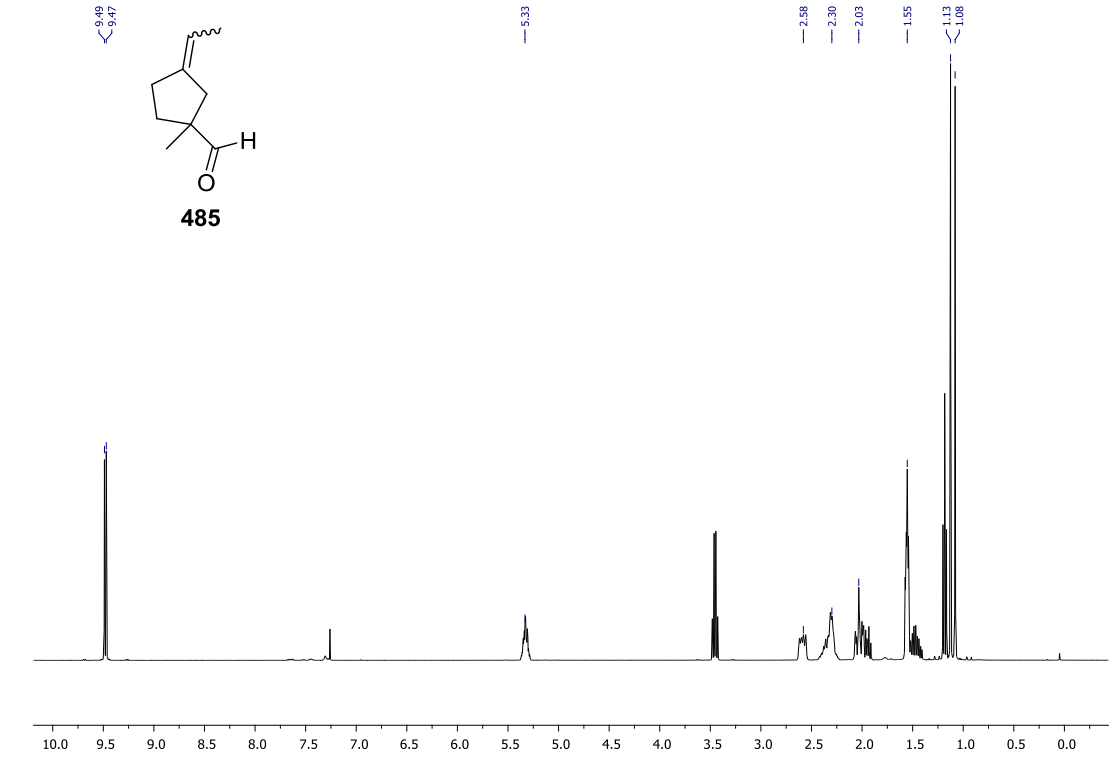



376
3.06
2.85
2.82
2.72
1.56
1.41
1.39
1.08
0.96
0.48
0.97
0.44
3.00
4.03
3.7
3.5
3.3
3.1
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
1.3
1.1
0.9
0.7
0.5
0.3

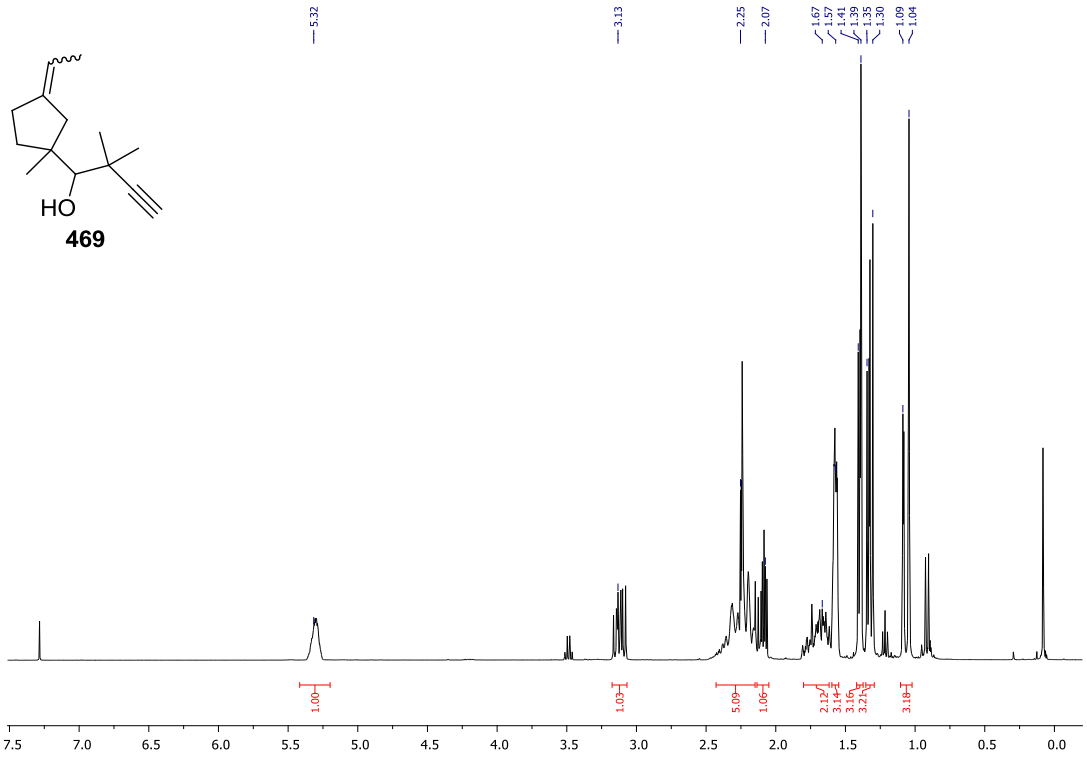

377a
2.99
2.81
2.76
2.32
1.85
1.30
3.00
0.98
0.99
1.01
1.03
3.06
3.5
3.3
3.1
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
1.3
1.1
0.9
0.7
0.5
0.3
0.1

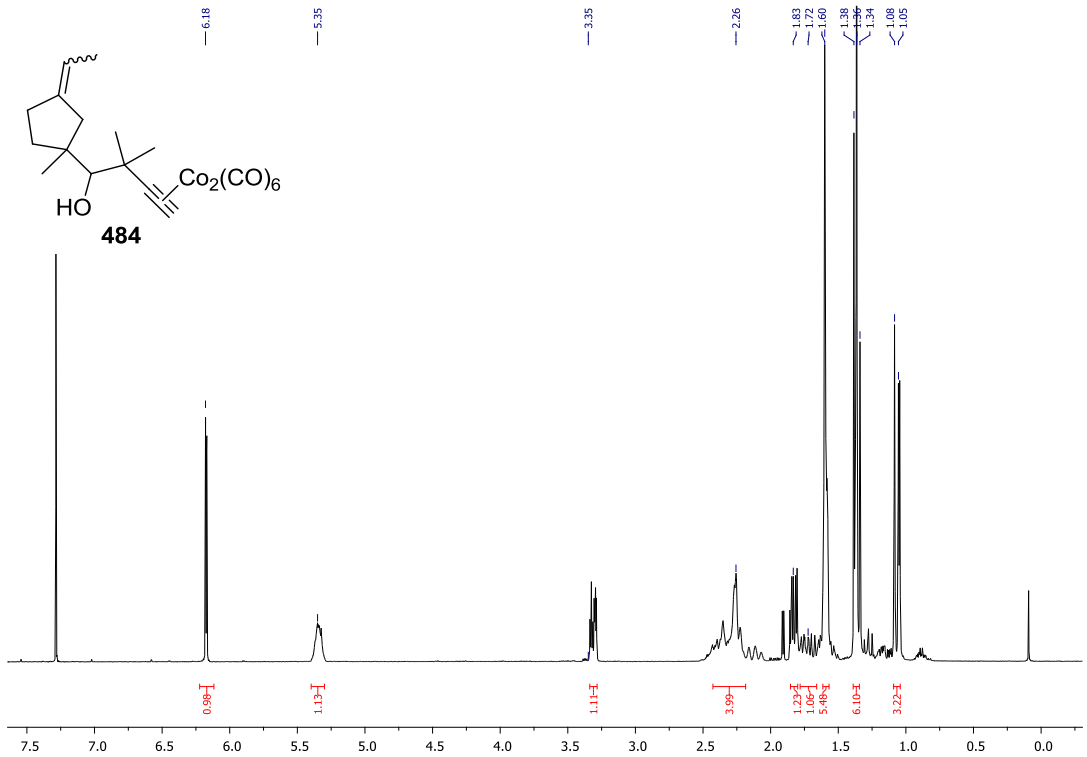

3.10
3.01
2.81
2.53
1.94
1.57
1.29
1.00
2.01
1.05
1.04
1.04
1.14
3.11
3.3
3.1
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
1.3
1.1
0.9
0.7
0.5
0.3
0.1
-0.1
-0.3

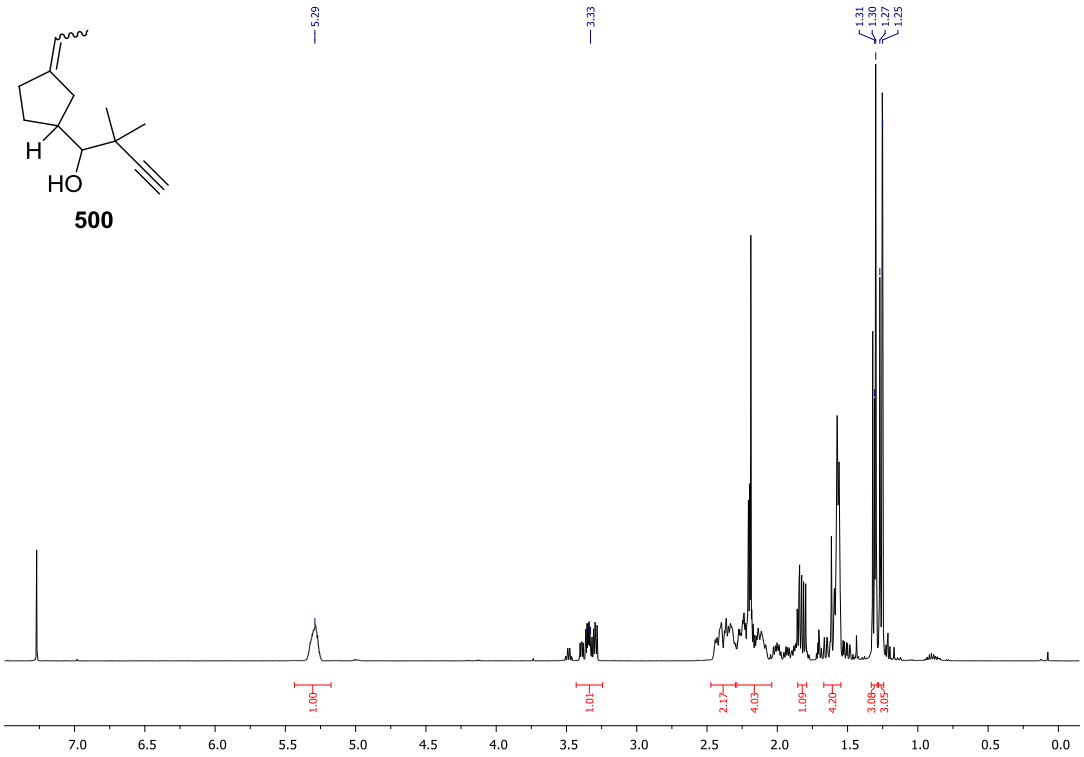
377b


9.49
9.47
5.33
2.58
2.30
2.03
1.55
1.13
1.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

485


HO
469
5.32
3.13
2.25
2.07
1.67
1.57
1.41
1.39
1.35
1.30
1.09
1.04
1.00
1.03
5.09
1.06
2.12
3.14
3.16
3.21
3.18
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


HO
Co2(CO)6
484
6.18
5.35
3.35
2.26
1.83
1.72
1.60
1.38
1.34
1.08
1.05
0.98
1.13
1.11
3.99
1.23
1.06
5.48
6.10
3.22
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


H
HO
5.29
3.33
1.31
1.30
1.27
1.25
1.00
1.01
2.17
4.03
1.09
4.20
3.08
3.05
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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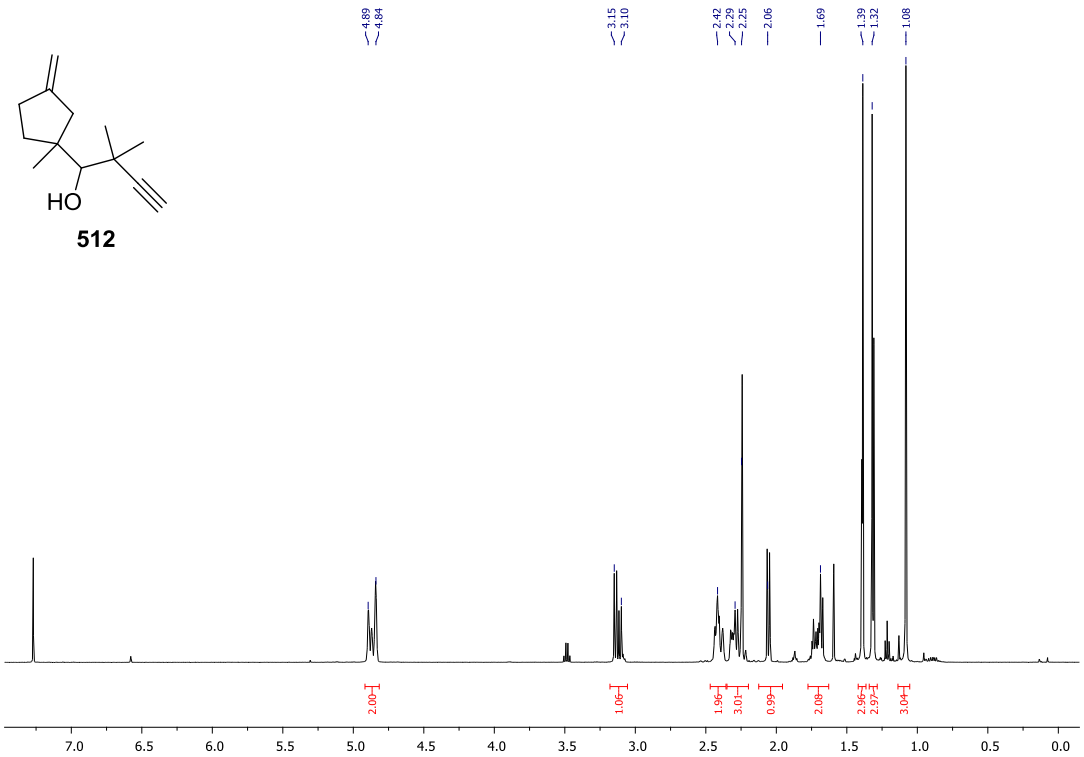
500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2.00
1.06
1.96
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2.96
2.97
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6.0
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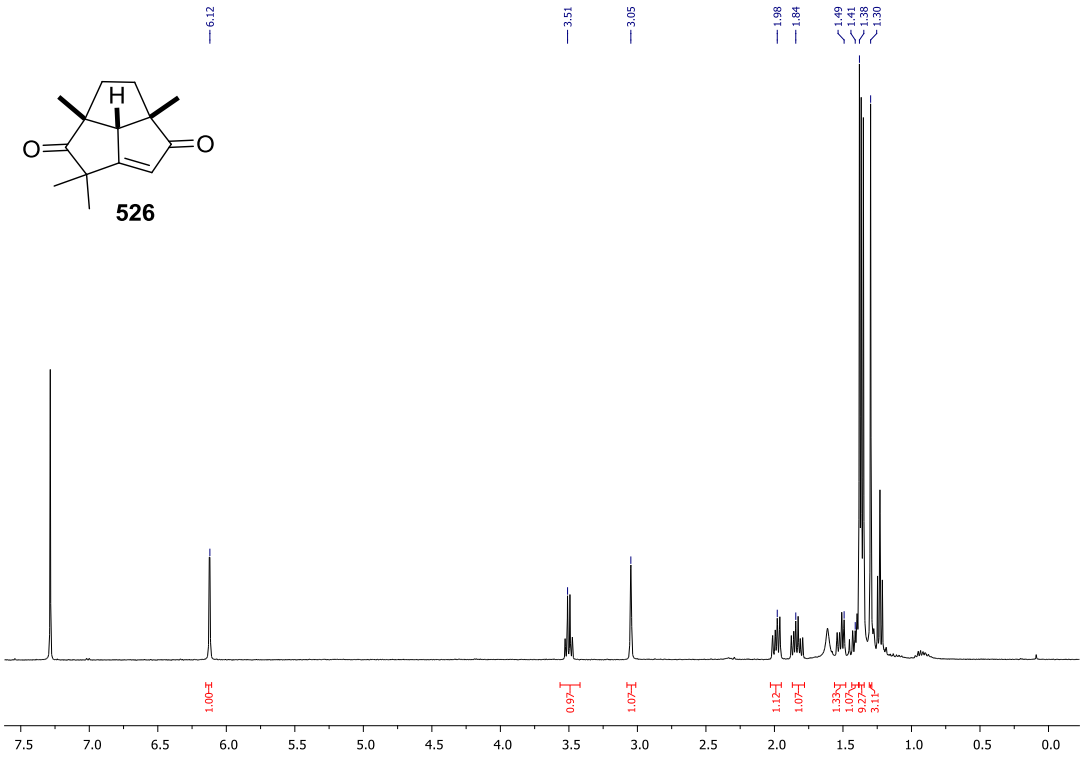
512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1.38
1.30
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O
O
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0.97
1.07
1.12
1.07
1.33
1.07
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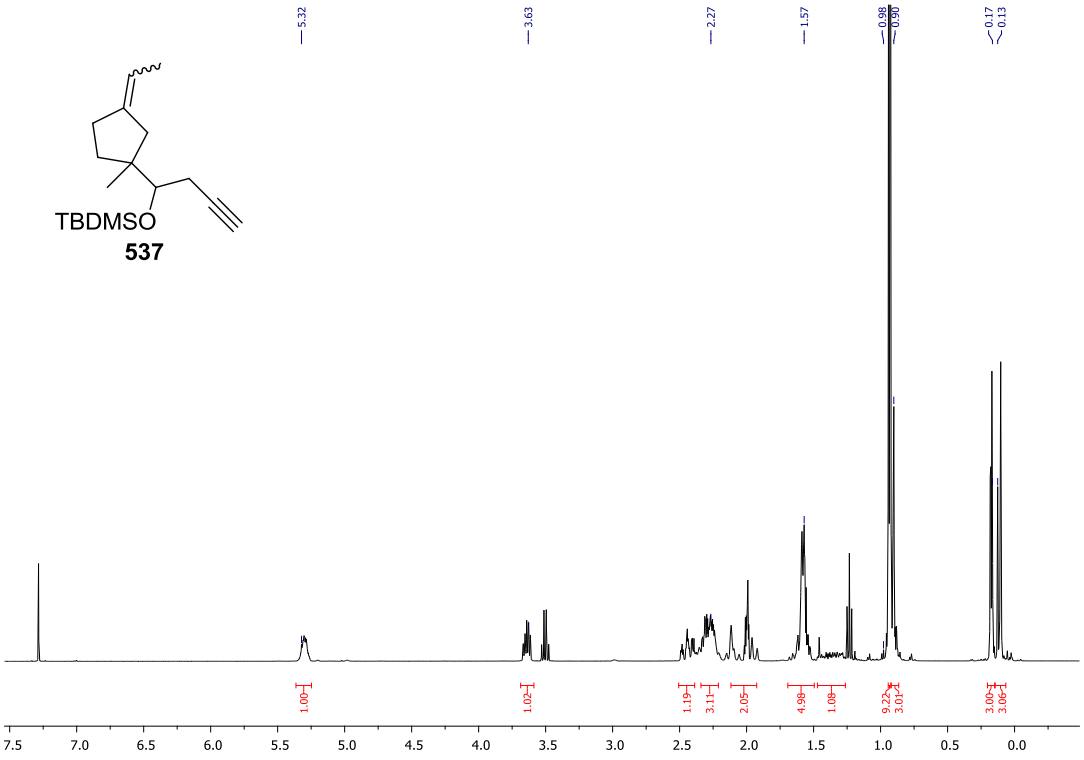
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3.11
2.05
4.90
1.08
9.22
3.01
3.00
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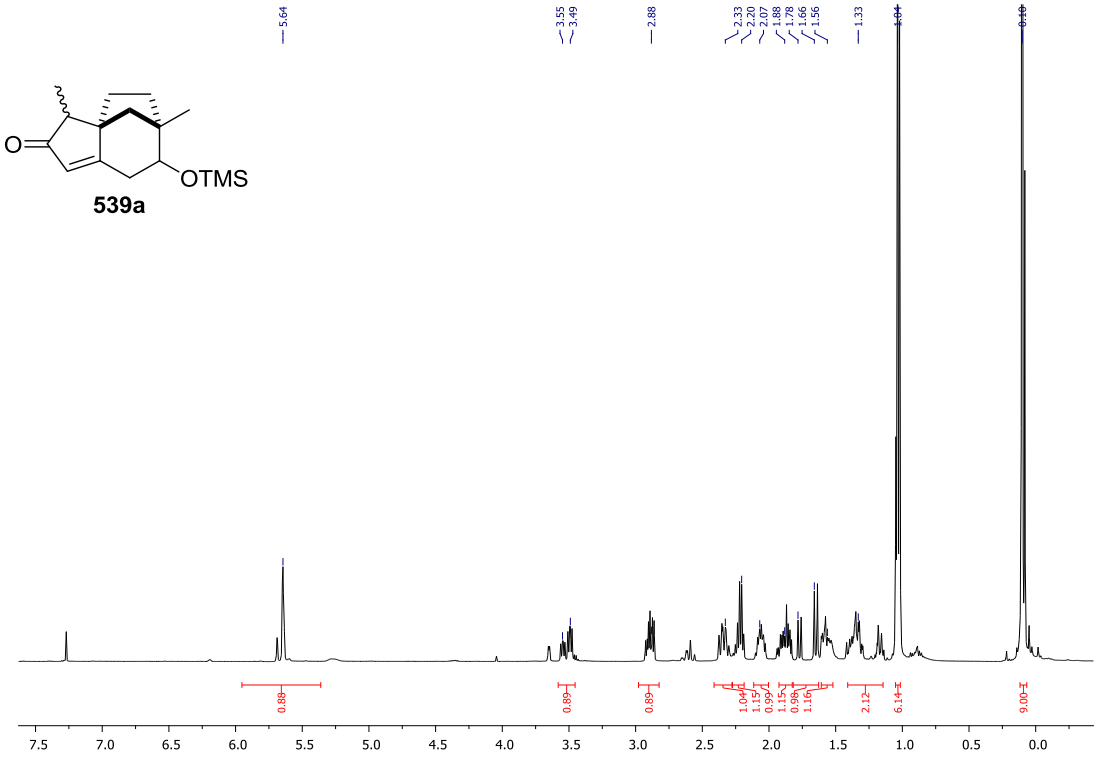
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2.33
2.20
2.07
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1.78
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1.56
1.33
0.88
0.89
0.89
1.04
1.15
0.98
1.16
2.12
6.14
9.00
7.5
7.0
6.5
6.0
5.5
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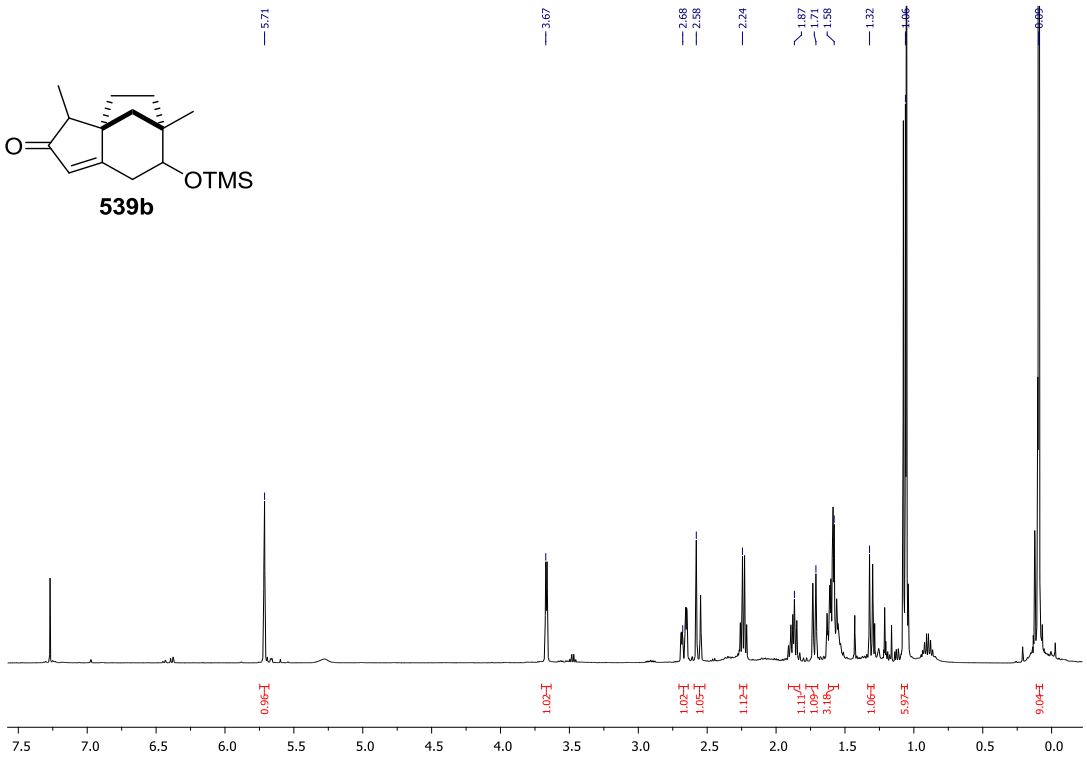
539a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3.67
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1.32
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0.96
1.02
1.02
1.05
1.12
1.14
1.09
3.18
1.06
5.97
9.04
7.5
7.0
6.5
6.0
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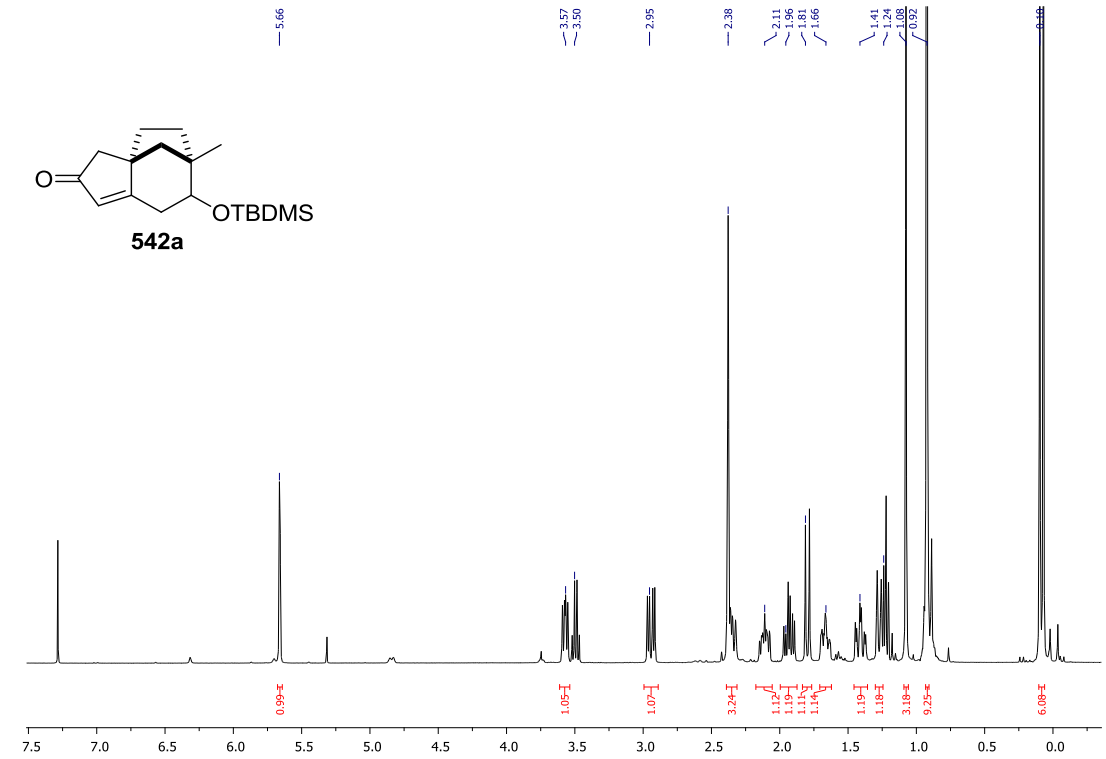
539b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542a
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1.81
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1.41
1.24
1.08
0.92
0.99
1.05
1.07
3.24
1.12
1.19
1.11
1.14
1.19
1.18
3.18
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6.08
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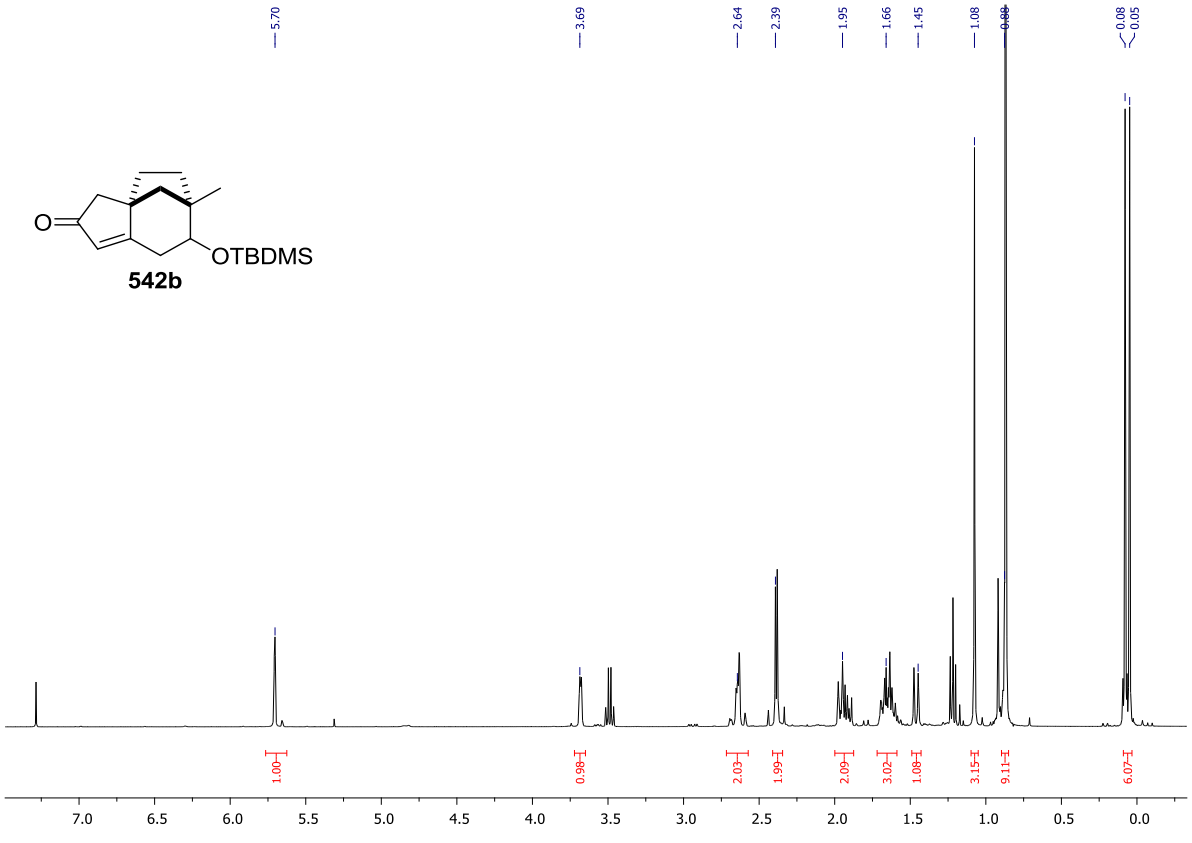
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542b
5.70
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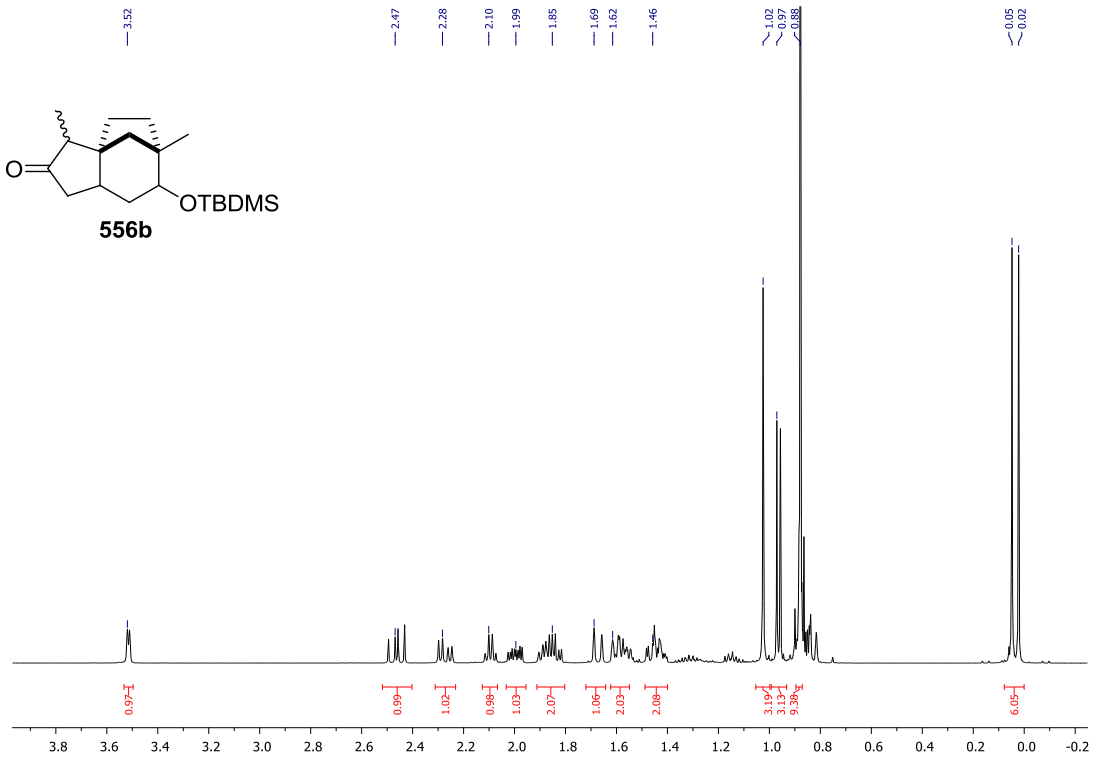
2.64
2.39
1.95
1.66
1.45
1.08
0.08
0.05
1.00
0.98
2.03
1.99
2.09
3.02
1.08
3.15
9.11
6.07
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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1.62
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1.02
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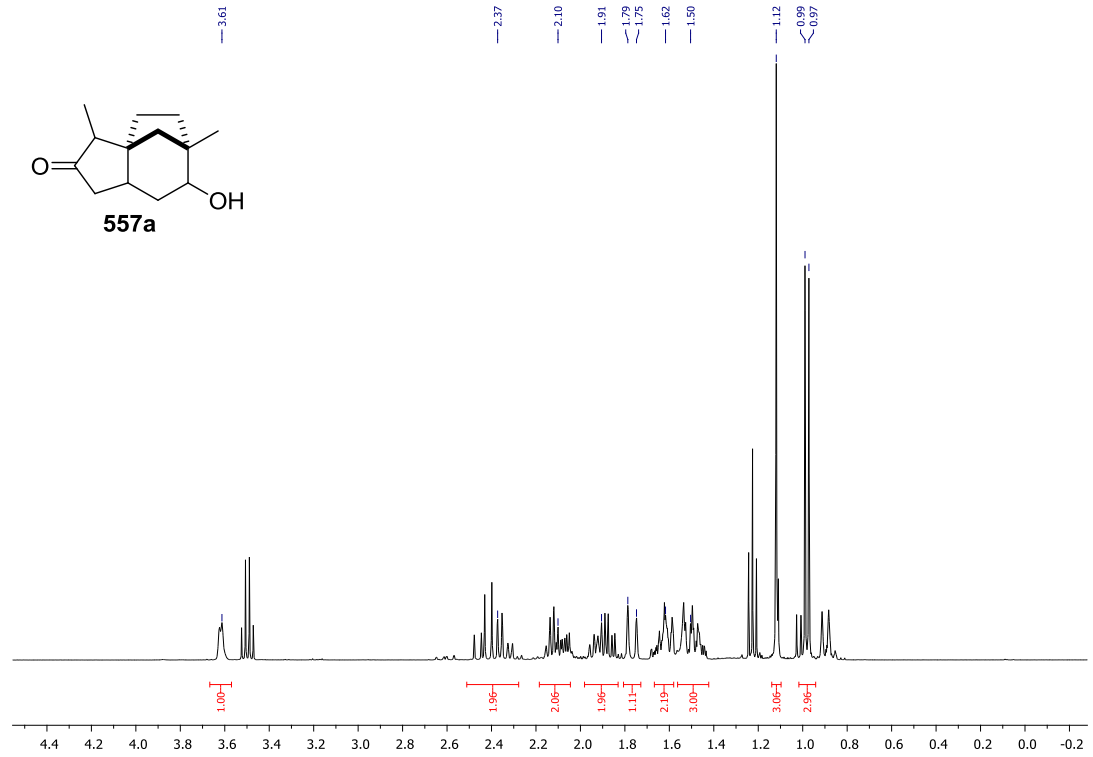
0.88
0.05
0.02
O
OTBDMS
556b
0.97
0.99
1.02
0.98
1.03
2.07
1.06
2.03
2.08
3.19
3.13
9.38
6.05
3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2 0.0 -0.2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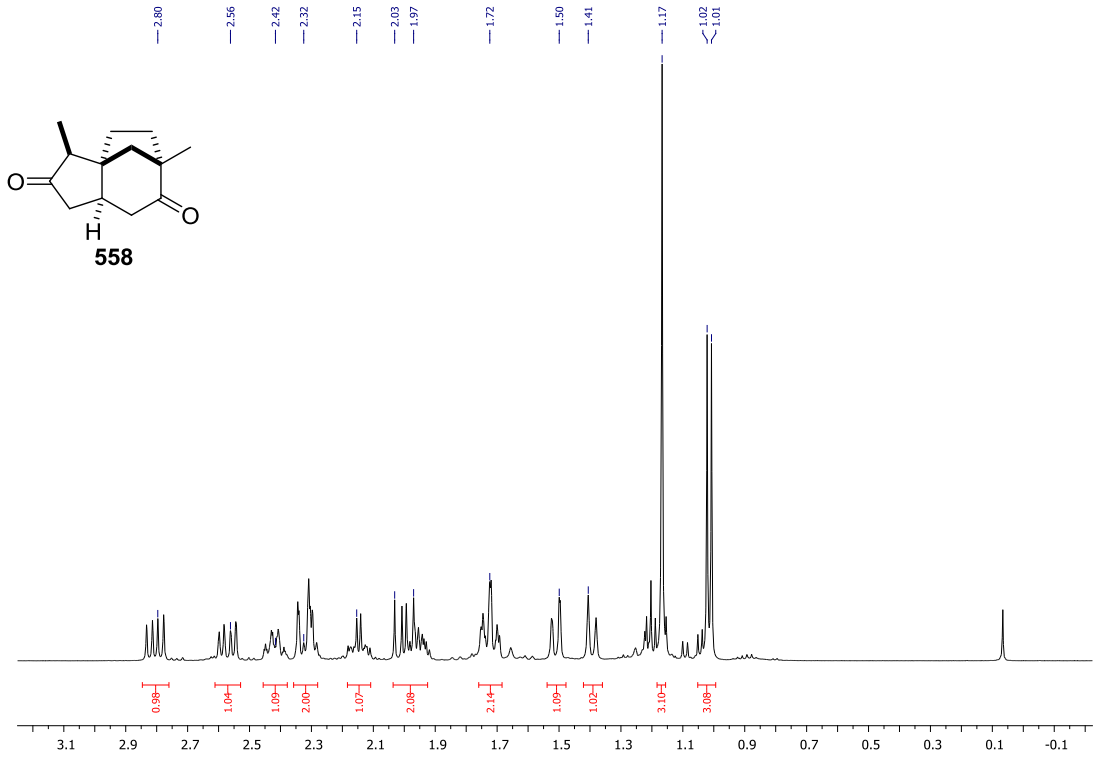
2.37
2.10
1.91
1.79
1.75
1.62
1.50
1.12
0.99
0.97
O
OH
557a
1.00
1.96
2.06
1.96
1.11
2.19
3.00
3.06
2.96
4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2 0.0 -0.2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2.32
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2.03
1.97
1.72
1.50
1.41
1.17
1.02
1.01
O
O
H
0.98
1.04
1.09
2.00
1.07
2.08
2.14
1.09
1.02
3.10
3.08
3.1
2.9
2.7
2.5
2.3
2.1
1.9
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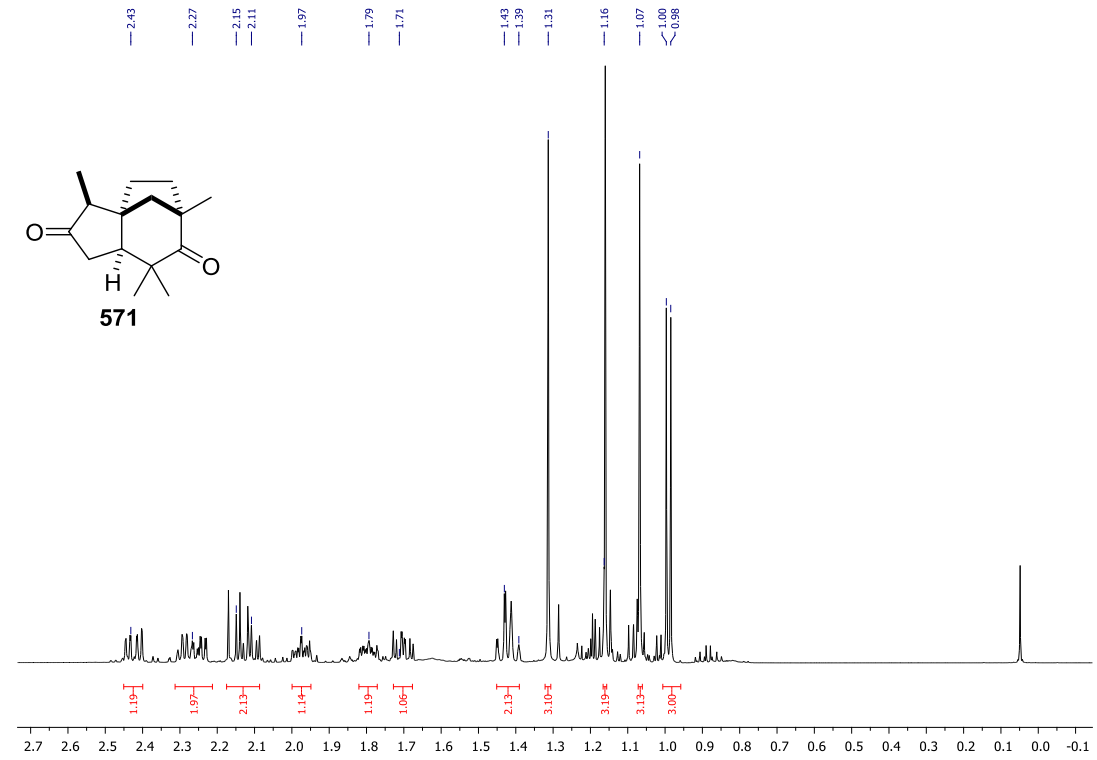
1.5
1.3
1.1
0.9
0.7
0.5
0.3
0.1
-0.1

558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1.79
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1.31
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1.00
0.98
O
O
H
1.19
1.97
2.13
1.14
1.19
1.06
2.13
3.10
3.19
3.13
3.00
2.7
2.6
2.5
2.4
2.3
2.2
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2.0
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1.8
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0.1
0.0
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571

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