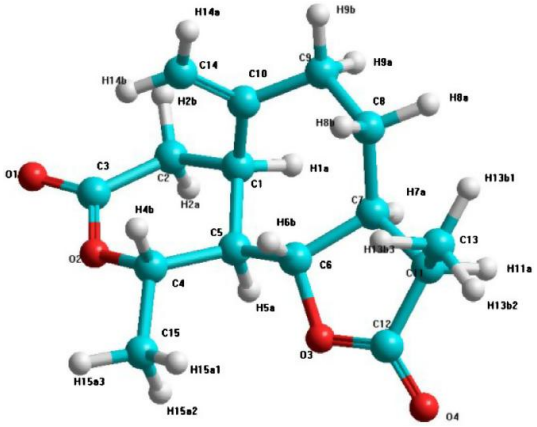
Rhodium(I)-Catalysed Carbocyclisation Reactions of Alkylidenecyclopropane tethered with Dienes for the Construction of *cis*-Fused 5,5-Bicyclic Ring and 5,7-Bicyclic Ring Systems: Synthetic Study towards the Total Synthesis of Zaluzanin E



Thesis submitted in accordance with the requirement of the University of Liverpool for the degree of Doctor in Philosophy

UNIVERSITY OF LIVERPOOL

Oluwarotimi Stephen Ayodipupo Ojo

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DEDICATION

...I thank God for making this success possible. With God, all things are possible.

The Lord grants success to the one whose behaviour He finds commendable.

- **Psalm 37:23**

..This thesis is also dedicated to Professor P. Andrew Evans on the occasion of his 50th birthday.

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I would like show my gratitude of thanks to Professor P. Andrew Evans for his guidance and unwavering support throughout the duration of my PhD study. I count it a privilege to have been under his mentorship and supervision. This has helped me to develop into a scientist that I dreamt of as a child. I would also like to thank Dr Christophe Aïssa for proof-reading this thesis.

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ABSTRACT

The construction of *cis*-fused 5,5-bicyclic and *cis*-fused 5,7-bicyclic systems

The construction of 5,5-bicyclic and 5,7-bicyclic systems, specifically, the *cis*-fused type, has become an increasingly important and growing area of research. Numerous synthetic methodologies have been developed towards the preparation of these attractive structural motifs, due to their presence in both structurally challenging and biologically important natural products. In our effort to contribute to the vast arsenal of synthetic approaches which are utilised for constructing these bicyclic systems, we herein report a highly selective synthesis of *cis*-fused 5,5-bicyclic and *cis*-fused 5,7-bicyclic systems *via* rhodium(I)-catalysed [3+2] and [4+3] carbocyclisation reactions of alkylidenecyclopropane and dienes, respectively. A novel diastereoselective version of these reactions was also developed for the synthesis of bicyclic systems with three stereogenic centres. The scope and limitation of these transformations was examined and it was utilised as a key strategy for the synthesis of 1-*epi*-dictamnol, a natural product which possesses a tertiary alcohol.

Synthetic Studies Towards the Total Synthesis of Zaluzanin E

The rhodium(I)-catalysed [4+3] carbocyclisation reaction was employed for the diastereoselective construction of a *cis*-fused 5,7-bicyclic ring with four stereogenic centres. Further synthetic manipulation of the 5,7-bicyclic ring provides an advanced late stage intermediate, a 5,7,5-tricyclic ring, towards the first total synthesis of zaluzanin E. This intermediate can also be used as an entry point to assemble other guaianolide natural products.

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ABBREVIATIONS

9-BBN	9-borabicyclo(3.3.1)nonane
2,2-DMP	2,2-dimethoxypropane
Å	angstrom
Ac	acetate
ACP	alkylidenecyclopropane
APT	attached proton test
β	beta
BCP	bicyclopropylidene
Bn	benzyl
BOC	*tert*-butoxycarbonyl
^{n}Bu	butyl
^{t}Bu	*tert*-butyl
Bs	4-bromobenzenesulfonyl
COD	1,5-cyclooctadiene
Cp	cyclopentadiene
CI	chemical ionisation
Cy	cyclohexyl
dba	*bis*(dibenzylidene acetone)
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine

DMDO	dimethyldioxirane
DME	ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppe	1,3-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereoisomeric ratio
e.e	enantiomeric excess
e.r	enantiomeric ratio
EI	electron ionisation
ESI	electrospray ionisation
Et	ethyl
g	gram
G	Grubbs
h	hour
HG	Hoveyda-Grubbs
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorus triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IC_{50}	half maximal inhibitory concentration
Ipc	isopinocamphenyl
IR	infra-red
L	litre
L1, L2, L3, L4	ligands
Ln	ligand set

LDA	lithium diisopropylamide
M	metal
MCP	methylenecyclopropane
mCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Min	minutes
MHz	megahertz
mL	millilitre
mmol	millimole
MS	molecular sieves
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect 1D-spectroscopy
NOESY	nuclear overhauser effect 2D-spectroscopy
Ph	phenyl
Piv	pivoyl
^{i}Pr	isopropyl
PPTS	pyridinium *p*-toluenesulfonate
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMM	trimethylenemethane
TMS	trimethylsilyl
Ts	4-toluenesulfonyl

UV	ultra-violet
VCP	vinylcyclopropane
μL	microlitre
σ	sigma
π	pi
η	hapticity
γ	gamma

Chapter 1

1. Transition Metal-Catalysed Carbocyclisation Reactions of Alkylidenecyclopropane, Methylenecyclopropane and Vinylcyclopropane for the Construction of 5,5-Bicyclic Ring and 5,7-Bicyclic Ring Systems

1.1 Transition Metal Chemistry of MCP

The reactions of methylenecyclopropane (MCP) and its derivatives alkylidenecyclopropane (ACP) and bicyclopropylidene (BCP) (**Figure 1**) with transition metals have been studied in great detail.[1] MCP can undergo a ring-opening process in the presence of various transition metals.[32] For this reason, they serve as an important synthetic building block in metal-catalysed reactions.

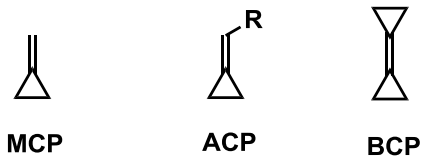
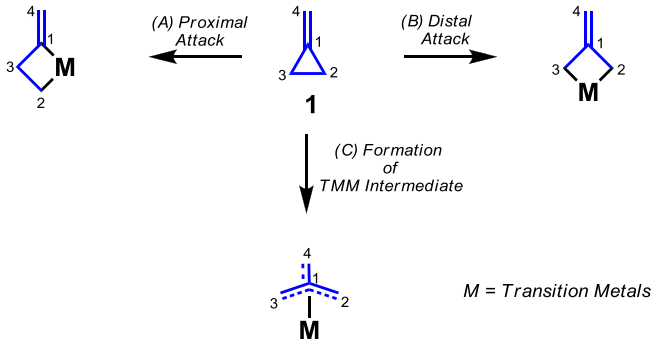


Figure 1: MCP, ACP and BCP

The MCP **1** ring opening process can occur *via* the oxidative addition of the transition metal into the (a) proximal C1-C2 bond or into the (b) distal C2-C3 bond or (c) the formation of a metal-TMM complex intermediate (**Scheme 1**).[2]



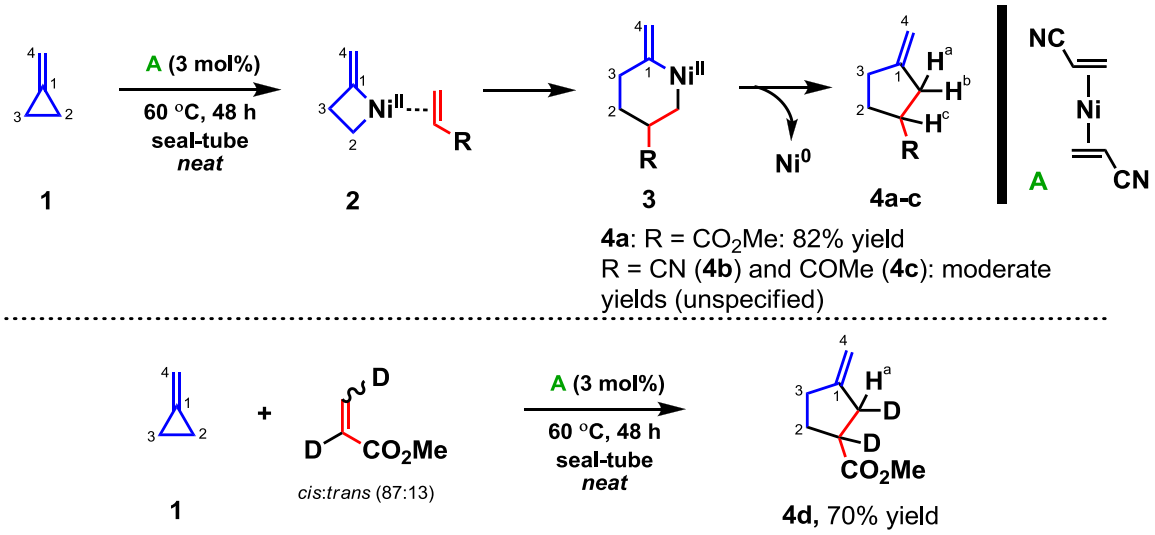
Scheme 1: Different modes of MCP ring opening by transition metals

1.2 Reaction of MCP

1.2.1 With Nickel Complex (Proximal Bond Cleavage)

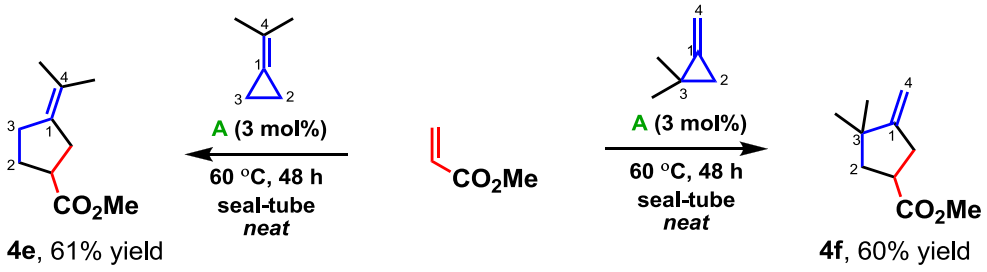
The reaction of nickel(0)-complex (**A**) with MCP **1** supposedly produced cyclobutanenickel **2**. The carbometallation of monosubstituted olefin (such as methyl acrylate, methyl vinyl ketone and acrylnitrile) into intermediate **2** could generate cyclohexanenickel **3** and subsequent reductive elimination possibly led to the formation of 5-membered rings **4a-c** (**Scheme 2**).[3]

The proton NMR spectra of 5,5-membered ring **4a** showed three overlapping peaks in the region of 2.4-2.8ppm, these peaks corresponds to H_a, H_b and H_c. However, the proton NMR spectra of 5,5-membered ring **4d** showed only one peak in this region. This deuterium labelling study suggests that the reaction pass through cyclobutanickel **2**.



Scheme 2: Proximal insertion of Ni^0 into MCP

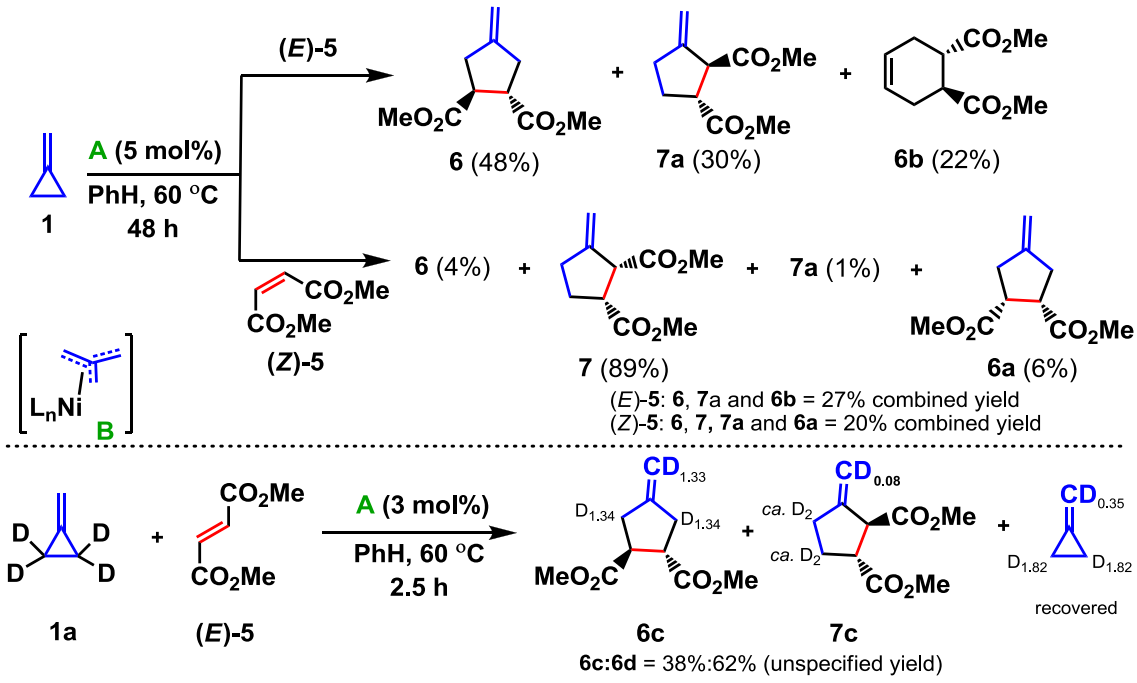
The reaction of substituted MCPs with methyl acrylate in the presence of nickel(0)-complex **A** produced 5-membered rings **4e-f** (**Scheme 3**). These results suggest that substitution on the MCP is tolerated and it also provides support for the initial proposal that MCP undergoes cycloaddition with nickel complexes *via* cyclobutanickel **2**.[4]



Scheme 3: Substituted MCP in nickel-catalysed reactions

The reaction of MCP with monosubstituted olefins in the presence of a nickel complex furnished a 5-membered ring **4**. In contrast, the reaction of MCP with 1,2-disubstituted olefin produced two 5-membered rings. For example, the reaction of MCP **1** with olefin (*E*)-**5** in the presence of a nickel complex produced 5-membered rings **6** and **7a** along with **6b** (**Scheme 4**).[4] Employing olefin (*Z*)-**5** gave rise to 5-membered rings **6**, **6a**, **7** and **7a**. Also, the reaction of MCP **1a** with (*E*)-**5** produced 5-membered rings **6c** and **6d**.

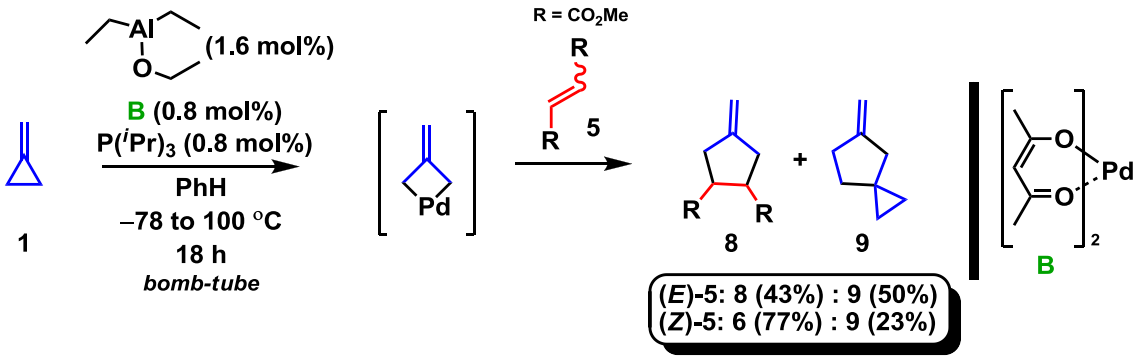
The scrambling of deuterium over three carbons suggests that 5-membered rings of type **6c** are formed *via* nickel-TMM complex **B**. In contrast, most of the deuterium atoms were located on two of the carbons in **7c**. This is in agreement with the previous proposal which suggest that 5-membered rings of type **7c** are formed *via* cyclobutanickel **2**.[5]



Scheme 4: Reaction of disubstituted olefins with MCP

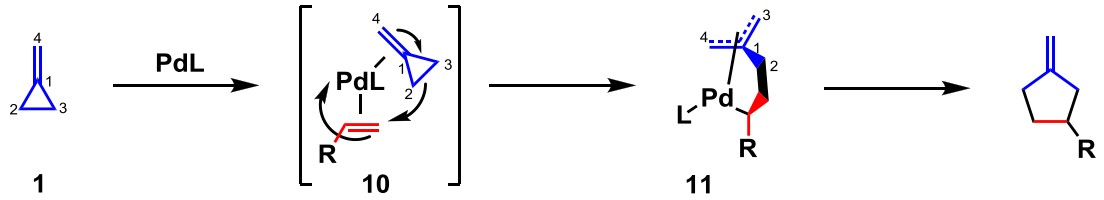
1.2.2 With Palladium Complex (Distal Bond Cleavage of MCP)

The reaction of a palladium complex with MCP **1** produced a 5-membered ring **8**, possibly *via* the distal cleavage of MCP **1**, accompanied by the codimerisation product **9** (**Scheme 5**).[6a] The product from the proximal bond cleavage was not observed. This is in contrast to the reaction of a nickel complex with MCP **1**.



Scheme 5: Distal insertion of palladium into the MCP

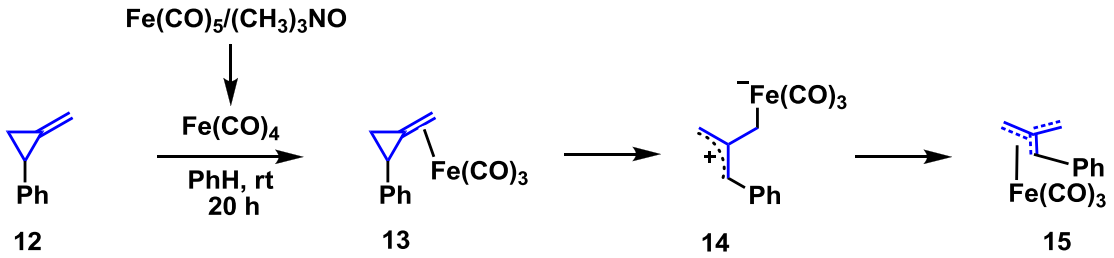
A recent density functional theory (DFT) calculation suggested that the cleavage of the distal bond is more favourable than the cleavage of the proximal bond with palladium complexes.[6b] On the other hand, Trost proposed that the pre-coordination of palladium to the MCP **1** occurred first, then direct attack of the distal bond on the olefin generated a π-allylpalladium complex **11** (**Scheme 6**).[6c] Reductive elimination of **11** would produce a 5-membered ring.



Scheme 6: Direct distal attack of MCP on olefins to form π-allyl complex

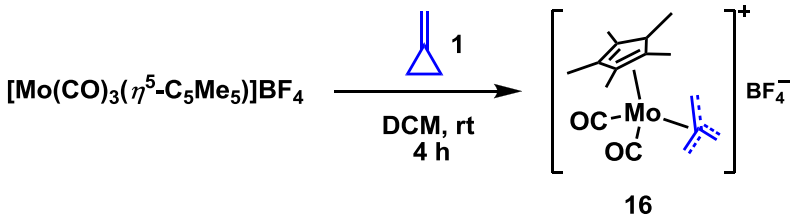
1.2.3 With Iron, Molybdenum and Palladium (The Formation of Metal-TMM complexes)

As described above, the mode of MCP ring opening depends on whether the metal attacks the distal bond or the proximal bond. In addition to this, MCP can also react with transition metals to form a metal-TMM complex. For example, the reaction of MCP **12** with iron tetracarbonyl led to the formation of trimethylenemethane iron (Fe-TMM) tricarbonyl complex **15** *via* a zwitterion intermediate **14** (**Scheme 7**). Complex **15** was isolated (> 57% yield) and its structure was confirmed by ^{1}H, ^{13}C and NOE analysis.[7]



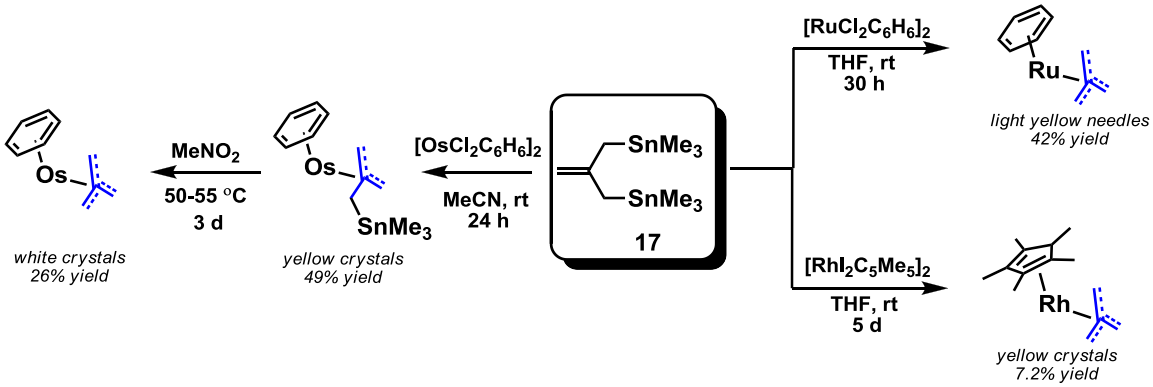
Scheme 7: The formation of Fe-TMM complex from MCP

Similarly, the reaction of MCP **1** with molybdenum carbonyl complex $[Mo(CO)_3(\eta^5\text{-}C_5Me_5)BF_4]$ produced $[Mo\text{-}TMM]BF_4$ **16** as a yellow crystalline complex in an unspecified yield (**Scheme 8**).[8a] Complex **16** was isolated and characterised using ^1H and ^{13}C NMR analysis.



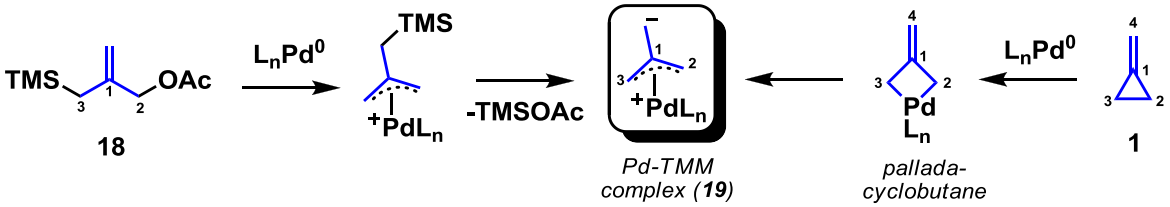
Scheme 8: The formation of $[Mo\text{-}TMM]BF_4$ complex from MCP

A seminal study reported the isolable trimethylenemethane complexes of ruthenium, osmium and rhodium. They are generated from the reaction of osmium, rhodium and ruthenium-complexes with compound $CH_2{=}C(CH_2SnMe_3)_2$ **17** (**Scheme 9**).[8b] X-ray crystallography was used to determine the structure of ruthenium-TMM and osmium-TMM complexes.[8b]



Scheme 9: The formation of Ru-, Rh-, Os-TMM complexes from compound **17**

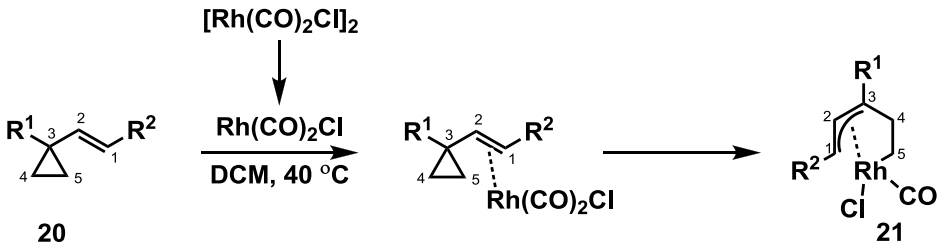
A mechanistic proposal suggested that the insertion of palladium into the distal bond of MCP **1** gave pallacyclobutane. Subsequent rearrangement could provide the Pd-TMM complex **19** (**Scheme 10**).[9] A complementary study has demonstrated that the same putative Pd-TMM complex **19** can be generated from compound **18**.[10]



Scheme 10: The formation of a Pd-TMM complex from MCP and compound **18**

1.2.4 Reaction of VCP with Rhodium-complexes

The reaction of VCP with a transition metal involves the C3-C5 proximal bond cleavage of the cyclopropane ring.[11d] The coordination of $Rh(CO)_2Cl$ complex to the olefin of the VCP **20**, followed by cyclopropane ring cleavage would produce σ-π-allylrhodium intermediate **21** (**Scheme 11**).[11a] The reaction of VCP of type **20** with Rh(I)-complexes has been studied in detail. The intramolecular reaction of VCP with π-systems catalysed by zirconium,[12a] ruthenium,[11b] nickel,[11c] iron,[12c] and palladium,[12b] have also been described.

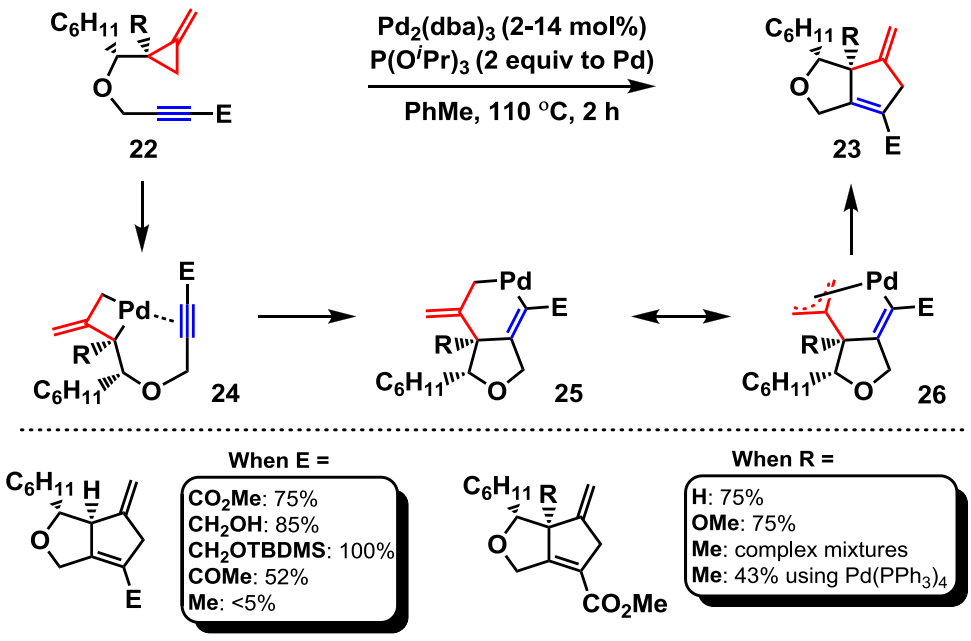


Scheme 11: The reaction of VCP **20** with a rhodium(I)-complex

1.3 Intramolecular [3+2] Carbocyclisation Reactions of Alkylidenecyclopropane and Methylenecyclopropane

1.3.1 Reaction with Alkynes

As described previously, the ring opening of MCP is governed by the selection of transition metal complexes. For example, nickel complexes favour either the proximal cleavage or the formation of a TMM complex, whereas palladium complexes selectively favour the distal cleavage. This MCP cleavage by transition metals has been investigated in metal-catalysed intramolecular reaction of MCP with π-systems, specifically, for the construction of bicyclic rings. For example, exposing substrate **22** to a palladium complex produced 5,5-bicyclic rings **23** exclusively as a single isomer (**Scheme 12**).[13]

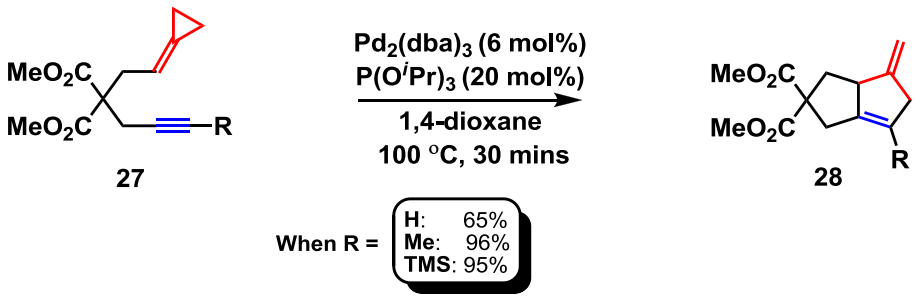


Scheme 12: Pd-catalysed [3+2] carbocyclisation reaction of MCP tethered with alkynes

The proposed mechanism suggested that the insertion of palladium into the MCP distal bond generated palladacyclobutane **24**. Subsequent carbometallation of **24** with the alkyne produced palladacyclohexane **25** or π-allyl palladium species **26**. Reductive elimination of **26** would furnish the 5,5-bicyclic ring **23**.

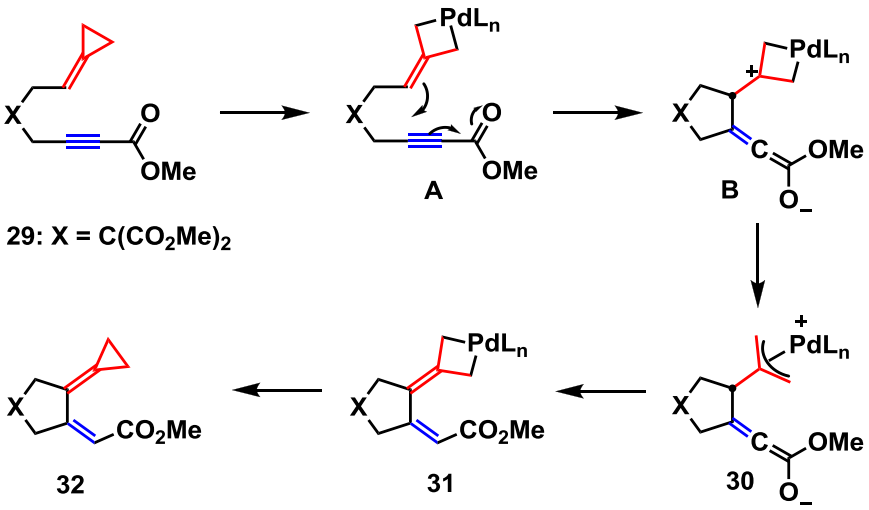
In relation to the scope of this reaction, complex mixtures were obtained when R = Me. However, 43% yield of the desired 5,5-bicyclic ring was obtained when 2-12 mol% of $Pd(PPh_3)_4$ complex was employed in place of $Pd_2(dba)_3$ complex. Substrates with R = H and OMe underwent efficient cyclisation in the presence of $Pd_2(dba)_3$ complex. Also, substrates with alkynes bearing hydroxymethyl, protected hydroxymethyl, ester or ketone underwent successful cyclisation to give the corresponding 5,5-bicyclic rings in good yields. However, methyl or TMS substituted alkynes and terminal alkynes did not cyclise efficiently.

In contrast to the results discussed above, ACP tethered with an alkyne **27** which bears methyl or TMS substituents and terminal alkynes underwent successfully cyclisation in the presence of $Pd_2(dba)_3$ complex to produce similar 5,5-bicyclic rings **28** (**Scheme 13**).[14a]



Scheme 13: Pd-catalysed [3+2] carbocyclisation reaction of ACP tethered with alkynes

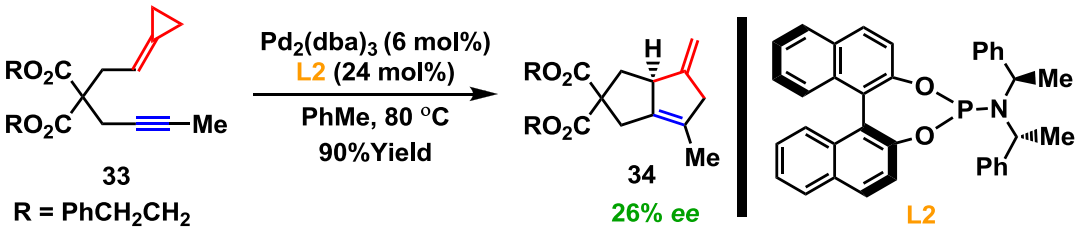
However, compound **29** with an electron-withdrawing group to the alkyne (R = CO_2Et) produced an unexpected product **32**. A related computational study provided an explanation for this transformation.[14b]



Scheme 14: Proposed reaction pathway for the transformation of **29** to **32**

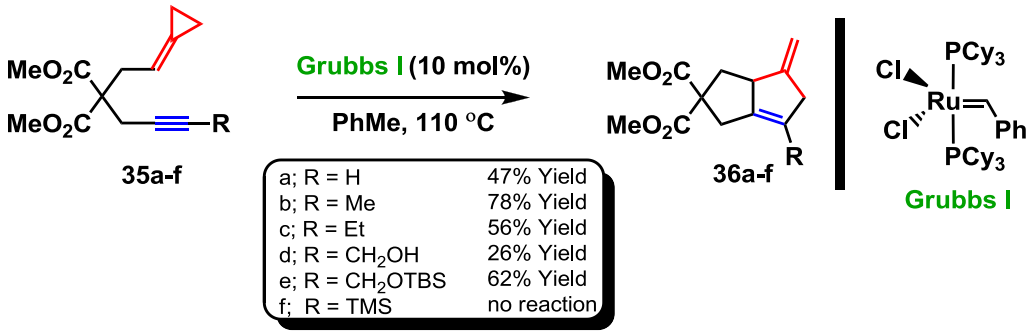
The study provided support for the insertion of palladium into the ACP distal bond of **29** to produce palladacyclobutane **A**. The calculation revealed that the presence of the ester carbonyl group promoted the cyclisation of **A** to **B**. Subsequent cleavage of the σ Pd-C bond of the pallacyclobutane **B** generated the π-allylpalladium zwitterionic species **30** which can rearrange to **31**. Reductive elimination of **D** provided the unexpected product **32** (**Scheme 14**).

The enantioselective version of the reaction depicted in **scheme 13** was developed by replacing achiral $P(O^iPr)_3$ with a chiral phosphoramidite ligand **L2**. The cyclisation of **33** was successful, providing 5,5-bicyclic ring **34** in excellent yield, albeit in 26% ee. This study showed that the reaction of ACP with alkynes can be carried out in an asymmetric manner (**Scheme 15**).[15]



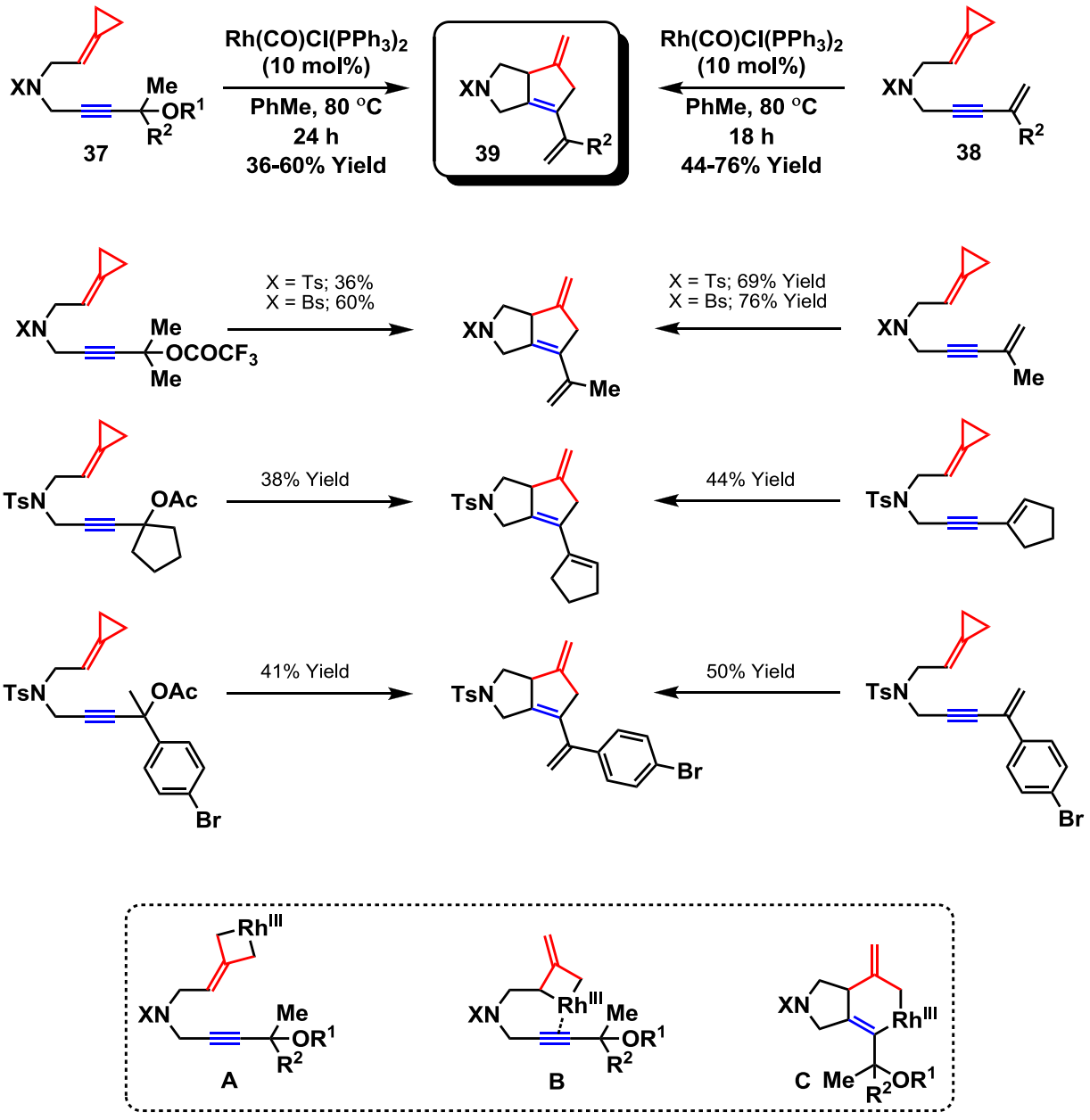
Scheme 15: Asymmetric Pd-catalysed [3+2] carbocyclisation reaction

An elegant study has showed that the cyclisation reaction of ACP tethered with alkynes **35a-e** to 5,5-bicyclic ring systems **36a-e** can be mediated by a ruthenium complex (**Scheme 16**).[16] Different substitutions on the alkyne are allowed in this reaction. However, the presence of a TMS-group at the alkyne terminus in **36f** inhibited the carbocyclisation process, whereas it was tolerated by the $Pd_2(dba)_3/P(O^iPr)_3$ system (**Scheme 13**).



Scheme 16: Ru-catalysed [3+2] carbocyclisation reactions of ACP tethered with alkynes

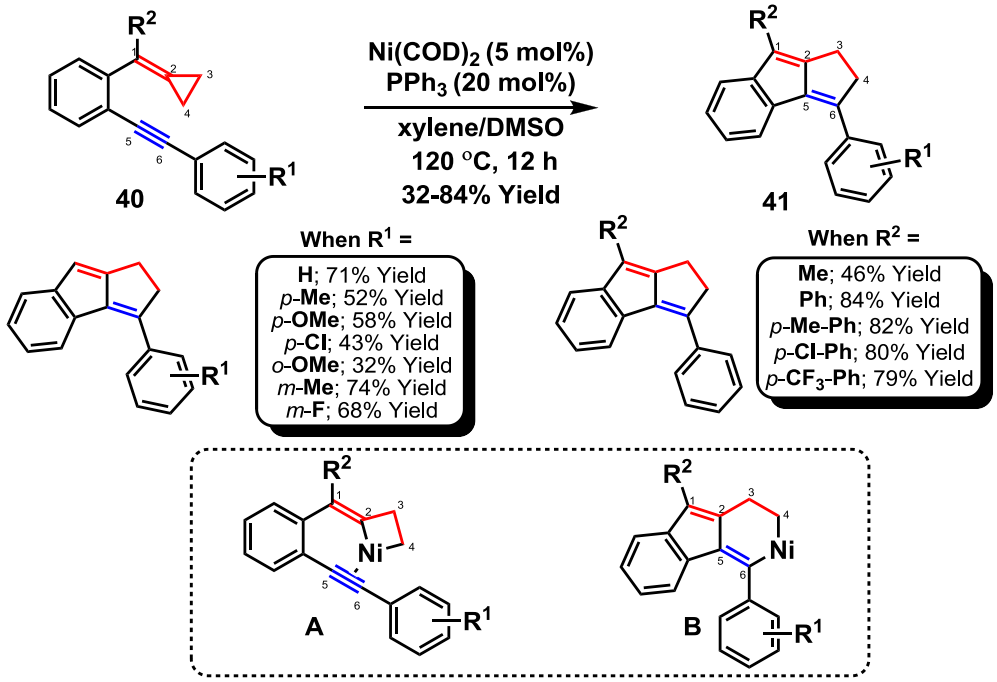
Palladium and ruthenium complexes have been shown to be effective promoters of the carbocyclisation reaction of ACP or MCP tethered with alkynes. In addition to this, rhodium complexes can also mediate this reaction. For example, ACP tethered with propargylic ester **37** and enyne **38** both cyclised efficiently in the presence of $Rh(CO)Cl(PPh_3)_2$ to furnish the same 5,5-bicyclic ring system **39** (**Scheme 17**).[17]



Scheme 17: Rh(I)-catalysed [3+2] carbocyclisation reactions of ACP tethered with alkynes

It was proposed that the rhodium(I)-complex inserted into the ACP distal bond to generate metallacycle **A**, which can presumably rearrange to metallacycle **B**. The carbometallation of the alkyne into **B** would afford **C**. Subsequent reductive elimination would produce **39** along with the release of R^1OH. Alternatively, the propargylic ester **37** could form **38** first, and then follow the aforementioned mechanistic sequence to generate **39**. For substrate **38** to produce **39**, the same mechanistic pattern will be in operation.

The reactions described above showed that the distal bond cleavage of ACP or MCP by palladium, ruthenium and rhodium complexes enabled the construction of 5,5-bicyclic rings which possess an exomethylene moiety. However, the nickel-catalysed intramolecular carbocyclisation of ACP with aryl alkynes proceeded *via* the proximal bond cleavage for the construction of a highly conjugated 5,5-bicyclic ring (**Scheme 18**).[18]



Scheme 18: Nickel-catalysed [3+2] carbocyclisation reaction of ACP with aryl alkyne

According to the proposed mechanism, the oxidative insertion of nickel(0) into the proximal bond of the ACP generated cyclobutanenickel **A**. Subsequent carbometallation of the alkyne into **A** furnished cyclohexanenickel **B**. Reductive elimination of metallycycle **B** produced the 5,5-bicyclic ring **41**.

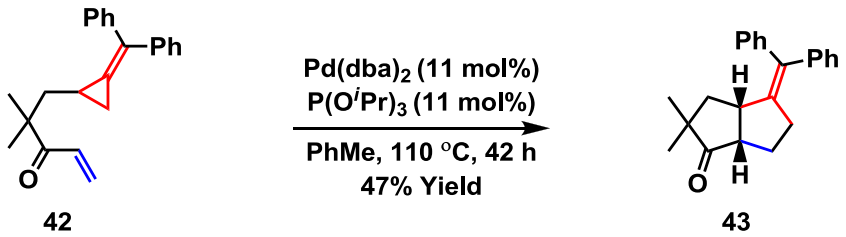
In relation to the scope of this reaction, alkyl alkynes did not participate in the cycloaddition reaction, in fact, aryl alkyne is mandatory for the success of this reaction. Additionally, 20 mol% of COD (1,5-cyclooctadiene) was preferred as a ligand instead of PPh_3 for the cyclisation of substituted ACP olefin (R^2) substrates.

The significant feature of this reaction stems from the tolerance of the aryl moiety as a tether in this reaction. Overall, the reaction enabled the construction of 5,5-bicyclic rings in moderate to good yields.

1.3.2 Reaction with Alkenes

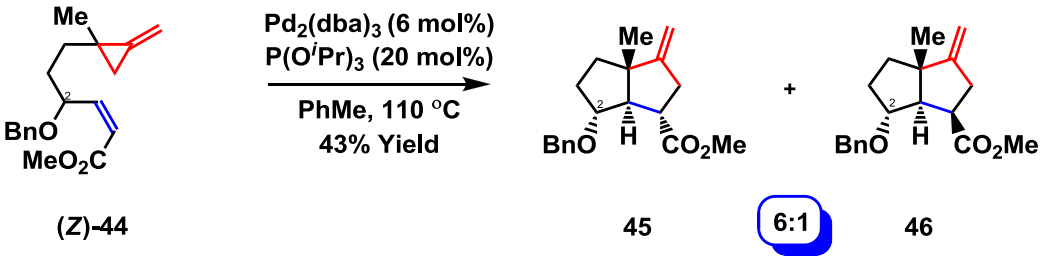
As described above, the metal-catalysed [3+2] carbocyclisation reactions of ACP and MCP tethered with alkynes generated 5,5-bicyclic ring systems *via* distal or proximal cleavage of the cyclopropyl σ carbon-carbon bond. However, the replacement of the alkyne with an alkene enabled the construction of a 5,5-bicyclic ring system with two or three stereogenic centres. The diastereoselective capability of these metal-catalysed reactions was tested in the studies described below.

The exposure of diphenylmethylenecyclopropane tethered with enone **42** to 11 mol% of $Pd(dba)_2$ and 11 mol% of $P(O^iPr)_3$ in toluene at 110 ˚C furnished a *cis*-fused 5,5-bicyclic ring **43** *via* distal bond cleavage, as a single isomer in 47% yield (**Scheme 19**).[20a]



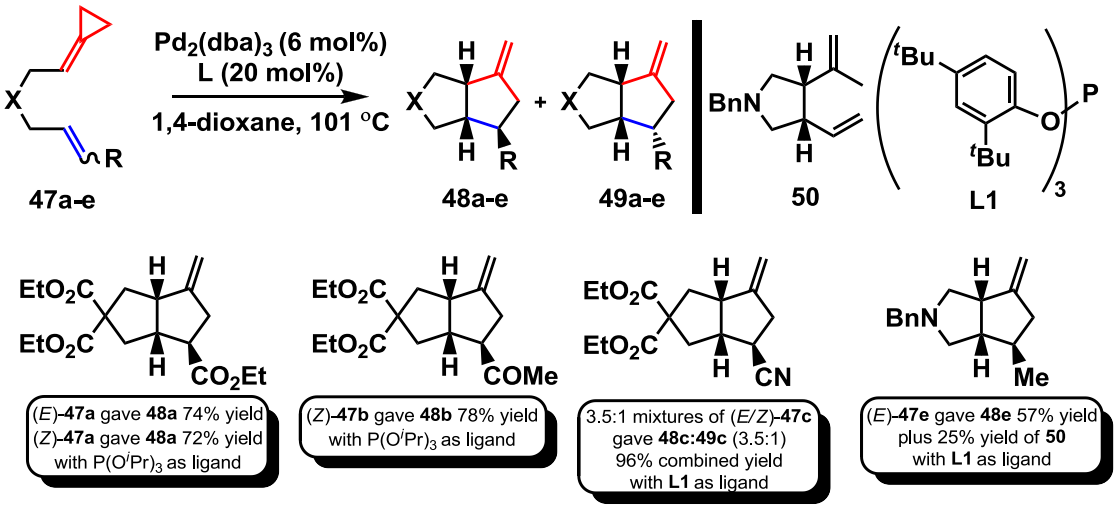
Scheme 19: Pd-catalysed [3+2] carbocyclisation reaction of MCP tethered with an alkene

A related study investigated the tolerance of substitution on the alkene and at the C2 carbon.[20b] Exposure of compound (*Z*)-**44** to 6 mol% of $Pd_2(dba)_3$ and 20 mol% of $P(O^iPr)_3$ in toluene at 110 °C afforded *trans*-fused 5,5-bicyclic rings **45** and **46** in 6:1 ratio and 43% combined yield (**Scheme 20**). The critical feature of this reaction is that 5,5-bicyclic ring **45** was observed as the major product, possibly as a consequence of the inversion of the stereochemistry of the *cis* double bond.



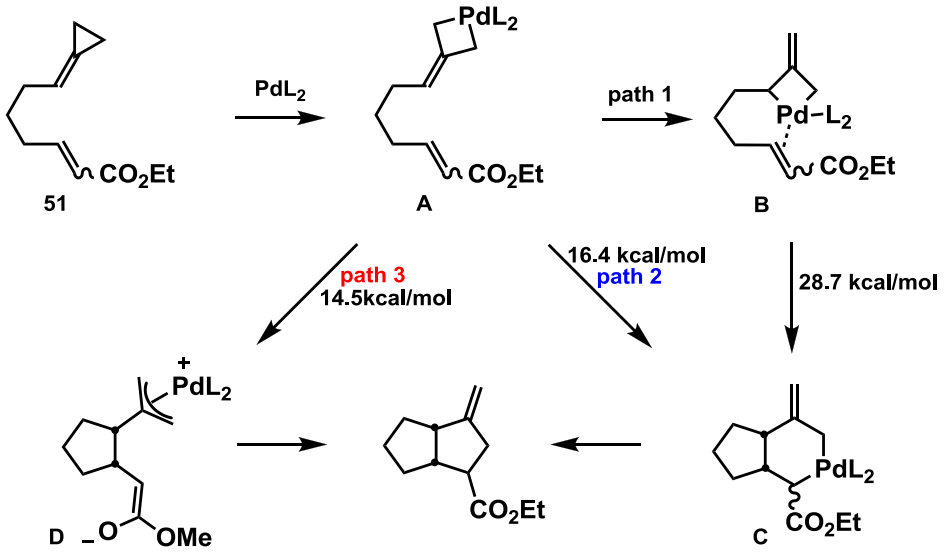
Scheme 20: Diastereoselective Pd-catalysed [3+2] carbocyclisation reaction of MCP tethered with alkenes

Interestingly, substrate (*E*)-**44** did not participate in this reaction. In contrast, (*E*) and (*Z*)-ACP tethered with alkenes underwent successful cyclisation in the presence of $Pd_2(dba)_3$ and **L1** (**Scheme 21**).[21] For example, both (*E*)-**47a** and (*Z*)-**47a** furnished the *cis*-fused 5,5-bicyclic ring **48a** selectively as a single isomer in excellent yield, when L = $P(O^iPr)_3$. The epimerisation of **49a** to **48a** was not detected and the observation of **48a** as the sole product was influenced by the reaction mechanism (**Scheme 22**).



Scheme 21: Pd-catalysed [3+2] carbocyclisation reactions of ACP tethered with an alkene

The DFT calculation on model substrate **51** provided a plausible rationale for the formation of **48a** from both (*E*)- and (*Z*)-**47a** (**Scheme 22**). Substrate (*E*)-**47a** appeared to go through pathway 2 with an energy barrier of 16.4 kcal/mol, whereas pathway 3 has an energy barrier of 14.5 kcal/mol for (*Z*)-**47a**.

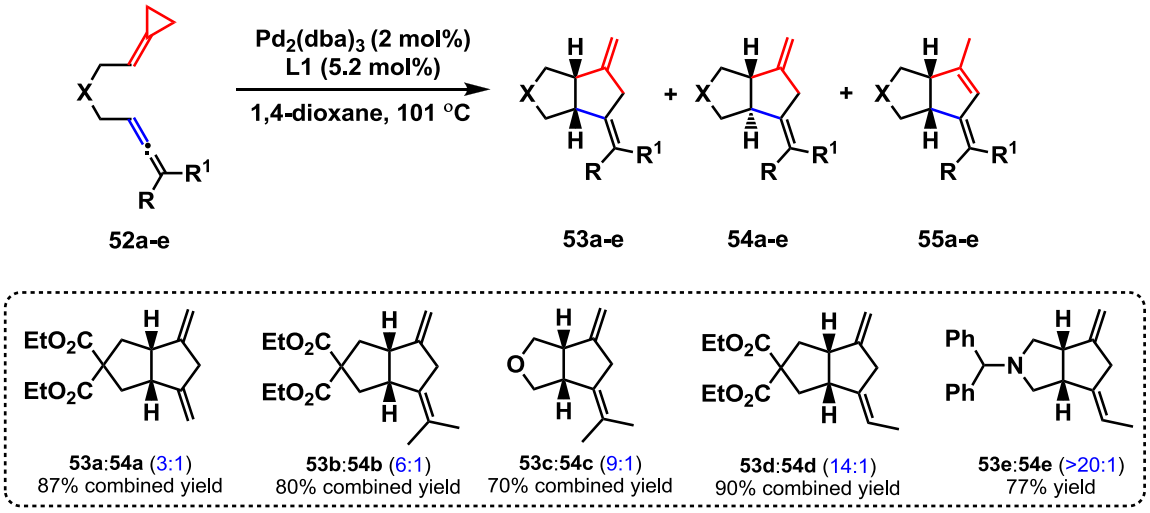


Scheme 22: Calculated mechanism for the Pd-catalysed [3+2] carbocyclisation reaction of **51**

The development of the scope of this reaction was achieved with two ligands, **L1** and $P(O^iPr)_3$. The significant limitation of this reaction is that alkenes with alkyl substitution (R = Me) at the terminal position experienced competing β-hydride elimination process which led to the formation of compound **50**.

1.3.3 Reaction with Allenes

The introduction of an allene in place of an alkene could circumvent the *β*-hydride elimination process. This was demonstrated in the reaction of ACP tethered with allenes for the construction of *cis*-fused 5,5-bicyclic ring systems which possess two exo methylene moieties (**Scheme 23**).[22]

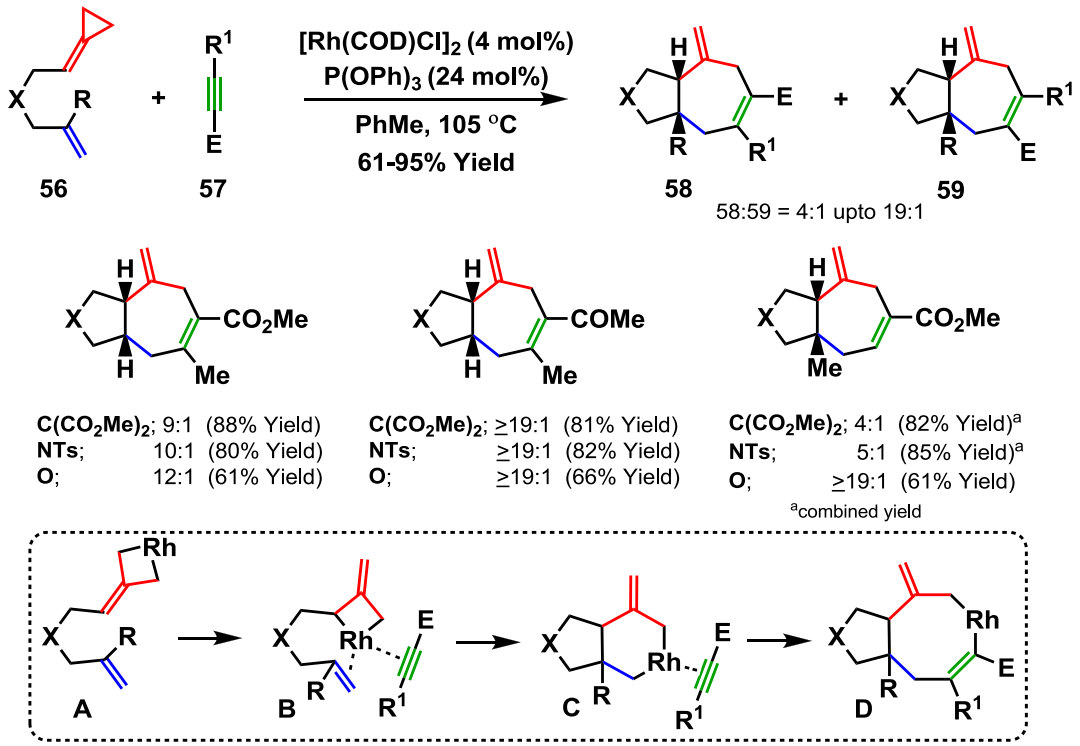


Scheme 23: Pd-catalysed [3+2] carbocyclisation reactions of ACP tethered with allenes

The treatment of substrate **52a** (unsubstituted allene) with 0.1 mol% of $Pd_2(dba)_3$ and 0.26 mol% of **L1** at 80 °C gave **53a** and **54a** with a trace of **55a** (5%). Prolonging the reaction time caused the *in situ* isomerisation of the *cis* adduct **53a** to **55a**. The reaction tolerated substituents on the external double bond of the allene using 2 mol% of $Pd_2(dba)_3$ and 5.2 mol% of **L1** at 110 °C. Mono-substituted allenes furnished **53** in excellent diastereoselectivity and in good yields, whereas, unsubstituted allenes performed worst in this reaction.

1.4 The [3+2+2] Carbocyclisation Reactions of Alkylidenecyclopropane with π-systems

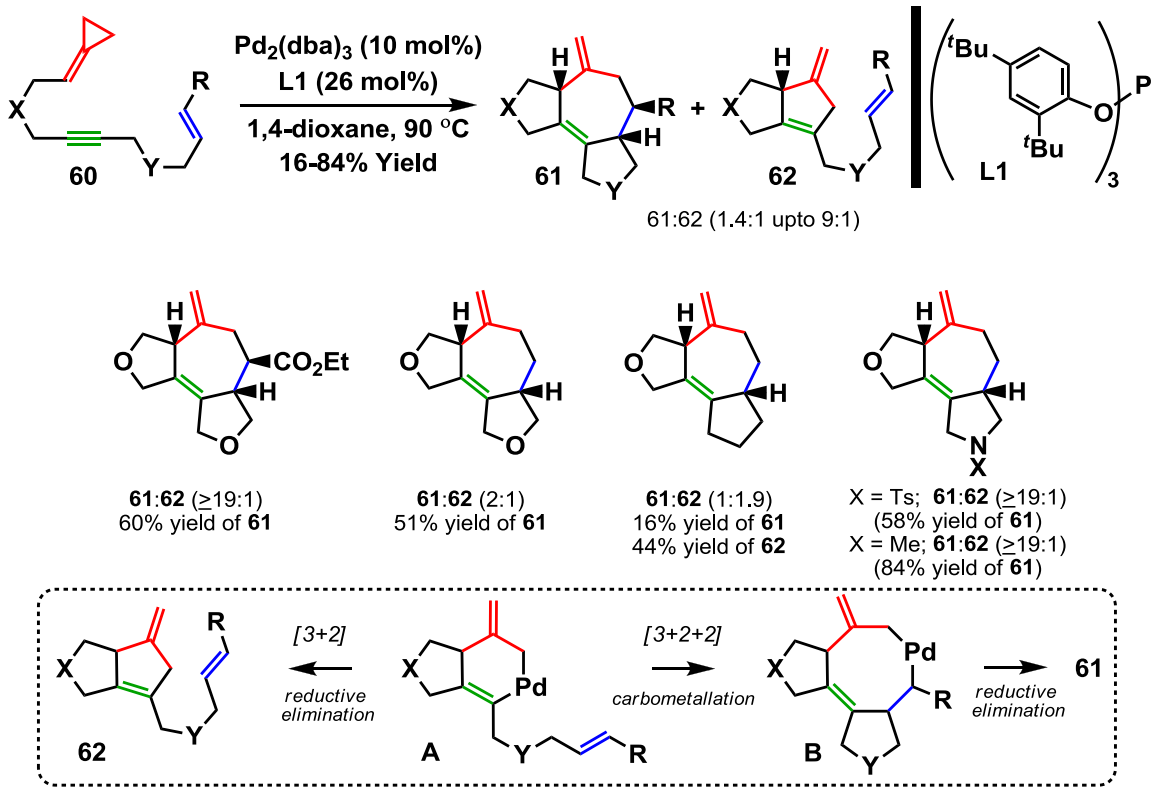
The metal-catalysed [3+2] intramolecular carbocyclisation reactions of ACP and MCP with π-systems such as alkynes, alkenes and allenes have been described. These reactions involve the distal or proximal bond cleavage of the cyclopropyl ring. When this ring opening process is coupled with a two carbon π-system, it provides a practical synthetic method to construct a variety of 5,5-bicyclic rings. However, the construction of a 5,7-bicyclic ring would require the introduction of an additional π-system. For example, the reaction of an ACP tethered with an alkene plus an additional alkyne enabled the construction of a *cis*-fused 5,7-bicyclic ring which possesses an α,β-unsaturated system (**Scheme 24**).[23]



Scheme 24: Rh(I)-catalysed [(3+2)+2] carbocyclisation reactions of ACP with alkynes

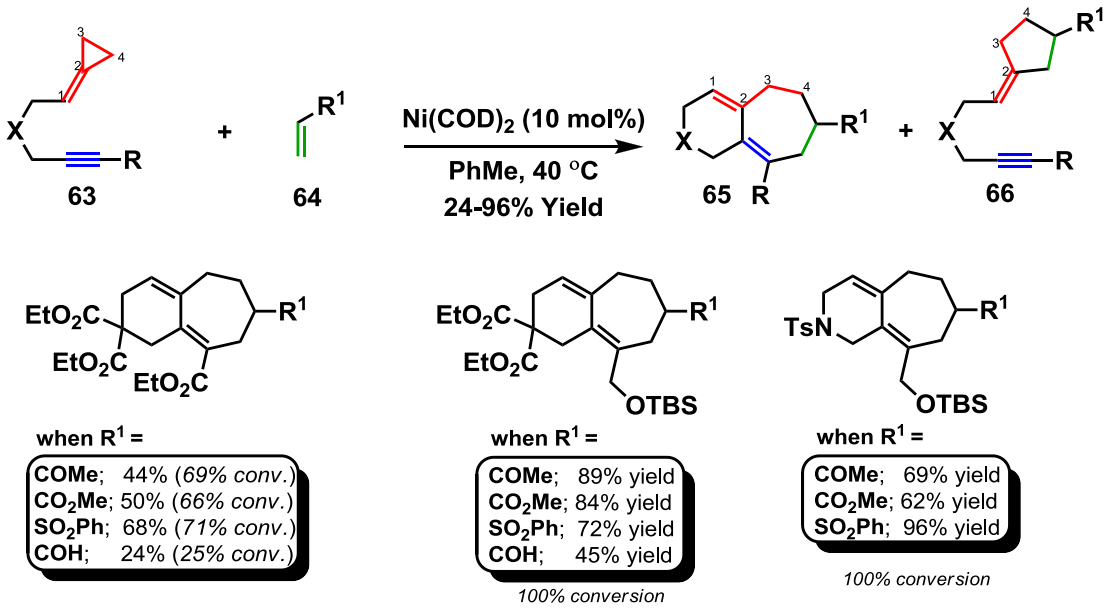
In this reaction, disubstituted alkynes and oxygen tethered substrates performed best. Additionally, excellent regioselectivity was obtained for ketone substituted alkynes when compared to ester substituted alkynes. The proposed mechanism showed that the oxidative insertion of rhodium into the distal bond of the ACP **56** produced intermediate **A**, which can possibly rearrange to produce **B**. Subsequent intramolecular carbometallation of the alkene into **B** would generate cyclohexanerhodium intermediate **C**. The intermolecular carbometallation of the alkyne would produce intermediate **D**, followed by reductive elimination to provide the 5,7-bicyclic ring **58**.

Alternatively, the reaction depicted in **scheme 24** can be carried out in a fully intramolecular fashion as shown in the spectacular palladium(I)-catalysed intramolecular [3+2+2] carbocyclisation reaction. ACP tethered with an alkyne and alkene **60** generated 5,7,5-tricyclic ring **61** along with 5,5-bicyclic ring **62** (**Scheme 25**).[24] In any case, three substrates (X = Y = O, R = CO_2Et and X = O, R = H, Y = NMe or NTs) furnished the 5,7,5-tricyclic ring **61** selectively, albeit in moderate yields. For these substrates, activated alkene (R = CO_2Et) and the choice of tether (Y = NTs or NMe) played an important role. The reaction is highly diastereoselective, furnishing **61** with the fused rings in a *cis* configuration. The observation of the 5,5-bicyclic ring **62** *via* the [3+2] pathway is probably due to the reductive elimination of the key intermediate **A**.



Scheme 25: Pd-catalysed [3+2+2] carbocyclisation reactions of ACP with alkyne and alkene

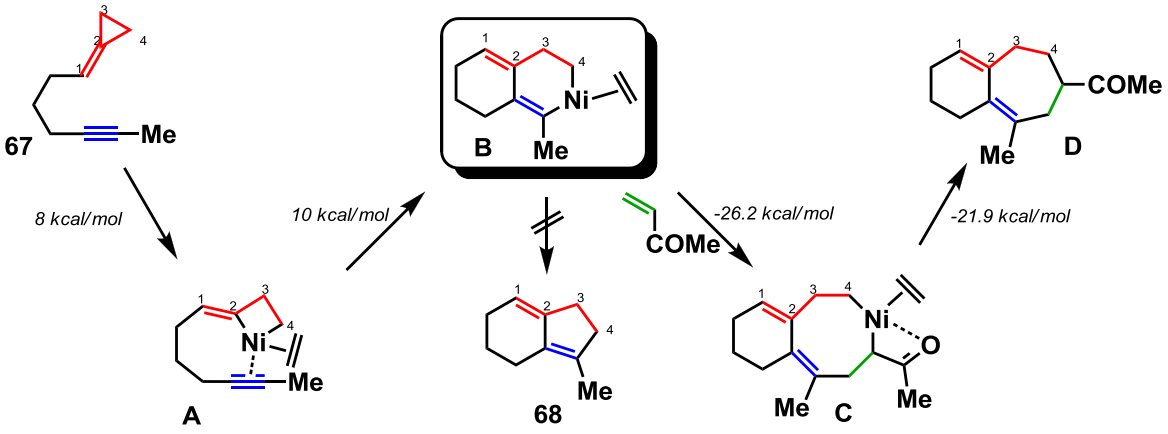
The palladium- and rhodium-catalysed [3+2+2] carbocylisation reaction of ACP with alkynes and alkenes involves the distal ring opening of the cyclopropane ring towards the construction of a 5,7-bicyclic ring (**Schemes 24** and **25**). In contrast, nickel-catalysed [3+2+2] carbocyclisation reaction of ACP with alkyne and an electron deficient alkene provided a 6,7-bicyclic ring *via* the proximal ring opening of the ACP cyclopropane ring (**Scheme 26**).[19]



Scheme 26: Ni-catalysed [3+2+2] carbocyclisation reaction of ACP with alkyne and activated alkenes

In relation to the scope of this reaction, alkynes with methyl and CH_2OAc substitution (R) produced the [3+2+2] cycloadduct **65** and [3+2] cycloadduct **66** in 4:1 ratio (72% and 91% combined yield, respectively). However, the selective formation of **65** was favoured by substrates with an electron withdrawing group (R = CO_2Et) on the alkyne, the competitive [3+2] cycloadduct **66** was not detected. On the downside, these substrates suffered from the lack of full conversion to the desired product **65** despite carrying out the reaction at 90 °C.

Remarkably, substrates with CH_2OTBS substituent on the alkyne provided full conversion, furnishing the 6,7-bicyclic ring selectively and in good yields. The presence of an electron withdrawing group (R^1) on the alkene is compulsory, as non-activated alkenes failed to participate in this reaction.



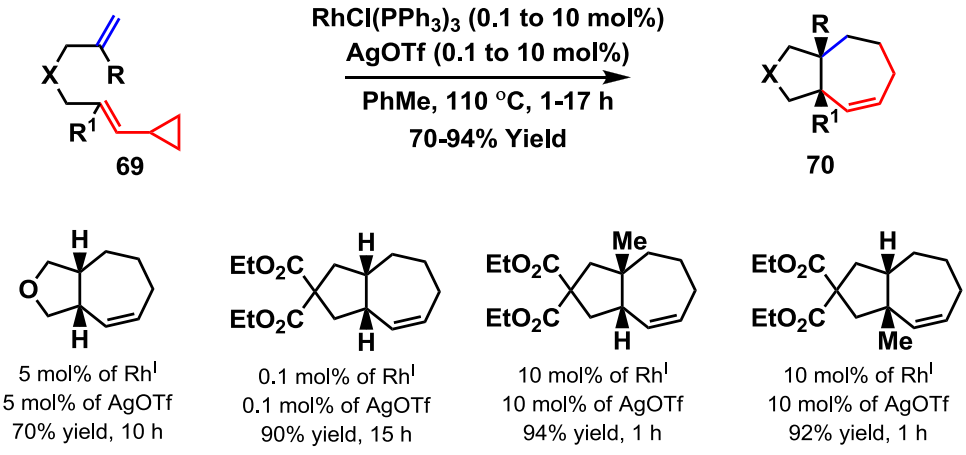
Scheme 27: Calculated intermediates in the Ni-catalysed [3+2+2] carbocyclisation reaction of **67**

The computational analysis on substrate **67** revealed that the energy barrier of the migratory insertion of the alkene (from intermediate **B** to **C**) to be -26.2 kcal/mol (**Scheme 27**). This pathway is favoured over other alternative reaction pathways that were calculated, owing to the stabilising coordination of the carbonyl oxygen atom to the nickel metal centre as shown in intermediate **C**. The reductive elimination of complex **B** to **68** was not observed theoretically and also the [3+2] cycloadduct **68** was not detected experimentally.

This reaction is an elegant example of a carbocyclisation reaction which involves the proximal cleavage of the ACP cyclopropane ring.

1.5 The [5+2] Carbocyclisation Reactions of Vinylcyclopropane with π-systems

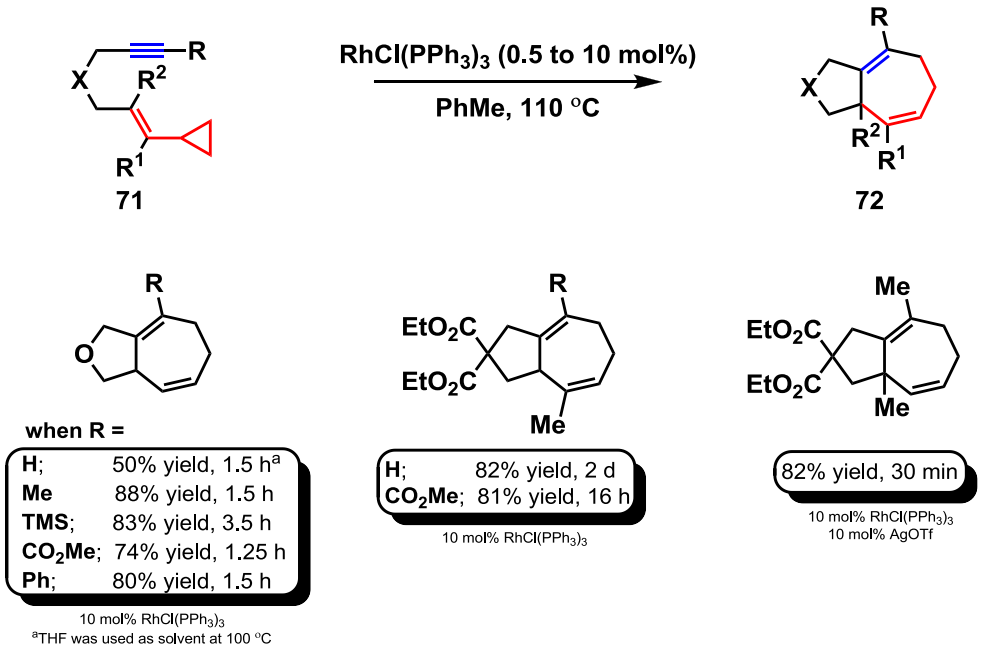
The distal or proximal opening of ACP and MCP coupled with a π-system furnished a 5,5-bicyclic ring efficiently. Additional π-systems enabled the construction of a 5,7- or 6,7-bicyclic ring. In a complimentary manner, vinylcyclopropane (VCP), a related small ring system, has been widely employed in metal-catalysed [5+2] carbocyclisation reactions for the construction of 5,7-bicyclic ring systems (**Scheme 28**).[25] For example, subjecting ene-vinylcyclopropane **69** (X = $C(CO_2Me)_2$, R = R^1 = H) to $RhCl(PPh_3)_3$ and AgOTf generated a *cis*-fused 5,7-bicyclic ring **70** in 86% yield as a single stereoisomer. The introduction of AgOTf is critical to the success of this reaction, decomposition occurred more rapidly than cyclisation without it. Likewise, substrates bearing a methyl group at the alkene terminus did not undergo efficient cyclisation, forming predominantly the *β*-hydride elimination product.



Scheme 28: Rh(I)-catalysed [5+2] carbocyclisation reactions of VCP tethered with alkenes

Overall, the reactions proceeded in good to excellent yields and was tolerant to substitution on the alkene (R and R^1), allowing access to 5,7-bicyclic rings with angular methyl substitution.

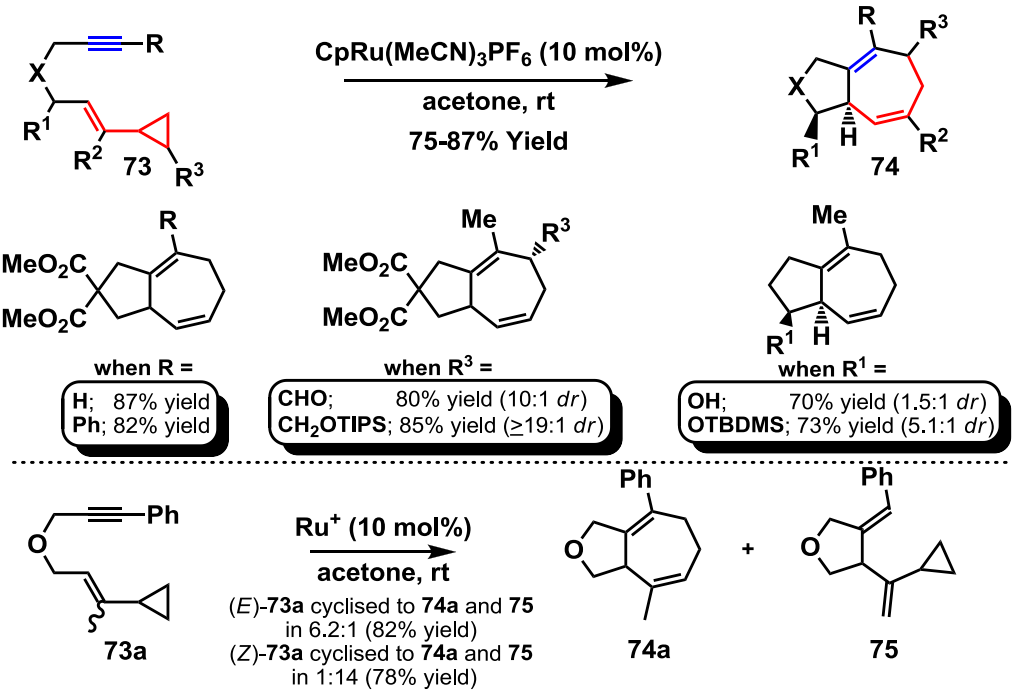
The [5+2] carbocyclisation reaction of VCP tethered with an alkyne also generated the 5,7-bicyclic ring in good yields (**Scheme 29**).[26] This reaction is relatively insensitive to steric and electronic effects introduced by substituent's on the alkyne. The attractiveness of this reaction is further enhanced due to its tolerance to substitution on the VCP alkene.



Scheme 29: Rh(I)-catalysed [5+2] carbocyclisation reactions of VCP tethered with an alkyne

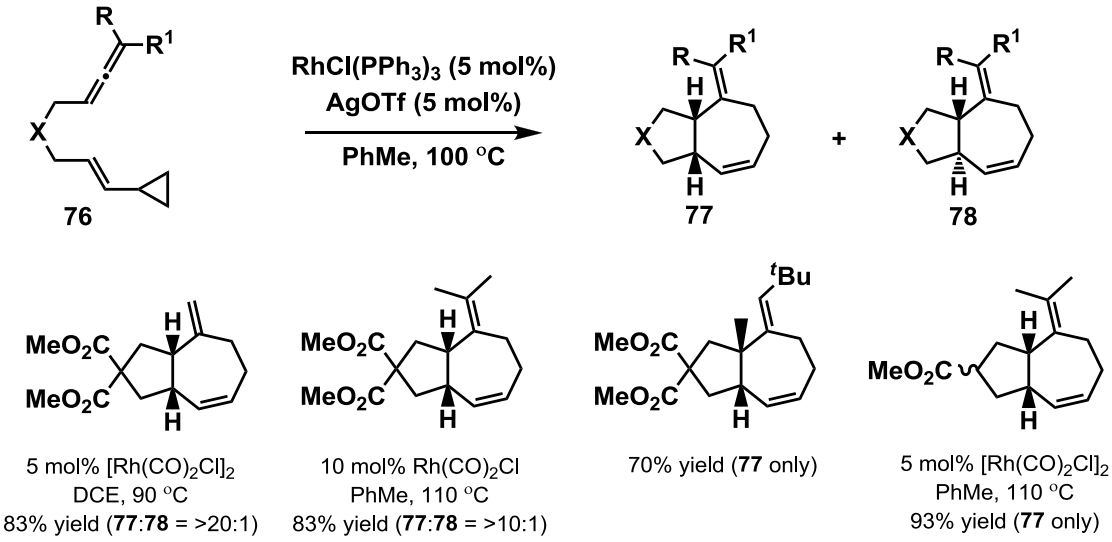
The [5+2] carbocyclisation reaction of VCP tethered with an alkyne can also be promoted by a cationic ruthenium complex (**Scheme 30**).[27] The important significance of this study is that the carbocyclisation reaction can be carried out at room temperature. In contrast, the related rhodium-catalysed [5+2] carbocyclisation reactions depicted in scheme **29** are carried out at 110 ^{0}C.

The ruthenium-catalysed [5+2] cycloaddition reaction is tolerant to substitution on the alkyne (R). However, substitution on the cyclopropane (R^3) and C2-position (R^1) creates diastereoselectivity issues. Additionally, substrates with a methyl group on the olefin (R^2) produced the 5,7-bicyclic ring **74a** along with a *β*-hydride elimination side product of type **75**. In any case, this reaction compliments the rhodium-catalysed [5+2] cycloaddition reaction, both methods permitted the construction of 5,7-bicyclic rings from VCP tethered with alkynes.



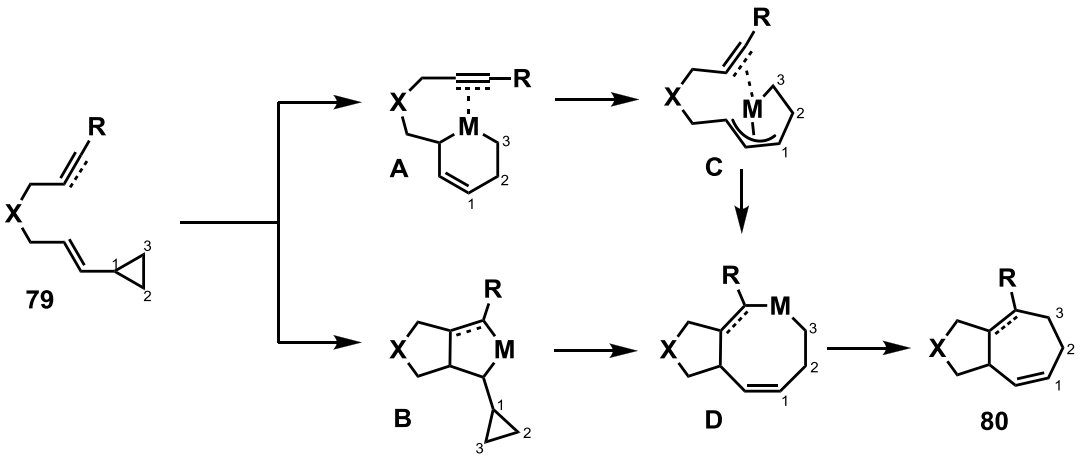
Scheme 30: Ru-catalysed [5+2] carbocyclisation reactions of VCP tethered with alkynes

The rhodium(I)-catalysed intramolecular [5+2] carbocyclisation reactions of VCP tethered with an allene provides an efficient method for the synthesis of a 5,7-bicyclic ring which possesses an exocyclic methylene (**Scheme 31**).[28] However, seven different reaction conditions were utilised to develop the scope of this study. The reactions worked efficiently with mono and disubstituted allenes furnishing the 5,7-bicyclic ring in good to excellent yields.



Scheme 31: Rh(I)-catalysed [5+2] carbocyclisation reactions of VCP tethered with an allene

The proposed mechanism of the metal-catalysed reactions of VCP with π-systems can proceed *via* (a) the formation of metallacyclohexene **A**, which can rearrange to **C.** Carbometallation of the π-system would produce intermediate **D**. Alternatively, the mechanism can proceed *via* (b) the formation of metallacyclopentene **B**, followed by cyclopropyl cleavage to produce intermediate **D**. Reductive elimination of intermediate **D** would produce the 5,7-bicyclic ring **80** (**Scheme 32**).[29]



Scheme 32: Proposed Mechanism of the [5+2] carbocyclisation reaction of VCP with π-systems

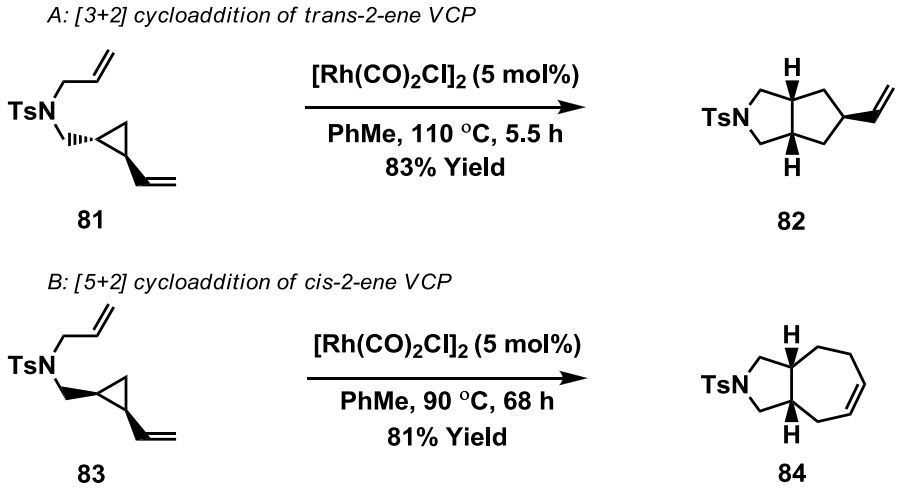
1.6 Competition Between The Formation of 5,5-bicyclic Ring and 5,7-Bicyclic Ring

The competition between the formation of a 5,7,5-tricyclic ring and 5,5-bicyclic ring was observed in the palladium catalysed [3+2+2] carbocyclisation reaction of ACP with alkynes and alkenes. This type of competition can be substrate dependent or influenced by the mechanism.

1.6.1 Substrate Dependent

VCP has been shown to be an effective five-carbon unit in metal-catalysed [5+2] carbocyclisation reactions. Additionally, it can also behave as a three-carbon unit in [3+2] reactions. This dual ability of VCP presumably led to the observed competition between the formation of a 5,5-bicyclic ring and a 5,7-bicyclic ring.

For example, *trans*-VCP tethered with an alkene successfully underwent intramolecular [3+2] carbocyclisation reaction to furnish a *cis*-fused 5,5-bicyclic ring system (**Scheme 33**; A).[30] Exposing *trans*-VCP-ene **81** to 5 mol% of $[Rh(CO)_2Cl]_2$ in toluene at 110 °C provided 5,5-bicyclic ring **82** in 83% yield.

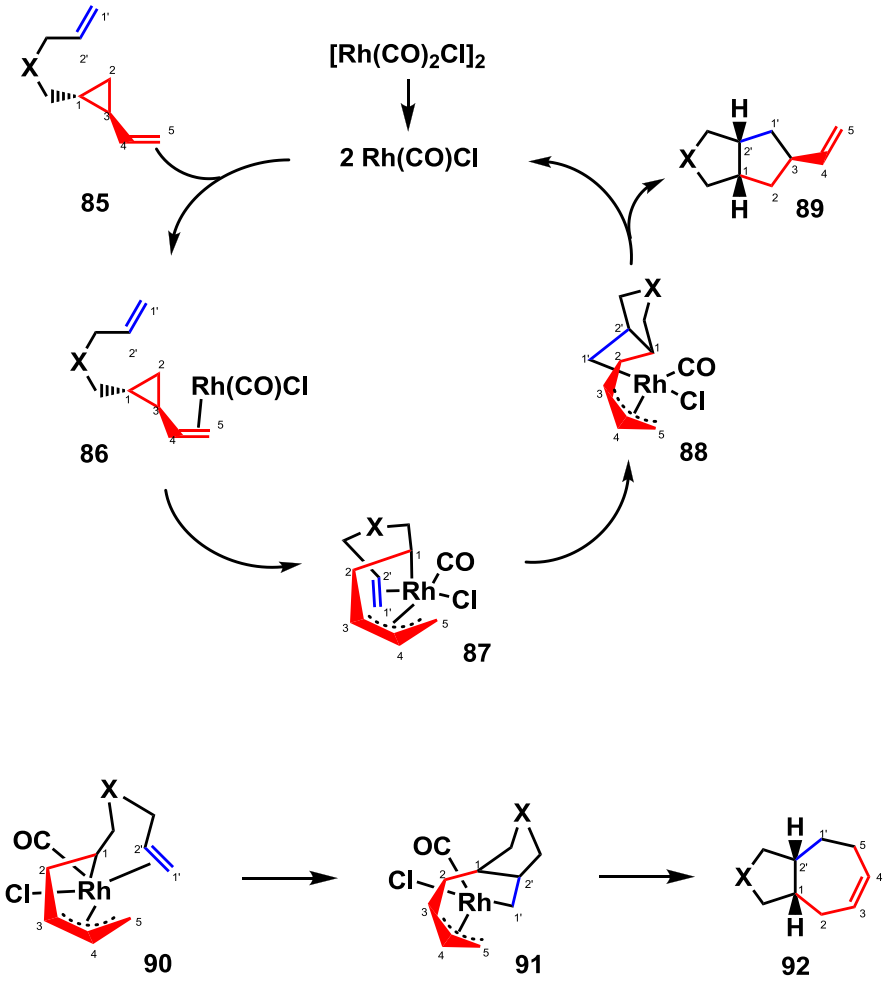


Scheme 33: Rh(I)-catalysed carbocyclisation reactions of *trans*-2-ene and *cis*-2-ene VCP

However, the examination of *cis*-ene-VCP **83** under the same rhodium reaction condition did not produce the expected [3+2] cycloadduct, instead a *cis*-fused 5,7-bicyclic ring system **84** was obtained in 81% yield, possibly *via* the [5+2] cycloaddition pathway (**Scheme 33**; B).[30]

The plausible mechanism for this reaction (**Scheme 34**) showed that, for *trans-2-ene*-VCP, the *cis* insertion of the alkene into the Rh–C1 bond in **87** led to the formation of intermediate **88**. The subsequent reductive elimination between the proximal carbons C1' and C3 furnished 5,5-bicyclic ring **89**.

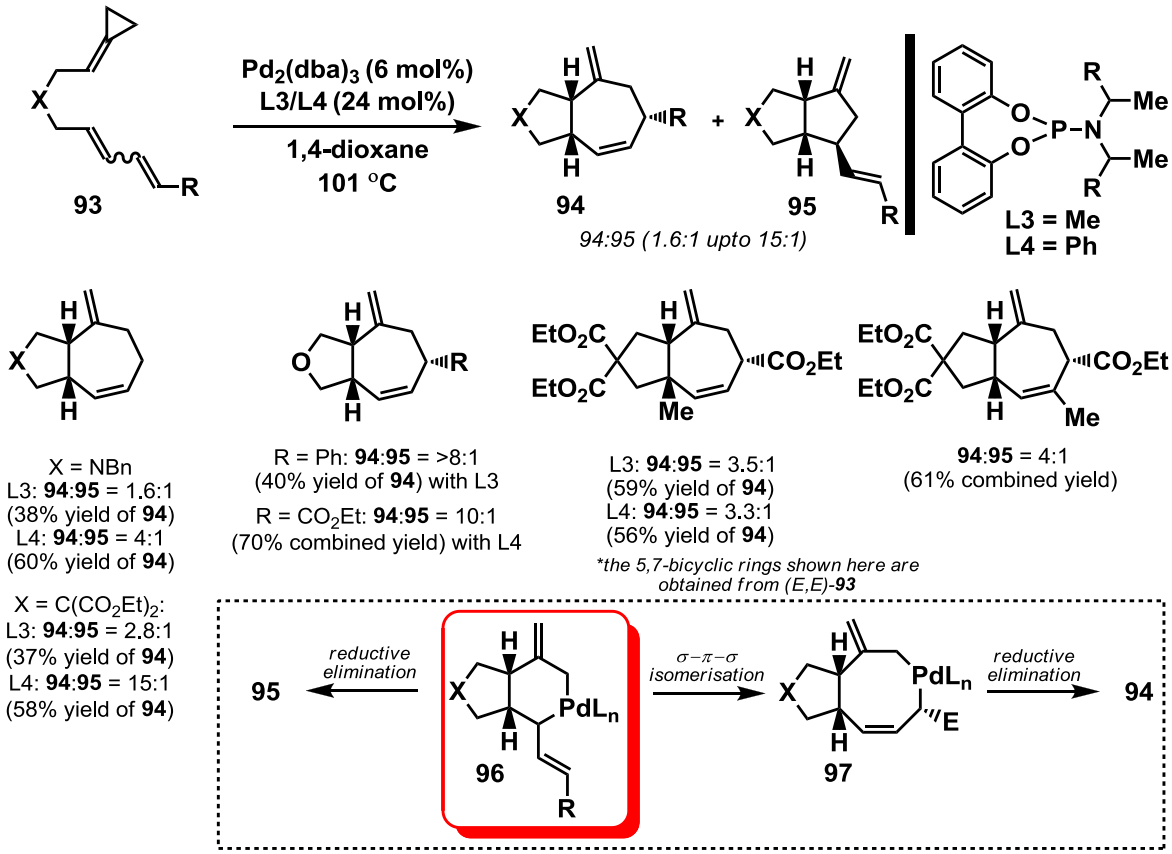
However, for *cis*-VCP-ene, the C1' and C5 carbons are in close proximity as shown in **91**. Hence, reductive elimination will lead to the formation of the C1'-C5 bond to produce the 5,7-bicyclic ring **92**. For *cis*-VCP-ene, the formation of the C1'-C3 bond is unfavoured, hence, the 5,5-bicyclic ring was not detected.



Scheme 34: Proposed mechanism for the carbocyclisation reaction of *trans*-VCP-ene and *cis*-VCP-ene

1.6.2 Pathway Dependent

The palladium catalysed [4+3] carbocyclisation reaction of ACP tethered with 1,3-dienes **93** furnished a 5,7-bicyclic ring **94** (**Scheme 35**).[31] However, the 5,7-bicyclic rings were obtained in poor to moderate selectivities and yields, using ligands **L3** and **L4**. The lack of complete selectivity for the 5,7-bicyclic ring **94** was due to the formation of the 5,5-bicyclic ring **95** possibly *via* the [3+2] pathway.

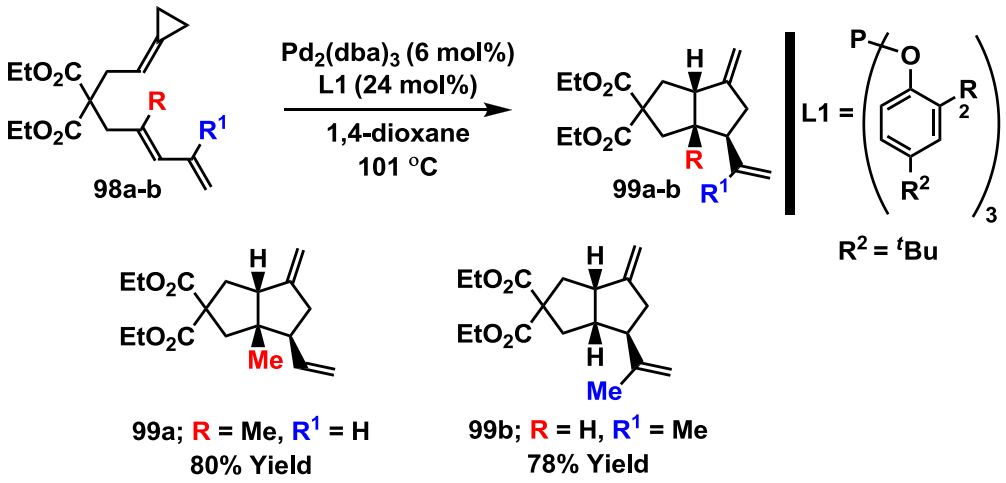


Scheme 35: Pd-catalysed [4+3] carbocyclisation reactions of ACP tethered with 1,3-diene

The use of 1,3-diene enabled the formation of the 5,7-bicyclic ring possibly *via* *σ*-*π*-*σ* isomerisation of palladacyclohexane **96** to palladacyclooctane **97**. Subsequent reductive elimination of **97** led to the formation of the 5,7-bicyclic ring **94** *via* the [4+3] pathway**.** The reductive elimination of **96** probably led to the formation of the 5,5-bicyclic ring **95** *via* the [3+2] pathway.

The inability to selectively favour the *σ*-*π*-*σ* isomerisation of **96** over the reductive elimination restricted the success of this reaction as a synthetic tool for the construction of 5,7-bicyclic ring systems.

The result of this study showed that when X = O, E = CO_2Et, (*E,E*)-**93** (10:1, 70% yield) the reaction performed more efficiently than (*Z,E*)-**93** (1.4:1, 32% yield). The (*E,E*)-**93** favoured *σ*-*π*-*σ* isomerisation of **96** over reductive elimination, when compared to the (*Z,E*)-**93**. It was noted in the study that two substrates (*E,E*)-**98** underwent selective [3+2] cyclisation to provide 5,5-bicyclic rings **99**, when **L1** was utilised as ligand (**Scheme 36**).



Scheme 36: Pd-catalysed [3+2] carbocyclisation reaction of ACP tethered with Diene

1.7 Conclusion

Alkylidenecyclopropane, methylenecyclopropane and vinylcyclopropane have found widespread applicability in numerous transition metal-catalysed carbocyclisation reactions, especially, for the construction of 5,5-, 5,6- and 5,7-bicyclic rings. The propensity of ACP and MCP to undergo metal-triggered ring opening process *via* distal or proximal bond cleavage or formation of metal-trimethylmethylene (metal-TMM) complexes greatly enhanced their application in metal-catalysed reactions. VCP was also shown to participate in metal-catalysed [3+2] or [5+2] carbocyclisation reactions for the construction of 5,5- or 5,7 bicyclic rings, respectively. Overall, transition metal-catalysed carbocyclisation reactions represent a powerful synthetic methodology for the rapid and efficient construction of bicyclic ring systems from ACP, MCP and VCPs tethered with π-systems.

1.8 References

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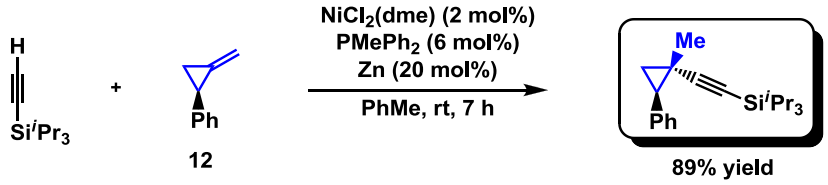
Hydroalkynylation of MCP: Ring-retaining metal catalysed reaction of MCP



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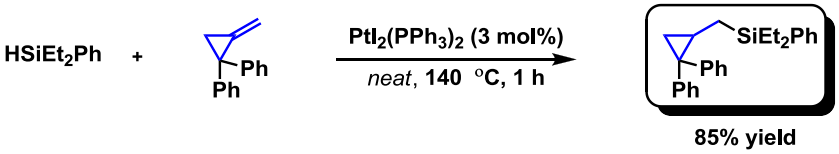
Hydrosilylation of MCP: Ring-retaining metal catalysed reaction of MCP



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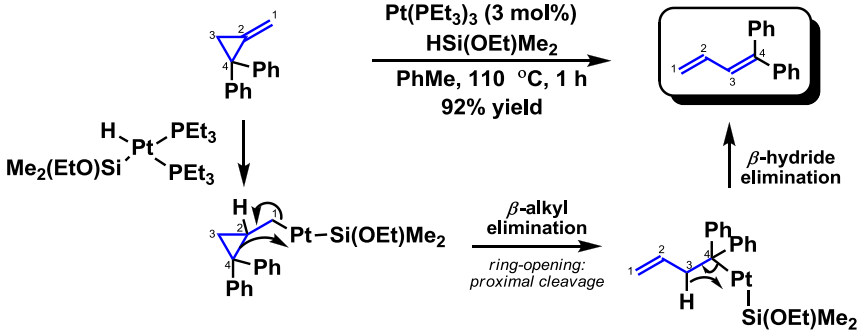
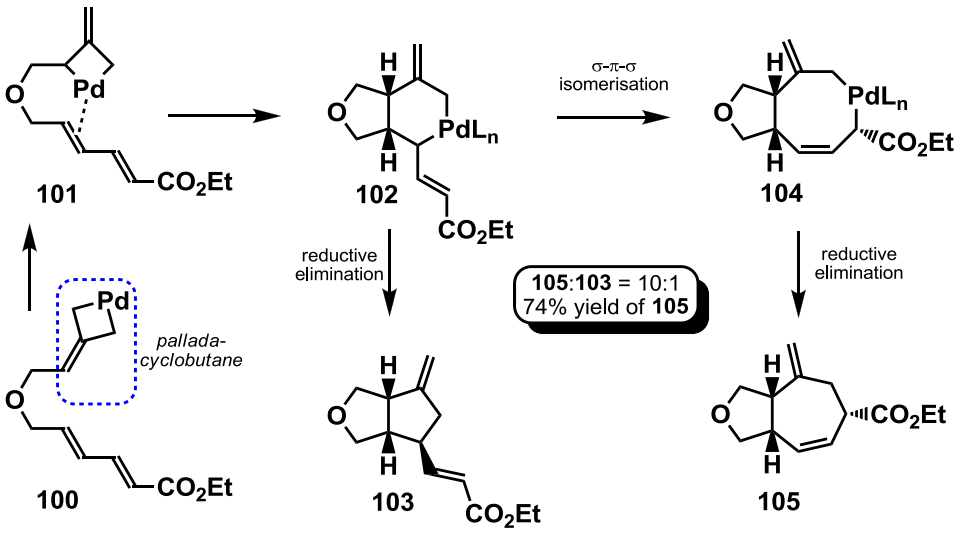


2. The Intramolecular Carbocyclisation Reactions of Alkylidenecyclopropane with Dienes for the Construction of *cis*-Fused 5,5-Bicyclic Ring and *cis*-Fused 5,7-Bicyclic Ring Systems

2.1 Background and Hypothesis

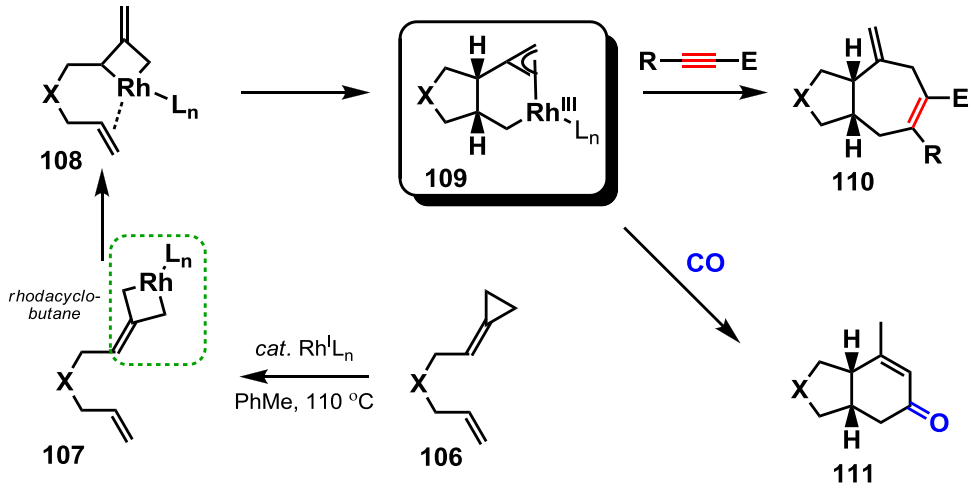
Some of the examples discussed in chapter 1 showed that the insertion of palladium complexes into the distal carbon-carbon bond of ACPs could lead to the formation of palladacyclobutanes.[1] The intramolecular reaction of this putative palladacyclobutanes with an alkene,[2a] an alkyne[2b] or an allene[2c] in the [3+2] carbocyclisation reactions furnished 5,5-bicyclic rings exclusively. However, the intramolecular reaction of the palladacyclobutane **100** with 1,3-diene led to the formation of a 5,5-bicyclic ring **103** and a 5,7-bicyclic ring **105** (**Scheme 35** chapter 1 and **Scheme 37**).[2d]



Scheme 37: The competition between σ-π-σ isomerisation and reductive elimination

The aim of the study was to utilise an ACP tethered with 1,3-diene as a substrate to construct 5,7-bicyclic ring systems. However, the observation of the 5,5-bicyclic ring **103** affected the selective formation of the 5,7-bicyclic ring **105**. This is due to the competition between reductive elimination and σ-π-σ isomerisation of palladacycle **102**.

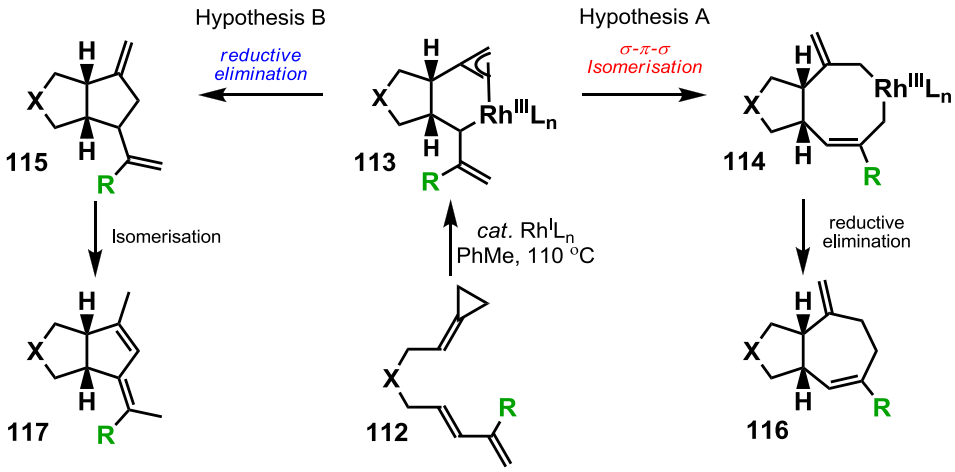
In a program directed towards the development of rhodium(I)-catalysed carbocyclisation reactions, our group has developed a carbocyclisation reaction between ACPs tethered with alkene an **106** and unsymmetrical alkynes for the construction of *cis*-fused 5,7-bicyclic rings **110** which posseses an exocyclic methylene.[3a] In a subsequent study, we replaced the unsymmetrical alkyne with CO. The ensuing stereoselective rhodium(I)-catalysed carbocyclisation reaction between ACP tethered with alkene **106** and CO furnished a *cis*-fused 5,6-bicyclic ring with an α,β-unsaturated system **111**.[3b] Both studies proposed the insertion of a rhodium(I)-complex into the ACP distal bond. The later study[3b] provided theoretical evidence for the *cis*-fused π-allylrhodium complex **109** (R = H; **Scheme 38**).



Scheme 38: Rh(I)-catalysed carbocyclisation reactions of ACP (**106**) with alkyne or CO

Therefore, we envisioned that this concept can be extended to the cyclisation of ACP tethered with dienes for the selective construction of both *cis*-fused 5,5- and *cis*-fused 5,7-bicyclic rings. The ubiquity of these bicyclic rings in bioactive natural products makes them an attractive synthetic target for organic chemists, thereby providing the incentive for the development of new methodologies for their expeditious synthesis.[3c]

Our main objective is to favour the *σ*-*π*-*σ* isomerisation **113** towards the selective construction of a *cis*-fused 5,7-bicyclic ring **116** (Hypothesis A; **Scheme 39**). This can be achieved by examining different rhodium(I)-complexes, ancilliary ligands and investigating the effect of weakly coordinating counterions. In addition, we intend to explore the possibility of favouring the reductive elimination of **113** over *σ*-*π*-*σ* isomerisation in order to achieve the selective construction of the *cis*-fused 5,5-bicyclic ring **117** (Hypothesis B; **Scheme 39**). We proposed that the distal bond cleavage by rhodium will be in operation in this reaction (**Figure 2**).



Scheme 39: Hypothesis for the Rh(I)-catalysed carbocyclisation reaction of ACP with dienes

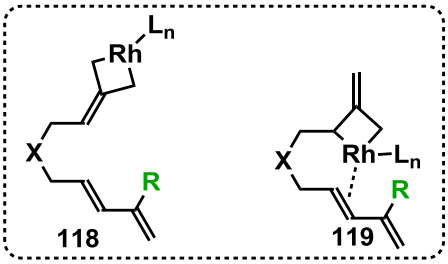


Figure 2: Distal bond cleavage by rhodium(I)-complex

The following discussion will describe how we overcame the current limitations associated with the selective construction of a *cis*-fused 5,7-bicyclic ring from an ACP-diene substrate, and how we also achieved the selective construction of a *cis*-fused 5,5-bicyclic ring without recourse to functional group manipulation, and with a broad scope.[4]

2.2 Synthesis of Model Substrates

The feasibility of the hypotheses depicted in **scheme 39** was tested with two model substrates (*E*)-**127** and (*E*)-**132** (**Figure 3**).

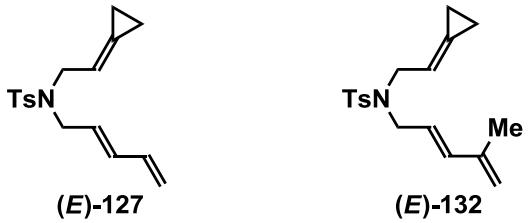
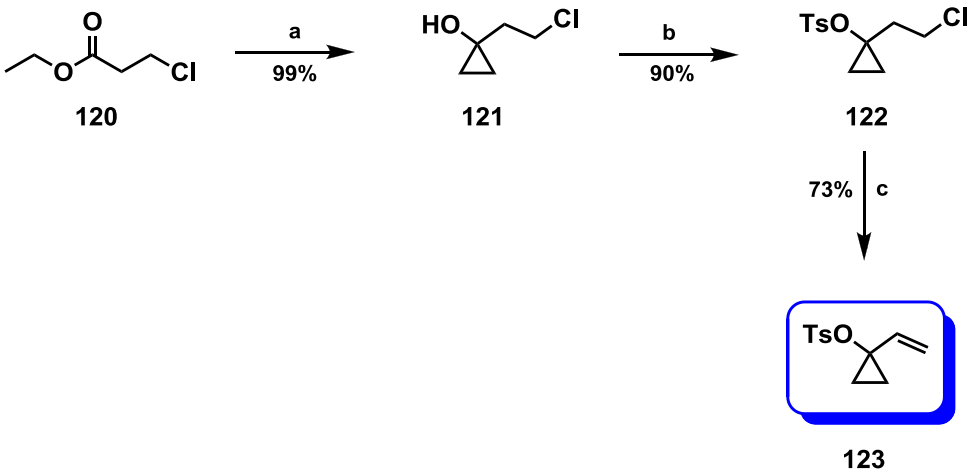


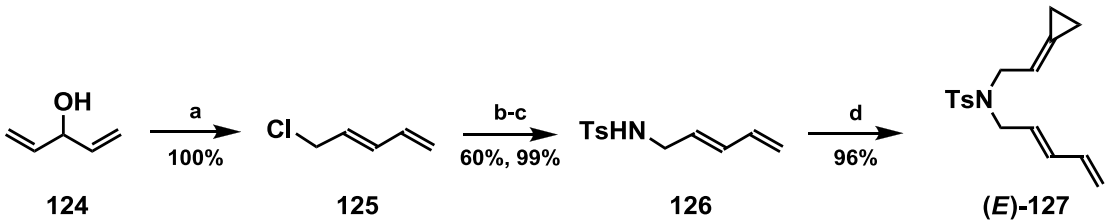
Figure 3: Model substrates: ACP-Dienes (*E*)-**127** and (*E*)-**132**

Compound **123** is a useful synthetic synthon for the installation of the alkylidenecyclopropane moiety.[5] The formation of chloroethyl cyclopropanol **121**[6] was mediated by 20 mol% of $Ti(O^iPr)_4$ and two equivalents of ethylmagnesium bromide at –10 ˚C. The tertiary alcohol **121** was subsequently reacted with tosyl chloride (TsCl) under basic condition to provide compound **122**.[7] Elimination, promoted by potassium *tert*-butoxide at 0 ˚C, led to the formation of compound **123** (**Scheme 40**).[7]



Scheme 40: Preparation of compound **123**: Reaction Conditions: a) EtMgBr (2 equiv), 20 mol% $Ti(O^iPr)_4$, Et_2O, –10 °C, 99% (b) TsCl (1.1 equiv), Et_3N (1 equiv), 4-DMAP (1 equiv), DCM, 0 °C, 90% (c) KO^tBu (1.3 equiv), THF, 0 °C, 73%

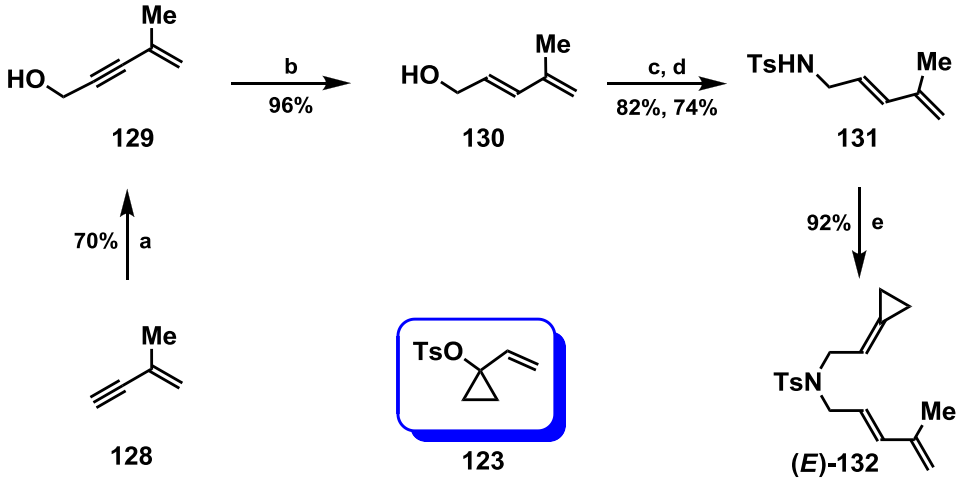
The synthesis of nitrogen atom-tethered ACP-diene (*E*)-**127** began from commercially available penta-1,4-dien-3-ol **124** (**Scheme 41**). Exposure of **124** to 12 M hydrochloric acid, stirred vigorously in water for 2 h, furnished the volatile (*E*)-5-chloropentadiene **125**.[8] The alkylation of commercially available *tert*-butyl tosylcarbamate (BocNHTs) with (*E*)-5-chloropentadiene **125** in the presence of 10 mol% of tetrabutylammonium iodide (TBAI), followed by deprotection of the Boc group, provided (*E*)-**126**.[8] The palladium-catalysed allylation of (*E*)-**126** with **123** furnished the nitrogen atom-tethered ACP-diene (*E*)-**127** in 96% yield.



Scheme 41: Preparation of ACP-Diene (*E*)-**127**: Reaction Conditions: a) 12 M HCl (3 equiv), THF, 0 ˚C, 100% (b) Cs_2CO_3 (2 equiv), BocNHTs (1 equiv), TBAI (0.1 equiv), anhydrous acetone, rt, 60% (c) K_2CO_3 (5 equiv), MeOH, 80 ˚C, 99% (d) (i) NaH (1.2 equiv), DMF (ii) 1 mol% $Pd_2(dba)_3$, 2 mol% dppe, **123** (1 equiv), THF, rt, 96%

The synthesis of nitrogen atom-tethered ACP-diene (*E*)-**132** is described as follows (**Scheme 42**). Treatment of commercially available enyne **128** with ^{n}BuLi generated an alkynyllithium species, which upon treatment with paraformaldehyde at –78 ˚C in THF furnished compound **129** in 70% yield.[9]

Next, treatment of propagyl alcohol **129** with $LiAlH_4$ in THF provided compound (*E*)-**130** in 96% yield.[10] The dienol (*E*)-**130** was converted to dienamine (*E*)-**131** using the Mitsunobu reaction protocol.[11] The treatment of commercially available BocNHTs with compound (*E*)-**130** using PPh_3 and diisopropyl azodicarboxylate (DIAD) at room temperature, followed by deprotection of the Boc group using potassium carbonate (K_2CO_3) at 80 ^{o}C produced (*E*)-**131** in 74% yield. The palladium-catalysed allylation reaction of dienamine (*E*)-**131** with **123** afforded nitrogen atom-tethered ACP-diene (*E*)-**132** in 92% yield.

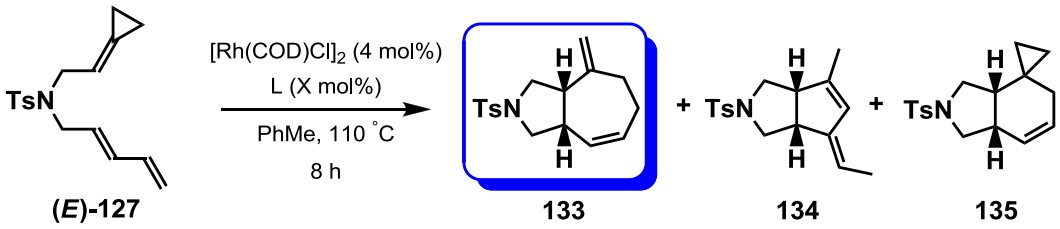


Scheme 42: Preparation of ACP-Diene (*E*)-**132**: Reaction Conditions: (a) ^{n}BuLi (1.2 equiv), $(HCOH)_n$ (5 equiv), THF, –78 ˚C, 70% (b) $LiAlH_4$ (2 equiv), THF, rt, 96% (c) BocNHTs (1.1 equiv), PPh_3 (1.1 equiv), DIAD (1.1 equiv), THF, rt, 82% (d) K_2CO_3 (5 equiv), MeOH, 80 ˚C, 74% (e) (i) NaH (1.1 equiv), DMF (ii) 1 mol% $Pd_2(dba)_3$, 2 mol% dppe, **123** (1 equiv), THF, rt, 92%

2.3 Optimisation of the Intramolecular Carbocyclisation Reaction of ACP with Diene

Preliminary studies focused on the development of the rhodium-catalysed [4+3] carbocyclisation reaction. We elected to use neutral chloro(1,5-cyclooctadiene)rhodium(I) dimer, $[Rh(COD)Cl]_2$ in toluene at 110 °C. This selection was based on the excellent results achieved with this reaction condition in a study carried out within the group on rhodium-catalysed *inter*molecular [(3+2)+2] carbocyclisation reaction of ACP with activated alkynes.[3a]

Table 1: Electronic effect of ligand on Rh(I)-catalysed intramolecular carbocyclisation reaction of ACP-diene **127**



(*E*)-127 **133** **134** **135**

Entry[a]	L	Rh:L	**133:134:135**[b]	Yield (%)[c]
1	-	-	-	-
2	dppp	1:0.5	1:1:4	24
3	PPh_3	1:1	1:1:2	16
4	$P(OPh)_3$	1:2	2:1:1	35[d]
5	$P(OPh)_3$	1:1	3:1:1	45
6	P(O-*o*-tolyl)$_3$	1:1	3:1:1	58
7	$P(OEt)_3$	1:1	3:1:1	60
8	***$P(OCH_2CF_3)_3$***	***1:1***	***4:1:0***	***69***

[a]All reactions were performed on a 0.25 mmol reaction scale using 4 mol% of $[Rh(COD)Cl]_2$ in PhMe (5 mL) for 8 h at 110 °C [b]Ratio of **133:134:135** was determined by HPLC on the crude reaction mixtures [c]HPLC yield of **133** [d]70% conversion after 8 h; entry 1, 2, 4, 5, 6, 7, 8 went to 100% completion. The HPLC selectivity and yields were calculated using HPLC assay see general information.

Initial studies examined the electronic effect of various phosphorus based ligands (**Table 1**). Firstly, we checked whether the transformation of ACP-diene **127** to **133** can occur in the absence of a transition metal. Heating compound (*E*)-**127** at 110 ˚C for 8 h with no rhodium(I)-complex and no ligand gave no reaction (entry 1). However, the introduction of 4 mol% of $[Rh(COD)Cl]_2$ and 4 mol% of dppp furnished 5,7-bicyclic compound **133** (24 % yield) and 5,5-bicycle **134** in 1:1 ratio including unexpected side-product **135** as the major product (entry 2).

This result suggested that the carbocyclisation reaction of an ACP tethered with diene can be catalysed by rhodium, in a similar fashion to palladium. The observed side-product **135** was formed possibly *via* rhodium-catalysed Diels-Alder reaction.[12] This assumption is based on the result obtained in entry 1, which suggested that the formation of cycloadduct **135** is not feasible in the absence of rhodium(I)-complex. Employing a monodentate electron donating σ-donor phosphine ligand gave no improvement in the selectivity between 5,7-bicycle and 5,5-bicycle (entry 3). Still, the formation of Diels-Alder cycloadduct **135** was favoured. The introduction of an electron deficient π-accepting phosphite ligands reversed the selectivity in favour of the formation of the desired bicycloheptadiene **135**, albeit with poor selectivity and in moderate yield (entries 4-7). For example, employing 8 mol% each of $P(OPh)_3$, $P(O\text{-}o\text{-tolyl})_3$ and $P(OEt)_3$ furnished **133** as the major product, albeit in 3:1:1 selectivities (entries 5-7). Gratigfyingly, strongly electron withdrawing trifluoroethyl phosphite proved to be the optimal ligand, and prevented the formation of the Diels-Alder cycloadduct **135** (entry 8).

Although the selectivity between **133** and **134** is still moderate, these results showed that *cis*-fused 5,7-bicyclic ring can be furnished from an ACP-diene with excellent diastereocontrol (*dr* ≥19:1, determined by ^{1}H NMR analysis) in the presence of a rhodium(I)-catalyst. The *syn*-stereochemistry of the two hydrogen atoms of the ring junction was unambiguously confirmed by X-ray crystallography (**Figure 4**).

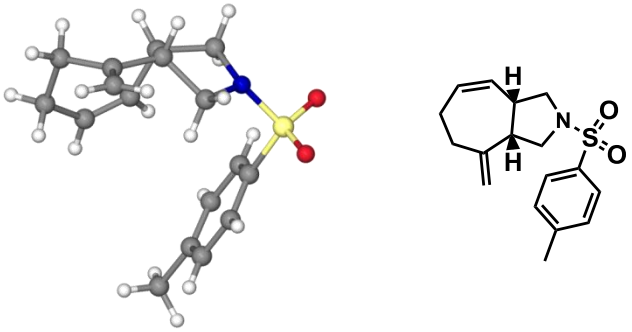


Figure 4: X-ray crystallography of *cis*-fused 5,7-bicyclic ring **133**

It is noteworthy that a 1:1 Rh:L ratio proved optimal for this reaction. The reaction became sluggish with a 1:2 ratio (**Table 1**; entry 4 vs 5). Presumably, with a 1:1 Rh:L ratio, vacant coordination sites are available on the metal centre which could be necessary for the oxidative addition of the metal into the ACP distal C-C bond (as drawn in **Figure 5**).

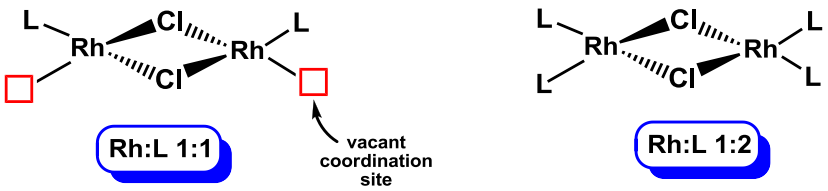
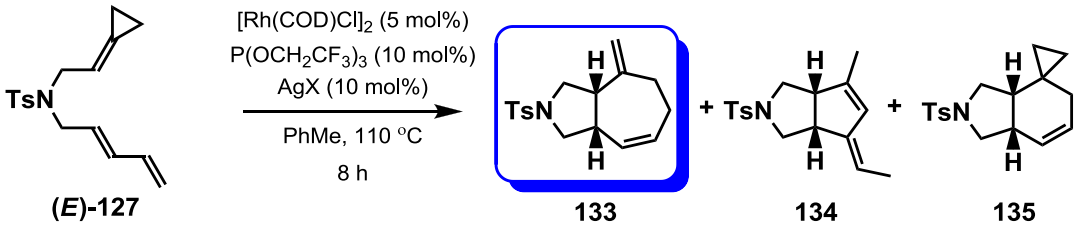


Figure 5: Rationale for the optimal reactivity with Rh:L 1:1 ratio – vacant coordination site

Based on our previous knowledge of the reactivity of cationic rhodium(I)-complex in carbocyclisation reactions,[13] we explored the effect of weakly co-ordinating outersphere counterions to improve the efficiency of this reaction (**Table 2**). Treatment of 5 mol% of the neutral $[Rh(COD)Cl]_2$ dimer with 10 mol% of silver salt provided a cationic rhodium(I)-complex and AgCl *in situ.* The cationic rhodium(I)-complex was formed through the salt metathesis of the Rh-Cl bond. Silver salts such as $AgNO_3$, Ag_2CO_3 and Ag_2SO_4 were ineffective (entries 1, 2 and 3). However, employing silver hexafluorophosphate (entry 4) and silver tetrafluoroborate (entry 5) gave a slight increase in *cis*-fused 5,7-bicyclic ring **133** selectivity.

Table 2: Effect of cationic Rh(I)-complex on the carbocyclisation reaction of ACP-diene **127**.



Entry[a]	Rh(I)	AgX[b]	**133:134**[c]	Yield (%)[d]
1	$[Rh(COD)Cl]_2$	$AgNO_3$	3:1	25
2	$[Rh(COD)Cl]_2$	Ag_2CO_3	3:1	45
3	$[Rh(COD)Cl]_2$	Ag_2SO_4	4:1	35
4	$[Rh(COD)Cl]_2$	$AgPF_6$	5:1	25
5	$[Rh(COD)Cl]_2$	$AgBF_4$	8:1	21
6	$[Rh(COD)Cl]_2$	$AgSbF_6$	15:1	40
7	***$[Rh(COD)_2]SbF_6$***	***none***	***≥99:1***	***92***
8	$[Rh(COD)_2]SbF_6$	AgCl	23:1	50
9	$[Rh(COD)_2]SbF_6$	$AgSbF_6$	20:1	55

[a]All reactions were performed on a 0.25 mmol reaction scale using 5 mol% $[Rh(COD)Cl]_2$, 10 mol% of $P(OCH_2CF_3)_3$ in PhMe (5 mL) for 8 h at 110 °C [b]10 mol% of AgX was used [c]Ratio of **133/134** was determined by HPLC on the crude reaction mixtures. [d]HPLC yield of **133** on crude mixtures

Encouraged by these results, we explored other silver salts such as silver hexafluoroantimonate. Gratifyingly, bicycloheptadiene **133** was obtained in 15:1 selectivity and in 40% yield (entry 6). Although, the cationic rhodium-complex produced the desired cycloadduct **133** in good selectivity, the yields were disappointingly poor (entries 4-6). To resolve this problem, we examined a pre-formed cationic rhodium(I)-complex, $[Rh(COD)_2]SbF_6$, which does not require the addition of a silver salt (entry 7). The salt free condition proved optimal and the bicycloheptadiene **133** was obtained in excellent selectivity and 92% yield.

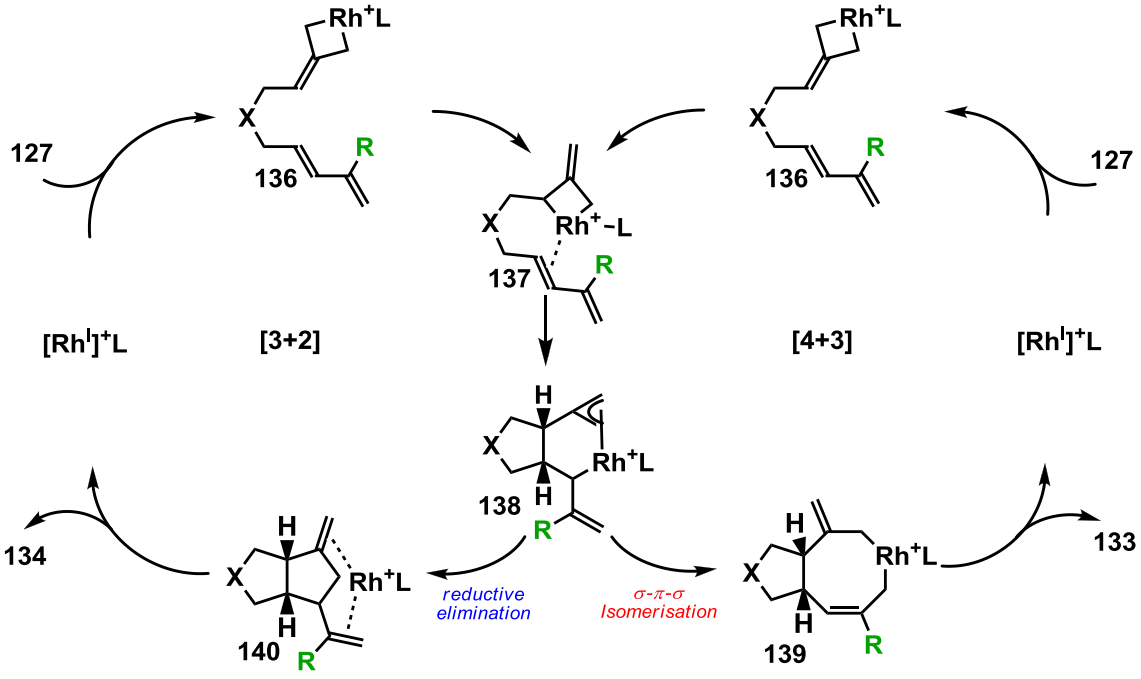
It is noteworthy that the presence of residual silver chloride salt is detrimental to the selectivity and yield of the reaction (entries 8 and 9). Previous studies have shown that silver salts behaved as one electron oxidants, specifically, in the reaction of silver salt with rhodium tetranuclear complexes.[14,15] The reaction vessels used for this reaction are always coated with a thin layer of metal when silver salts are employed.

We examined whether this reaction can be carried out at lower temperature than 110 ˚C. Treatment of ACP-diene **127** with 10 mol% of $[Rh(COD)_2]SbF_6$ and 10 mol% of $P(OCH_2CF_3)_3$ in toluene at 100 ˚C led to a sluggish reaction. The reaction also failed to proceed at 80 ˚C after 8 h, mostly starting material was recovered.

In summary, the combination of cationic rhodium(I)-complex, $[Rh(COD)_2]SbF_6$, with a strongly electron deficient π-acceptor ligand, $P(OCH_2CF_3)_3$ in toluene at 110 ˚C enabled the construction of a *cis*-fused 5,7-bicyclic ring **133** in ≥99:1 (determined by HPLC) and 92% yield. This is in line with our aim, which is to furnish a *cis*-fused 5,7-bicyclic ring system selectively from an ACP tethered with a diene.

Following up on our hypothesis, we turned our efforts toward the selective formation of the 5,5-bicyclic ring **134**. We postulated that this can be achieved by preventing the *σ*-*π*-*σ* isomerisation step of the proposed [4+3] mechanistic pathway (**Scheme 43**).

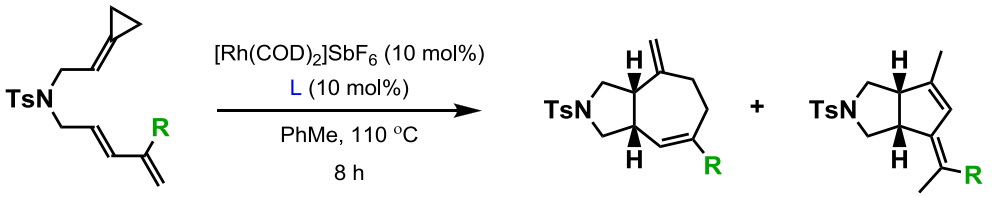
Oxidative insertion of rhodium-complex into the distal bond of ACP-diene **127** should produce alkylidene rhodacyclobutane **136**, followed by rearrangement to give rhodium complex **137**.[16] Carbometallation of the alkene should afford η^3 rhodacycle complex **138**, which could undergo *σ*-*π*-*σ* isomerisation to furnish metallocycle **139**, then reductive elimination would furnish the *cis*-fused 5,7-bicyclic product **133**.



Scheme 43: Proposed mechanism for the [3+2] and [4+3] carbocyclisation reactions

This proposed catalytic cycle suggested that either a 5,7-bicyclic ring or a 5,5-bicyclic ring could be formed from rhodacycle intermediate **138**. Ancilliary ligands and their electronic properties do have a huge impact on the rate of reductive elimination steps in organometallic chemistry.[17] Based on this knowledge, we examined different ligands. $P(OCH_2CF_3)_3$, an electron withdrawing phosphite ligand[18] favoured the [4+3] cycloadduct **133** (**Table 3**; entry 1, **R** = H).

Table 3: Effect of PPh_3 and Methyl Substitution, for the construction of 5,5-bicyclic ring **134** and **142**



(*E*)-127; R = H
(*E*)-132; R = Me

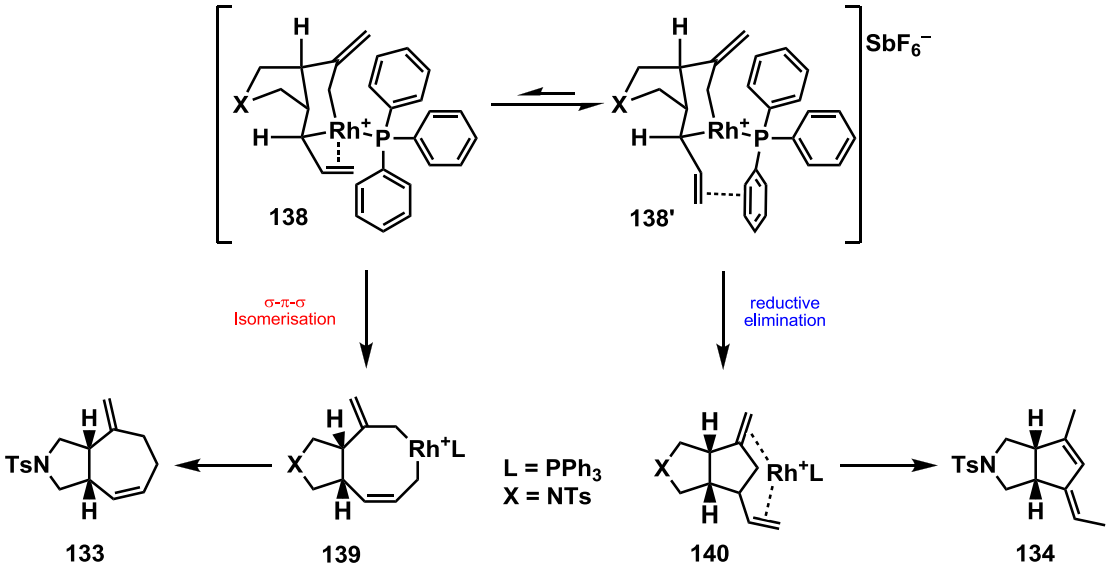
133; R = H
141; R = Me

134; R = H
142; R = Me

Entry[a]	L	R = H 133:134[b]	Yield of 133[c]	Entry[a]	R = Me 141:142[b]	Yield of 142[c]
1	***$P(OCH_2CF_3)_3$***	***>19:1***	***88***	7	3:1	70[e]
2	$P(OEt)_3$	>19:1	68	8	5:1	68[e]
3	$P(OPh)_3$	>19:1	60	9	3:1	72[e]
4	PCy_3	>19:1	60	10	3:1	55[e]
5	PPh_3	1:8	71[d]	***11***	***<1:19***	***89***
6	P(*p*-OMe-Ph)$_3$	1:8	72[d]	12	<1:19	73

[a]All reactions were carried out on a 0.25 mmol scale 8 h [b]Ratios were determined by 500 MHz ^{1}H NMR on the crude reaction mixtures [c]Isolated yield of **133/125** [d]Combined yield of **133** and **134** [e]Combined yield of **141** and **142**

Similarly, $P(OEt)_3$ and $P(OPh)_3$ also favoured the formation of **133** (entries 2 and 3; **R** = H). Also, the electron-donating σ-donor alkyl phosphine ligand[19] (entry 4, **R** = H) favoured the formation of bicycloheptadiene **133**. These results (entries 1-4) suggested that the *σ-π-σ* isomerisation is presumably facile.[20] However, PPh_3 and P(*p*-OMe-Ph)$_3$ reversed the selectivity in favour of the 5,5-bicyclic ring albeit in 1:8 ratio (entry 5-6, **R** = H). This could possibly due to the stabilising π/π interaction between the olefin and the phenyl ring of the PPh_3 (**138'**, **Scheme 44**).[21] Noteworthily, the Diels-Alder side-product was not observed in these reactions. The use of the cationic rhodium(I)-complex prevented its formation.



Scheme 44: Rationale for the switch from 5,7-bicyclic product **133** to 5,5-bicyclic product **134**

A previous study has showed that substitution on the diene reduces the stability of olefin complexes of rhodium(I), *i.e.* a substituted olefin does not bind tightly with rhodium(I) complexes when compared to an unsubstituted olefin.[22] A related study has also highlighted the destabilising effect of an alkyl substituted allyl moiety on the stability of π-allylmetal complexes.[23]

Therefore, we propose that replacing the hydrogen atom, highlighted in green, with a methyl group might prevent the coordination of the olefin to the rhodium(III)-metal centre (**Figure 6**). The rotation around the carbon-carbon bond would possibly introduce $A^{1,2}$ allylic strain. This could cause metallacycle intermediate **138a** (or **138b**) to undergo reductive elimination to produce a 5,5-bicyclic ring.

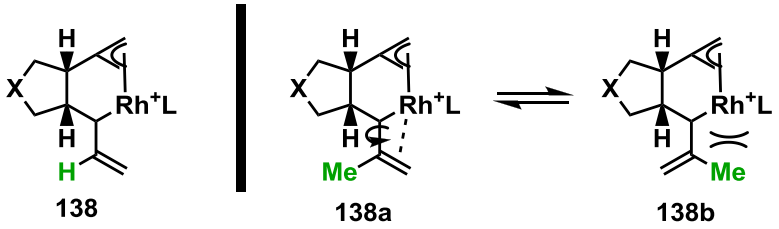


Figure 6: Replacement of H-group with Me-group in rhodium(III)-complex

To test this hypothesis, ACP-diene (*E*)-**132** was treated with 10 mol% of $[Rh(COD)_2]SbF_6$ and 10 mol% of $P(OCH_2CF_3)_3$ in toluene at 110 ˚C, which furnished 5,7-bicyclic compound **141** and 5,5-bicyclic compound **142** in 3:1 ratio and 70% combined yield (entry 7). This result suggested that the positioning of a Me-group on the diene caused the reductive elimination to some great extent (entry 1 *vs* 7). Notably, placing the Me-group on the terminal double bond of the diene produced the *β*-hydride elimination product. Substitution on other sites of the diene led to either decomposition or furnished the 5,7-bicyclic rings selectively, albeit in poor yield.[24]

Furthermore, employing $P(OEt)_3$, $P(OPh)_3$ or PCy_3 as the ligand furnished **141** and **142** in 5:1, 3:1 and 3:1 ratios, respectively (entries 8-10). These results confirmed our initial suggestion that a methyl substitutent on the diene can prevent the coordination of the olefin to the rhodium(III)-metal centre in metallacycle **138b** (**Figure 6**). The presence of the methyl group presumably introduces $A^{1,2}$ strain,[25,26] hence, the reductive elimination of **138b** to generate the 5,5-bicyclic ring (entries 1 *vs* 7, 2 *vs* 8, 3 *vs* 9, 4 *vs* 10). Although, the *cis*-fused 5,5-bicyclic ring was obtained as a minor product, the X-ray crystallography unambiguously confirmed its structure and stereochemistry (**Figure 7**).

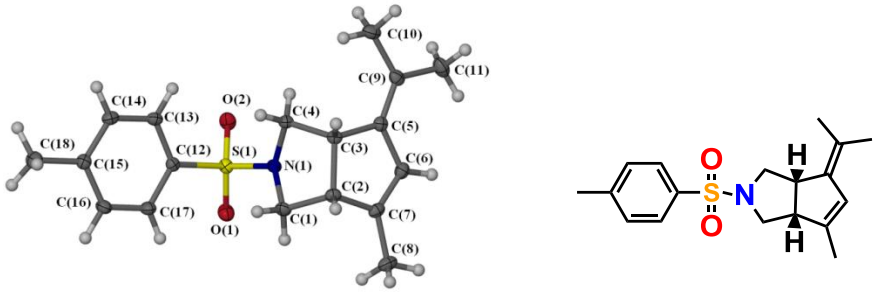
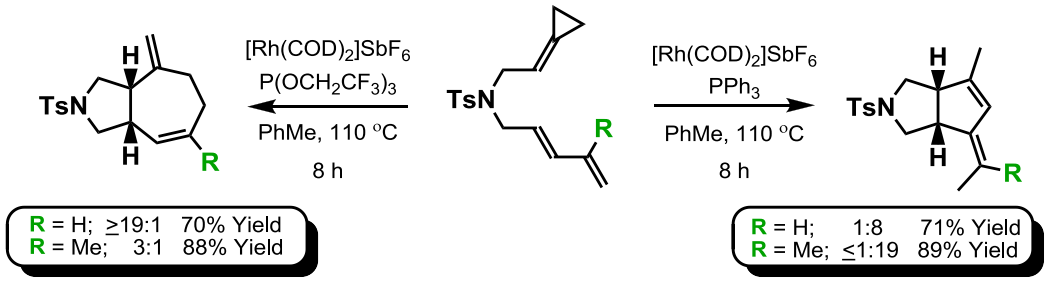


Figure 7: X-ray crystallography of *cis*-fused 5,5-bicyclic ring **142**

Following up on our aim, which was to selectively construct a *cis*-fused 5,5-bicyclic ring from an ACP tethered to a diene, we envisaged that the synergistic effect of substituted diene and PPh_3 could improve the selectivity of the 5,5-bicyclic compound **142**. Gratifyingly, treatment of ACP-diene (*E*)-**132** with 10 mol% of $[Rh(COD)_2]SbF_6$ and 10 mol% of PPh_3 in toluene at 110 ˚C, furnished the 5,5-bicyclic compound **142** in excellent chemoselectivity and yield (entry 11). A similar result was also obtained when P(*p*-OMe-Ph)$_3$ was employed (entry 12). The summary of our results (**Scheme 45**) shows a switch from the selective formation of a *cis*-fused 5,7-bicyclic compound to the selective formation of a *cis*-fused 5,5-bicyclic ring.



Scheme 45: Selective construction of *cis*-fused 5,7-bicyclic ring **133** and *cis*-fused 5,5-bicyclic rings **142** from ACP tethered with 1,3-diene

2.4 Scope of the Rhodium(I)-Catalysed [3+2] and [4+3] Carbocyclisation Reactions

The [3+2] and [4+3] carbocyclisation optimised reaction conditions were extended to oxygen atom- and carbon atom-tethered ACP-diene substrates, (*E*)-**143**, (*E*)-**144**, (*E*)-**145**, (*E*)-**146**, (*E*)-**147** and (*E*)-**148** (**Figure 8**).

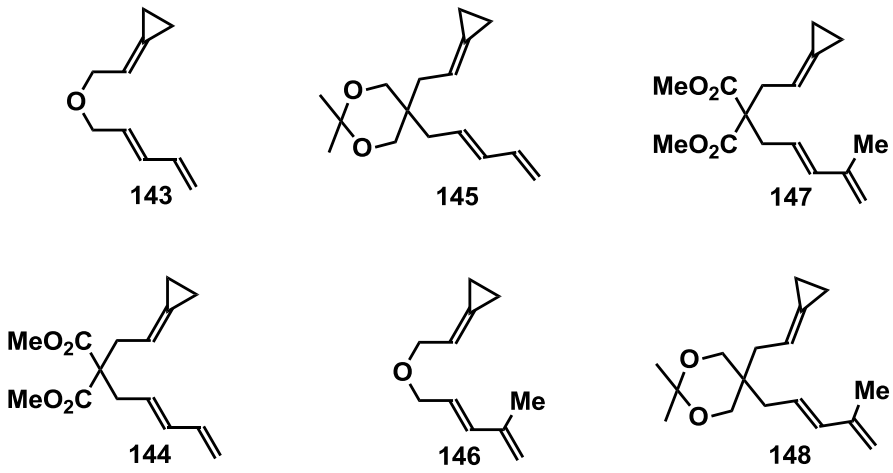
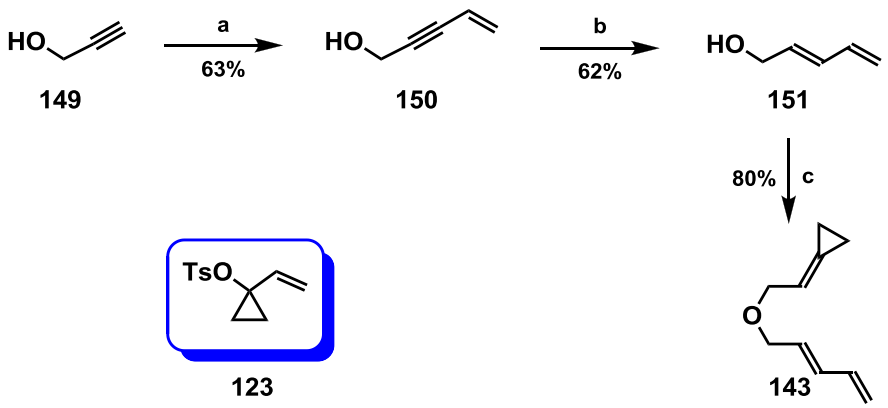


Figure 8: Acetal, ether and malonate ACP-diene substrates

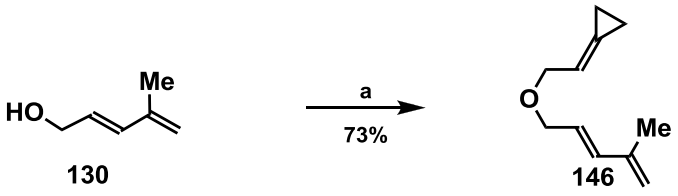
2.4.1 Substrate Synthesis

The synthesis of oxygen-atom tethered ACP-diene (*E*)-**143** commenced from commercially available propargyl alcohol **149** (**Scheme 46**). The Sonogoshira cross-coupling reaction of propargyl alcohol **149** with vinyl bromide using 10 mol% $PdCl_2$, 20 mol% CuI and diisopropylamine furnished the enyn-1-ol **150** in 63% yield.[27] Reduction of **150** with $LiAlH_4$ furnished (*E*)-pentadienol **151** in 62% yield.[28] Subsequent allylation reaction of (*E*)-**128** with **123** furnished ACP-diene (*E*)-**143** in 80% yield.[5]



Scheme 46: Preparation of ACP-Diene (*E*)-**143**: Reaction Conditions: a) $^{i}Pr_2NH$ (2 equiv), 20 mol% CuI, 10 mol% $PdCl_2$, 20 mol% PPh_3, vinyl bromide (5 equiv), THF, rt, 63% (b) $LiAlH_4$ (2 equiv), THF, rt, 62% (c) (i) NaH (1 equiv), THF (ii) 10 mol% $Pd_2(dba)_3$, 20 mol% dppe, **123** (1 equiv), THF, rt, 80%

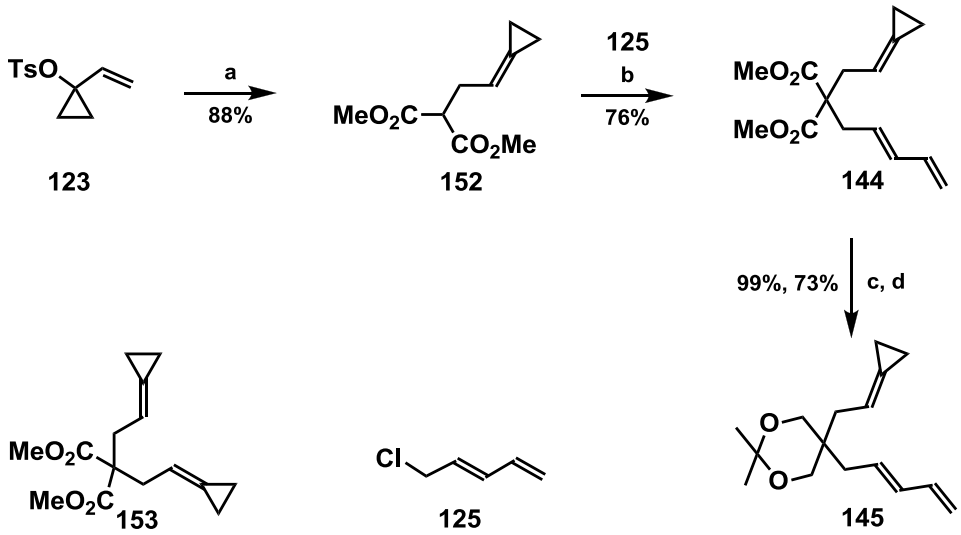
Similarly, the allylation of (*E*)-**130** (synthesis in **scheme 42**) with ACP **123** using 10 mol% $Pd_2(dba)_3$, 20 mol% dppe in THF at room temperature for 12 h produced oxygen-atom tethered ACP-diene (*E*)-**146** (**Scheme 47**).[5] The allylation reaction required higher catalyst loading (10 mol%) and longer reaction time (12 h) to afford oxygen atom- tethered ACP-dienes in good yields; when compared to the allylation reaction of nitrogen atom- tethered ACP-dienes which required 1 mol% of palladium catalyst and 2 h reaction time.



Scheme 47: Preparation of ACP-Diene (*E*)**-146**: Reaction Conditions: a) (i) NaH (1.2 equiv), THF (ii) 10 mol% $Pd_2(dba)_3$, 20 mol% dppe, **123**, THF, rt, 73%

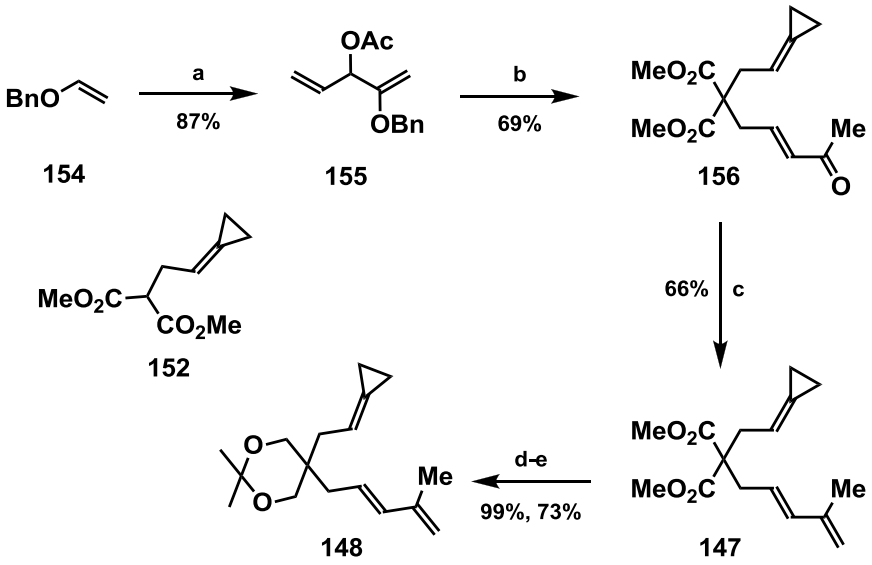
Allylation of dimethyl malonate with vinylcyclopropyl tosylate **123** furnished ACP-malonate **152** in 88% yield (**Scheme 48**).[5] The double-allylation side product **153** was observed when one equivalent of dimethly malonate and one equivalent of sodium hydride (NaH) were used. The formation of malonate tethered ACP-diene (*E*)-**144** was achieved by alkylating **152** with the volatile (*E*)-chloropentadiene **125**.[2]

Treatment of (*E*)-**144** with DIBAL-H in dichloromethane at –78 °C produced a diol, which was subsequently protected as an acetal by employing 8 mol% of pyridinium *p*-toluenesulfonate (PPTS) in 2,2-dimethoxypropane as solvent, generating compound (*E*)-**145** in 73% yield.[29]



Scheme 48: Preparation of ACP-Dienes (*E*)-**144** and (*E*)-**145**: Reaction Conditions: a) (i) NaH (1 equiv), dimethyl malonate (2.5 equiv), THF, rt (ii) 1 mol% $Pd_2(dba)_3$, 2 mol% dppe, THF, 88% (b) **125** (2.5 equiv), NaH (1 equiv), THF, rt, 76% (c) DIBAL–H (4.2 equiv), DCM, –78 °C, 99% (d) PPTS (8 mol%), 2,2-dimethoxypropane, rt, 73%

The synthesis of carbon atom- tethered ACP-dienes (*E*)-**147** and (*E*)-**148** commenced from commercially available compound **154** (**Scheme 49**). Lithiation of ((vinyloxy)methyl) benzene **154** with ^{t}BuLi at –78 ˚C in pentane/THF gave the corresponding α-benzyloxy vinyllithium.[30] Subsequent addition of acrolein generated an allylic alcohol, which was treated *in situ* with acetic anhydride to afford **155** in 87% yield. Compound **155** was purified by short-path vacuum distillation using a Kugelrohr apparatus. Palladium-catalysed allylation reaction of **155** with the sodium anion of **152**, resulted in the formation of compound **156** in 69% yield.[5] Wittig olefination on **156** using the ylide derived from phosphonium salt, $Ph_3P^{+}MeBr^{-}$, produced ACP-diene (*E*)-**147** in 66% yield.[31] DIBAL-H reduction of the two ester groups gave a diol, which was protected as an acetal to give ACP-diene (*E*)-**148** in 73% yield.



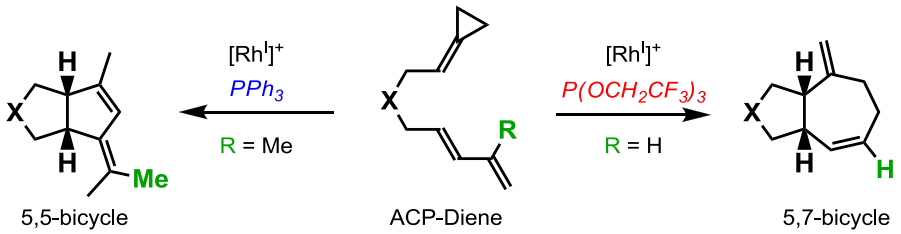
Scheme 49: Preparation of ACP-Dienes (*E*)-**147** and (*E*)-**148**: Reaction Conditions: a) (i) ^{t}BuLi (1 equiv), acrolein (1 equiv), THF, -78 ˚C (ii) DMAP (0.01 equiv), pyridine (2 equiv), acetic anhydride (2 equiv), rt, 87% (b) (i) NaH (1 equiv), **152** (1 equiv), THF, rt (ii) 2 mol% $Pd_2(dba)_3$, 8 mol% PPh_3, THF, 69% (c) K^{t}OBu (1.5 equiv), $Ph_3P^{+}MeBr^{-}$ (1.5 equiv), benzene, –20 ˚C, 66% (d) DIBAL–H (4.2 equiv), DCM, –78 ˚C, 99% (e) PPTS (8 mol%), 2,2-dimethoxypropane, rt, 73%

Table 4 summarises the results of the scope of the [3+2] and [4+3] carbocyclisation reactions. The nitrogen atom-, oxygen atom-, carbon atom-tethered ACP-diene substrates (*E*)-**127,** (*E*)-**143,** (*E*)-**144** and (*E*)-**145** successfully underwent [4+3] carbocyclisation reaction to produce the corresponding bicycloheptadienes **157**, **158**, **159** and **160** respectively in excellent yields (**R** = H; entry 1-4).

Similarly, ACP-diene substrates (*E*)-**132**, (*E*)-**146** and (*E*)-**147** successfully underwent [3+2] carbocyclisation reaction to produce the corresponding bicyclopentadienes **161**, **162** and **163** respectively in good yields (**R** = Me; entry 5-7). Substrate (*E*)-**148** underwent [3+2] carbocyclisation reaction successfully but **164** was obtained as an inseparable 3:1 mixture of regioisomers (**R** = Me; entry 8).

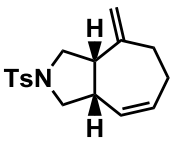
It is noteworthy that the carbocyclisation reaction of these substrates can be carried out with similar efficiency using lower loadings of Rh-catalyst (5-6 mol%). These results highlight how the product distribution of the carbocyclisation reaction can be influenced by the choice of ligand and the diene substitution.

Table 4: Scope of the Cationic Rhodium(I)-Catalysed Intramolecular Carbocyclisation Reactions of ACP with Diene



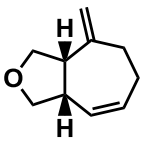
Entry[a]	X	R	ACP-diene	5,7:5,5[b]		Yield(%)[c]
1	NTs	H	**127**	≥19:1	**133**	92
2	O	"	**143**	≥19:1	**158**	70
3	$C(CO_2Me)_2$	"	**144**	≥19:1	**159**	92
4	$C[(CH_2O)_2C(Me)_2]$	"	**145**	≥19:1	**160**	80
5	NTs	Me	**132**	≤1:19	**142**	89
6	O	"	**146**	≤1:19	**162**	68
7	$C(CO_2Me)_2$	"	**147**	≤1:19	**163**	89
8	$C[(CH_2O)_2C(Me)_2]$	"	**148**	≤1:19	**164**	78[d]

[a]All reactions were carried out using 10 mol% $[Rh(COD)_2]SbF_6$, 10 mol% of ligand in PhMe at 110 °C on a 0.25 mmol scale 8 h [b]Ratios of **5,7/5,5** were determined by 500 MHz ^{1}H NMR on the crude reaction mixtures. [c]Isolated yield [d]Combined yield of regioisomers, 3:1 ratio.



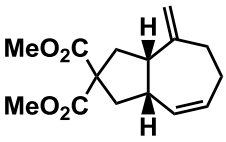
133

≥19:1 , 88%



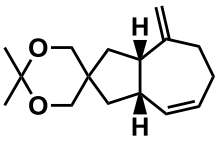
158

≥19:1 , 70%



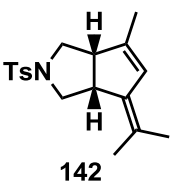
159

≥19:1 , 92%



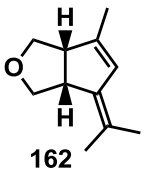
160

≥19:1 , 80%



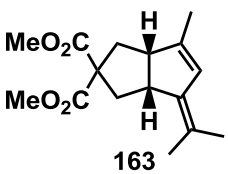
142

≤1:19 , 89%



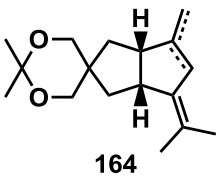
162

≤1:19 , 68%



163

≤1:19 , 89%



164

≤1:19 , 78%

2.5 The Diastereoselective Cationic Rhodium(I)-Catalysed Intramolecular Carbocyclisation Reactions of ACP with Diene

The scope of the [3+2] and [4+3] carbocyclisation reaction was extended to diastereoselective reactions of various ACP-dienes with methyl- or phenyl substituent at the C-2 position (**Figure 9**).

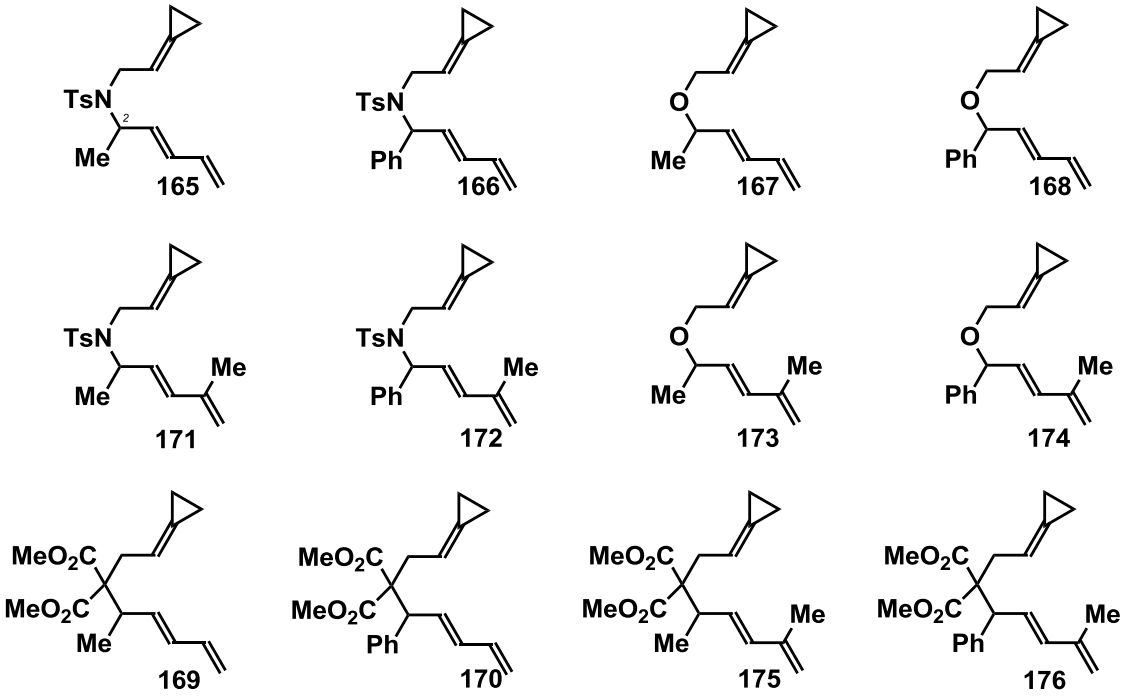
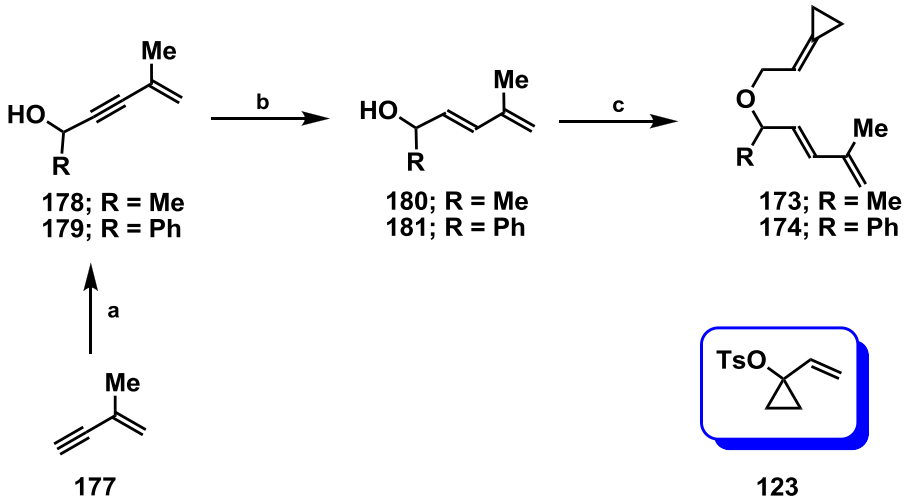


Figure 9: Methyl and phenyl C-2 substituted ACP-diene substrates

The syntheses of these precursors are delineated below. The formation of oxygen atom-tethered ACP-dienes (*E*)-**173** and (*E*)-**174** commenced from commercially available enyne **177** (**Scheme 50**).

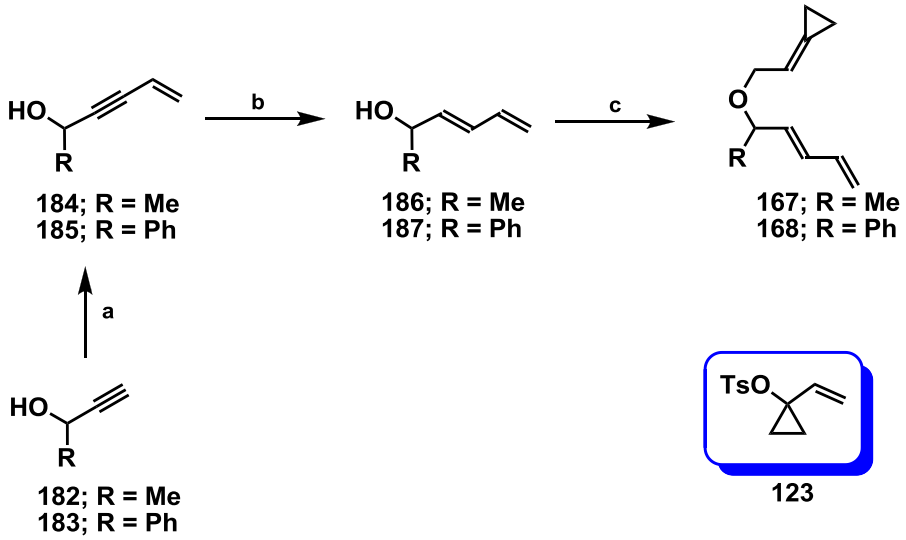
Treatment of enyne **177** with ^{n}BuLi in THF at –78 ^{o}C generated the corresponding alkynyllithium, and quenching with acetyladehyde or benzaldehyde generated alcohols **178** or **179** in 96% and 89% yield, respectively.[32] Compounds (*E*)-**180**[33] and (*E*)-**181**[34] were obtained by reduction of precursors **178** and **179** with $LiAlH_4$ in THF at 0 ˚C.[32] Successive palladium-catalysed allylation of (*E*)-**180** and (*E*)-**181** with compound **123** furnished (*E*)-**173** and (*E*)-**174** in 56% and 51% yields, respectively.[5]



Scheme 50: Preparation of ACP-Dienes (*E*)-**173** and (*E*)-**174**; Reaction Conditions (a) ^{n}BuLi (1.2 equiv), THF, acetaldehyde (1 equiv) or benzaldehyde (1 equiv), –78 ˚C (96%; **178**) (89%; **179**) (b) $LiAlH_4$ (1.2 equiv), THF, 0 ˚C (78%; **180**) (50%; **181**) (c) (i) NaH (1.2 equiv), THF (ii) 10 mol% $Pd_2(dba)_3$, 20 mol% dppe, **123** (1 equiv), THF, rt (56%; **173**) (51%; **174**)

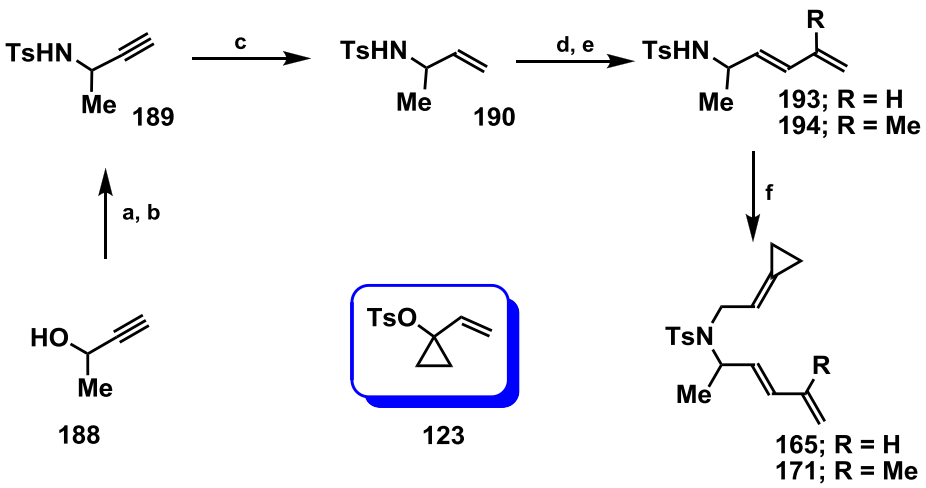
The synthesis of (*E*)-**167** and (*E*)-**168** commenced from commercially available propargyl alcohols **154** or **155** (**Schemes 51**). Sonogoshira coupling[35] of alkynes **182** and **183** with vinyl bromide furnished enynes **184** and **185** in 54% and 80% yield, respectively. Subsequent $LiAlH_4$ reduction of the substituted propargyl alcohols **184** and **185** gave compounds (*E*)-**186**[36a] and (*E*)-**187**[36b] in 63% and 70% yield, respectively.[37]

Installation of the ACP moiety was achieved through palladium-catalysed allylation of **123** with dienes (*E*)-**186** and (*E*)-**187** produced oxygen atom-tethered ACP-dienes (*E*)-**167** and (*E*)-**168** in 45% and 50% yield, respectively.[5]



Scheme 51: Preparation of ACP-Dienes (*E*)-**167** and (*E*)-**168**; Reaction Conditions (a) $^{i}Pr_2NH$ (2 equiv), 4 mol% CuI, 5 mol% $Pd(PPh_3)_4$, vinyl bromide (5 equiv), THF, rt (80%; **185**) (54%; **184**) (b) $LiAlH_4$ (1.2equiv), THF, 0 ˚C (63%; **186**) (70%; **187**) (c) (i) NaH (1.2 equiv), THF (ii) 10 mol% $Pd_2(dba)_3$, 20 mol% dppe, **123** (1equiv), THF, rt (45%; **167**) (50%; **168**)

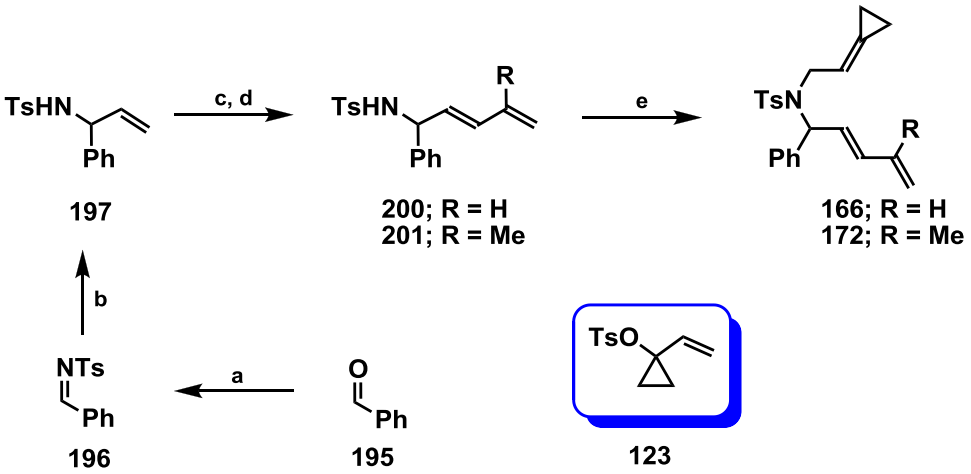
The synthesis of ACP-dienes (*E*)-**165** and (*E*)-**171** was achieved in five synthetic steps. Mitsunobu reaction, deprotection, $LiAlH_4$ reduction of alkyne, cross metathesis,[38] and Wittig olefination on propargyl alcohol **188** furnished (*E*)-**193** and (*E*)-**194** in excellent yields. The palladium-catalysed allylation reaction of **123** with (*E*)-**193** and (*E*)-**194** afforded nitrogen-atom tethered ACP-dienes (*E*)-**165** and (*E*)-**171** in 79% and 86% yield, respectively (**Scheme 52**).



Scheme 52: Preparation of ACP-Dienes (*E*)-**165** and (*E*)-**171**; Reaction Conditions (a) BocNHTs (1.1 equiv), PPh_3 (1.1 equiv), DEAD (1.1 equiv), THF, rt, 82% (b) K_2CO_3 (5 equiv), MeOH, 80 ˚C, 89% (c) $LiAlH_4$ (4 equiv), THF, 0 ˚C, 92% (d) 1 mol% Hoveyda-Grubbs II, methyl vinylketone (5 equiv) or crotonaldehyde (5 equiv), DCM, 60 ˚C, (97%, **192**; 99%, **191**) (e) ^{n}BuLi (2 equiv), $Ph_3P^+MeBr^-$ (2 equiv), THF, –20 ˚C, (71%, **193**; 83%, **194**) (f) (i) NaH (1.1 equiv), DMF, rt (ii) 1 mol% $Pd_2(dba)_3$, 2 mol% dppe, **123**, THF, rt, (79%, **165**; 86%, **171**)

The nitrogen atom-tethered ACP-dienes (*E*)-**166** and (*E*)-**172** were both accessed from benzaldehyde **195** (**Scheme 53**). The imine precursor **196** was obtained from the condensation of 4-toluenesulfonamide (H_2NTs) with commercially available benzaldehyde **196**, mediated by 10 mol% of iron(III)-chloride ($FeCl_3$).

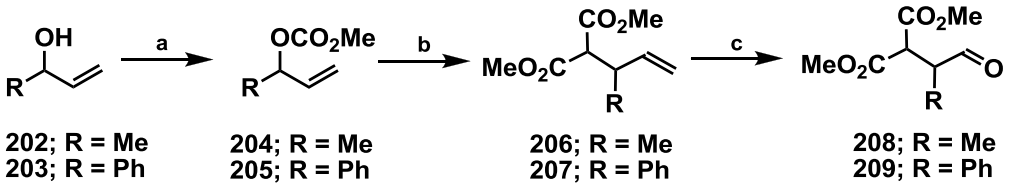
Compound **168** was subjected to a three step synthetic sequence consisting of; Grignard addition,[39] cross metathesis and Wittig olefination, providing (*E*)-**200** and (*E*)-**201** in 72% and 67% yield, respectively. The allylation reaction of (*E*)-**200** and (*E*)-**201** with **123** successfully furnished (*E*)-**166** and (*E*)-**172** in 86% and 64% yield, respectively.



Scheme 53: Preparation of ACP-Dienes (*E*)-**166** and (*E*)-**172**; Reaction Conditions (a) 10 mol% $FeCl_3$, H_2NTs (1 equiv), DCM, rt, 66% (b) Vinylmagnesium bromide (2 equiv), THF, 0 ˚C, 68% (c) 1 mol% Hoveyda-Grubbs II, (2 equiv) crotonaldehyde or methyl vinyl ketone (2 equiv), DCM, 60 ˚C, (92%; **198**, 60%; **199**) (d) ^{n}BuLi (2 equiv), $Ph_3P^{+}MeBr^{-}$ (2 equiv), THF, –20 ˚C (72%, **200**; 67%, **201**)(e) (i) NaH (1.1 equiv), DMF, rt (ii) 1 mol% $Pd_2(dba)_3$, 2 mol% dppe, **123**, THF, rt (86%, **166**, 64%, **172**)

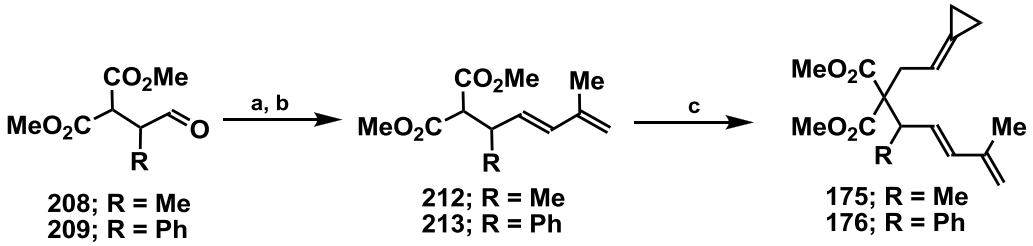
The carbon atom-tethered ACP-diene series were constructed *via* aldehyde precursors **208**[40] and **209** (**Scheme 54**). The commercially available allylic alcohols **202** and **203** were protected under basic condition using methyl chloroformate, produced compounds **204** and **205** in 68% and 85% yield, respectively.

The rhodium(I)-catalysed allylic substitution[41] of **204** and **205** with dimethyl malonate furnished compounds **206** and **207** in 92% and 85% yield, respectively. Ozonolysis[42a] of **206** and **207** furnished aldehydes **208** and **209** in 87% and 88% yield, respectively.



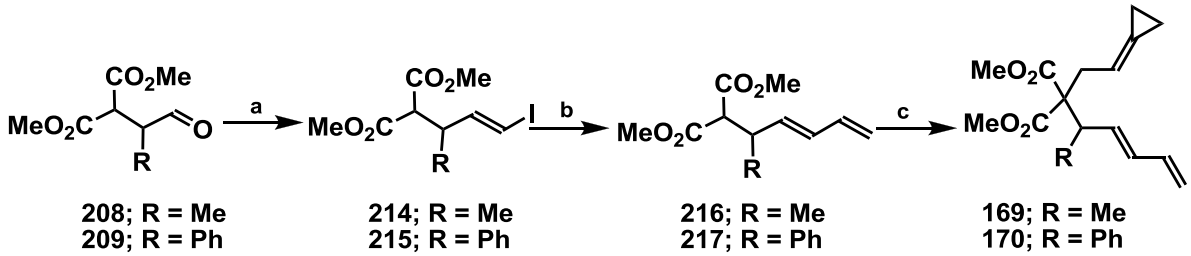
Scheme 54: Preparation of aldehydes **208** and **209**; Reaction Conditions (a) Methyl chloroformate (2 equiv), Et_3N (2 equiv), DMAP (10 mol%), DCM, rt (85%; **205**) (68%; **204**) (b) (i) NaH (1.5 equiv), dimethyl malonate (1 equiv), THF (ii) 5 mol% $RhCl(PPh_3)_3$, 20 mol% $P(OMe)_3$, rt, (85%; **207**) (92%; **206**) (c) Ozone, DCM, –78 ˚C (87%; **208**) (88%; **209**)

Two consecutive Wittig olefinations[42b] on **208** and **209** furnished dienes (*E*)-**212** and (*E*)-**213** in 69% and 68% yield, respectively. Installation of the ACP moiety onto these dienes was achieved under palladium-catalysed allylation with compound **123**, generated the malonate tethered ACP-dienes (*E*)-**175** and (*E*)-**176** in 89% and 87% yield, respectively (**Scheme 55**).



Scheme 55: Preparation of ACP-Dienes (*E*)-**175** and (*E*)-**176**; Reaction Conditions: (a) $Ph_3PCHCOMe$ (2 equiv), toluene, 120 ˚C (65%; **211**) (82%; **210**) (b) ^nBuLi (2 equiv), $Ph_3P^+MeBr^-$ (2 equiv), THF, –20 ˚C (69%; **212**) (68%; **213**) (c) (i) NaH (1.1 equiv), THF, rt (ii) 1 mol% $Pd_2(dba)_3$, 2 mol% dppe, **123**, THF, rt, (89%, **175**; 87%, **176**)

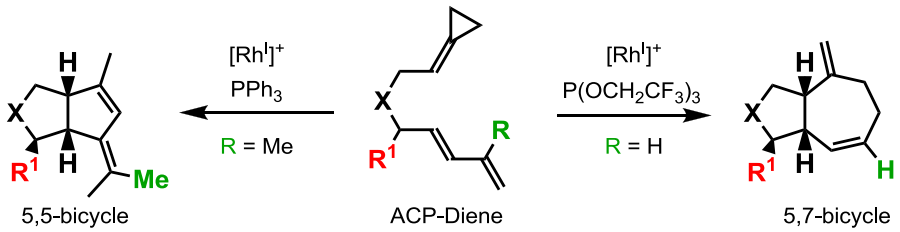
Compounds **208** and **209** were also used to synthesise ACP-dienes **169** and **170**. Takai olefination on aldehydes **208** and **209** using chromium(II)-chloride and iodoform produced vinyl iodides (*E*)-**214** and (*E*)-**215** in moderate yields.[43] Stille cross coupling,[44] with tributylvinylstannane furnished (*E*)-**216** and (*E*)-**217** in 92% and 90% yield, respectively. Installation of the ACP moiety onto these dienes was achieved under palladium-catalysed allylation reaction condition using compound **123** to generate ACP-dienes (*E*)-**169** and (*E*)-**170** in 84% and 80% yield, respectively (**Scheme 56**).



Scheme 56: Preparation of ACP-Dienes (*E*)-**169** and (*E*)-**170**; Reaction Conditions: (a) $CrCl_2$ (7 equiv), CHI_3 (2 equiv), THF, rt, (65%; **214**) (54%; **215**) (b) 5 mol% $Pd(PPh_3)_4$, tributylvinylstannane (2 equiv), DMF, rt, (92%; *E*/*Z* = ≥19:1, **216**) (90%; *E*/*Z* = 13:1, **217**) (c) (i) NaH (1.1equiv), THF, rt (ii) 1 mol% $Pd_2(dba)_3$, 2 mol% dppe, **123** (1 equiv), THF, rt, (84%, **169**; 80%; **170**)

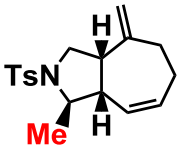
The ACP-diene substrates synthesised in **schemes 50-56** were subjected to the rhodium-catalysed [3+2] and [4+3] carbocyclisation optimised reaction conditions. As shown in Table 5, these reactions proceeded with high degree of diastereocontrol (≥19:1 determined by ^1H NMR analysis) affording the desired carbocycles selectively and in excellent yields. The reactions worked efficiently with various nitrogen atom-, carbon atom-, and oxygen atom-tethered ACP-dienes. Both phenyl and methyl substituents at the C-2 position are tolerated.

Table 5: The Diastereoselective Intramolecular Carbocyclisation Reactions of ACP with dienes

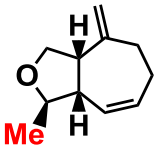


Entry[a]	X	R	R^1	ACP-Diene	Ratio[b] of **5,7:5,5**	*dr*	Product	Yield of Product[c]
1	NTs	H	Me	**165**	≥19:1	≥19:1	**218**	70
2	"	"	Ph	**166**	≥19:1	≥19:1	**219**	80
3	O	"	Me	**167**	≥19:1	≥19:1	**220**	58
4	"	"	Ph	**168**	≥19:1	≥19:1	**221**	72
5	$C(CO_2Me)_2$	"	Me	**169**	≥19:1	≥19:1	**222**	78[d]
6	"	"	Ph	**170**	≥19:1	≥19:1	**223**	81
7	NTs	Me	Me	**171**	≤1:19	≥19:1	**224**	76
8	"	"	Ph	**172**	≤1:19	≥19:1	**225**	72
9	O	"	Me	**173**	≤1:19	≥19:1	**226**	67
10	"	"	Ph	**174**	≤1:19	≥19:1	**227**	60
11	$C(CO_2Me)_2$	"	Me	**175**	≤1:19	≥19:1	**228**	68
12	"	"	Ph	**176**	≤1:19	≥19:1	**229**	75

[a]All reactions were carried out using 10 mol% $[Rh(COD)_2]SbF_6$, 10 mol% of ligand in PhMe at 110 [o]C on a 0.25 mmol scale 8h [b]Ratios of **5,7/5,5** and *dr* were determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixtures. [c]Isolated yield [d]$P(OEt)_3$ was used as ligand



218



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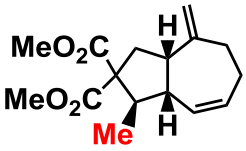
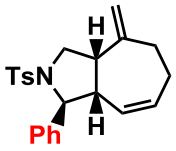
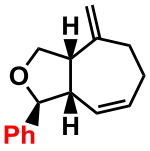


222

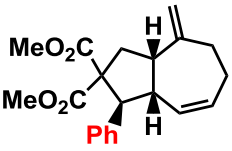
dr, yield ≥19:1, 70% ≥19:1, 58% ≥19:1, 78%



219

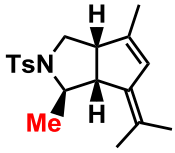


221

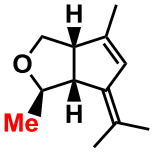


223

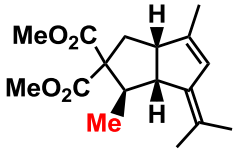
dr, yield ≥19:1, 80% ≥19:1, 72% ≥19:1, 81%



224

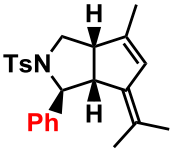


226

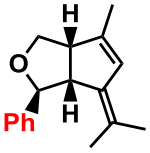


228

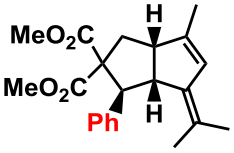
dr, yield ≥19:1, 76% ≥19:1, 67% ≥19:1, 68%



225



227



229

dr, yield ≥19:1, 72% ≥19:1, 60% ≥19:1, 75%

Overall, this study described an efficient procedure for the selective construction of both *cis*-fused five-seven and five-five bicyclic structures in a highly chemo- and diastereoselective manner. These bicyclic motifs represent useful synthons for target directed synthesis. The stereochemistry of some of these bicyclic products were confirmed by ^{3}J ^{1}H-^{1}H coupling constants and nOe correlation between the hydrogen atoms at the ring junction (determined by ^{1}H NMR analysis) and X-ray crystallography (**Figure 10**).

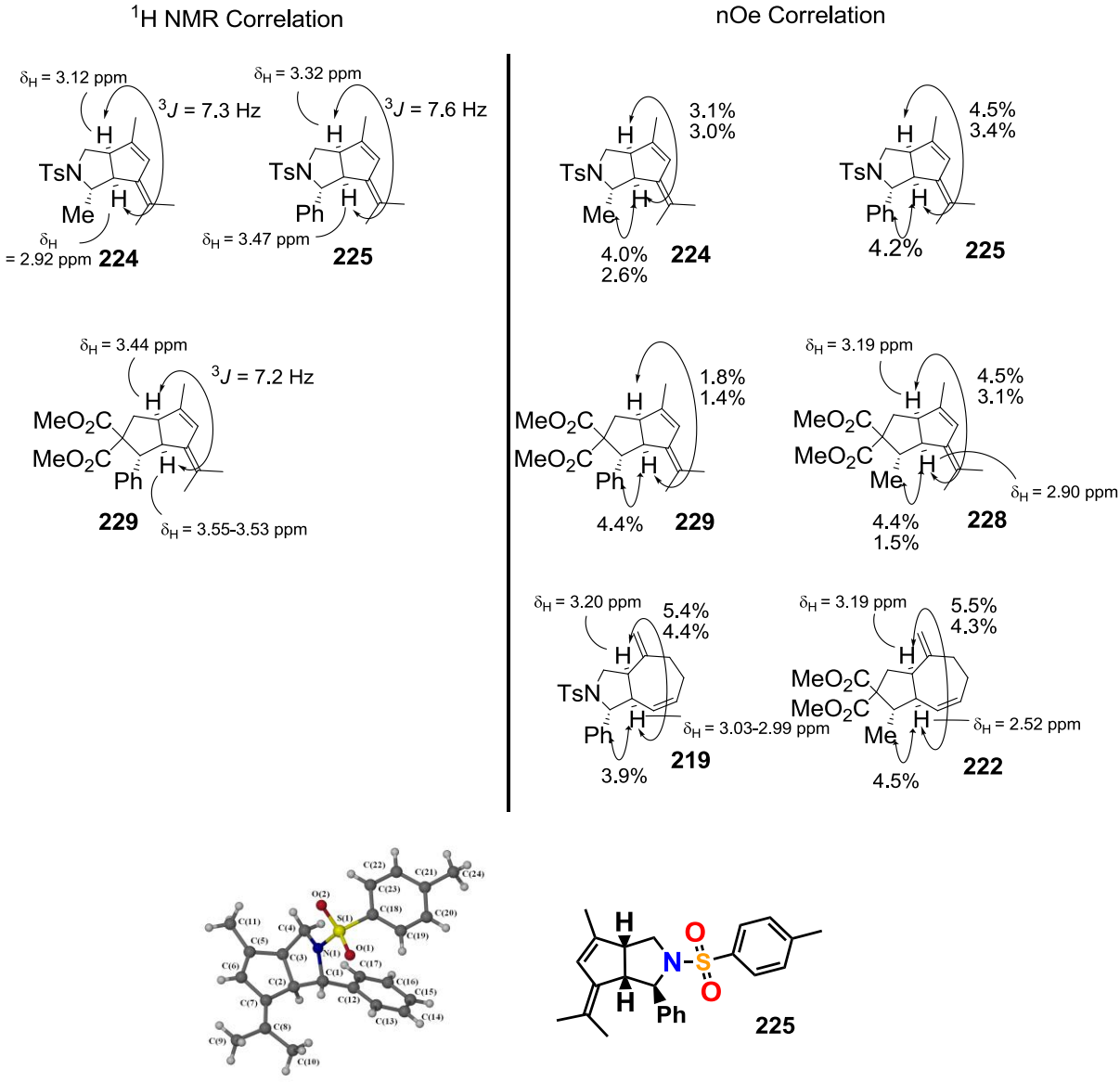


Figure 10: $^{3}J_{H\text{-}H}$ couplings, nOe Correlation and X-ray Crystallography

As shown in Table 5, a *cis*-fused 5,7 bicyclic ring system with three stereocentres is accessible *via* the diastereoselective [4+3] carbocyclisation strategy. We extended the scope of this highly diastereoselctive [4+3] carbocyclisation reaction to substrate (*E*)-**234** with a quaternary centre at the C2-position.

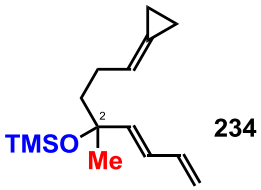
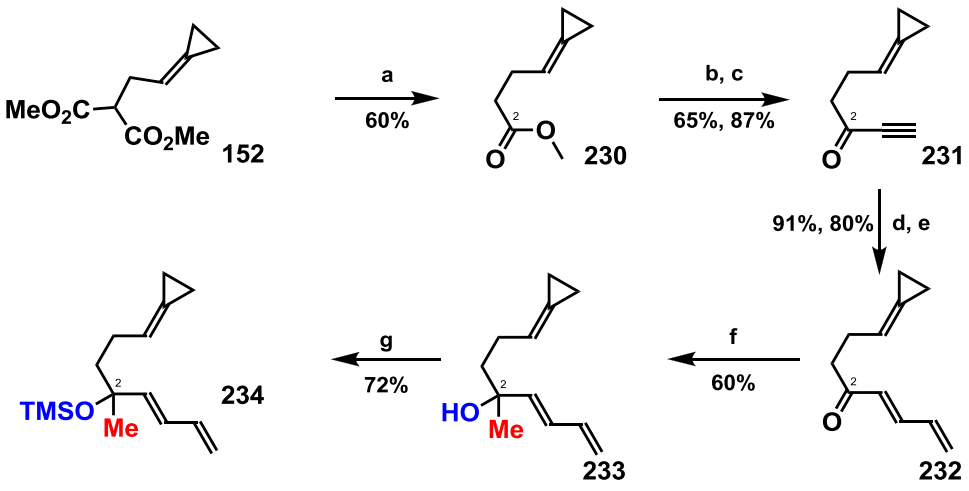


Figure 11: ACP-diene substrate with quaternary centre at the C-2 position

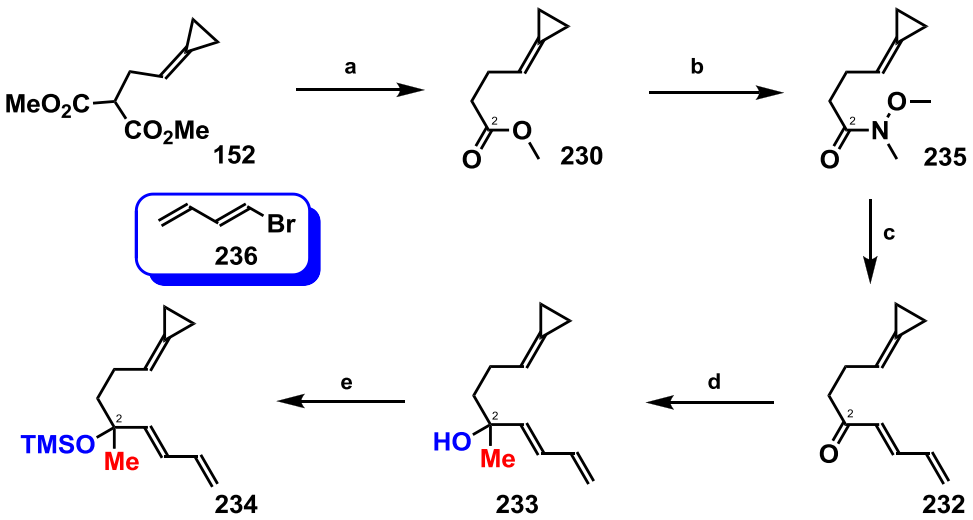
Scheme 57 delineates the eight-step synthesis of substrate **234**. Decarboxylation of **152** at 150 ˚C in DMSO furnished **230** in 60% yield. Treatment of compound **230** with MeONHMe·HCl and isopropylmagnesium chloride (^{i}PrMgCl) afforded the corresponding Weinreb amide which reacted successfully with ethynylmagnesium bromide to generate ynone **231.**[45]



Scheme 57: Preparation of ACP-Diene (*E*)-**234:** Reaction Conditions: (a) LiCl (2 equiv), DMSO, 150 ˚C, 60% (b) *N*,*O*-dimethylhydroxylamine.HCl (1.5 equiv), ^{i}PrMgCl 2 M in THF (3 equiv), –20 ˚C to rt, THF, 65% (c) Ethynylmagnesium chloride (1.5 equiv), THF, –10 ˚C to rt, 87% (d) Acetic acid (200 equiv), NaI (1.3 equiv), *neat*, rt, 91% (e) CuI (1.3 equiv), 5 mol% $Pd(PPh_3)_4$, tributyl(vinyl)stannane (1.3 equiv), DMF, rt, 80%, (*E*/*Z* 12:1) (f) MeMgBr (1.5 equiv), THF, 0 ˚C to rt, 60% (g) Imidazole (2 equiv), HMPT (1.2 equiv), TMSOTf (2 equiv), –20 ˚C to rt, 72%

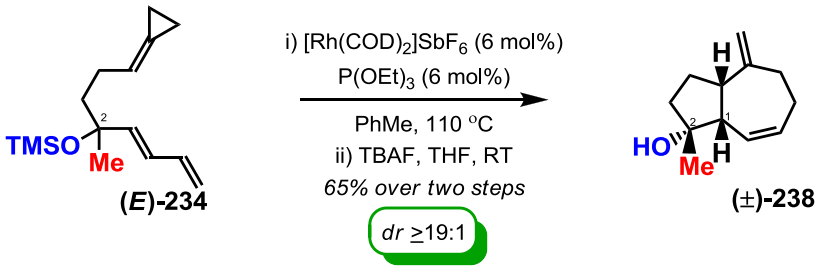
The addition of compound **231** to a light yellow homogeneous solution of sodium iodide in neat acetic acid produced the corresponding *β*-halovinyl ketone. It was observed that the *E*/*Z* ratio was 1:1 after 1 hr (determined by ^{1}H NMR analysis on crude mixture). Interestingly, further stirring in neat acetic acid for 12 h furnished the *β*-halovinyl ketone in *E*/*Z* ≥19:1 in 91% yield.[46] The (*E*)-vinyl iodide was coupled with vinystannane to produce the dienone **232** (*E*/*Z* 12:1) in 80% yield.

The addition of methylmagnesium bromide (MeMgBr) to dienone **232** afforded a tertiary alcohol **233** in 60% yield. Subsequent protection using TMSOTf furnished silyl ether (*E*)-**234** in 72% yield. A more concise synthetic route for (*E*)-**234** is described in **Scheme 58**. Lithiation of commercially available (*E*)-bromobutadiene **236** with *tert*-butyllithium at –78 ˚C in THF generated a vinyllithium species, quenched with Weinreb amide **235** afforded dienone **232** (*E*/*Z* ≥19:1) in 73% yield.[47]



Scheme 58: Alternative route for the preparation of (*E*)-**234:** Reaction Conditions: (a) LiCl (1.5 equiv), DMSO, 150 ˚C, 60% (b) *N*,*O*-dimethylhydroxylamine.HCl (1.5 equiv), ^{i}PrMgCl 2 M in THF (3 equiv), –20 ˚C to RT, THF, 65% (c) ^{t}BuLi 1.6 M in pentane (1.2 equiv)), **236** (1.2equiv), THF, –78 ˚C to rt, 73% (d) MeMgBr (1.5 equiv), THF, 0 ˚C to RT, 60% (e) Imidazole (2 equiv), HMPT (1.2 equiv), TMSOTf (2 equiv), –20 ˚C to rt, 72%

The ACP-diene substrate (*E*)-**234** underwent the [4+3] carbocyclisation reaction successfully. Subjecting (*E*)-**234** to the cationic rhodium catalytic system, $[Rh(COD)_2]SbF_6$ (6 mol%) and triethylphosphite (6 mol%), afforded the 5,7-bicyclic product **237** in 71% yield (5,7:5,5 ≥19:1) with excellent diastereocontrol (≥19:1; determined ^1H NMR analysis). Protodesilylation furnished 1-*epi*-dictamnol (±)-**238** in 60% yield (**Scheme 59**).



Scheme 59: Diastereoselective [4+3] carbocyclisation reaction of of (*E*)-**234**

The excellent diastereoselectivity of this reaction reaffirms the results obtained in Table 5. The diastereoselectivity was determined by ^1H NMR analysis of the crude mixture and the stereochemistry was determined by nOe analysis of the pure compound (**Figure 12**).

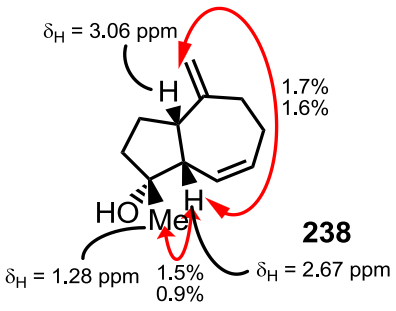
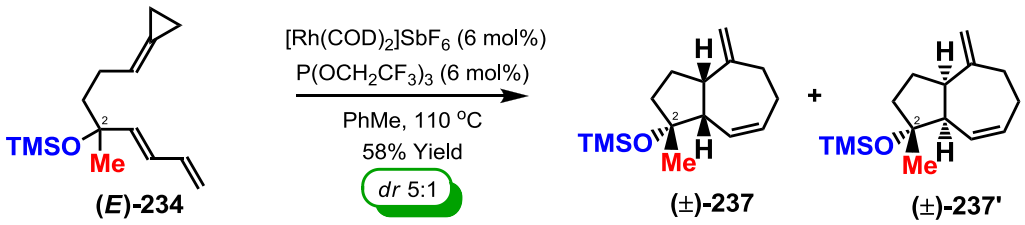


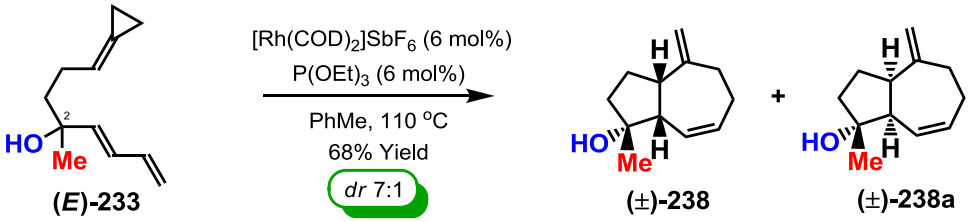
Figure 12: 1D nOe of **238** (Proof of Stereochemistry)

Further to our investigation, employing a strongly electron withdrawing phosphite $P(OCH_2CF_3)_3$ as a ligand, 5,7-bicyclic products **237** and **237'** was obtained as a mixture of inseparable diastereoisomers in 5:1 ratio (**Scheme 60**).



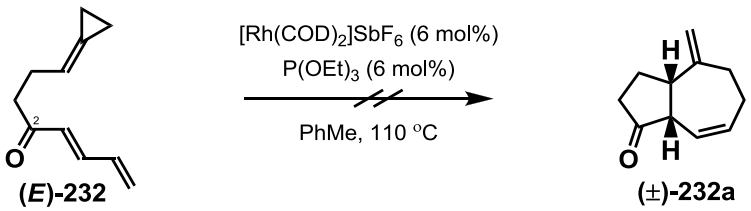
Scheme 60: Diastereoselective [4+3] carbocyclisation reaction of (*E*)-**234**

Additionally, subjecting substrate **233** to 6 mol% $[Rh(COD)_2]SbF_6$ and 6 mol% of $P(OEt)_3$ furnished the corresponding inseparable diastereomeric mixtures of 5,7-cycloadducts **238** and **238a** in 7:1 ratio (**Scheme 61**).



Scheme 61: Diastereoselective [4+3] carbocyclisation reaction of (*E*)-**233**

Substrate **232** failed to undergo carbocyclisation reaction under similar reaction conditions (**Scheme 62**). A plausible rationale for this observation is probably due to the difference in the electrophilicity of dienone and dienes.[48,49]

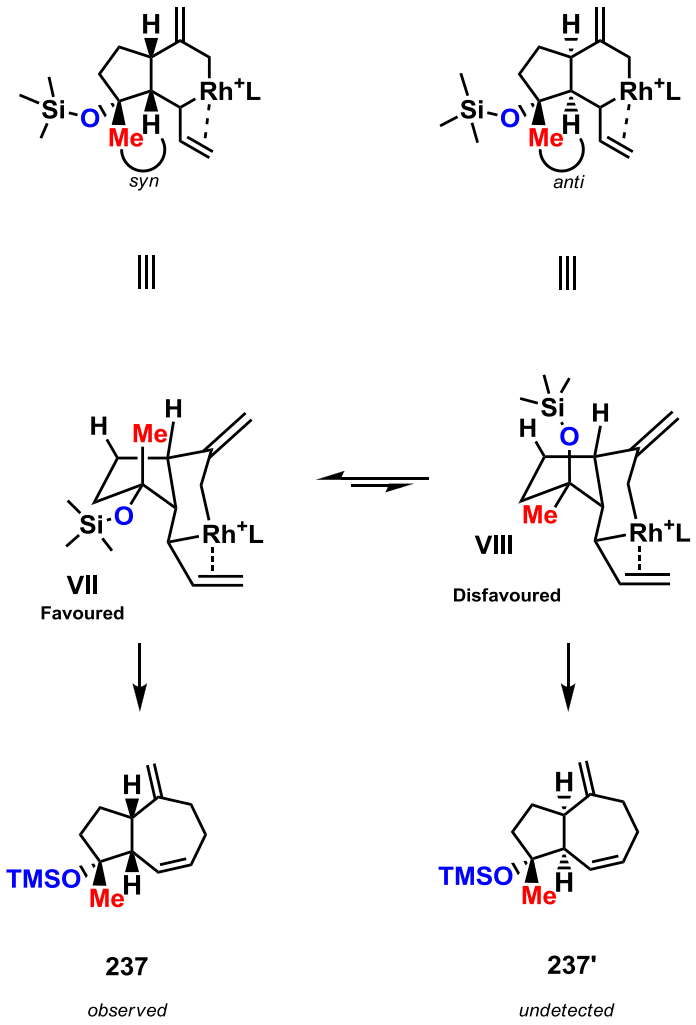


(*E*)-232 (±)-232a

Scheme 62: Attempted [4+3] carbocyclisation reaction of (*E*)-**232**

A plausible mechanistic rationale for the excellent diastereoselectivity observed in **scheme 59** is descrbied in **scheme 63**. The $OSi(CH_3)_3$ group is larger in size than CH_3, however, positioning the CH_3-substituent in the axial position is disfavoured.[50] This is due to the A-value of CH_3, 1.7 kcal/mol. The A-value for $OSi(CH_3)_3$ is 0.74 kcal/mol.[51] A-values are used to predict substituents steric effect and not the physical size.

Additionally, the hydrogen bond interaction could possibly stabilised conformation **VII.** The carbon-silicon bond (C-Si bond 1.89Å) is longer than carbon-carbon bond;[52] this means less interaction of trimethylsilyl with neighbouring substituents. These factors presumably enabled the conformer **VII** to proceed to the observed 5,7-bicyclic ring **237** with a high degree of diastereocontrol.



Scheme 63: Rationale for the observed diastereoselectivity for 5,7-bicyclic ring **237**

2.6 Conclusion

In conclusion, we have developed a general and highly diastereoselective cationic rhodium(I)-catalysed [3+2] and [4+3] carbocyclisation reactions of ACP tethered with dienes. This work demonstrates the importance of counterions in facilitating the selective construction of 5,7-bicyclic rings and the detrimental effect of residual silver chloride salt on the yield of the reaction. Furthermore, we provided compelling evidence for the *cis* fusion of the bicyclic systems.

In addition, this study highlighted the dramatic switch in selectivity from 5,7-bicyclic ring to 5,5-bicyclic ring through the modification of the cationic rhodium(I)-complex with triphenylphosphine. The ligand-substrate interaction (π/π-stacking) presumably prevented the facile *σ*-*π*-*σ* isomerisation, causing the premature reductive elimination to occur to produce the 5,5-bicyclic ring as the major product. Also, the placement of substitution (*i.e.* methyl group) at a specific position on the diene led to a sharp decrease in the selectivity for the 5,7-bicyclic ring. The methyl group presumably introduced 1,2-allylic strain, obstructing the *σ*-*π*-*σ* isomerisation in the process.

Our investigation showed that the synergistic effect of the Me-group and triphenylphosphine enabled the selective construction of the 5,5-bicyclic ring.

Finally, the limitation of the diastereoselective [4+3] carbocyclicsation reaction was tested in the synthesis of 1-*epi*-dictamnol **238**. Overall, this methodology proved to be a convenient and predictable strategy for the selective construction of *cis*-fused 5,5-bicyclic and *cis*-fused 5,7-bicyclic systems.

2.7 General Information

All reactions were carried out under ambient atmosphere (except from where temperature is specified) of argon in a balloon. Commercially available reagents were purchased from *Aldrich*, *Alfa-Aesar*, *Acros* and were used as received, unless otherwise noted. Magnesium sulfate (or sodium sulfate) was used in its anhydrous form as drying agents. All solvents used were HPLC (High Performance Liquid Chromatography) graded and their anhydrous form was obtained by passing degassed solvents through two activated alumina columns in a solvent purification system (*PureSolv MD-6* of *Innovative Technology Inc.*). All compounds were purified by flash chromatography using HPLC graded petroleum ether (boiling point 30-40 ˚C) and silica gel (60 Å pore size; 40-63 μm diameter, from *FluoroChem*) and gave spectroscopic data consistent with being ≥95% the assigned structure. Analytical thin layer chromatography (TLC) was performed on pre-coated 0.25 mm thick silica gel 60-F_{254} plates (*Whatman PE SIL G/UV*); Ultra-Violet light and by treatment with a $KMnO_4$, *p*-anisaldehyde and Hanessian's dip, followed by heating. The melting points (uncorrected) were obtained from a *Griffin Melting Point Instrument*. Optical rotations ($[\alpha]_{20}$) were measured on *a Perkin-Elmer Model 343 plus* polarimeter with a sodium lamp (D line, 589 nm) at ambient temperature (indicated in ˚C as superscript) using a 1 mL quartz cell of 100 mm length; solution concentration (*c*) are given in g/100 mL. IR spectra were recorded on a *Perkin-Elmer FT-IR (Fourier transform infra-red) Spectrum 100* (ATR) spectrometer; wavenumbers (ν) are given in cm^{-1}; and the abbreviations w (weak, < 25%), m (medium, 25-50%), s (strong, 51-75%), (very strong, > 75%) and br (broad) are used to describe the relative intensities

of the IR absorbance bands. Mass spectra were obtained through the chemistry department mass spectrometry service, University of Liverpool and EPSRC national mass spectrometry service centre (Swansea, UK). High resolution chemical ionization (CI) and electrospray ionisation (ESI) mass spectra were recorded on a *Fisons Trio-1000 or LTQ Orbitrap*, and *Micromass LTC* mass spectrometers, respectively. ^{1}H NMR and ^{13}C NMR spectra were recorded on a *Bruker Avance DRX-500* spectrometer in $CDCl_3$ at ambient temperature; chemical shifts (δ) are given in ppm and calibrated using the signal of residual undeuterated solvent as internal reference (δ_H = 7.26 ppm and δ_C = 77.16 ppm). ^{1}H NMR data are reported as follows: chemical shift (multiplicity, 2nd order spin system if available, coupling constant, and integration). Coupling constants (*J*) are reported in Hz and apparent splitting patterns are designated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad), app. (apparent) and the appropriate combinations. ^{13}C NMR spectra with complete proton decoupling were described with the aid of an Attached Proton Test (APT) sequence, separating methylene and quaternary carbons (e, even), from methyl and methine (o, odd). All glassware's were flamed-dried and cooled under vacuum before use.

During the course of optimising the carbocyclisation reaction of ACP-diene **133**, the yields and selectivities of 5,7-bicyclic ring **133**, 5,5-bicyclic ring **134** and the side product **135** were calculated using an HPLC assay. The assay was set-up as follows; 10 mg, 20 mg, 30 mg, 40 mg and 50 mg of **133** were dissolved in accurate amount of hexame (1 mL) in separate vials. Specific amount of TsCl (15 mg), employed as a standard, was added to each vial. Each sample was run three times. An achiral column, Agilent Zorbax RX-SIL, eluting with hexane/isopropanol, 99:1 was used.

Each HPLC report produced a value for **133**. This value corresponds to the area of **133** which increases as mass increases, while the value of TsCl remained constant. This value was inputed into a Microsoft excel spreadsheet with a pre-existing formula to generate the graph shown below.

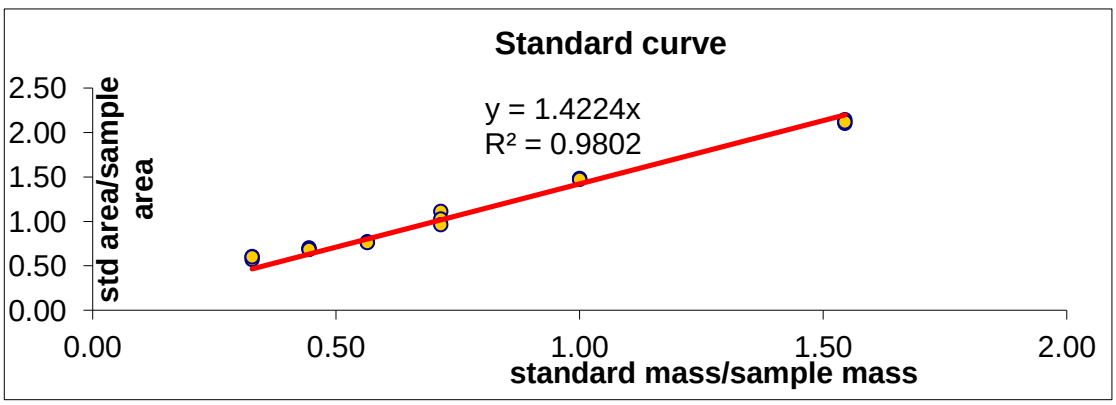
The HPLC yield was calculated using this formula;

$$\text{HPLC Yield} = \frac{\text{Product mass}}{\text{Substrate mass}} \times 100$$

The selectivity of the bicycloheptadiene **133** was calculated using this formula;

$$\text{Selectivity} = \frac{A}{(A \times B \times C)}$$

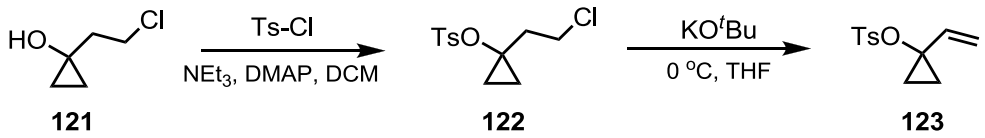
A: Area of **133**; B: Area of **134**; C: Area of **135**



In a separate vial, compounds **133**, **134**, **135**, **127** and TsCl were dissolved in hexane (1 mL). This mixture was run in HPLC to obtain separation and retention time for each compound. This exercise lasted for two months. This is due to difficulty in finding the appropriate eluent to obtain separation, hexane:isopropanol (99:1) proved optimal. For every carbocyclisation reaction, after completion, 15 mg of TsCl was always added then the mixture was concentrated *in vacuo*. A small portion of the crude mixture was dissolved in hexane (1 mL) and run using HPLC. The areas of **133**, **134** and **135** were inputed into the Microsoft excel spreadsheet, which then calculate the yields and selectvities specifically for **133**, using the aforementioned formula.

2.8 Experimental Section and Spectra Data

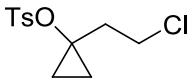
2.8.1 Experimental Procedure for the Preparation of 1-Vinylcyclopropyl 4-methylbenzenesulfonate 123



121 **122** **123**

Triethylamine (36.7 mL, 263 mmol) and dimethylaminopyridine (29.20 g, 239 mmol) were added to a solution of 1-(2-chloroethyl)cyclopropanol[1] **121** (28.85 g, 239 mmol) in DCM (1 L). The resulting colourless mixture was stirred at room temperature for 15 min, followed by the addition of 4-toluenesulfonyl chloride (52.50 g, 275 mmol). The bright-yellow homogenous solution was stirred overnight at room temperature (t.l.c. control). The reaction mixture solvent was reduced to minimum volume, quenched with water (200 mL) and partitioned with diethyl ether (300 mL). The yellow aqueous layer was neutralised with saturated aqueous solution of NH_4Cl (150 mL) then extracted with diethyl ether twice (2 x 150 mL). The combined organics were washed with water (200 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5-10% diethyl ether/petroleum ether) furnished 1-(2-chloroethyl)cyclopropyl 4-methylbenzenesulfonate **122** as a colourless oil (59.15 g, 215 mmol, 90%).

[1] Kulinkovich, O. G.; Kozyrkov. Y. Y.; Bekish, A. V.; Matiushenkov, E. A.; Lysenko, I. L. *Synthesis* **2005**, *10*, 1713.



1-(2-Chloroethyl)cyclopropyl 4-methylbenzenesulfonate 122.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 3.69 (t, *J* = 7.1 Hz, 2H), 2.44 (s, 3H), 2.23 (t, *J* = 7.1 Hz, 2H), 1.13-1.11 (m, 2H), 0.73-0.70 (m, 2H).

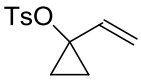
^{13}C NMR (125 MHz, $CDCl_3$) δ 145.10 (e), 134.98 (e), 130.00 (o), 127.64 (o), 64.54 (e), 40.78 (e), 39.22 (e), 21.80 (o), 11.59 (e).

IR (Neat) 2963 (w), 1596 (w), 1454 (w), 1359 (s), 1227 (m), 1170 (s), 1093 (m), 1034 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$): calcd. for $C_{12}H_{15}O_3ClSNa$ 297.0317, found 297.0328.

Potassium *tert*-butoxide (53.10 g, 474 mmol) was added at once to a solution of 1-(2-chloroethyl)cyclopropyl 4-methylbenzenesulfonate **122** (59.15 g, 215 mmol) in THF (1 L) at 0 ˚C. The resulting pale-red suspension was stirred at same temperature for 1 h. The resulting brown-red suspension was diluted with water (150 mL) then partitioned with diethyl ether (250 mL). The aqueous layer was neutralised with saturated aqueous $NaHCO_3$ (100 mL), then re-extracted with diethyl ether twice (2 x 150 mL). The combined organics were washed with water (150 mL), followed by brine (150 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10-20% diethyl ether/petroleum ether) furnished 1-vinylcyclopropyl 4-methylbenzenesulfonate **123** as a light green-yellow oil (37.40 g, 157 mmol, 73%).

1-Vinylcyclopropyl 4-methylbenzenesulfonate 123.



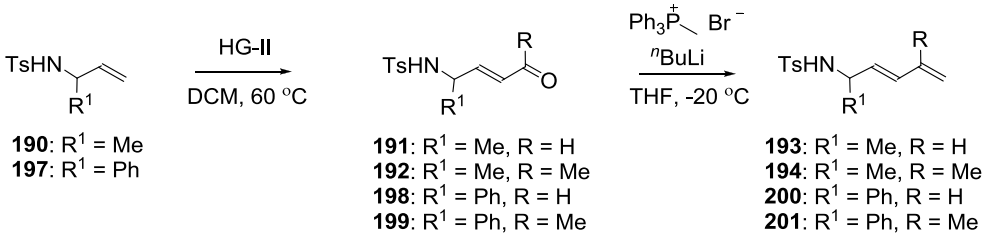
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2 H), 5.88 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.10 (d, *J* = 17.1 Hz, 1H), 5.01 (d, *J* = 11.0 Hz, 2H), 2.44 (s, 3H), 1.36-1.33 (m, 2H), 0.93-0.90 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.84 (e), 136.59 (o), 135.01 (e), 129.98 (o), 127.92 (o), 113.52 (e), 65.48 (e), 21.74 (o), 14.04 (e).

IR (Neat) 2925 (w), 1645 (w), 1598 (w), 1495 (w), 1448 (w), 1421 (w), 1361 (s), 1167 (s), 1095 (s), 1026 (m) cm^{-1}.

HRMS (ESI**,** $[M+NH_4]^+$): calcd. for $C_{12}H_{18}O_3NS$ 256.1002, found 256.1003.

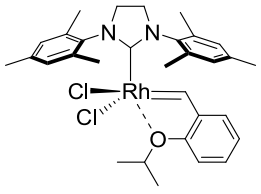
2.8.2 Representative Experimental Procedure for the Preparation of Nitrogen-atom tethered ACP-Dienes (*E*)-127, (*E*)-132, (*E*)-165, (*E*)-166, (*E*)-171, (*E*)-172



190: R^1 = Me
197: R^1 = Ph

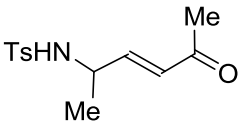
191: R^1 = Me, R = H
192: R^1 = Me, R = Me
198: R^1 = Ph, R = H
199: R^1 = Ph, R = Me

193: R^1 = Me, R = H
194: R^1 = Me, R = Me
200: R^1 = Ph, R = H
201: R^1 = Ph, R = Me



HG-II

A solution of compound **190**[2] (2.00 g, 8.88 mmol) in DCM (15 mL) was added to the green solution of Hoveyda-Grubbs II (0.056 g, 0.089 mmol) in DCM (20 mL) at room temperature. Subsequently, methyl vinyl ketone (3.60 mL, 44.4 mmol) in DCM (10 mL) was added. The resulting mixture was heated up to 60 ˚C and left to stir for 3 h. After the reaction had reached completion (t.l.c. control), the resulting orange-red solution was allowed to cool to room temperature and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% diethyl ether/petroleum ether) afforded (*E*)-**192** as a pale brown oil (2.31 g, 8.64 mmol, 97%).



(*E*)-4-methyl-*N*-(5-oxohexa-3-en-2-yl)benzenesulfonamide 192.

Stereochemistry: *E/Z* = ≥19:1 (^{1}H NMR analysis)

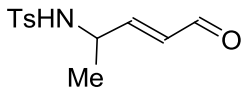
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (app. d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.46 (dd, *J* = 16.0, 8.0 Hz, 1H), 6.00 (d, *J* = 16.0 Hz, 1H), 5.12 (d, *J* = 7.7 Hz, 1H), 4.03 (ddq, *J* = 8.0, 7.7, 6.9 Hz, 1H), 2.40 (s, 3H), 2.11 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 3H),

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.27 (e), 146.64 (o), 143.90 (e), 137.57 (e), 130.08 (o), 129.90 (o), 127.31 (o), 50.56 (o), 27.32 (o), 21.64 (o), 21.13 (o).

IR (Neat) 3137 (m), 2978 (w), 2886 (w), 1663 (m), 1640 (m), 1597 (w), 1494 (w), 1466 (w), 1438 (w), 1361 (w), 1329 (s), 1266 (s), 1159 (s), 1146 (s), 1091 (s), 1068 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{17}NO_3NaS$ 290.0827, found 290.0825.

[2] References for compounds **190** and **197** see; (a) Garzon, C.; Attolini, M.; Maffei, M. *Eur. J. Org. Chem.* **2013**, 3653–3657 (b) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Tamioka, K. *J. Org. Chem.* **2004**, *69*, 1531–1534 respectively.



(*E*)-4-methyl-*N*-(5-oxopent-3-en-2-yl)benzenesulfonamide 191.

Colour and State: Yellow oil

Stereochemistry: *E/Z* = ≥19:1 (^{1}H NMR analysis)

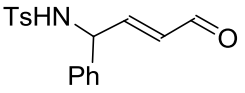
Compound (*E*)-**191** (99% yield on 4.44 mmol scale) was prepared according to the experimental procedure as described for the synthesis of compound (*E*)-**192**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 6.57 (dd, *J* = 15.7, 7.1 Hz, 1H), 6.05 (dd, *J* = 15.7, 7.8 Hz, 1H), 5.12 (d, *J* = 7.5 Hz, 1H), 4.12 (ddq, *J* = 7.8, 7.5, 6.9 Hz, 1H), 2.41 (s, 3H), 1.24 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 193.28 (e), 156.56 (o), 144.15 (e), 137.22 (e), 131.55 (o), 129.99 (o), 127.27 (o), 50.47 (o), 21.70 (o), 20.92 (o).

IR (Neat) 3216 (br), 1668 (s), 1598 (w), 1435 (w), 1435 (w), 1325 (m), 1303 (s), 1159 (s), 1141 (s), 1091 (s), 1020 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{12}H_{15}NO_3NaS$ 276.0671, found 276.0671.



(*E*)-4-methyl-*N*-(4-oxo-1-phenylbut-2-enyl)benzenesulfonamide 198.

Colour and State: Light brown oil

Stereochemistry: *E/Z* = ≥19:1 (^{1}H NMR analysis)

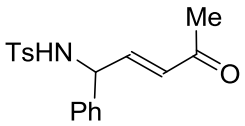
Compound (*E*)-**198** (92% yield on 3.48 mmol scale) was prepared according to the experimental procedure as described for the synthesis of compound (*E*)-**192**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.22-7.27 (m, 5H), 7.07-7.05 (m, 2H), 6.77 (dd, *J* = 15.6, 7.0 Hz, 1H), 6.13 (ddd, *J* = 15.6, 7.7, 3.5 Hz, 1H), 5.25 (d, *J* = 6.9 Hz, 1H), 5.11 (app. t, *J* = 6.2 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 192.96 (e), 154.26 (e), 144.13 (e), 137.25 (e), 136.91 (e), 132.51 (o), 129.86 (o), 129.37 (o), 128.92 (o), 127.35 (o), 127.23 (o), 58.87 (o), 21.70 (o).

IR (Neat) 3265 (br), 2829 (w), 1685 (s), 1598 (m), 1494 (w), 1458 (w), 1443 (w), 1349 (w), 1326 (m), 1306 (m), 1152 (s), 1135 (m), 1089 (m), 1078 (m), 1040 (m), 1022 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{17}NO_3NaS$ 315.3872, found 315.3870.



(*E*)-4-methyl-*N*-(4-oxo-1-phenylpent-2-enyl)benzenesulfonamide 199.

Colour and State: Yellow oil

Stereochemistry: *E/Z* = ≥19:1 (^{1}H NMR analysis)

Compound (*E*)-**199** (60% yield on 2.44 mmol scale) was prepared according to the experimental procedure described for the synthesis of compound (*E*)-**192**.

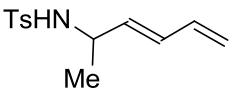
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.26-7.21 (m, 5H), 7.06-7.04 (m, 2H), 6.68 (dd, *J* = 15.8, 7.2 Hz, 1H), 6.10 (app. d, *J* = 15.9 Hz, 1H), 5.24 (d, *J* = 7.1 Hz, 1H), 5.03 (app. t, *J* = 6.4 Hz, 1H), 2.39 (s, 3H), 2.15 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.01 (e), 144.49 (o), 143.91 (e), 137.75 (e), 137.16 (e), 131.03 (o), 129.77 (o), 129.21 (o), 128.67 (o), 127.37 (o), 127.19 (o), 58.84 (o), 27.63 (o), 21.67 (o).

IR (Neat) 3257 (w), 1664 (s), 1623 (m), 1598 (w), 1494 (w), 1455 (m), 1328 (s), 1309 (m), 1254 (w), 1162 (vs) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for, $C_{18}H_{20}NO_3S$ 329.4130 found 329.4128.

^{n}BuLi (0.62 mL, 2.5 M in Hexane, 1.54 mmol) was slowly added to a suspension of methyltriphenylphosphonium bromide salt (0.55 g, 1.54 mmol) in THF (10 mL) at –20 °C. The resulting yellow mixture was stirred at –20 °C for 3 h, followed by the slow addition of a solution of compound (*E*)-**191** (0.19 g, 0.77 mmol) in THF (6 mL). The resulting mixture was warmed up to room temperature and stirred for further 1 h. Afterwards, the mixture was quenched with saturated solution of NH_4Cl (10 mL) and partitioned with diethyl ether (15 mL). The organic layer was washed with water (10 mL), followed by brine (10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% diethyl ether/petroleum ether) afforded (*E*)-**193** as a yellow oil (0.14 g, 0.55 mmol, 71%).



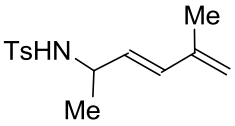
(*E*)-*N*-(hexa-3,5-dien-2-yl)-4-methylbenzenesulfonamide 193.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.08 (dt, *J* = 16.8, 7.7 Hz, 1H), 5.93 (dd, *J* = 15.1, 8.5 Hz, 1H), 5.38 (dd, *J* = 15.2, 7.2 Hz, 1H), 5.22 (d, *J* = 7.7 Hz, 1H), 5.05 (d, *J* = 16.8 Hz, 1H), 4.99 (d, *J* = 5.1 Hz, 1H), 3.89 (ddq, *J* = 8.5, 6.8, 5.1 Hz, 1H), 2.37 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.25 (e), 137.95 (e), 135.99 (o), 134.26 (o), 131.12 (o), 129.60 (o), 127.26 (o), 117.73 (e), 51.18 (o), 21.71 (o), 21.54 (o).

IR (Neat) 3281 (m), 1660 (w), 1596 (m), 1494 (w), 1456 (w), 1422 (m), 1322 (s), 1287 (s), 1155 (vs), 1138 (vs) 1090 (s), 1054 (s), 1009 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{13}H_{17}NO_2NaS$ 274.0887, found 274.0887.



(*E*)-4-methyl-*N*-(5-methylhexa-3,5-dien-2-yl)benzenesulfonamide 194.

Colour and State: Light yellow oil

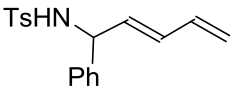
Compound (*E*)-**194** (83% yield on 8.45 mmol scale) was prepared according to the experimental procedure described for the synthesis of compound (*E*)-**193**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (app. d, *J* = 8.2 Hz, 2H), 7.27-7.26 (m, 2H), 6.04 (d, *J* = 15.7 Hz, 1H), 5.26 (app. d, *J* = 15.7, 7.4 Hz, 1H), 4.92 (s, 1H), 4.86 (s, 1H), 4.40 (app. d, *J* = 7.4 Hz, 1H), 3.99 (dq, *J* = 7.4, 6.7 Hz, 1H), 2.40 (s, 3H), 1.62 (s, 3H), 1.20 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.19 (e), 141.04 (e), 138.09 (e), 133.28 (o), 130.19 (o), 129.53 (o), 127.31 (o), 116.98 (e), 51.68 (o), 21.91 (o), 21.52 (o), 18.27 (o).

IR (Neat) 3289 (m), 2983 (w), 1812 (w), 1610 (w), 1596 (w), 1495 (w), 1421 (m), 1373 (m), 1318 (s), 1302 (s), 1287 (s), 1146 (vs), 1089 (s), 1065 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{14}H_{19}NO_2NaS$ 288.1034, found 288.1032.



(*E*)-4-methyl-*N*-(1-phenylpenta-2,4-dienyl)benzenesulfonamide 200.

Colour and State: Colourless oil

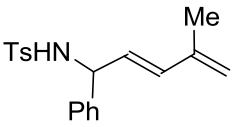
Compound (*E*)-**200** (72% yield on 2.06 mmol scale) was prepared according to the experimental procedure as described for the synthesis of compound (*E*)-**193**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (app. d, *J* = 8.3 Hz, 2H), 7.22-7.18 (m, 5H), 7.12-7.10 (m, 2H), 6.18 (dt, *J* = 13.6, 7.5 Hz, 1H), 5.99 (dd, *J* = 15.1, 8.5 Hz, 1H), 5.65-5.60 (m, 1H), 5.10 (d, *J* = 16.9 Hz, 1H), 5.07 (d, 10.1 Hz, 1H), 4.97-4.96 (m, 2H), 2.38 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.40 (e), 139.63 (e), 137.66 (e), 135.78 (o), 132.96 (o), 132.26 (o), 129.55 (o), 128.80 (o), 127.94 (o), 127.41 (o), 127.14 (o), 118.66 (e), 59.44 (o), 21.64 (o).

IR (Neat) 3274 (m), 1652 (w), 1596 (w), 1495 (w), 1455 (m), 1436 (m), 1334 (m), 1321 (s), 1289 (m), 1154 (vs), 1091 (vs), 1073 (s), 1006 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{19}NO_2NaS$ 336.1034, found 336.1045.



(*E*)-4-methyl-*N*-(4-methyl-1-phenylpenta-2,4-dienyl)benzenesulfonamide 201.

Colour and State: Colourless oil

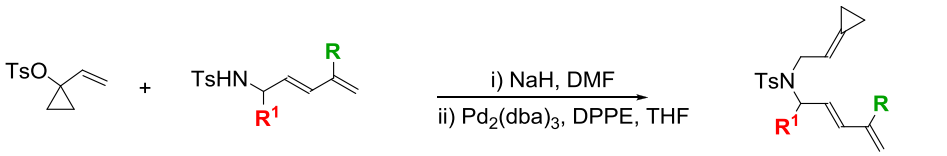
Compound (*E*)-**201** (67% yield on 0.57 mmol scale) was prepared according to the experimental procedure as described for the synthesis of compound (*E*)-**193**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (app. d, *J* = 8.2 Hz, 2H), 7.23-7.14 (m, 7H), 6.06 (d, *J* = 15.6 Hz, 1H), 5.51 (dd, *J* = 15.6, 7.5 Hz, 1H), 5.39 (d, *J* = 7.4 Hz, 1H), 4.99 (app. t, *J* = 7.1 Hz, 1H), 4.92 (s, 1H), 4.84 (s, 1H), 2.36 (s, 3H), 1.64 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.22 (e), 140.94 (e), 139.89 (e), 137.76 (e), 134.95 (o), 129.44 (o), 128.68 (o), 128.27 (o), 127.74 (o), 127.37 (o), 127.07 (o), 117.72 (e), 60.52 (o), 21.55 (o), 18.41 (o).

IR (Neat) 3270 (m), 2922 (w), 1608 (w), 1597 (w), 1495 (w), 1454 (m), 1411(m), 1318 (s), 1306 (s), 1153 (vs), 1092 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{21}NO_2NaS$ 350.1191, found 350.1175.

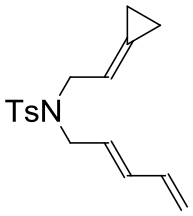


123

126: R^1 = H, R = H
131: R^1 = H, R = Me
193: R^1 = Me, R = H
194: R^1 = Me, R = Me
200: R^1 = Ph, R = H
201: R^1 = Ph, R = Me

127: R^1 = H, R = H
132: R^1 = H, R = Me
165: R^1 = Me, R = H
171: R^1 = Me, R = Me
166: R^1 = Ph, R = H
172: R^1 = Ph, R = Me

A solution of (*E*)-**126** (1.13 g, 4.80 mmol) in DMF (8 mL) was added to a suspension of sodium hydride (0.19 g, 60% in mineral oil, 4.80 mmol) in DMF (12 mL) at room temperature. The resulting mixture was stirred for 1 h. In a separate vessel, $Pd_2(dba)_3$ (0.043 g, 0.047 mmol) and DPPE (0.035 g, 0.087 mmol) were dissolved in THF (20 mL), stirred for 5 min, then a solution of 1-vinylcyclopropyl 4-methylbenzenesulfonate **123** (1.04 g, 4.36 mmol) in THF (10 mL) was added. The reaction was stirred until the dark red solution turned green (*ca.* 30 min). The electrophile (green solution) was then transferred *via* Teflon® cannula to the vessel containing the nucleophile (solution of NaH and **126**). The resulting mixture was allowed to stir at room temperature for 4 h (t.l.c. control), quenched with water (30 mL) then partitioned with diethyl ether (50 mL). The aqueous layer was diluted with 1 M HCl (20 mL), and then re-extracted with diethyl ether (60 mL). The combined organic layers were washed with brine (35 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% diethyl ether/petroleum ether) afforded (*E*)-**127** as a yellow oil (1.27 g, 4.20 mmol, 96%).



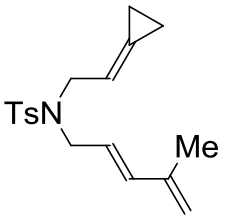
(*E*)-*N*-(2-Cyclopropylideneethyl)-4-methyl-*N*-(penta-2,4-dienyl)benzenesulfonamide 127.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.23 (dt, *J* = 16.9, 10.3 Hz, 1H), 6.01 (dd, *J* = 15.2, 10.5 Hz, 1H), 5.57 (tquin, *J* = 6.8, 2.2 Hz, 1H), 5.47 (dd, *J* = 15.2, 6.7 Hz, 1H), 5.13 (d, *J* = 16.9 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 3.92 (d, *J* = 6.8 Hz, 2H), 3.81 (d, *J* = 6.7 Hz, 2H), 2.42 (s, 3H), 1.07-1.03 (m, 2H), 0.98-0.94 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.24 (e), 137.60 (e), 135.05 (o), 134.46 (o), 129.75 (o), 128.27 (o), 127.51 (e), 127.30 (o), 117.88 (e), 112.78 (o), 48.63 (e), 48.42 (e), 21.66 (o), 2.60 (e), 1.96 (e).

IR (Neat): 2982 (w), 2922 (w), 1599 (w), 1494 (w), 1440 (w), 1336 (s), 1304 (m), 1155 (s), 1094 (m), 1004 (m) cm^{-1}.

HRMS (ESI**,** $[M+Na]^+$): calcd for $C_{17}H_{21}NO_2NaS$ 326.1186, found 326.1191.



(*E*)-*N*-(2-Cyclopropylideneethyl)-4-methyl-*N*-(4-methylpenta-2,4-dienyl)benzenesulfonamide 132.

Colour and State: Colourless oil.

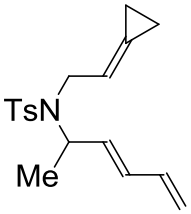
Compound (*E*)-**132** (92% yield on 1.30 mmol scale) was prepared according to the representative experimental procedure as described for compound (*E*)-**127**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.07 (d, *J* = 15.6 Hz, 1H), 5.58 (tquin, *J* = 6.7, 2.1 Hz, 1H), 5.39 (dt, *J* = 15.6, 6.7 Hz, 1H), 4.93 (s, 1H), 4.87 (s, 1H), 3.93 (d, *J* = 6.7 Hz, 2H), 3.84 (d, *J* = 6.7 Hz, 2H), 2.41 (s, 3H), 1.71 (s, 3H), 1.05-1.02 (m, 2H), 0.98-0.94 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) 143.19 (e), 141.28 (e), 137.79 (e), 136.52 (o), 129.71 (o), 127.37 (e), 127.33 (o), 124.18 (o), 116.97 (e), 112.96 (o), 49.03 (e), 48.45 (e), 21.60 (o), 18.52 (o), 2.59 (e), 1.96 (e).

IR (Neat) 2981 (w), 1610 (w), 1598 (w), 1494 (w), 1439 (m), 1337 (s), 1157 (s), 1089 (m), 1033 (w), 1011 (w) cm^{-1}.

HRMS (ESI, $[M+Na]^+$): calcd for $C_{18}H_{23}NO_2NaS$ 340.1347, found 340.1347.



(*E*)-*N*-(2-Cyclopropylideneethyl)-*N*-(hexa-3,5-dien-2-yl)-4-methylbenzenesulfonamide 165.

Colour and State: Yellow oil.

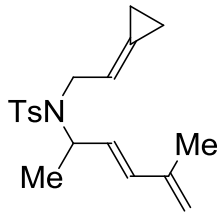
Compound (*E*)-**165** (79% yield on 1.60 mmol scale) was prepared according to the representative experimental procedure as described for compound (*E*)-**127**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.19 (dt, *J* = 16.9, 10.2 Hz, 1H), 5.96 (dd, *J* = 15.4, 10.3 Hz, 1H), 5.76 (tquin, *J* = 6.6, 2.0 Hz, 1H), 5.49 (dd, *J* = 15.5, 5.5 Hz, 1H), 5.12 (d, *J* = 17.0 Hz, 1H), 5.05 (d, *J* = 10.1 Hz, 1H), 4.61 (dq, *J* = 6.9, 5.5 Hz, 1H), 3.93 (ddt, A of $ABXY_2$, J_{AB} = 15.6 Hz, J_{AX} = 6.6 Hz, J_{AY} = 1.1 Hz, 1H), 3.84 (ddt, B of $ABXY_2$, J_{AB} = 15.6, J_{BX} = 6.6 Hz, J_{BY} = 1.1 Hz, 1H), 2.41 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.05-0.98 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.04 (e), 138.54 (e), 136.32 (o), 133.77 (o), 132.17 (o), 129.63 (o), 127.28 (o), 125.17 (e), 117.81 (e), 116.09 (o), 54.28 (o), 45.48 (e), 21.65 (o), 18.41 (o), 2.45 (e), 1.93 (e).

IR (Neat) 2979 (w), 1653 (w), 1599 (w), 1494 (w), 1450 (w), 1335 (s), 1150 (s), 1102 (m), 1088 (m), 1002 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{23}NO_2NaS$ 340.1349, found 340.1347.



(*E*)-*N*-(2-Cyclopropylideneethyl)-4-methyl-*N*-(5-methylhexa-3,5-dien-2-yl)-4-benzenesulfonamide 171.

Colour and State: Yellow oil

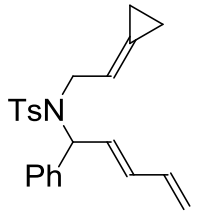
Compound (*E*)-**171** (86% yield on 4.20 mmol scale) was prepared according to the representative experimental procedure as described for compound (*E*)-**127**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.27-7.25 (m, 2H), 6.03 (dd, *J* = 15.9, 1.3 Hz, 1H), 5.77 (tquin, *J* = 6.5, 2.2 Hz, 1H), 5.43 (dd, *J* = 16.0, 5.6 Hz, 1H), 4.93 (s, 1H), 4.87 (s, 1H), 4.63 (dq, *J* = 6.8, 6.4 Hz, 1H), 3.92 (dd, A of ABX, J_{AB} = 15.6 Hz, J_{AX} = 6.6 Hz, 1H), 3.86 (dd, B of ABX, J_{AB} = 15.6 Hz, J_{BX} = 6.5 Hz, 1H), 2.41 (s, 3H), 1.68 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.05-1.01 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.02 (e), 141.37 (e), 138.65 (e), 134.02 (o), 129.65 (o), 129.61 (o), 127.33 (o), 125.04 (e), 117.02 (e), 116.25 (o), 54.52 (o), 45.47 (e), 21.62 (o), 18.52 (o), 18.48 (o), 2.47 (e), 1.95 (e).

IR (Neat) 2979 (w), 1609 (m), 1494 (w), 1452 (w), 1338 (s), 1153 (s), 1088 (m), 1001 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{25}NO_2NaS$ 354.1491, found 354.1504.



(*E*)-*N*-(2-Cyclopropylideneethyl)-4-methyl-*N*-(1-phenylpenta-2,4-dienyl)-4-benzenesulfonamide 166.

Colour and State: Pale yellow oil

Compound (*E*)-**166** (86% yield on 0.63 mmol scale) was prepared according to the representative experimental procedure as described for compound (*E*)-**127**.

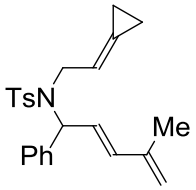
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.20 Hz, 2H), 7.26-7.22 (m, 7H), 6.27 (dt, *J* = 16.9, 10.2 Hz, 1H), 6.00 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.83 (dd, *J* = 15.3, 7.6 Hz, 1H), 5.69 (d, *J* = 7.6 Hz, 1H), 5.47 (tquin, *J* = 6.6, 2.5 Hz, 1H), 5.12 (d, *J* = 17.0 Hz, 1H),

5.09 (d, *J* = 10.0 Hz, 1H), 3.90 (dt, *J* = 15.6, 6.5 Hz, 2H), 2.40 (s, 3H), 0.99-0.74 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.05 (e), 139.06 (e), 138.29 (e), 136.04 (o), 135.00 (o), 129.72 (o), 129.42 (o), 128.42 (o), 128.27 (o), 127.73 (o), 127.63 (o), 125.39 (e), 118.43 (e), 115.26 (o), 62.65 (o), 46.92 (e), 21.60 (o), 2.41 (e), 1.71 (e).

IR (Neat) 2980 (w), 2254 (w), 1599 (w), 1494 (w), 1449 (w), 1336 (s), 1156 (s), 1093 (m), 1005 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{23}H_{25}O_2Na$ 402.1500, found 402.1504.



(*E*)-*N*-(2-Cyclopropylideneethyl)-4-methyl-*N*-(4-methyl-1-phenylpenta-2,4-dienyl)-4-benzenesulfonamide 172.

Colour and State: Colourless oil.

Compound (*E*)-**172** (64% yield on 0.40 mmol scale) was prepared according to the representative experimental procedure as described for compound (*E*)-**127**.

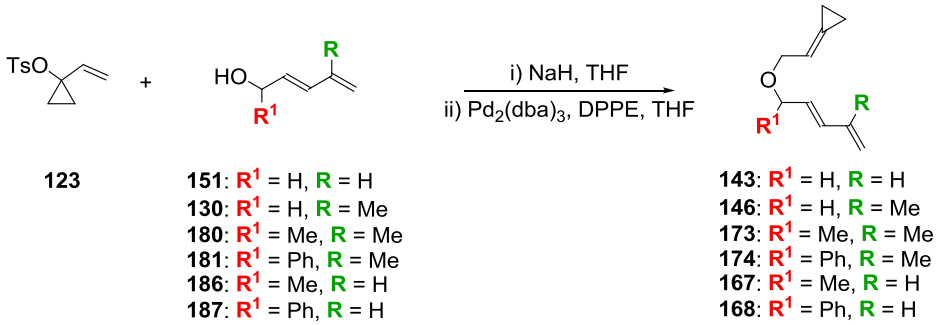
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.28-7.22 (m, 7H), 6.08 (d, *J* = 14.6 Hz, 1H), 5.75 (dd, *J* = 14.6, 7.8 Hz, 1H), 5.72 (d, *J* = 7.9 Hz, 1H), 5.50 (tquin, *J* = 6.6, 2.5 Hz, 1H), 4.98 (s, 1H), 4.87 (s, 1H), 3.96 (dd, A of ABX, J_{AB} = 15.6 Hz, J_{AX} = 6.5 Hz, 1H), 3.89 (dd, B of ABX, J_{AB} = 15.7 Hz, J_{BX} = 6.6 Hz, 1H), 2.39 (s, 3H), 1.76 (s, 3H), 0.96-0.74 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.01 (e), 141.00 (e), 139.21 (e), 138.15 (e), 136.96 (o), 129.35 (o), 128.35 (o), 128.15 (o), 127.63 (o), 127.56 (o), 125.49 (o), 125.19 (e), 117.61 (e), 115.34 (o), 62.86 (o), 46.83 (e), 21.54 (o), 18.52 (o), 2.37 (e), 1.66 (e).

IR (Neat) 2979 (w), 1599 (w), 1494 (w), 1450 (m), 1337 (s), 1159 (s), 1092 (m), 1004 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{27}NO_2NaS$ 416.1665, found 416.1660.

2.8.3 Representative Experimental Procedure for the Preparation of Oxygen tethered ACP-Dienes (*E*)-143, (*E*)-146, (*E*)-173, (*E*)-174, (*E*)-167, (*E*)-168

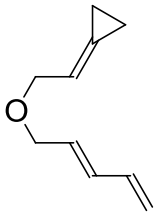


123

151: R^1 = H, R = H
130: R^1 = H, R = Me
180: R^1 = Me, R = Me
181: R^1 = Ph, R = Me
186: R^1 = Me, R = H
187: R^1 = Ph, R = H

143: R^1 = H, R = H
146: R^1 = H, R = Me
173: R^1 = Me, R = Me
174: R^1 = Ph, R = Me
167: R^1 = Me, R = H
168: R^1 = Ph, R = H

A solution of (*E*)-dien-ol **151**[28] (0.13 g, 1.63 mmol) in THF (10 mL) was added to a suspension of sodium hydride (0.065 g, 60% in mineral oil, 1.63 mmol) in THF (10 mL). The resulting mixture was stirred at room temperature for 1 h. In a separate vessel, $Pd_2(dba)_3$ (0.15 g, 0.12 mmol) and DPPE (0.10 g, 0.25 mmol) were dissolved in THF (15 mL), stirred for 5 min, then a solution of 1-vinylcyclopropyl 4-methylbenzenesulfonate **123** (0.30 g, 1.25 mmol) in THF (5 mL) was added. The reaction was stirred until the dark red solution turned green (*ca.* 30 min). The electrophile (green solution) was then transferred *via* Teflon® cannula to the vessel containing the nucleophile (solution of NaH and **151**). The resulting mixture was allowed to stir at room temperature for 12 h (t.l.c. control), quenched with water (10 mL) then partitioned with diethyl ether (35 mL). The resulting aqueous layer was diluted with 1 M HCl (25 mL) and extracted with diethyl ether (35 mL). The combined organic layers were washed with water (20 mL), followed by brine (15 mL), then dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% diethyl ether/ petroleum ether) afforded compound (*E*)-**143** as a colourless oil (0.15 g, 1.00 mmol, 80%).



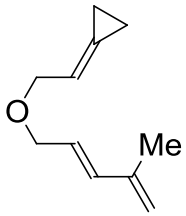
(*E*)-(2-(Penta-2,4-dienyloxy)ethylidene)cyclopropane 143.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (dt, *J* = 10.3, 6.5 Hz, 1H), 6.24 (dd, *J* = 15.2, 10.6 Hz, 1H), 5.94 (tquin, *J* = 6.6, 2.0 Hz, 1H), 5.79 (dt, *J* = 15.2, 6.3 Hz, 1H), 5.19 (d, *J* = 16.5 Hz, 1H), 5.08 (d, *J* = 10.1 Hz, 1H), 4.11 (dquin, *J* = 6.6, 1.1 Hz, 2H), 4.01 (d, *J* = 6.1 Hz, 2H), 1.13-1.05 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.53 (o), 133.23 (o), 130.42 (o), 127.02 (e), 117.52 (e), 114.91 (o), 70.46 (e), 70.14 (e), 2.41 (e), 1.89 (e).

IR (Neat): 2983 (w), 2849 (w), 2245 (w), 1604 (w), 1449 (w), 1357 (w), 1300 (w), 1106 (m), 1063 (m), 1002 (s) cm^{-1}.

HRMS (ESI, $[M+NH_4+H]^+$): calcd for $C_{10}H_{19}ON$ 170.1045, found 170.1057.



(*E*)-(2-(4-Penta-2,4-dienyloxy)ethylidene)cyclopropane 146.

Colour and State: Colourless oil.

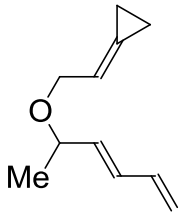
Compound (*E*)-**146** (73% yield on 2.52 mmol scale) was prepared according to the representative experimental procedure as described for compound (*E*)-**143**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (d, *J* = 15.7, 1H), 5.93 (tquin, *J* = 6.7, 1.9 Hz, 1H), 5.73 (dt, *J* = 15.7, 6.2 Hz, 1H), 4.94 (s, 2H), 4.10 (dt, *J* = 6.7, 1.0 Hz, 2H), 4.02 (d, *J* = 6.2 Hz, 2H), 1.83 (s, 3H), 1.11-1.03 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) 141.47 (e), 135.35 (o), 126.91 (e), 126.15 (o), 116.73 (e), 114.84 (o), 70.52 (e), 70.37 (e), 18.55 (o), 2.32 (e), 1.78 (e).

IR (Neat) 2982 (w), 2849 (w), 1610 (w), 1452 (w), 1357 (m), 1108 (s), 1066 (s), 1017 (m) cm^{-1}.

HRMS (ESI, $[M+NH_4]^+$): calcd for $C_{11}H_{20}ON$ 182.1539, found 182.1541.



(*E*)-(2-(Hexa-3,5-dien-2-yloxy)ethylidene)cyclopropane 167.

Colour and State: Colourless oil

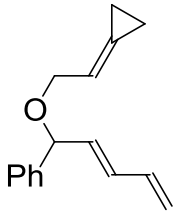
Compound (*E*)-**167** (45% yield on 1.26 mmol scale) was prepared according to the representative experimental procedure as described for compound (*E*)-**143**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.16 (dd, *J* = 15.3, 10.5 Hz, 1H), 5.92 (tquin, *J* = 6.7, 2.0 Hz, 1H), 5.62 (dd, *J* = 15.3, 7.6 Hz, 1H), 5.20 (d, *J* = 16.9 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 4.12 (ddquin, A of $ABXY_4$, J_{AB} = 11.2 Hz, J_{AX} = 6.3 Hz, J_{AY} = 1.2 Hz, 1H), 4.02-3.92 (m, 2H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.12-1.03 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.61 (o), 136.23 (o), 131.99 (o), 126.48 (e), 117.38 (e), 115.35 (o), 75.29 (o), 68.50 (e), 21.64 (o), 2.40 (e), 1.90 (e).

IR (Neat) 2978 (m), 2929 (w), 2856 (w), 1605 (w), 1448 (w), 1369 (w), 1338 (w), 1143 (m), 1096 (s), 1070 (s), 1002 (s) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{11}H_{17}O$ 165.1273, found 165.1274.



(*E*)-(1-(2-Cyclopropylideneethoxy)penta-2,4-dienyl)benzene 168.

Colour and State: Yellow oil.

Compound (*E*)-**168** (50% yield on 1.26 mmol scale) was prepared according to the experimental procedure described for the synthesis of compound (*E*)-**143**.

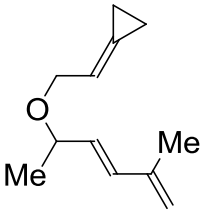
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H), 6.35 (dt, *J* = 16.8, 10.3 Hz, 1H), 6.25 (dd, *J* = 14.9, 10.5 Hz, 1H), 5.99 (tquin, J = 6.6, 1.9 Hz, 1H), 5.84 (dd, *J* = 15.1,

7.0 Hz, 1H), 5.22 (dd, *J* = 16.9, 1.5 Hz, 1H), 5.10 (dd, *J* = 10.0, 1.5 Hz, 1H), 4.88 (d, *J* = 7.0 Hz, 1H), 4.16-4.09 (m, 2H), 1.14-1.02 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.38 (e), 136.52 (o), 134.71 (o), 132.19 (o), 128.33 (o), 127.53 (o), 126.74 (o), 126.30 (e), 117.80 (e), 115.10 (o), 81.22 (o), 68.63 (e), 2.40 (e), 1.95 (e).

IR (Neat) 2924 (m), 2854 (m), 1680 (w), 1603 (w), 1492 (w), 1452 (m), 1299 (w), 1102 (m), 1057 (m), 1002 (s).

HRMS (ESI, $[M+H]^+$) calcd for $C_{16}H_{19}O$ 227.1431, found 227.1431.



(*E*)-(2-(Hexa-3,5-dien-2-yloxy)ethylidene)cyclopropane 173.

Colour and State: Pale yellow oil.

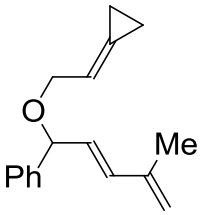
Compound (*E*)-**173** (56% yield on 2.73 mmol scale) was prepared according to the experimental procedure described for the synthesis of compound (*E*)-**143**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (d, *J* = 15.7 Hz, 1H), 5.93 (tquin, *J* = 6.8, 2.0 Hz 1H), 5.57 (dd, *J* = 15.7, 7.6 Hz, 1H), 4.97 (s, 1H), 4.96 (s, 1H), 4.15-4.10 (m, 1H), 4.03-3.94 (m, 2H), 1.85 (s, 3H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.13-1.03 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.56 (e), 134.07 (o), 131.95 (o), 126.28 (e), 116.55 (e), 115.34 (o), 75.64 (o), 68.34 (e), 21.76 (o), 18.65 (o), 2.31 (e), 1.80 (e).

IR (Neat) 2975 (m), 2928 (w), 2857 (w), 1601 (w), 1446 (w), 1369 (m), 1341 (w), 1303 (m), 1149 (m), 1101 (m), 1069 (s), 1036 (m).

HRMS (ESI, $[M+H]^+$) calcd for $C_{12}H_{19}O$ 179.1430, found 179.1431.



(*E*)-(1-(2-Cyclopropylideneethoxy)penta-2,4-dienyl)benzene 174.

Colour and State: Yellow oil.

Compound (*E*)-**174** (51% yield on 1.19 mmol scale) was prepared according to the experimental procedure described for the synthesis of compound (*E*)-**143**.

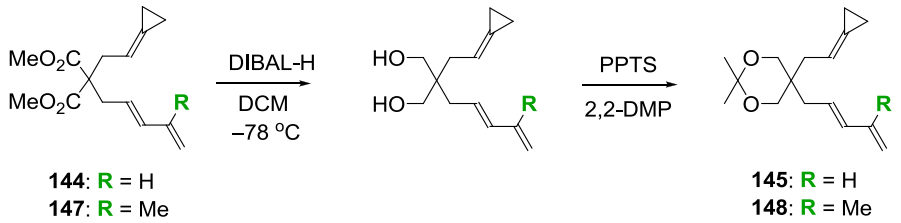
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 6.33 (d, *J* = 15.6 Hz, 1H), 5.99 (tquin, *J* = 6.5, 2.0 Hz, 1H), 5.78 (dd, *J* = 15.7, 7.2 Hz, 1H), 4.99 (s, 2H), 4.91 (d, *J* = 7.2 Hz, 1H), 4.16-4.09 (m, 2H), 1.84 (s, 3H), 1.13-1.08 (m, 2H), 1.05-1.01 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 141.63 (e), 141.61 (e), 134.48 (o), 130.62 (o), 128.55 (o), 127.65 (o), 127.04 (o), 126.81 (e), 117.15 (e), 115.08 (o), 81.69 (o), 68.59 (e), 18.68 (o), 2.41 (e), 1.93 (e).

IR (Neat) 3028 (w), 2981 (w), 2857 (w), 1609 (w), 1493 (w), 1452 (m), 1375 (w), 1303 (w), 1105 (m), 1057 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{20}ONa$ 263.1420, found 263.1412.

2.8.4 Experimental Procedure for the Preparation of Carbon-atom (Acetal) tethered ACP-Dienes (*E*)-145 and (*E*)-148

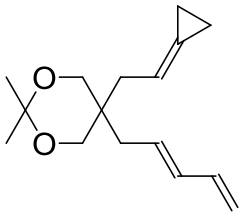


144: R = H
147: R = Me

145: R = H
148: R = Me

DIBAL–H (11.22 mL, 1 M in hexane, 11.22 mmol) was slowly added to a solution of compound (*E*)-**144**[7] (0.70 g, 2.67 mmol) in DCM (25 mL) at –78 ˚C and then stirred for 2 h. After the reaction had reached completion (t.l.c. control), saturated aqueous solution of sodium potassium tartarate (30 mL) was added slowly until the precipitate turned to a suspension. The aqueous layer was extracted with DCM twice (20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The diol (0.55 g, 2.64 mmol, 99%) was used without further purification.

The diol (0.55 g, 2.65 mmol) was dissolved in 2,2-dimethoxypropane (2,2-DMP) (8 mL) followed by the addition of pyridinium *para*-toluenesulfonate (PPTS) (0.053 g, 0.21 mmol). The reaction mixture was stirred at room temperature for 3 h, and then at refluxed for 1 h. After completion (t.l.c. control), excess 2,2-dimethoxylpropane (2,2-DMP) was removed *in vacuo*. Purification by flash chromatography (silica gel, 5% diethyl ether/hexane) afforded (*E*)-**145** as a colourless oil (0.48 g, 1.93 mmol, 73%).



(*E*)-*5*-(2-Cyclopropylideneethyl)-2,2-dimethyl-5-(penta-2,4-dienyl)-1,3-dioxane 145.

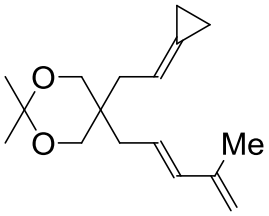
Stereochemistry: *E*:*Z* = 17:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.09 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.74-5.64 (m, 2H), 5.09 (d, *J* = 17.0 Hz, 1H), 4.97 (d, *J* = 10.0 Hz, 1H), 3.60 (d, *J* = 11.6 Hz, 2H), 3.54 (d, *J* = 11.6 Hz, 2H), 2.21 (d, *J* = 7.7 Hz, 2H), 2.18 (d, *J* = 7.5 Hz, 2H), 1.39 (s, 6H), 1.09-1.06 (m, 2H), 1.01-0.98 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) 137.07 (o), 134.43 (o), 129.83 (o), 125.30 (e), 115.64 (e), 112.65 (o), 98.06 (e), 67.60 (e), 36.93 (e), 35.52 (e), 34.89 (e), 25.10 (o), 22.84 (o), 2.99 (e), 2.07 (e).

IR (Neat) 2990 (w), 2857 (w), 1650 (w), 1601 (w), 1438 (w), 1369 (m), 1255 (m), 1224 (m), 1195 (s), 1156 (m), 1095 (m), 1078 (s), 1033 (m), 1003 (s) cm^{-1}.

HRMS (ESI**,** $[M+H]^+$): calcd for $C_{16}H_{25}O_2$ 249.1776, found 249.1849



(*E*)-5-(2-Cyclopropylideneethyl)-2,2-dimethyl-5-(4-methylpenta-2,4-dienyl)-1,3-dioxane 148.

Stereochemistry: *E*:*Z* = ≥19:1 (^{1}H NMR analysis)

Colour and State: Colourless oil.

Compound (*E*)-**148** (73% yield on 1.13 mmol scale) was prepared according to the experimental procedure described for the synthesis of compound (*E*)-**145**.

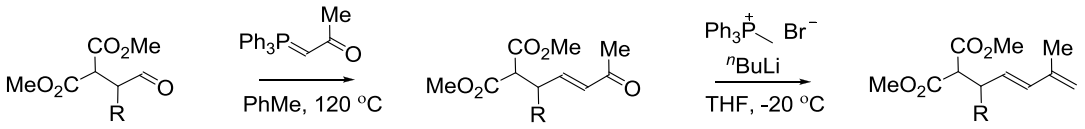
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (d, *J* = 15.5 Hz, 1H), 5.77-5.72 (m, 1H), 5.64 (dt, *J* = 15.5, 7.7 Hz, 1H), 4.88 (s, 2H), 3.59 (d, *J* = 11.5 Hz, 2H), 3.57 (d, *J* = 11.5 Hz, 2H), 2.24 (d, *J* = 7.7 Hz, 2H), 2.20 (d, *J* = 7.5 Hz, 2H), 1.83 (s, 3H), 1.41 (s, 6H), 1.10-1.07 (m, 2H), 1.02-0.99 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.95 (e), 136.27 (o), 125.36 (o), 125.21 (e), 115.10 (e), 112.80 (o), 98.09 (e), 67.59 (e), 37.00 (e), 35.76 (e), 35.02 (e), 25.02 (o), 22.96 (o), 18.85 (o), 2.99 (e), 2.06 (e).

IR (Neat) 2990 (m), 2941 (w), 2857 (w), 1741 (w), 1609 (w), 1452 (w), 1437 (w), 1369 (m), 1255 (m), 1194 (s), 1157 (m), 1096 (m), 1081 (s), 1035 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$): calcd for $C_{17}H_{26}O_2Na$ 285.1831, found 285.1831.

2.8.5 Representative Experimental Procedure for the Preparation of Malonate tethered ACP-Dienes (*E*)-169, (*E*)-170, (*E*)-175, (*E*)-176



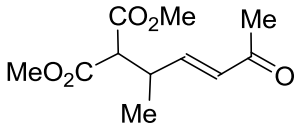
208; R = Me
209; R = Ph

210; R = Me
211; R = Ph

212; R = Me
213; R = Ph

A suspension of $Ph_3PCHCOMe$ (3.55 g, 11.16 mmol) in toluene (15 mL) was heated up to 120 ˚C. The resulting pale-yellow solution was treated with a solution of aldehyde **208**[3] (0.70, 3.72 mmol) in toluene (5 mL), then left to stir for 12 h at same temperature. After the reaction had reached completion (t.l.c. control), the resulting orange-red solution was allowed to cool to room temperature and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5-10% diethyl ether/petroleum ether) afforded (*E*)-**210** as a pale yellow oil (0.70 g, 3.07 mmol, 82%).

[3] References for known aldehydes **208** and **209**, see; Lassaletta, J. M.; Vázquez, J. V.; Prieto, A.; Fernández, R.; Raabe, G.; Enders, D. *J. Org. Chem.* **2003**, *68*, 2698–2703 and Tuloup, R.; Danion-Bougot, R.; Danion, D. *Tetrahedron Lett.* **1988**, 29, 6249–6252 respectively.



(*E*)-dimethyl 2-(5-oxohex-3-en-2-yl)malonate 210.

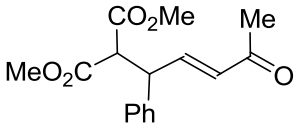
Stereochemistry: *E/Z* = ≥19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (dd, *J* = 16.0, 8.0 Hz, 1H), 6.01 (d, *J* = 16.0 Hz, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 3.35 (d, *J* = 8.2 Hz, 1H), 3.04 (dq, *J* = 14.6, 7.3 Hz, 1H), 2.17 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.48 (e), 168.13 (e), 168.09 (e), 147.94 (o), 131.22 (o), 56.52 (o), 52.65 (o), 52.56 (o), 36.50 (o), 27.02 (o), 17.42 (o).

IR (Neat) 2956 (w), 1732 (vs), 1698 (s), 1675 (s), 1628 (m), 1435 (s), 1359 (m), 1251 (s), 1194 (s), 1154 (s), 1019 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{11}H_{16}O_5Na$ 251.0895, found 251.0904.



(*E*)-dimethyl 2-(4-oxo-1-phenylpent-2-enyl)malonate 211.

Colour and State: Yellow oil

Stereochemistry: *E/Z* = ≥19:1 (^{1}H NMR analysis)

The experimental procedure described for the synthesis of compound (*E*)-**210** was followed. Compound (*E*)-**211** (65% yield on 2.12 mmol scale) was prepared from aldehyde **209**[3] in DCM (20 mL) with acetic acid (0.012 mL, 0.0212 mmol) at room temperature.

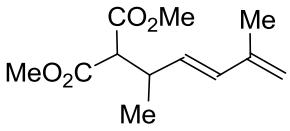
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 7.27-7.20 (m, 3H), 6.90 (dd, *J* = 15.9, 8.0 Hz, 1H), 6.07 (d, *J* = 15.9 Hz, 1H), 4.25 (dd, *J* = 10.6, 8.2 Hz, 1H), 3.92 (d, *J* = 10.8 Hz, 1H), 3.74 (s, 3H), 3.50 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.33 (e), 167.90 (e), 167.42 (e), 145.68 (o), 138.06 (e), 131.75 (o), 129.13 (o), 128.22 (o), 127.95 (o), 56.64 (o), 53.03 (o), 52.81 (o), 48.13 (o), 27.46 (o).

IR (Neat) 2954 (w), 1735 (vs), 1698 (s), 1674 (vs), 1626 (m), 1495 (w), 1454 (s), 1434 (m), 1360 (m), 1314 (m), 1252 (s), 1193 (s), 1151 (s), 1021 (m) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{16}H_{19}O_5$ 291.1227, found 291.1232.

^{n}BuLi (2.18 mL, 2.5 M in Hexane, 5.45 mmol) was slowly added to a suspension of methyltriphenylphosphonium bromide salt (1.94 g, 5.45 mmol) in THF (20 mL) at –20 °C. The resulting yellow mixture was stirred at –20 °C for 3 h, followed by the slow addition of a solution of compound (*E*)-**210** (0.62 g, 2.73 mmol) in THF (5 mL). The resulting mixture was warmed up to room temperature and stirred for a further 1 h. Afterwards, the mixture was quenched with saturated solution of NH_4Cl (10 mL) and partitioned with diethyl ether (25 mL). The organic layer was washed with water (15 mL), followed by brine (10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10-20% ethyl acetate/petroleum ether) afforded (*E*)-**212** as a yellow oil (0.42 g, 1.86 mmol, 69%).



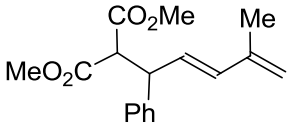
(*E*)-dimethyl 2-(5-methylhexa-3,5-dien-2-yl)malonate 212.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (d, *J* = 15.6 Hz, 1H), 5.50 (dd, *J* = 15.6, 8.0 Hz, 1H), 4.86 (s, 2H), 3.69 (app. d, *J* = 0.7 Hz, 3H), 3.63 (app. d, *J* = 0.6 Hz, 3H), 3.28 (d, *J* = 8.9 Hz, 1H), 2.96 (ddq, *J* = 8.6, 7.5, 6.8 Hz, 1H), 1.75 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.71 (e), 168.67 (e), 141.60 (e), 133.71 (o), 131.00 (o), 116.09 (e), 57.91 (o), 52.44 (o), 52.31 (o), 37.54 (o), 18.59 (o), 18.57 (o).

IR (Neat) 2954 (w), 1734 (vs), 1609 (w), 1434 (m), 1374 (w), 1240 (s), 1192 (m), 1145 (s), 1068 (w), 1021 (m) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{12}H_{19}O_4$ 227.1278, found 227.1279.



(*E*)-dimethyl 2-(4-methyl-1-phenylpenta-2,4-dienyl)malonate 213.

Colour and State: Yellow oil

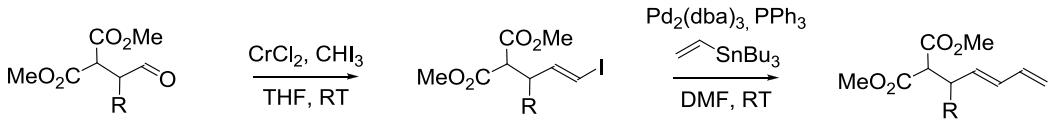
Compound (*E*)-**213** (68% yield on 0.71 mmol scale) was prepared from (*E*)-**211** according to the experimental procedure as described for the synthesis of compound (*E*)-**212**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.25-7.20 (m, 3H), 6.21 (d, *J* = 15.5 Hz, 1H), 5.75 (dd, *J* = 15.5, 8.0 Hz, 1H), 4.91 (br s, 2 H), 4.15 (dd, *J* = 10.7, 6.5 Hz, 1H), 3.88 (d, *J* = 10.9 Hz, 1H), 3.71 (s, 3H), 3.49 (s, 3H), 1.78 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.30 (e), 167.89 (e), 141.45 (e), 140.48 (e), 134.77 (o), 128.97 (o), 128.78 (o), 127.92 (o), 127.19 (o), 116.86 (e), 57.83 (o), 52.67 (o), 52.53 (o), 49.11 (o), 18.63 (o).

IR (Neat) 2953 (w), 1758 (s), 1735 (vs), 1608 (w), 1496 (w), 1453 (w), 1433 (m), 1315 (m), 1254 (s), 1221 (s), 1191 (m), 1143 (s), 1025 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{20}O_4Na$ 311.1248, found 311.1259.

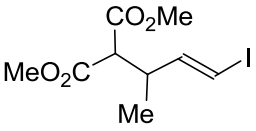


208; R = Me
209; R = Ph

214; R = Me
215; R = Ph

216; R = Me
217; R = Ph

Chromium(II) chloride (1.37 g, 11.16 mmol) was weighed into a reaction vessel, followed by the addition of THF (15 mL) and a solution of iodoform (1.25 g, 3.19 mmol) in THF (10 mL). The resulting dark red suspension, protected from direct light was stirred vigorously (*ca.* 5 min), then a solution of aldehyde **208** (0.30 g, 1.59 mmol) in THF (5 mL) was added at room temperature. After the reaction had reached completion (t.l.c. control), water (15 mL) was added and partitioned with ethyl acetate (3 x 35 mL). The combined organic layers were washed with saturated solution of $Na_2S_2O_3$ (15mL), followed by brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (silica gel, 20% ethyl acetate/petroleum ether) afforded vinyl iodide (*E*)-**214** as a light yellow oil (0.32 g, 1.03 mmol, 65%).



(*E*)-dimethyl 2-(4-iodobut-3-en-2-yl)malonate 214.

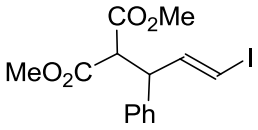
Stereochemistry: *E/Z* = ≥19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (dd, *J* = 14.4, 7.7 Hz, 1H), 6.15 (d, *J* = 14.4 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.27 (d, *J* = 8.7 Hz, 1H), 2.94 (ddq, *J* = 8.5, 7.5, 6.8 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.21 (e), 168.12 (e), 146.80 (o), 77.14 (o), 56.73 (o), 52.63 (o), 52.62 (o), 40.68 (o), 17.52 (o).

IR (Neat) 2953 (w), 1731 (vs), 1605 (w), 1434 (m), 1323 (m), 1268 (m), 1237 (m), 1197 (m), 1152 (s), 1018 (m) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_9H_{14}O_4I$ 312.9939, found 312.9936.



(*E*)-dimethyl 2-(3-iodo-1-phenylallyl)malonate 215.

Colour and State: deep yellow oil

Stereochemistry: *E/Z* = ≥19:1 (^{1}H NMR analysis)

Compound (*E*)-**215** (54% yield on 1.99 mmol scale) according to the experimental procedure as described for the synthesis of compound (*E*)-**214**.

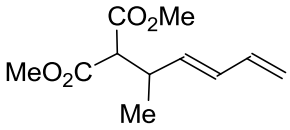
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.24-7.18 (m, 3H), 6.68 (dd, *J* = 14.3, 7.6 Hz, 1H), 6.21 (dd, *J* = 14.3, 0.6 Hz, 1H), 4.12-4.08 (m, 1H), 3.84 (d, *J* = 10.8 Hz, 1H), 3.74 (s, 3H), 3.47 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.85 (e), 167.19 (e), 144.61 (o), 138.19 (e), 128.88 (o), 127.89 (o), 127.56 (o), 78.69 (o), 56.65 (o), 52.89 (o), 52.58 (o), 51.83 (o).

IR (Neat) 3029 (w), 2952 (w), 1733 (vs), 1603 (w), 1494 (w), 1453 (w), 1433 (m), 1313 (m), 1257 (s), 1198 (s), 1148 (s), 1083 (w) 1021 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{14}H_{15}O_4NaI$ 396.9923, found 396.9913.

$Pd_2(dba)_3$ (0.18 g, 0.20 mmol) and PPh_3 (0.10 g, 0.41 mmol) were dissolved in degassed DMF (10 mL) in a flame dried flask. To the resulting black suspension, tributyl(vinyl)stannane (0.65 g, 2.06 mmol) and a solution of vinyl iodide (*E*)-**214** (0.32 g, 1.03 mmol) in de-gassed DMF (10 mL) were added simultaneously. The resulting dark brown solution was stirred at room temperature for 2 h (t.l.c. control) and then quenched with saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with diethyl ether (2 x 25 mL). The combined organic layers were washed with water (15 mL) followed by brine (20 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (silica gel, 10% diethyl ether/petroleum ether) afforded (*E*)-**216** as a light yellow oil (0.19 g, 0.92 mmol, 90%).



(*E*)-dimethyl 2-(hexa-3,5-dien-2-yl)malonate 216.

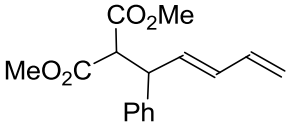
Stereochemistry: *E/Z* = 13:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (ddd, *J* = 16.9, 10.0, 7.8 Hz, 1H), 6.07 (dd, *J* = 15.1, 8.5 Hz, 1H), 5.59 (dd, *J* = 15.1, 7.8 Hz, 1H), 5.11 (app. dd, *J* = 16.9, 0.8 Hz, 1H), 4.99 (app. dd, *J* = 10.0, 0.8 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.28 (d, *J* = 8.9 Hz, 1H), 2.96 (ddq, *J* = 8.4, 7.5, 6.8 Hz, 1H), 1.08 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.70 (e), 168.64 (e), 136.73 (o), 135.25 (o), 131.82 (o), 116.75(e), 57.73 (o), 52.49 (o), 52.41 (o), 37.28 (o), 18.29 (o).

IR (Neat) 3030 (w), 2953 (w), 2847 (w), 1757 (vs), 1735 (vs), 1649 (w), 1602 (w), 1524 (w), 1495 (w), 1454 (w), 1434 (m), 1313 (m), 1254 (m), 1194 (s), 1145 (s), 1004 (s) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{11}H_{17}O_4$ 213.2422, found 275.2419.



(*E*)-dimethyl 2-(1-phenylpenta-2,4-dienyl)malonate 217.

Colour and State: Colourless oil

Stereochemistry: *E/Z* = ≥19:1 (^{1}H NMR analysis)

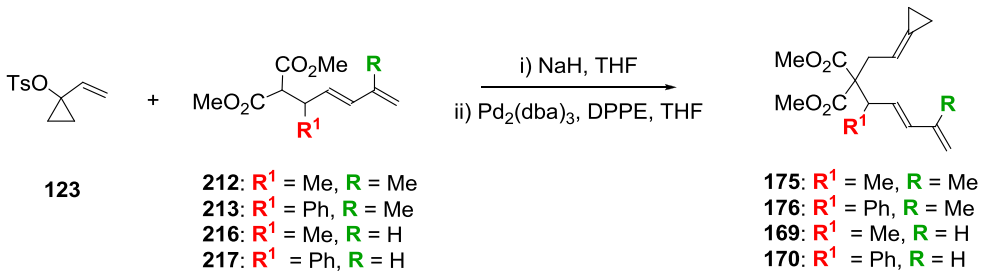
Compound (*E*)-**217** (92% yield on 2.24 mmol scale) was prepared according to the experimental procedure as described for the synthesis of compound (*E*)-**216**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.22-7.18 (m, 3H), 6.25 (ddd, *J* = 16.9, 10.0, 7.4 Hz, 1H), 6.10 (dd, *J* = 15.1, 8.5 Hz, 1H), 5.82 (dd, *J* = 15.1, 7.8 Hz, 1H), 5.13 (app. dd, *J* = 16.8, 1.2 Hz, 1H), 5.02 (app. d, *J* = 10.0, 1.2 Hz, 1H), 4.15-4.10 (m, 1H), 3.86 (d, *J* = 10.9 Hz, 1H), 3.71 (s, 3H), 3.48 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.23 (e), 167.80 (e), 140.12 (e), 136.46 (o), 133.11 (o), 132.82 (o), 128.76 (o), 127.94 (o), 127.23 (o), 117.47 (e), 57.63 (o), 52.70 (o), 52.51 (o), 48.84 (o).

IR (Neat) 2954 (w), 2923 (w), 2872 (w), 2850 (w), 1735 (vs), 1650 (w), 1604 (w), 1520 (w), 1455 (w), 1434 (m), 1341 (m), 1241 (m), 1196 (m), 1154 (s), 1065 (w), 1006 (s) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{16}H_{19}O_4$ 275.3121, found 275.3119.

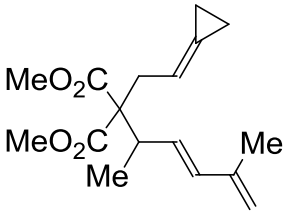


123

212: R^1 = Me, R = Me
213: R^1 = Ph, R = Me
216: R^1 = Me, R = H
217: R^1 = Ph, R = H

175: R^1 = Me, R = Me
176: R^1 = Ph, R = Me
169: R^1 = Me, R = H
170: R^1 = Ph, R = H

A solution of dienylmalonate (*E*)-**212** (0.42 g, 2.13 mmol) in THF (8 mL) was added to a suspension of sodium hydride (0.093 g, 60% in mineral oil, 2.30 mmol) in THF (7 mL). The mixture was stirred at room temperature for 1 h. In a separate vessel, $Pd_2(dba)_3$ (0.015 g, 0.018 mmol) and diphenylphosphine ethane (DPPE) (0.014g, 0.036 mmol) were dissolved in THF (7 mL), stirred for 5 min, then a solution of 1-vinylcyclopropyl 4-methylbenzenesulfonate **123** (0.42 g, 1.77 mmol) in THF (10 mL) was added. The reaction was stirred until the dark red solution turned green (*ca.* 30 min). The electrophile (green solution) was then transferred *via* Teflon® cannula to the vessel containing the nucleophile (NaH and **212**). The resulting mixture was stirred at room temperature for 4 h. The reaction was quenched with water (10 mL) and partitioned with diethyl ether (35 mL). The aqueous layer was diluted with 1 M HCl (15 mL), and re-extracted with diethyl ether (25 mL). The combined organic layers were washed with brine (15 mL) then dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% diethyl ether/petroleum ether) afforded (*E*)-**175** as a yellow oil (0.41 g, 1.49 mmol, 84%).



(*E*)-Dimethyl 2-(2-cyclopropylideneethyl)-2-(5-methylhexa-3,5-dien-2-yl)malonate 175.

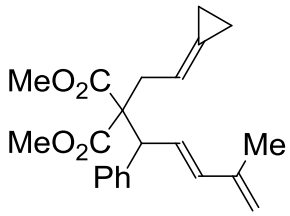
Colour and State: Pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (d, *J* = 15.6 Hz, 1H), 5.64 (tquin, *J* = 8.1, 2.1 Hz, 1H), 5.53 (dd, *J* = 15.6, 9.0 Hz, 1H), 4.85 (s, 1H), 4.84 (s, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 2.90 (ddq, *J* = 9.5, 6.9, 2.4 Hz, 1H), 2.75-2.70 (m, 2H), 1.76 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.01-0.98 (m, 2H), 0.93-0.89 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.18 (e), 171.04 (e), 141.92 (e), 134.11 (o), 130.65 (o), 125.78 (e), 115.61 (e), 112.59 (o), 61.72 (e), 52.06 (o), 52.01 (o), 40.99 (o), 36.72 (e), 18.68 (o), 17.06 (o), 2.85 (e), 1.71 (e).

IR (Neat) 2980 (w), 2951 (w), 1727 (s), 1609 (w), 1435 (m), 1374 (w), 1296 (w), 1272 (m), 1246 (m), 1200 (s), 1103 (m), 1073 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{24}O_4Na$ 315.1571, found 315.1572.



(*E*)-Dimethyl 2-(2-cyclopropylideneethyl)-2-(4-methyl-1-phenylpenta-2-4-dienyl)malonate 176.

Colour and State: Colourless oil.

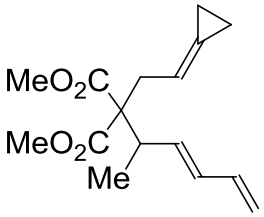
Compound (*E*)-**176** (87% yield on 0.34 mmol scale) was prepared according to the experimental procedure as described for the synthesis of compound (*E*)-**175**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.16 (m, 5H), 6.17 (dd, *J* = 15.4, 8.5 Hz, 1H), 6.10 (d, *J* = 15.5 Hz, 1H), 5.69 (ddquin, *J* = 7.8, 5.9, 2.0 Hz, 1H), 4.87 (s, 1H), 4.83 (s, 1H), 4.11 (d, *J* = 8.4 Hz, 1H), 3.71 (s, 3H), 3.60 (s, 3H), 2.74 (ddquin, A of $ABXY_4$, J_{AB} = 14.2 Hz, J_{AX} = 6.4 Hz, J_{AY} = 1.2 Hz, 1H), 2.63 (ddquin, B of $ABXY_4$, J_{AB} = 14.3 Hz, J_{BX} = 7.8 Hz, J_{BY} = 1.1 Hz, 1H), 1.83 (s, 3H), 1.03 (dt, *J* = 7.8, 1.2 Hz, 2H), 0.96-0.86 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.97 (e), 170.85 (e), 142.02 (e), 139.63 (e), 135.11 (o), 129.35 (o), 129.27 (o), 128.36 (o), 127.22 (o), 125.97 (e), 115.97 (e), 112.77 (o), 63.11 (e), 53.41 (o), 52.20 (o), 52.18 (o), 37.51 (e), 18.80 (o), 2.93 (e), 1.81 (e).

IR (Neat) 2981 (w), 2951 (w), 1727 (s), 1607 (w), 1496 (w), 1453 (w), 1433 (m), 1201 (s), 1177 (s), 1085 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{22}H_{26}O_4Na$ 377.1741, found 377.1729.



(*E*)-Dimethyl 2-(2-cyclopropylideneethyl)-2-(hexa-3,5-dien-2-yl)malonate 169.

Colour and State: Colourless oil

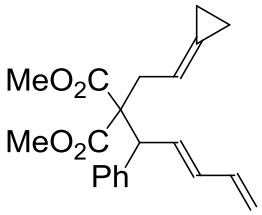
Compound (*E*)-**169** (84% yield on 1.78 mmol scale) was prepared according to the experimental procedure as described for the synthesis of compound (*E*)-**175**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (dt, *J* = 16.9, 10.3 Hz, 1H), 6.03 (dd, *J* = 15.1, 10.5 Hz, 1H), 5.69-5.62 (m, 2H), 5.10 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.99 (dd, *J* = 10.1, 0.9 Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 2.91 (dq, *J* = 8.7, 6.9 Hz, 1H), 2.77-2.74 (m, 2H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.06-1.03 (m, 2H), 0.98-0.93 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.27 (e), 171.16 (e), 137.18 (o), 135.17 (o), 132.34 (o), 125.98 (e), 116.27 (e), 112.70 (o), 61.86 (e), 52.20 (o), 52.17 (o), 40.96 (o), 36.85 (e), 16.90 (o), 2.97 (e), 1.89 (e).

IR (Neat) 2980 (w), 2952 (w), 1727 (s), 1603 (w), 1434 (m), 1202 (s), 1091 (m), 1071 (m), 1003 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{16}H_{22}O_4Na$ 301.1407, found 301.1416.



(*E*)-Dimethyl 2-(2-cyclopropylideneethyl)-2-(1-phenylpenta-2-4-dienyl)malonate 170.

Colour and State: Colourless oil

Compound (*E*)-**170** (80% yield on 0.92 mmol scale) was prepared according to the experimental procedure described for the synthesis of compound (*E*)-**175**.

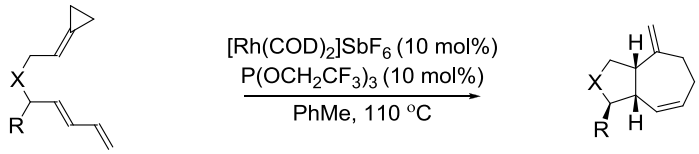
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.20 (m, 3H), 7.14 (m, 2H), 6.32 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.24 (dd, *J* = 15.1, 8.6 Hz, 1H), 5.99 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.69 (ddquin, *J* = 7.9, 6.4, 2.1 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 4.98 (d, *J* = 10.2 Hz, 1H), 4.08 (d, *J* = 8.6 Hz, 1H), 3.71 (s, 3H), 3.61 (s, 3H), 2.72 (dd, A of ABX, J_{AB} = 14.2 Hz, J_{AX} = 6.4 Hz, 1H), 2.61 (dd, B of ABX, J_{AB} = 14.1 Hz, J_{BX} = 7.9 Hz, 1H), 1.03 (app. t, *J* = 7.7 Hz, 2H), 0.91 (dq, *J* = 16.0, 7.3 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.02 (e), 170.84 (e), 139.37 (e), 137.15 (o), 133.68 (o), 133.31 (o), 129.38 (o), 128.41 (o), 127.32 (o), 126.08 (e), 116.56 (e), 112.79 (o), 63.10 (e), 53.37 (o), 52.26 (o), 52.22 (o), 37.57 (e), 2.96 (e), 1.89 (e).

IR (Neat) 2981 (w), 2951 (w), 1726 (s), 1601 (w), 1496 (w), 1453 (w), 1434 (m), 1203 (s), 1178 (s), 1085 (m), 1003 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{21}H_{24}O_4Na$ 363.1580, found 363.1572.

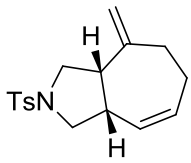
2.8.6 Representative Experimental Procedure for the Rhodium(I)-Catalysed [4+3] Carbocyclisation Reaction



127: R = H, X = NTs
143: R = H, X = O
144: R = H, X = $C(CO_2Me)_2$
145: R = H, X = $C[(CH_2O)_2C(Me)_2]$
165: R = Me, X = NTs
166: R = Ph, X = NTs
167: R = Me, X = O
168: R = Ph, X = O
169: R = Me, X = $C(CO_2Me)_2$
170: R = Ph, X = $C(CO_2Me)_2$

133: R = H, X = NTs
158: R = H, X = O
159: R = H, X = $C(CO_2Me)_2$
160: R = H, X = $C[(CH_2O)_2C(Me)_2]$
218: R = Me, X = NTs
219: R = Ph, X = NTs
220: R = Me, X = O
221: R = Ph, X = O
222: R = Me, X = $C(CO_2Me)_2$
223: R = Ph, X = $C(CO_2Me)_2$

$Rh(COD)_2SbF_6$ (0.014 g, 0.025 mmol) was inserted into a flamed dried reaction vessel, followed by the addition of toluene (2 mL). The vessel was placed under vacuum and backfilled with argon, $P(OCH_2CF_3)_3$ (0.0088 g, 0.025 mmol) was introduced, then heated up to 110 ˚C for 10 min. The requisite ACP-diene (*E*)-**127** (0.076 g, 0.25 mmol) in toluene (3 mL) was added *via* syringe pump over a period of 6 h (0.5 mL/h) to the bright yellow solution 110 ˚C. The reaction mixture was stirred for 1-2 h at same temperature after the addition had completed (t.l.c. control), then cooled to room temperature, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% diethyl ether/petroleum ether) furnished *cis*-fused bicycloheptadiene **133** as a light yellow oil (0.070 g, 0.23 mmol, 92%).



(3a*S*,8a*S*)-4-methylene-2-tosyl-1,2,3,3a,4,5,6,8a octahydrocyclohepta[*c*]pyrrole 133.

Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

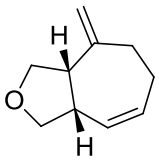
Relative stereochemistry: X-ray Crystallography (**Figure 4**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.52-5.48 (m, 1H), 5.09-5.06 (m, 1H), 4.80 (s, 1H), 4.54 (s, 1H), 3.50 (dd, A of ABX, J_{AB} = 9.6 Hz, J_{AX} = 7.5 Hz, 1H), 3.43 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 6.2 Hz, 1H), 3.27 (dd, A of ABX, J_{AB} = 9.7 Hz, J_{AX} = 7.2 Hz, 1H), 3.14 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 4.8 Hz, 1H), 2.99-2.94 (m, 2H), 2.42 (s, 3H), 2.33-2.22 (m, 3H), 2.09-2.01 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.77 (e), 143.46 (e), 134.34 (e), 130.66 (o), 129.76 (o), 128.83 (o), 127.56 (o), 111.91 (e), 54.19 (e), 51.15 (e), 47.72 (o), 40.76 (o), 34.14 (e), 29.66 (e), 21.64 (o).

IR (Neat) 3022 (w), 2949 (w), 2883 (w), 2830 (w), 1638 (m), 1596 (w), 1457 (w), 1339 (s), 1323 (m), 1220 (m), 1157 (s), 1135 (s), 1087 (m), 1030 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{21}NO_2NaS$ 326.1292, found 326.1191.



(3a*S*,8a*S*)-4-methylene-3,3a,4,5,6,8a-hexahydro-1*H*-cyclohepta[*c*]furan 158.

Colour and State: Light yellow oil

Compound **158** (70% yield on 0.25 mmol scale) was prepared according to the representative [4+3] carbocyclisation reaction experimental procedure.

Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

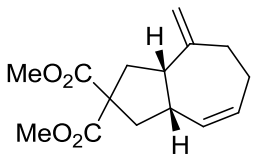
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66-5.61 (m, 1H), 5.39 (d, *J* = 11.8 Hz, 1H), 4.87 (s, 1H), 4.75 (s, 1H), 4.03-3.99 (m, 2H), 3.85 (dd, A of ABX, J_{AB} = 8.3 Hz, J_{AX} = 6.0 Hz,

1H), 3.59 (dd, B of ABX, J_{AB} = 7.9 Hz, J_{AX} = 6.3 Hz, 1H), 3.14-3.12 (m, 2H), 2.45-2.34 (m, 3H), 2.20-2.13 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.18 (e), 129.73 (o), 128.98 (o), 111.39 (e), 74.33 (e), 71.95 (e), 48.35 (o), 42.23 (o), 34.53 (e), 29.07 (e).

IR (Neat) 2927 (w), 2249 (w), 1643 (w), 1457 (w), 1062 (w) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{10}H_{15}O$ 151.1117, found 151.1115.



(3a*S*, 8a*S*)-dimethyl-8methylene-3,3a,4,6,8,8a-hexahydroazulene-2,2-(1*H*)-dicarboxylate 159.

Colour and State: Yellow oil

Compound **159** (92% yield on 0.25 mmol scale) was prepared according to the representative [4+3] carbocyclisation reaction experimental procedure.

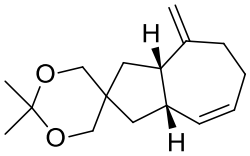
Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53-5.49 (m, 1H), 5.33 (d, *J* = 11.5 Hz, 1H), 4.79 (s, 1H), 4.74 (app. q, *J* = 1.5 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.03 (br s, 1H), 2.93 (q, *J* = 8.4 Hz, 1H), 2.36-2.19 (m, 5H), 2.46 (dt, *J* = 13.4, 7.2 Hz, 2H), 2.15-2.08 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.19 (e), 172.66 (e), 150.36 (e), 132.26 (o), 129.11 (o), 111.09 (e), 59.00 (e), 52.90 (o), 52.82 (o), 48.81 (o), 41.44 (e), 41.11 (o), 38.05 (e), 33.89 (e), 29.71 (e).

IR (Neat) 2951 (m), 1731 (vs), 1640 (w), 1434 (m), 1249 (vs), 1196, (vs), 1158 (vs), 1120 (m), 1067 (m), 1028 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{20}O_4Na$ 287.1362, found 287.1246.



(3a*S*, 8a*S*)-2',2'-dimethyl-4-methylene-3,3a,4,4,5,6,8a-hexahydro-1*H*-spiro[azulene-2,5'-[1,3]dioxane] 160.

Colour and State: Colourless oil

Compound **160** (80% yield on 0.25 mmol scale) was prepared according to the representative [4+3] carbocyclisation reaction experimental procedure.

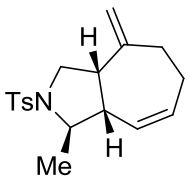
Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54-5.49 (m, 1H), 5.31 (app. dt, *J* = 11.4, 2.5 Hz, 1H), 4.79 (s, 1H), 4.74 (app. t, *J* = 1.4 Hz, 1H), 3.68 (app. d, *J* = 1.1 Hz, 2H), 3.60 (s, 2H), 3.03-2.99 (m, 1H), 2.87 (dt, *J* = 10.7, 7.3 Hz, 1H), 2.40-2.34 (m, 1H), 2.33-2.23 (m, 2H), 2.19-2.09 (m, 1H), 1.87 (dd, A of ABX, J_{AB} = 13.3 Hz, J_{AX} = 7.3 Hz, 1H), 1.78 (dd, B of ABX, J_{AB} = 13.5 Hz, J_{BX} = 7.5 Hz, 1H), 1.60-1.53 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.88 (e), 134.01 (o), 128.95 (o), 110.61 (e), 97.82 (e), 70.47 (e), 69.56 (e), 48.99 (o), 41.43 (e), 41.03 (o), 40.80 (e), 37.61 (e), 33.82 (e), 30.46 (e), 24.28 (o), 23.76 (o).

IR (Neat) 2991 (w), 2933 (m), 2855 (m), 1638 (m), 1452 (m), 1381 (m), 1368 (m), 1251 (m), 1198 (s), 1155 (m), 1104 (m), 1069 (m), 1034 (m) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{16}H_{24}O_2$ 249.1849, found 249.1848.



(1*R*,3a*S*,8a*S*)-1-methyl-4-methylene-2-tosyl-1,2,3,3a,4,5,6,8a-octahydrocyclohepta[*c*]pyrrole 218.

Colour and State: Pale yellow oil

Compound **218** (70% yield on 0.25 mmol scale) was prepared according to the representative [4+3] carbocyclisation reaction experimental procedure.

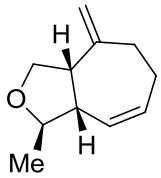
Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.31-7.29 (m, 2H), 5.23-5.18 (m, 1H), 4.83-4.82 (m, 1H), 4.65 (app. t, *J* = 1.5 Hz, 1H), 4.55-4.52 (m, 1H), 3.65 (dd, A of ABX, J_{AB} = 8.7 Hz, J_{AX} = 7.2 Hz, 1H), 3.56 (dq, *J* = 6.5, 2.0 Hz, 1H), 3.27-3.31 (m, 1H), 3.07 (dd, B of ABX, J_{BX} = 10.3 Hz, J_{AB} = 8.7 Hz, 1H), 2.74-2.71 (m, 1H), 2.42 (s, 3H), 2.36-2.31 (m, 1H), 2.27-2.16 (m, 2H), 2.07-1.98 (m, 1H), 1.36 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.02 (e), 143.32 (e), 134.81 (e), 130.58 (o), 129.93 (o), 129.63 (o), 127.66 (o), 112.37 (e), 63.86 (o), 51.55 (e), 46.93 (o), 46.90 (o), 32.97 (e), 31.19 (e), 22.98 (o), 21.69 (o).

IR (Neat) 2929 (w), 1642 (w), 1598 (w), 1494 (w), 1457 (w), 1377 (w), 1340 (s), 1304 (w), 1162 (s), 1093 (m), 1057 (m), 1017 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{23}NO_2NaS$ 340.1347, found 340.1347.



(1*R*,3a*S*,8a*S*)-1-methyl-4-methylene-3,3a,4,5,6,8a-hexahydro-[1*H*]-cyclohepta[*c*]furan 220.

Colour and State: Pale yellow oil

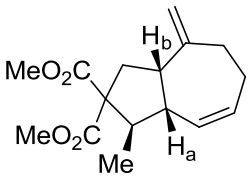
Compound **220** (58% yield on 0.25 mmol scale) was prepared according to the representative [4+3] carbocyclisation reaction experimental procedure. Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68-5.63 (m, 1H), 5.37 (dd, *J* = 11.2, 4.3 Hz, 1H), 4.85 (s, 1H), 4.79 (s, 1H), 4.08 (ddd, A of ABXY, J_{AB} = 8.6 Hz, J_{AX} = 7.3 Hz, J_{AY} = 1.3 Hz, 1H), 3.85 (ddd, B of ABXY, J_{AB} = 8.8 Hz, J_{BX} = 5.9 Hz, J_{BY} = 1.1 Hz, 1H), 3.70 (ddq, *J* = 9.0, 6.0, 1.1 Hz, 1H), 3.17 (app. q, *J* = 7.2 Hz, 1H), 2.54 (app. t, *J* = 8.9 Hz, 1H), 2.43-2.30 (m, 3H), 2.19-2.13 (m, 1H), 1.28 (dd, *J* = 6.0, 1.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.53 (e), 129.43 (o), 127.84 (o), 111.08 (e), 80.77 (o), 71.36 (e), 49.74 (o), 48.16 (o), 34.64 (e), 28.49 (e), 19.67 (o).

IR (Neat) 2968 (m), 2928 (m), 2865 (m), 1643 (m), 1455 (w), 1380 (m), 1220 (w), 1106 (m), 1080 (m), 1033 (m) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{11}H_{17}O$ 165.1201, found 165.1270.



(3*R*,3a*R*,8a*S*)-dimethyl 3-methyl-8-methylene-3,3a,6,7,8,8a-hexahydroazulene-2,2 (1*H*)-dicarboxylate 222.

Colour and State: Pale yellow oil

Compound **222** (78% yield on 0.25 mmol scale) was prepared according to the representative [4+3] carbocyclisation reaction experimental procedure.

Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

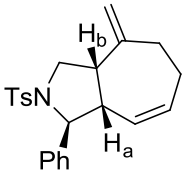
Relative Stereochemistry (nOe analysis): Me to H_a (4.5%), H_a to H_b (5.5%) and H_b to H_a (4.3%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64-5.59 (m, 1H), 5.46 (dd, *J* = 11.0, 4.5 Hz, 1H), 4.77 (s, 1H), 4.65 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.19 (app. q, *J* = 7.9 Hz, 1H, **H_b**), 2.66-2.61 (m, 1H), 2.52 (dd, *J* = 13.8, 7.9 Hz, 1H, **H_a**), 2.44 (dq, *J* = 13.6, 6.8 Hz, 1H), 2.35-2.21 (m, 3H), 2.15-2.07 (m, 2H), 1.07 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.59 (e), 172.09 (e), 150.53 (e), 130.89 (o), 128.86 (o), 110.34 (e), 62.58 (e), 52.55 (o), 52.17 (o), 47.71 (o), 46.81 (o), 45.59 (o), 38.53 (e), 34.56 (e), 28.22 (e), 15.00 (o).

IR (Neat) 2952 (w), 1728 (s), 1641 (w), 1456 (w), 1434 (m), 1378 (w), 1352 (w), 1247 (s), 1199 (m), 1179 (m), 1133 (w), 1094 (w), 1066 (w), 1048 (w), 1014 (w) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{16}H_{22}O_4Na$ 301.1425, found 301.1416.



(1*S*,3a*S*,8a*S*)-4-methylene-1-phenyl-2-tosyl-1,2,3,3a,4,5,6,8a-octahydrocyclohepta[*c*]pyrrole 219.

Colour and State: Pale yellow oil

Compound **219** (80% yield on 0.25 mmol scale) was prepared according to the representative [4+3] carbocyclisation reaction experimental procedure. Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

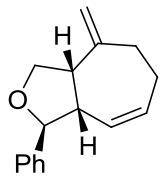
Relative Stereochemistry (nOe analysis): Phenyl hydrogen(s) to H_a (3.9%), H_a to H_b (5.4%) and H_b to H_a (4.4%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.31-7.26 (m, 7H), 5.30-5.26 (m, 1H), 4.84 (s, 1H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.68 (s, 1H), 4.64 (s, 1H), 3.84 (t, A of ABX, J_{AB} = 8.7 Hz, 1H), 3.37 (t, B of ABX, J_{AB} = 8.7 Hz, 1H), 3.20 (app. q, *J* = 8.9 Hz, 1H, **H_b**), 3.03-2.99 (m, 1H, **H_a**), 2.42 (s, 3H), 2.29-2.14 (m, 3H), 2.08-2.01 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.66 (e), 143.38 (e), 142.03 (e), 135.18 (e), 130.85 (o), 129.56 (o), 129.11 (o), 128.37 (o), 127.58 (o), 127.31 (o), 126.36 (o), 112.60 (e), 70.44 (o), 51.73 (e), 49.95 (o), 45.97 (o), 33.21 (e), 30.95 (e), 21.66 (o).

IR (Neat) 2932 (w), 1638 (w), 1598 (w), 1493 (w), 1451 (w), 1340 (s), 1303 (w), 1289 (w), 1160 (s), 1117 (m), 1089 (m), 1026 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{23}H_{25}NO_2NaS$ 402.1512, found 402.1504.



(1*S*,3a*S*,8a*S*)-4-methylene-1-phenyl-3,3a,4,5,6,8a-hexahydro-1*H*-cyclohepta[*c*]furan 221.

Colour and State: Pale yellow oil

Compound **221** (72% yield on 0.25 mmol scale) was prepared according to the representative [4+3] carbocyclisation reaction experimental procedure.

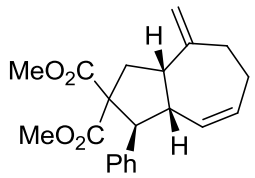
Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 5.71-5.66 (m, 1H), 5.36 (dd, *J* = 11.1, 3.5 Hz, 1H), 4.94 (s, 1H), 4.90 (s, 1H), 4.62 (d, *J* = 8.5 Hz, 1H), 4.32 (dd, A of ABX, J_{AB} = 8.7 Hz, J_{AX} = 7.0 Hz, 1H), 4.10 (dd, B of ABX, J_{AB} = 8.7 Hz, J_{BX} = 5.3 Hz, 1H), 3.28 (app. q, *J* = 6.3 Hz, 1H), 2.97-2.92 (m, 1H), 2.50-2.36 (m, 3H), 2.22-2.15 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.25 (e), 141.88 (e), 129.65 (o), 128.48 (o), 127.74 (o), 127.56 (o), 126.35 (o), 111.31 (e), 86.37 (o), 72.36 (e), 51.26 (o), 47.78 (o), 35.04 (e), 28.40 (e).

IR (Neat) 2930 (w), 2867 (w), 1720 (w), 1642 (m), 1603 (w), 1493 (w), 1454 (m), 1358 (w), 1215 (w), 1060 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{16}H_{18}ONa$ 249.1265, found 249.1255.



(3*S*,3a*S*,8a*S*)-dimethyl 8-methylene-3-phenyl-3,3a,6,7,8,8a-hexahydroazulene-2,2(1*H*)-dicarboxylate 223.

Colour and State: Pale yellow oil

Compound **223** (81% yield on 0.25 mmol scale) was prepared according to the representative [4+3] carbocyclisation reaction experimental procedure. Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

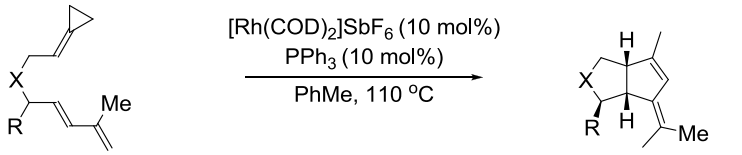
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19-7.30 (m, 5H), 5.51-5.56 (m, 1H), 5.19 (dd, *J* = 11.3, 3.7 Hz, 1H), 4.90 (s, 1H), 4.66 (s, 1H), 3.80 (d, *J* = 12.1 Hz, 1H), 3.73 (s, 3H), 3.36-3.46 (m, 2H), 3.23 (s, H), 2.90 (dd, A of ABX, J_{AB} = 14.4 Hz, J_{BX} = 8.0 Hz, 1H), 2.33-2.46 (m, 3H), 2.26 (dd, B of ABX, J_{AB} = 14.4 Hz, J_{BX} = 5.0 Hz, 1H), 2.07 (ddd, *J* = 13.5, 9.5, 3.6 Hz, 1H),

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.69 (e), 171.82 (e), 150.61 (e), 138.35 (e), 130.02 (o), 129.17 (o), 128.70 (o), 128.13 (o), 127.22 (o), 110.48 (e), 64.13 (e), 55.71 (o), 52.68 (o), 51.97 (o), 46.40 (o), 44.73 (o), 38.79 (e), 36.11 (e), 27.33 (e).

IR (Neat) 2950 (w), 1725 (s), 1642 (w), 1602 (w), 1497 (w), 1454 (w), 1433 (m), 1253 (s), 1206 (m), 1177 (m), 1107 (w), 1084 (w), 1036 (w) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{21}H_{24}O_4Na$ 363.1588, found 363.1572.

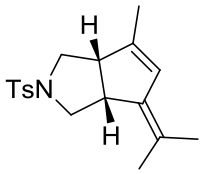
2.8.7 Representative Experimental Procedure for the Rhodium(I)-Catalysed [3+2] Carbocyclisation Reaction



132: R = H, X = NTs
146: R = H, X = O
147: R = H, X = $C(CO_2Me)_2$
148: R = H, X = $C[(CH_2O)_2C(Me)_2]$
171: R = Me, X = NTs
172: R = Ph, X = NTs
173: R = Me, X = O
174: R = Ph, X = O
175: R = Me, X = $C(CO_2Me)_2$
176: R = Ph, X = $C(CO_2Me)_2$

142: R = H, X = NTs
162: R = H, X = O
163: R = H, X = $C(CO_2Me)_2$
164: R = H, X = $C[(CH_2O)_2C(Me)_2]$
224: R = Me, X = NTs
225: R = Ph, X = NTs
226: R = Me, X = O
227: R = Ph, X = O
228: R = Me, X = $C(CO_2Me)_2$
229: R = Ph, X = $C(CO_2Me)_2$

$Rh(COD)_2SbF_6$ (0.014 g, 0.025 mmol) and PPh_3 (0.0065 g, 0.025 mmol) were inserted into a flamed dried reaction vessel, followed by the addition of toluene (2 mL). The vessel was placed under vacuum and backfilled with argon, heated up to 110 ˚C for 10 min to produce a brown-yellowish solution. The requisite ACP-diene (*E*)-**132** (0.079 g, 0.25 mmol) in toluene (3 mL) was added *via* syringe pump over a period of 6 h (0.5 mL/h). The reaction mixture was stirred at the same temperature for 1-2 h after the addition had been completed (t.l.c. control). The reaction mixture was allowed to cool to room temperature, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% diethyl ether/petroleum ether) furnished *cis*-fused bicyclopentadiene **142** as a colourless oil (0.071 g, 0.22 mmol, 89%).



(3a*R*,6a*S*)-6-methyl-4-(propan-2-ylidene)-2-tosyl-1,2,3,3a,4,6a-hexahydrocyclopenta[*c*]pyrrole 142.

Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

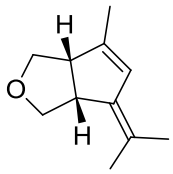
Relative stereochemistry: X-ray crystallography (**Figure 7**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 5.91 (s, 1H), 3.36 (app. t, A of ABX, J_{AB} = 9.4 Hz, 1H), 3.30 (q, *J* = 6.9 Hz, 1H), 3.13-3.21 (m, 2H), 3.03 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 3.1 Hz, 1H), 2.87 (dd, B of ABX, J_{AB} = 9.3 Hz, J_{BX} = 5.0 Hz, 1H), 2.43 (s, 3H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.63 (e), 141.18 (e), 132.33 (e), 129.63 (o), 128.17 (o), 127.78 (o), 121.30 (e), 54.24 (e), 52.06 (o), 50.95 (e), 44.81 (o), 21.68 (o), 21.37 (o), 20.81 (o), 15.76 (o).

IR (Neat) 2970 (w), 2922 (w), 2839 (m), 1597 (m), 1333 (s), 1159 (s), 1097 (s), 1026 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{23}NO_2NaS$ 340.1347 found, 340.1353.



(3a*R*,6a*S*)-6-methyl-4-(propan-2-ylidene)-3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan 162.

Colour and State: Pale yellow oil

Compound **162** (68% yield on 0.25 mmol scale) was prepared according to the representative [3+2] carbocyclisation reaction experimental procedure.

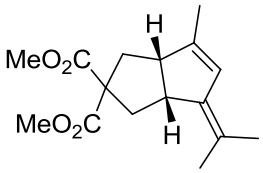
Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 3.90 (t, *J* = 8.1 Hz, 1H), 3.73 (dd, A of ABX, J_{AB} = 8.9 Hz, J_{AX} = 4.0 Hz, 1H), 3.70 (dd, *J* = 8.8, 5.2 Hz, 1H), 3.62 (dd, B of ABX, J_{AB} = 8.6 Hz, J_{AX} = 3.9 Hz, 1H), 3.41-3.37 (m, 1H), 3.26 (app. t, *J* = 7.7 Hz, 1H), 1.81 (s, 3H), 1.73 (s, 3H), 1.67 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.70 (e), 142.18 (e), 127.59 (o), 120.52 (e), 74.93 (e), 70.83 (e), 54.03 (o), 46.49 (o), 21.39 (o), 20.84 (o), 16.04 (o).

IR (Neat) 2966 (m), 2907 (m), 2849 (m), 1622 (w), 1440 (m), 1372 (w), 1254 (w), 1166 (w), 1075 (m) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{11}H_{17}O$ 165.1201, found 165.1212



(3a*R*,6a*S*)-dimethyl 4-methyl-6-(propan-2-ylidene)-3,3a,6,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate 163.

Colour and State: Pale yellow oil

Compound **163** (89% yield on 0.25 mmol scale) was prepared according to the representative [3+2] carbocyclisation reaction experimental procedure.

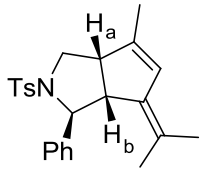
Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (s, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.25 (q, J = 8.4 Hz, 1H), 3.16 (q, J = 7.7 Hz, 1H), 2.64 (dd, A of ABX, J_{AB} = 12.9 Hz, J_{AX} = 8.7 Hz, 1H), 2.49 (dd, B of ABX, J_{AB} = 13.0 Hz, J_{BX} = 8.6 Hz, 1H), 1.99 (dd, A of ABX, J_{AB} = 13.2 Hz, J_{AX} = 6.6 Hz, 1H), 1.95 (dd, B of ABX, J_{AB} = 13.1 Hz, J_{BX} = 7.0 Hz, 1H), 1.77 (s, 3H), 1.70 (br s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.72 (e), 171.97 (e), 146.39 (e), 142.68 (e), 125.53 (o), 119.97 (e), 62.00 (e), 52.89 (o), 52.57 (o), 52.30 (o), 45.08 (o), 40.78 (e), 38.36 (e), 21.36 (o), 20.82 (o), 15.68 (o).

IR (Neat) 2953 (w), 2909 (w), 1732 (s), 1621 (w), 1434 (m), 1255 (s), 1224 (m), 1200 (s), 1161 (m), 1088 (m), 1061 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{16}H_{22}O_4Na$ 301.1416, found 301.1429.



(3*S*,3a*R*,6a*S*)-6-methyl-3-phenyl-4-(propan-2-ylidene)-2-tosyl-1,2,3,3a,4,6a-hexahydrocyclopenta[*c*]pyrrole 225.

Colour and State: Pale yellow oil

Compound **225** (72% yield on 0.25 mmol scale) was prepared according to the representative [3+2] carbocyclisation reaction experimental procedure.

Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

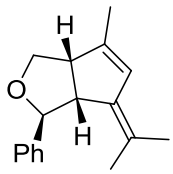
Relative stereochemistry: ^{1}H NMR analysis $^3J_{Ha\text{-}Hb}$ = 7.6 Hz; nOe analysis, Ph to H_b (4.2%), H_a to H_b (4.5%), H_b to H_a (3.4%); X-ray Crystallography (**Figure 10**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.2 Hz, 2H), 7.30-7.21 (m, 5H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.68 (s, 1H), 4.65 (d, *J* = 3.3 Hz, 1H), 3.65 (dd, A of ABX, J_{AB} = 11.4 Hz, J_{AX} = 1.8 Hz, 1H), 3.57 (dd, B of ABX, J_{AB} = 11.3 Hz, J_{BX} = 7.6 Hz, 1H), 3.47 (app. d, *J* = 7.6 Hz, 1H, **H_b**), 3.32 (app. t, *J* = 7.6 Hz, 1H, **H_a**), 2.37 (s, 3H), 1.68 (s, 3H), 1.65 (s, 3H), 1.45 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.20 (e), 142.65 (e), 142.34 (e), 141.56 (e), 136.76 (e), 128.96 (o), 128.60 (o), 127.95 (o), 127.61 (o), 127.55 (o), 127.36 (o), 121.80 (e), 70.89 (o), 54.63 (o), 52.78 (o), 50.04 (e), 21.99 (o), 21.59 (o), 21.10 (o), 15.66 (o).

IR (Neat) 3031 (w), 2907 (w), 1599 (w), 1494 (w), 1444 (w), 1342 (s), 1305 (m), 1157 (s), 1095 (s), 1028 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{24}H_{27}NO_2NaS$ 416.1656, found 416.1660.



(3*S*,3a*R*,6a*S*)-6-methyl-3-phenyl-4-(propan-2-ylidene)-3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan 227.

Colour and State: Pale yellow oil

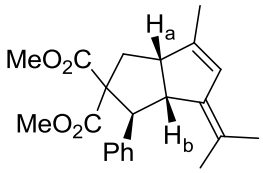
Compound **227** (60% yield on 0.25 mmol scale) was prepared according to the representative [3+2] carbocyclisation reaction experimental procedure. Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.34 (app. t, *J* = 7.1 Hz, 2H), 7.29 (d, *J* = 7.1 Hz, 1H), 6.04 (s, 1H), 4.44 (d, *J* = 4.3 Hz, 1H), 4.16 (app. t, *J* = 7.1 Hz, 1H), 3.72 (d, *J* = 7.8 Hz, 1H), 3.46 (br s, 2H), 1.84 (s, 3H), 1.73 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.68 (e), 141.85 (e), 139.46 (e), 128.54 (o), 127.87 (o), 127.38 (o), 126.56 (o), 122.34 (e), 87.32 (o), 70.28 (e), 54.83 (o), 54.51 (o), 21.82 (o), 21.14 (o), 15.98 (o).

IR (Neat) 2906 (m), 2852 (m), 1441 (m), 1373 (m), 1165 (w), 1058 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{20}ONa$ 263.1416, found 263.1412.



(1*S*,3a*S*,6a*S*)-dimethyl 4-methyl-1-phenyl-6-(propan-2-ylidene)-3,3a,6,6a-tetrahydropentalene-2,2 (1*H*)-dicarboxylate 229.

Colour and State: Pale yellow oil

Compound **229** (75% yield on 0.25 mmol scale) was prepared according to the representative [3+2] carbocyclisation reaction experimental procedure. Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

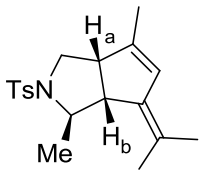
Relative stereochemistry: nOe analysis, Ph to H_b (4.4%), H_a to H_b (1.8%), H_b to H_a (1.4%) – **Figure 10**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.29 (m, 2H), 7.19-7.22 (m, 3H), 5.95 (s, 1H), 4.01 (d, *J* = 3.2 Hz, 1H), 3.61 (s, 3H), 3.55-3.53 (m, 1H, **H_b**), 3.44 (app. t, *J* = 9.2 Hz, 1H, **H_a**), 3.28 (s, 3H), 2.69 (dd, A of ABX, J_{AB} = 14.0 Hz, J_{AX} = 9.1 Hz, 1H), 2.41 (dd, B of ABX, J_{AB} = 14.0 Hz, J_{AX} = 1.4 Hz, 1H), 1.78 (s, 3H), 1.71 (s, 3H), 1.42 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.36 (e), 169.91 (e), 145.00 (e), 143.27 (e), 142.01 (e), 128.85 (o), 128.13 (o), 127.68 (o), 126.96 (o), 120.67 (e), 66.47 (e), 57.92 (o), 53.23 (o), 52.54 (o), 52.28 (o), 52.16 (o), 34.62 (e), 21.84 (o), 21.00 (o), 15.35 (o).

IR (Neat) 2951 (w), 2907 (w), 1735 (s), 1603 (w), 1495 (w), 1433 (m), 1258 (s), 1211 (s), 1155 (s), 1069 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{22}H_{26}O_4Na$ 377.1727, found 377.1729.



(3*R*,3a*R*,6a*S*)-3,6-dimethyl-4-(propan-2-ylidene)-2-tosyl-1,2,3,3a,4,6a-hexahydrocyclopenta[*c*]pyrrole 224.

Colour and State: Pale yellow oil

Compound **224** (76% yield on 0.25 mmol scale) was prepared according to the representative [3+2] carbocyclisation reaction experimental procedure.

Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

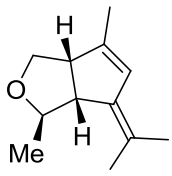
Relative stereochemistry: ^{1}H NMR analysis $^3J_{Ha\text{-}Hb}$ = 7.3 Hz; nOe analysis, Me to H_b (4.0%), H_a to H_b (3.1%), H_b to H_a (3.0%), H_b to Me (2.6%), **Figure 10**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.38 (s, 1H), 3.88 (dq, *J* = 6.6, 1.9 Hz, 1H), 3.51 (dd, A of ABX, J_{AB} = 12.0 Hz, J_{AX} = 1.4 Hz, 1H), 3.45 (dd, B of ABX, J_{AB} = 12.0 Hz, J_{BX} = 7.2 Hz, 1H), 3.12 (app. t, *J* = 7.3 Hz, 1H, **H_a**), 2.92 (d, *J* = 7.3 Hz, 1H, **H_b**), 2.40 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H), 1.35 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.93 (e), 142.77 (e), 142.35 (e), 137.65 (e), 129.01 (o), 128.03 (o), 127.35 (o), 120.75 (e), 63.55 (o), 53.51 (o), 52.78 (o), 48.10 (e), 22.15 (o), 21.60 (o), 21.52 (o), 20.97 (o), 15.56 (o).

IR (Neat) 3053 (w), 2977 (w), 2901 (m), 2853 (w), 1624 (w), 1445 (m), 1331 (m), 1302 (m), 1156 (s), 1138 (s), 1108 (m), 1089 (s), 1032 (m), 1016 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{25}NO_2NaS$ 354.1495, found 354.1504.



(3*R*,3a*R*,6a*S*)-3,6-Dimethyl-4-(propan-2-ylidene)-3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan 226.

Colour and State: Pale yellow oil

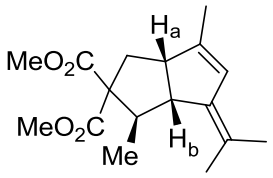
Compound **226** (67% yield on 0.25 mmol scale) was prepared according to the representative [3+2] carbocyclisation reaction experimental procedure. Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (s, 1H), 3.94 (app. t, *J* = 8.1 Hz, 1H), 3.77 (quin, *J* = 6.2 Hz, 1H), 3.66 (dd, *J* = 8.9, 3.3 Hz, 1H), 3.00-2.98 (m, 1H), 3.31 (app. t, 7.8 Hz, 1H), 1.80 (s, 3H), 1.74 (s, 3H), 1.71 (s, 3H), 1.30 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.89 (e), 141.00 (e), 126.91 (o), 121.11 (e), 81.78 (o), 68.44 (e), 54.54 (o), 53.62 (o), 21.78 (o), 21.05 (o), 20.30 (o), 15.90 (o).

IR (Neat) 2967 (m), 2908 (m), 2852 (s), 1624 (w), 1442 (m), 1372 (m), 1111 (s), 1065 (m), 1039 (m), 1018 (m) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{12}H_{19}O$ 179.1358, found 179.1364



(1*R*,3a*S*,6a*R*)-dimethyl-1,4-dimethyl-6-(propan-2-ylidene)-3,3a,6,6a tetrahydropentalene-2,2(1*H*)-dicarboxylate 228.

Colour and State: Pale yellow oil

Compound **228** (68% yield on 0.25 mmol scale) was prepared according to the representative [3+2] carbocyclisation reaction experimental procedure. Stereochemistry Assignment: *dr* ≥ 19:1 (^{1}H NMR analysis)

Relative stereochemistry: nOe analysis, Me to H_b (4.4%), H_a to H_b (4.5%), H_b to H_a (3.1%), H_b to Me (1.5%).

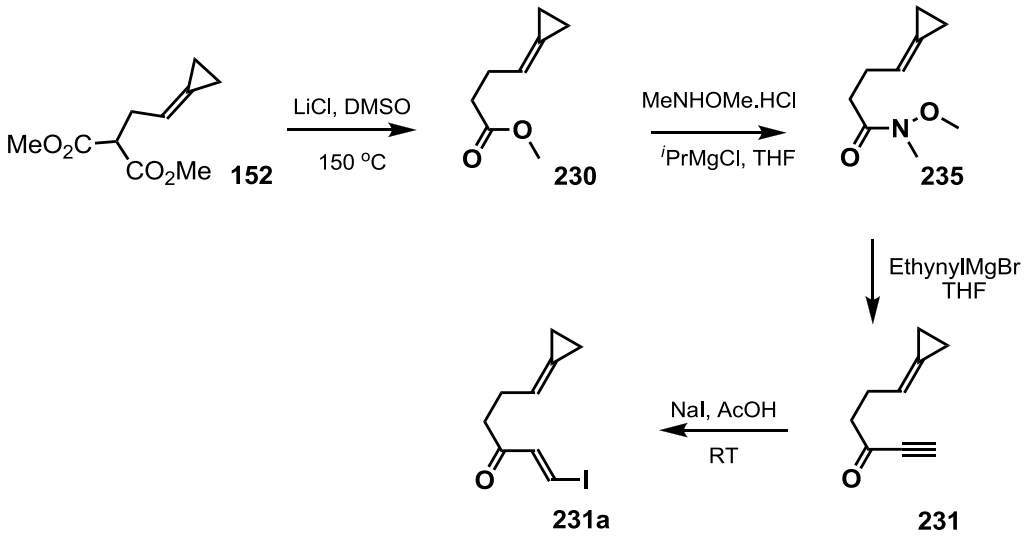
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 3.70 (s, 3H), 3.61 (s, 3H), 3.19 (app. t, *J* = 7.8 Hz, 1H, **H_a**), 2.90 (app. t, *J* = 6.6 Hz, 1H, **H_b**), 2.62 (quin, *J* = 6.5 Hz, 1H), 2.48 (dd, A of ABX, J_{AB} = 13.6 Hz, J_{AX} = 7.6 Hz, 1H), 2.11 (dd, B of ABX, J_{AB} = 13.6 Hz, J_{BX} = 5.6 Hz, 1H), 1.72 (s, 9H), 1.05 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.81 (e), 171.32 (e), 145.90 (e), 142.21 (e), 126.64 (o), 120.31 (e), 64.81 (e), 52.86 (o), 52.39 (o), 52.36 (o), 51.09 (o), 46.20 (o), 34.83 (e), 22.07 (o), 21.03 (o), 17.61 (o), 15.27 (o).

IR (Neat) 2953 (w), 2908 (w), 1730 (s), 1623 (w), 1434 (m), 1378 (w), 1245 (s), 1227 (m), 1203 (s), 1161 (m), 1089 (m), 1504 (m) cm^{-1}.

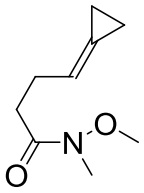
HRMS (ESI, $[M+Na]^+$) calcd for $C_{17}H_{24}O_4Na$ 315.1558, found 315.1572.

2.8.8 Experimental Procedure for the Preparation of Hydroazulenol (1-*epi*-Dictamnol) 238



Lithium chloride (0.42 g, 10.09 mmol) was added at once to a solution of dimethyl 2-(2-cyclopropylideneethyl)malonate **152** (1.00 g, 5.05 mmol) in DMSO (25 mL) at room temperature. The resulting mixture was heated to 150 °C for 16 h. After completion (t.l.c. control), the mixture was allowed to cool to room temperature (*ca.* 1 h), water (50 mL) was added and extracted twice with diethyl ether (2 x 100 mL). The combined organic layers were washed with brine (75 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 2% diethyl ether/petroleum ether) furnished methyl 4-cyclopropylidenebutanoate **230** as a colourless oil (0.42 g, 3.05 mmol, 60%).

Methyl 4-cyclopropylidenebutanoate **230** (2.75 g, 19.62 mmol) and *N*,*O*-dimethylhydroxylamine•HCl (3.83 g, 39.20 mmol) were dissolved in THF (25 mL) at room temperature. The resulting clear solution was cooled to –20 ˚C, followed by slow addition of *iso*-propylmagnesium chloride (29.40 mL, 2.0 M in THF, 58.90 mmol). Afterwards, the reaction mixture was allowed to warm to room temperature until completion (t.l.c. control), then quenched with aqueous NH_4Cl (20 mL) and partitioned with diethyl ether (50 mL). The organic layer was washed with brine (20 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (silica gel, 10% ethyl acetate/petroleum ether) afforded Weinreb amide **235** as a colourless oil (2.15 g, 12.71 mmol, 65%).



4-Cyclopropylidene-*N*-methoxy-*N*-methylbutanamide 235.

Colour and State: Colourless oil

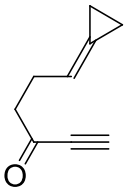
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (tquin, *J* = 6.4, 1.9 Hz, 1H), 3.68 (s, 3H), 3.18 (s, 3H), 2.61-2.57 (m, 2H), 2.53-2.48 (m, 2H), 1.01-1.03 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.41 (e), 122.14 (e), 116.96 (o), 61.32 (o), 32.25 (o), 31.64 (e), 26.96 (e), 2.17 (e), 2.06 (e).

IR (Neat) 2978 (w), 2938 (w), 1662 (s), 1462 (m), 1443 (m), 1413 (m), 1383 (m), 1314 (w), 1177 (m), 1112 (w) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_9H_{16}O_2N$ 170.1171, found 170.1176.

To a cooled solution of Weinreb amide **235** (2.15 g, 12.71 mmol) in THF (50 mL) at 0 ˚C, ethylnylmagnesium bromide (38.1 mL, 0.5 M in THF, 19.06 mmol) was slowly added. The resulting homogeneous yellowish-red solution was allowed to warm to room temperature (*ca.* 15 min) then stirred for a further 2 h (t.l.c. control). The reaction mixture was quenched with 1 M aqueous HCl (25 mL) and extracted with diethyl ether twice (2 x 30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (25 mL) followed by brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% diethyl ether/petroleum ether) afforded **231** as a yellow oil (1.48 g, 11.03 mmol, 87%).



6-Cyclopropylidenehex-1-yn-3-one 231.

Colour and State: Yellowish red oil

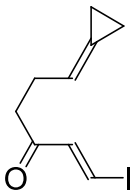
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (tquin, *J* = 6.2, 2.2 Hz, 1H), 3.22 (s, 1H), 2.76 (t, *J* = 7.3 Hz, 2H), 2.54 (q, *J* = 6.8 Hz, 2H), 1.05-0.98 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 187.27 (e), 122.92 (e), 115.54 (o), 81.47 (e), 78.61 (e), 44.81 (e), 26.06 (e), 2.28 (e), 2.12 (e).

IR (Neat) 3260 (w), 2981 (w), 2092 (m), 1677 (s), 1403 (w), 1363 (w), 1218 (w), 1105 (m), 1045 (w) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_9H_{11}O$ 135.0804 found 135.0805.

In a flame dried vessel, NaI (1.92 g, 12.86 mmol) was dried under vacuum with stirring for 10 min, and then the vessel was backfilled with argon followed by the addition of AcOH (35 mL). After stirring for 15 min, the white suspension turned to a light-yellow homogenous solution. 6-Cyclopropylidenehex-1-yn-3-one **231** (1.32 g, 9.89 mmol) was added and stirred for 12 h (t.l.c. control). The reaction mixture was diluted with diethyl ether (75 mL) and neutralised slowly with 3 M NaOH (30 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL). The combined organic layers were washed with water (50 mL) followed by brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (silica gel, 5% diethyl ether/petroleum ether) afforded vinyl iodide (*E*)-**231a** as a dark yellow oil (2.35 g, 8.97 mmol, 91%).



(*E*)-6-Cyclopropylidene-1-iodohex-1-en-3-one 231a.

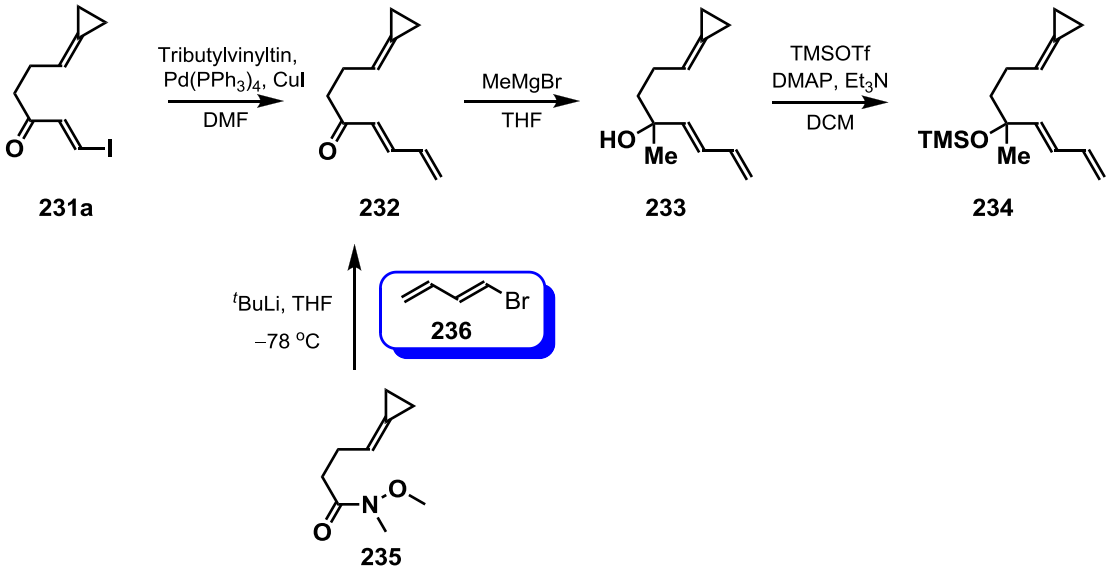
Stereochemistry assignment: *E*/*Z* = ≥19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 15.0 Hz, 1H), 7.15 (d, *J* = 14.9 Hz, 1H), 5.76-5.71 (m, 1H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.46 (q, *J* = 7.6 Hz, 2H), 0.99-0.98 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.97 (e), 144.59 (o), 122.51 (e), 116.15 (o), 98.82 (o), 39.86 (e), 26.02 (e), 2.12 (e).

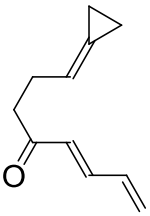
IR (Neat) 3052 (w), 2977 (w), 2907 (w), 1673 (s), 1563 (s), 1187 (m), 1150 (m), 1084 (m) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_9H_{12}IO$ 262.9927, found 262.9933.



$Pd(PPh_3)_4$ (0.51 g, 0.44 mmol) and CuI (2.22 g, 11.66 mmol) were dissolved in degassed DMF (30 mL) in a flame dried flask. To the resulting black suspension, tributyl(vinyl)stannane (3.13 g, 9.86 mmol) and a solution of vinyl iodide (*E*)-**231a** (2.35 g, 8.97 mmol) in de-gassed DMF (10 mL) were added simultaneously. The reaction mixture was stirred vigorously for 4 h (t.l.c. control) then quenched with water (20 mL). The aqueous layer was extracted twice with diethyl ether (2 x 35 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (30 mL), followed by brine (20 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (silica gel, 2% diethyl ether/petroleum ether) afforded (*E*)-**232** as a light yellow oil (1.17 g, 7.21 mmol, 80%).

A solution of (*E*)-1-bromobuta-1,3-diene (*E*)-**236** (0.047 g, 0.35 mmol) in THF (1 mL) was cooled to –78 ˚C, followed by slow addition of *tert*-butylithium (0.22 mL, 1.6 M in pentane, 0.35 mmol) at the same temperature. The resulting solution was stirred for 15 min and then a solution of Weinreb amide **235** (0.050 g, 0.29 mmol) in THF (1 mL) was added. After the reaction had reached completion (t.l.c. control), the mixture was quenched with saturated aqueous NH_4Cl (3 mL) and extracted with diethyl ether twice (2 x 5 mL). The organic layer was washed with water (2 mL), followed by brine (3 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 2% diethyl ether/petroleum ether) afforded dienone (*E*)-**232** as a light yellow oil (0.035g, 0.21 mmol, 73%).



(*E*)-6-Cyclopropylidene-1-iodohex-1-en-3-one 232.

Colour and State: Yellow oil

Stereochemistry assignment: ^{1}H NMR $E/Z \geq 19{:}1$

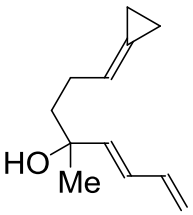
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 15.6, 10.9 Hz, 1H), 6.45 (dt, *J* = 16.9, 10.7 Hz, 1H), 6.19 (d, *J* = 15.6 Hz, 1H), 5.78 (tquin, *J* = 6.0, 2.1 Hz, 1H), 5.64 (d, *J* = 16.9 Hz, 1H), 5.52 (d, *J* = 10.0 Hz, 1H), 2.73 (t, *J* = 7.4 Hz, 2H), 2.50 (q, *J* = 6.5 Hz, 2H), 1.00 (br s, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.39 (e), 142.47 (o), 135.43 (o), 130.47 (o), 126.28 (e), 122.23 (e), 116.67 (o), 40.17 (e), 26.54 (e), 2.14 (e).

IR (Neat) 2979 (w), 2923 (w), 1689 (m), 1664 (s), 1621 (m), 1590 (s), 1411 (w), 1256 (m), 1190 (m), 1142 (m), 1098 (m), 1005 (s) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{11}H_{15}O$ 163.1117, found 163.1116.

Methylmagnesium bromide (4.81 mL, 3 M in THF, 14.42 mmol) was added slowly to a solution of dienone (*E*)-**232** (1.17 g, 7.21 mmol) in THF (35 mL) at 0 ˚C. The reaction mixture was allowed to warm to room temperature, and then stirred for 3 h (t.l.c. control). Afterwards, the mixture was quenched with saturated aqueous NH_4Cl (15 mL), extracted with diethyl ether twice (2 x 25 mL). The combined organic layers were washed with water (20 mL), followed by brine (15 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 15% diethyl ether/petroleum ether) afforded tertiary alcohol (*E*)-**233** as a colourless oil (0.780 g, 4.38 mmol, 60%).



***(E)*-1-Cyclopropylidene-4-methylocta-5,7-dien-4-ol 233.**

Colour and State: Colourless oil

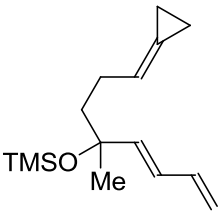
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (dt, *J* = 16.8, 10.1 Hz, 1H), 6.23 (dd, *J* = 15.3, 10.4 Hz, 1H), 5.79-5.74 (m, 2H), 5.20 (dd, *J* = 16.9, 1.5 Hz, 1H), 5.07 (dd, *J* = 10.9, 1.6 Hz, 1H), 2.28-2.17 (m, 2H), 1.767-1.77 (m, 2H), 1.31 (s, 3H), 1.01-1.02 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.89 (o), 136.75 (o), 128.24 (o), 121.72 (e), 118.09 (o), 116.93 (e), 73.15 (e), 41.94 (e), 28.22 (o), 26.83 (e), 2.30 (e), 2.08 (e).

IR (Neat) 3388 (br), 2977 (m), 2926 (w), 1603 (w), 1450 (w), 1411 (w), 1370 (w), 1095 (m), 1003 (s) cm^{-1}.

HRMS (ESI, $[M\text{-}H_2O+NH_4]^+$) calcd for $C_{12}H_{20}N$ 178.1590, found 178.1590.

Imidazole (2.83 g, 41.6 mmol) and DMAP (5.08 g, 41.6 mmol) were dissolved in THF (15 mL), then a solution of (*E*)-**233** (0.74 g, 4.16 mmol) in THF (5 mL) was added. The resulting reaction mixture was stirred for 30 min, and then cooled to –20 °C. Trimethylsilyl trifluoromethanesulfonate (1.84 g, 8.31 mmol) was added to the reaction mixture at –20 °C. After 20 min, the reaction was warmed up to room temperature and then left to stir overnight (t.l.c. control). The resulting brown solution was quenched with NH_4Cl (10 mL) and extracted with diethyl ether (25 mL). The organic layer was washed with water (15 mL), followed by brine (10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 2% diethyl ether/petroleum ether) afforded (*E*)-**208** as a colourless oil (0.75 g, 2.99 mmol, 72%).



(*E*)-(1-Cyclopropylidene-4-methylocta-5,7-dien-4-yloxy)trimethylsilane 234.

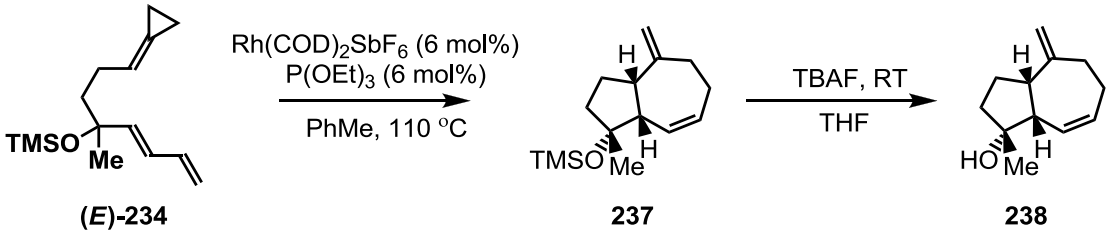
Colour and State: Colourless oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (dt, *J* = 16.9, 10.2 Hz, 1H), 6.15 (dd, *J* = 15.3, 10.4 Hz, 1H), 5.76-5.72 (m, 2H), 5.18 (dd, *J* = 16.9, 1.4 Hz, 1H), 5.05 (dd, *J* = 10.1, 1.3 Hz, 1H), 2.25-2.11 (m, 2H), 1.67 (tq, *J* = 10.7, 6.5 Hz, 2H), 1.34 (s, 3H), 1.01 (br s, 4H), 0.12 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.72 (o), 137.08 (o), 128.24 (o), 120.85 (e), 118.48 (o), 116.46 (e), 75.57 (e), 43.29 (e), 27.90 (o), 26.84 (e), 2.65 (o), 2.22 (e), 2.08 (e).

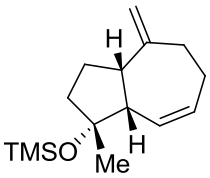
IR (Neat) 2977 (w), 1603 (w), 1451 (w), 1412 (w), 1371 (w), 1304 (w), 1249 (m), 1104 (m), 1051 (m), 1002 (s) cm^{-1}.

HRMS (ESI, $[M]^+$) calcd for $C_{15}H_{26}OSi$ 250.1747, found 250.1752.



(*E*)-234 **237** **238**

$Rh(COD)_2SbF_6$ (0.008 g, 0.015 mmol) was inserted into a flame dried vessel, followed by the addition of toluene (2 mL). The vessel was placed under vacuum and backfilled with argon. $P(OEt)_3$ (0.005 g, 0.015 mmol) was introduced, then heated up to 110 °C for 10 min, which produced a bright yellow solution. The requisite ACP-diene (*E*)-**234** (0.063 g, 0.25 mmol) in toluene (3 mL) was added *via* syringe pump over a period of 6 h (0.5 mL/h). The reaction mixture was stirred for a further 1-2 h, at same temperature after the addition had completed. The reaction mixture was concentrated *in vacuo*, and an NMR analysis was performed on the crude mixture. Purification by flash chromatography (silica gel, 5% diethyl ether/petroleum ether) furnished the (octahydroazulen-1-yloxy)silane **237** as a deep purple oil (0.045 g, 0.18 mmol, 72%).



Trimethyl ((1*R*,3a*S*,8a*S*)-1-methyl-4-methylene-1,2,3,3a,4,5,6,8a-octahydroazulen-1-yloxy)silane 237.

Stereochemistry assignment: *dr* ≥19:1 (^{1}H NMR analysis)

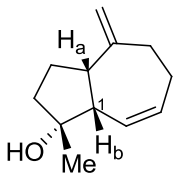
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (dd, *J* = 10.5, 4.1 Hz, 1H), 5.63-5.58 (m, 1H), 4.73 (s, 2H), 2.94 (q, *J* = 9.1 Hz, 1H), 2.58 (ddd, *J* = 10.0, 4.1, 1.7 Hz, 1H), 2.46-2.40 (m, 1H), 2.29-2.14 (m, 3H), 1.94-1.80 (m, 2H), 1.76-1.70 (m, 1H), 1.61-1.53 (m, 1H), 1.35 (s, 3H), 0.10 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.24 (e), 128.66 (o), 128.23 (o), 109.62 (e), 82.92 (e), 52.87 (o), 48.31 (o), 40.59 (e), 33.18 (e), 30.12 (e), 28.08 (e), 27.73 (o), 2.50 (o).

IR (Neat) 2955 (w), 2886 (w), 1642 (w), 1453 (w), 1373 (w), 1248 (m), 1084 (m), 1029 (m), 1008 (m), 835 (s) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{15}H_{27}OSi$ 250.1826, found 251.1825.

TBAF (0.27 mL, 1 M in THF, 0.27 mmol) was added to a solution of compound **237** (0.045 g, 0.180 mmol) in THF (3 mL). The resulting mixture was allowed to stir at room temperature for 2 h. Upon completion (t.l.c. control), the mixture was poured into water (5 mL) and extracted with diethyl ether twice (2 x 15 mL). The combined organic layers were washed with brine (5 mL) and dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 25% diethyl ether/petroleum ether) afforded hydroazulenol **212** as a colourless oil (0.027 g, 0.15 mmol, 85%).



(1*R*,3a*S*,8a*S*)-1-methyl-4-methylene-1,2,3,3a,4,5,6,8a-octahydroazulen-1-ol (1-*epi*-Dictamnol) 238.

Relative Stereochemistry: nOe analysis, Me to H_b (1.5%), H_a to H_b (1.7%), H_b to H_a (1.6%), H_b to Me (0.9%). (**Figure 12**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86-5.81 (m, 1H), 5.59-5.54 (m, 1H), 4.80 (s, 1H), 4.74 (s, 1H), 3.06 (dt, *J* = 10.5, 7.8 Hz, 1H, **H_a**), 2.67 (dd, *J* = 8.7, 7.4 Hz, 1H, **H_b**), 2.58-2.50 (m, 1H), 2.19-2.27 (m, 3H), 1.95-2.01 (m, 2H), 1.81-1.75 (m, 1H), 1.64 (dt, *J* = 10.8, 7.5 Hz, 1H), 1.28 (s, 3H, **Me**).

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.66 (e), 132.44 (o), 125.77 (o), 110.11 (e), 80.52 (e), 53.28 (o), 49.09 (o), 40.41 (e), 32.72 (e), 30.51 (e), 29.39 (e), 27.13 (o).

IR (Neat) 3470 (br), 2956 (m), 164 (w), 1456 (m), 1373 (m), 1269 (w), 1147 (w), 1104 (w), 1069 (m), 883 (s) cm^{-1}.

HRMS (ESI, $[M+NH_3]^+$) calcd for $C_{12}H_{22}ON$ 196.1696, found 196.1693.

2.9 References

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3. Synthetic Studies Towards the Total Synthesis of Zaluzanin E

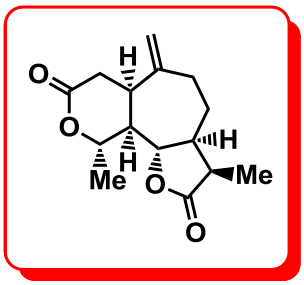
3.1 Introduction

In chapter 2, a highly diastereoselective and efficient rhodium(I)-catalysed [4+3] carbocyclisation reaction for the construction of 5,7-bicyclic rings was described. Herein, we applied the aforementioned methodology to construct a bicyclic ring system which possesses four stereogenic centres and is a key intermediate in our synthetic study towards the first total synthesis of zaluzanin E. The total synthesis of zaluzanin E would alleviate its scarcity and enable the delineation of its biological properties. The synthetic sample of zaluzanin E would also enable the confirmation of its structure.

3.2 Isolation of Zaluzanin E

Zaluzanin E was isolated from the aerial part of *Microliabum polymnioides* plant (**Figure 13**).[1] Its relative stereochemistry was established by proton coupling constant analysis, 2D NOESY correlations and molecular modelling. Although, no X-crystallography data is available yet, density functional theory (DFT) calculations revealed the lowest energy conformer of zaluzanin E at B3LYP/6-31G** level.[2] Also, no report on the biological activity of this scarce compound is available yet.

(A)



(B)

Figure 13: (A) *Microliabum polymnioides* (B) chemical structure of Zaluzanin E

3.3 Hypothesis

We were attracted to this molecule based on the known biological and pharmacological profile of guaianolides (**section 3.4**) and because zaluzanin E represents a rare type of guaianolide, with its two lactone moieties. Additionally, this molecule posed an interesting synthetic challenge because of its unique 6,7,5-tricyclic structure which possesses six-stereogenic centres. The installation of the *cis*-fused six-membered and *trans*-fused five-membered lactones onto the seven-membered ring will possibly be the most challenging aspect of this synthesis.

3.4 Selected Examples of Biologically Active Guaianolides

Guaianolide natural products have been found in modern therapeutic drugs, and some derivatives are currently in clinical trials.[3] For example, salograviolide A inhibits the proliferation of a host of colon-derived cells.[4] Rupicolin A-8-O-acetate possesses *in vitro* anti-plasmodial activity (IC_{50} = 10.8–12.5 μg/mL).[5] Repin induces neurotoxicity in rodents[6] and compound **239** exhibits toxicity towards liver and lung cancer cell lines (**Figure 14**).[7]

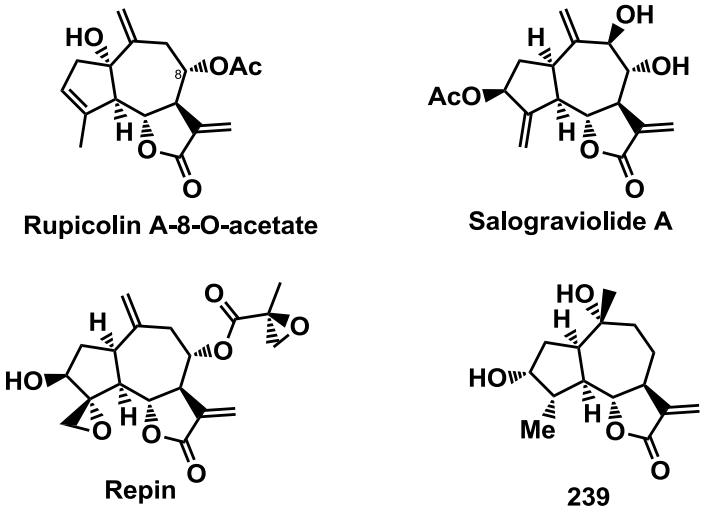


Figure 14: Biologically active guaianolides

3.4.1 Selected Examples of Recently Isolated Guaianolides

The compounds shown in **figure 15** have significant cytotoxicity against human cervix carcinoma KB cancer cell lines.[8] Extensive structural elucidation of these compounds revealed a highly oxygenated molecular architecture, with a C-2–O–C-4 ether bridge specifically found in **240** and **241**.

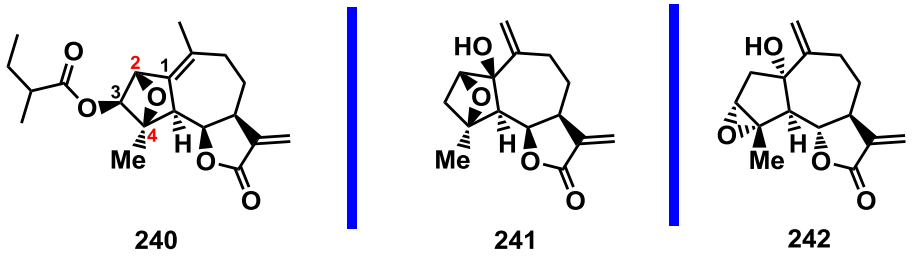


Figure 15: Recently isolated guaianolides

In addition, three highly oxygenated guaianolides rupin A, chrysartemin B and epoxy-trihydroxy-guaianolide (**Figure 16**) were recently isolated from the aerial parts of *Achillea falcate* found in the mountainous areas of Lebanon.[9a] These compounds showed promising anti-cancer activity against human colorectal carcinoma (HCT)-116 cell line. The biological activities of these compounds are related to their basic skeletons, *i.e.* the 5,7-bicyclic ring[9b] and α-methylene γ-butyrolactone,[9c] as well as the presence of the epoxide and the hydroxyl functional groups.

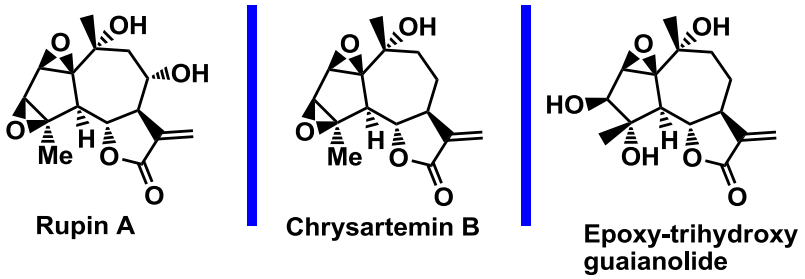
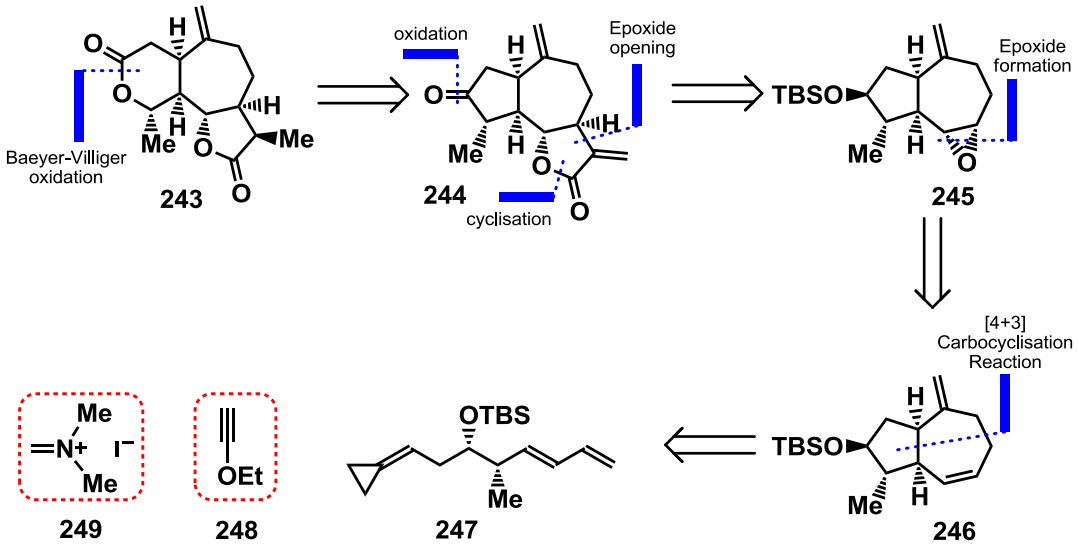


Figure 16: Highly oxygenated guaianolides

3.5 Retrosynthesis of Zaluzanin E

At the outset of our synthetic study, we were prompted to design a retrosynthetic pathway that can be modified to prepare other structurally similar bioactive guaianolides. Towards this end, the total synthesis of zaluzanin E **243** was proposed *via* a *cis*-fused 5,7-bicyclic ring which is present as a core motif in guaianolides. For instance, a pivotal dissection of the six-membered lactone in zaluzanin E **243** would unveil a novel guaianolide estafiatone[10a] **244** (**Scheme 64**). We anticipate that zaluzanin E can be obtained by the chemo- and regioselective Baeyer-Villiger oxidation of estafiatone **244.**[10b] The chemoselectivity is expected to be influenced by the presence of a Lewis acid, and the regiochemical outcome is expected to be controlled by the presence of the methyl substituent.

The construction of the 5-membered lactone in estafiatone **244** could be achieved by opening the epoxide in **245** using **248** in the presence of a base and Lewis acid followed by *in-situ* intramolecular cyclisation. We expect the regioselectivity of the epoxide opening to be controlled by steric factors. The attack of the nucleophile should take place at the least hindered position.[40]

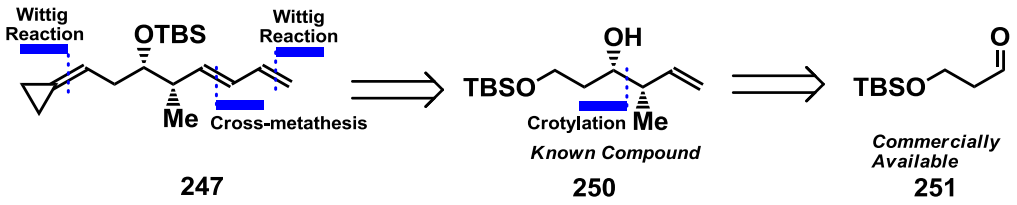


Scheme 64: Retrosynthetic analysis of zaluzanin E **243**

The α-methylene unit on the lactone in **244** can be installed through an enolate reaction with Eschenmoser salt **249** followed by elimination.[39,41] Additionally, the ketone group in **244** can be obtained *via* deprotection followed by oxidation of the silyl protected alcohol in **245**.

The epoxidation of the *cis*-fused 5,7-bicyclc compound **246** is expected to be possible under Jacobsen-Katsuki reaction condition,[30] using Mn(III)salen complex to produce compound **245**. The intermediate **247** which possesses the requisite functional groups, ACP and diene, will be subjected to the diastereoselective [4+3] carbocyclisation reaction for the construction of a highly functionalised *cis*-fused 5,7-bicyclic compound **246**.

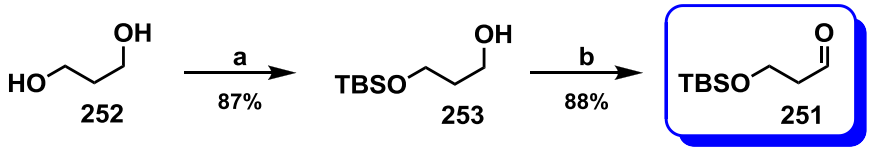
The ACP moiety of **247** will be installed using a Wittig reaction,[11a] and its diene through the combination of cross-metathesis[11b] and a Wittig reaction on compound **250**[11c] (**Scheme 65**). The incorporation of the two stereogenic centres of **250** in a *syn*-fashion could be achieved *via* Brown's crotylation[12] on aldehyde **251**.



Scheme 65: Retrosynthetic analysis of ACP-diene **247**

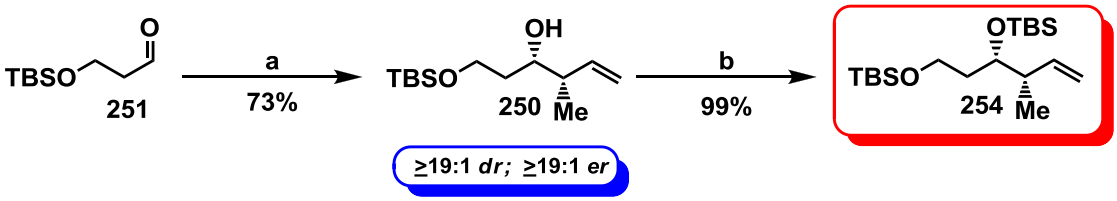
3.6 Synthesis of ACP-Diene 247

The construction of ACP-Diene **247** commenced from the commercially available diol **252** (**Scheme 66**). The selective mono protection of diol **252** under basic condition furnished **253**, subsequent Swern oxidation[13] afforded aldehyde **251** in excellent yield.



Scheme 66: Preparation of aldehyde **251**; Reaction Conditions: a) NaH (1 equiv), TBS-Cl (1 equiv), THF, 0 ˚C to rt, 87% (b) Oxalyl chloride (2 equiv), DMSO (5 equiv), DIPEA (4 equiv), DCM, −78 ˚C, 88%

The aldehyde **251** was subjected to Brown's crotylation using (+)-$(Ipc)_2B(OMe)$ and (*Z*)-$MeCH{=}CHCH_2Li$, which afforded homoallylic alcohol **250** as a single diastereoisomer (82%, ≥19:1 *dr*, ≥19:1 *er*, $[\alpha]_D$ = -0.84).[14] The protection of the secondary hydroxyl group in **250** as a silyl ether was achieved using TBSOTf and 2,6-lutidine[15] to provide compound **254** (**Scheme 67**).



Scheme 67: Preparation of Intermediate **254**: Reaction Conditions: (a) (i) ^{t}BuOK (1.2 equiv), *cis*-2-butene (13 equiv), ^{n}BuLi (1.3 equiv), (+)-$(Ipc)_2B(OMe)$ (1.4 equiv), $BF_3.OEt_2$ (1.7 equiv), THF, –78 °C (ii) 3M NaOH (5 equiv), H_2O_2 (5 equiv), 12 h , –78 °C to rt, 73% (b) TBSOTf (1.2 equiv), 2,6-lutidine (3 equiv), DCM, –78 °C, 99%

Brown crotylation reaction allowed the installation of the two stereogenic centres in one step. Other elegant crotylation reagents that can be utilised are Leighton's strained silacycles,[16] Soderquist TMS-9-BBN reagents,[17] Krische's Ru-catalysed transfer hydrogenation crotylation with butadiene,[18] Panek's chiral crotylsilanes,[19] and Roush's tartrate derived boronates[20] (**Figure 17**).

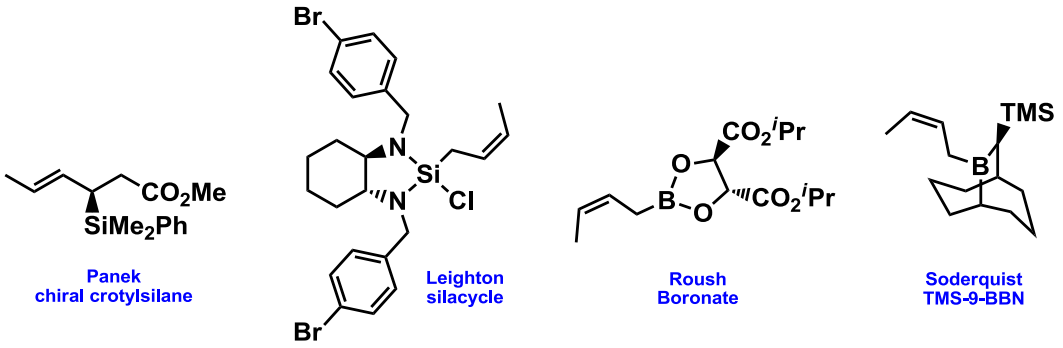
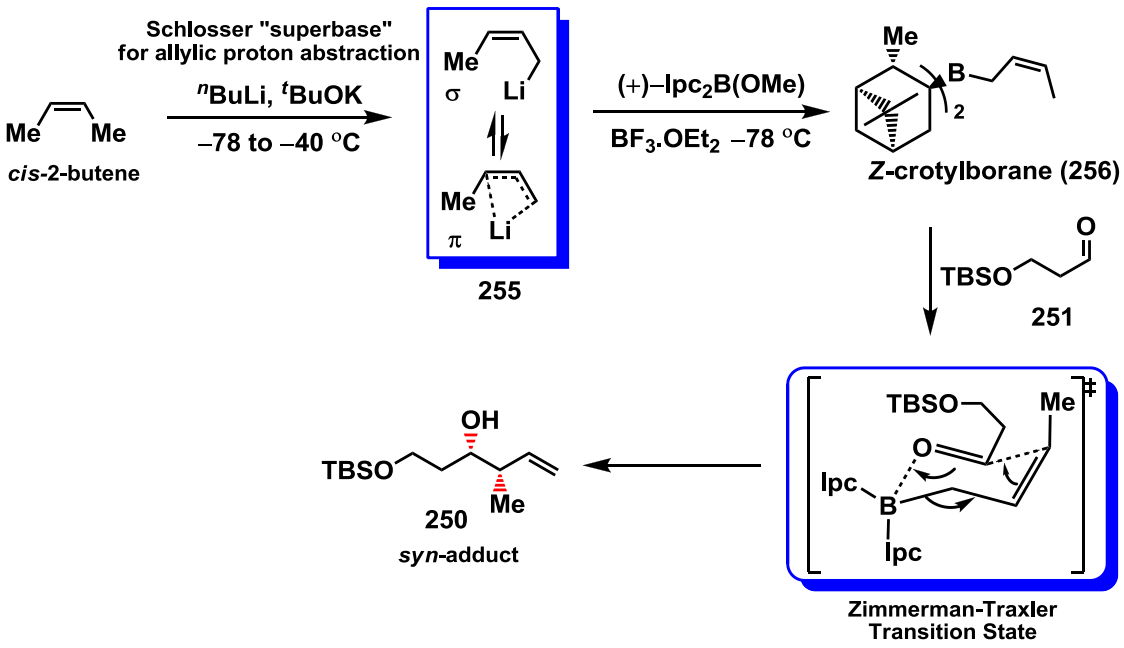


Figure 17: Alternative reagents for the crotylation reaction

The Brown's crotylation strategy was chosen preferentially because it is convenient, requires cheap and commercially available reagents such as *n*-butyl lithium, *tert*-potassium butoxide, *cis*-2-butene and enantiopure borane (+)-$(Ipc)_2B(OMe)$. Additionally, the crotylborane reagent **256** can be prepared in 2 h without employing an organocatalyst or a transition metal. **Scheme 68** explains the mechanism of the crotylation reaction and the rationale for the excellent diastereoselectivity observed in this reaction.

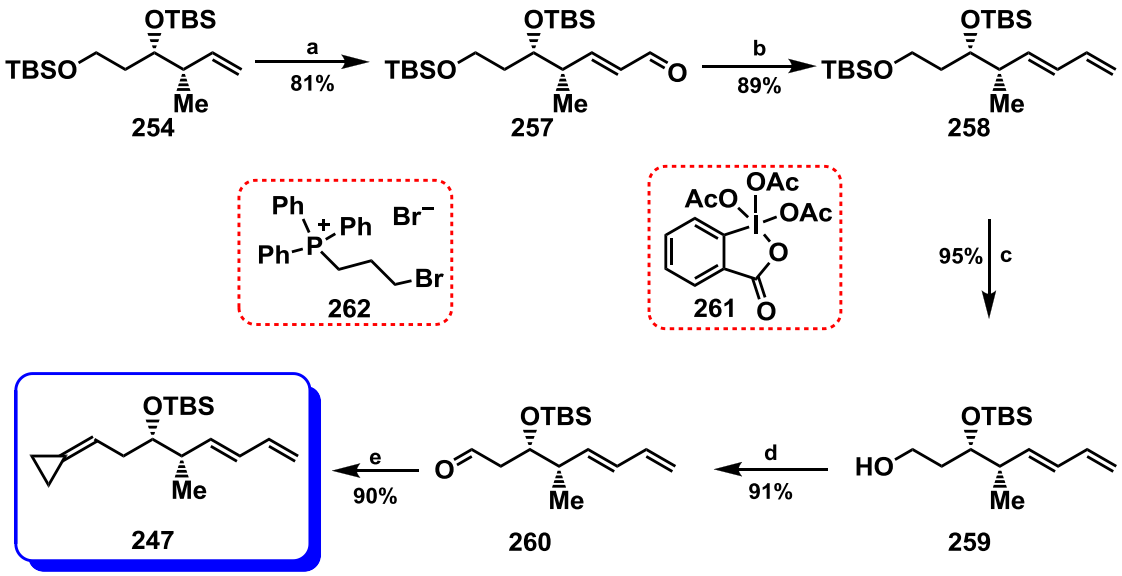


Scheme 68: Proposed mechanism of the crotylation reaction

Allylic deprotonation of the *cis*-2-butene by Schlosser base[21] provided a *cis*-allyllithium species **255**, which reacts with (+)-$(Ipc)_2B(OMe)$ to produce (*Z*)-crotylborane **256**. The reaction of crotylborane **256** with aldehyde **251** produced *syn*-adduct **250**.

The reaction is shown to proceed *via* a chair-like transition state (Zimmerman-Traxler model), with the aldehyde side-chain adopting a pseudo equatorial position to minimise steric repulsion. Previous reports have shown that *trans*-2-butene would generate (*E*)-crotylborane, which upon reaction with an aldehyde would furnish the corresponding *anti*-adduct.[10b]

Scheme 69 shows the complete synthesis of key intermediate ACP-diene **247**. The cross-metathesis[11b] of compound **254** with crotonaldehyde, mediated by 5 mol% of Hoveyda Grubbs 2nd generation (HG-II) catalyst, furnished the α,β-unsaturated aldehyde **257** in 81% yield ($E/Z \geq 19:1$, determined by ^{1}H NMR analysis).



Scheme 69: Preparation of ACP-Diene (*E*)-**247;** Reaction Conditions: a) 5 mol% HG-II, crotonaldehyde (2 equiv), DCM, 60 ˚C, 81% (b) Ph_3PMeBr (3 equiv), ^{n}BuLi (3 equiv), THF, –40 ˚C to rt, 89% (c) HF.pyr (3 equiv), THF, 0 ˚C to rt, 95% (d) Dess-Martin Periodinane **261** (1.2 equiv), DMSO/DCM (1:1), 0 ˚C to rt, 91% (e) (3-bromopropyl)triphenylphosphonium bromide **262** (3 equiv), ^{t}BuOK (6 equiv), THF, 70 ˚C, 90%

We discovered that Grubbs 2nd generation (G-II) catalyst was ineffective in this reaction; compound **254** was recovered after 12 h. Previous report suggested that G-II catalyst requires activation through dissociation of PCy_3 ligand.[22] Hence, the released phosphine can intercept and deactivate the active Ru-carbene complex **263**. Additionally, G-II reactivity also depends on how fast the catalyst binds to the olefin after the loss of PCy_3. In contrast, HG-II is activated through the dissociation of Ru–O chelation, followed by olefin metathesis (**Figure 18**).[23] A seminal report has showed that ruthenium-complexes such as HG-II operates a release (dissociation) and return (association) mechanistic process.[24a]

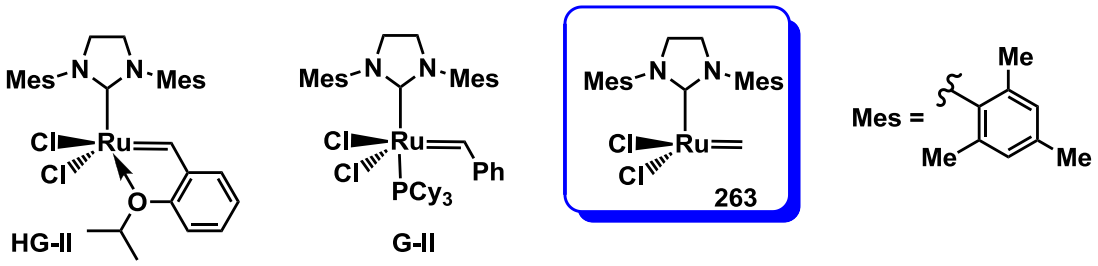
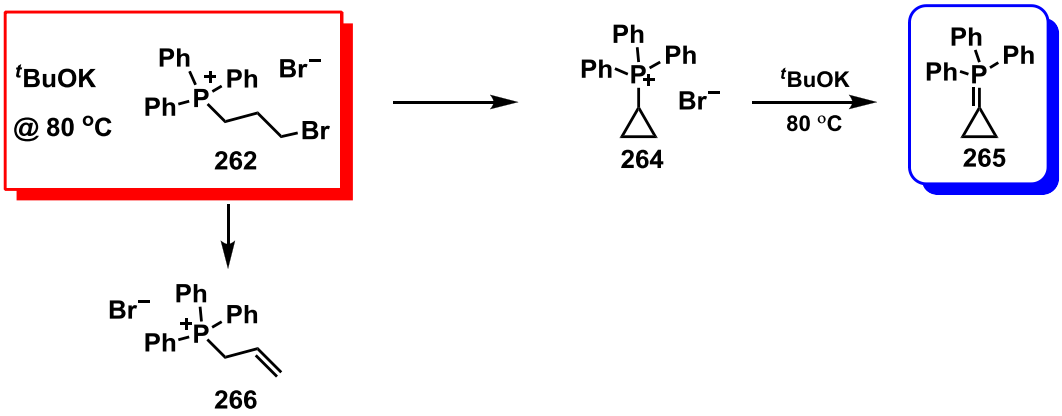


Figure 18: HG-II, G-II and Active Ru-complex specie **263**

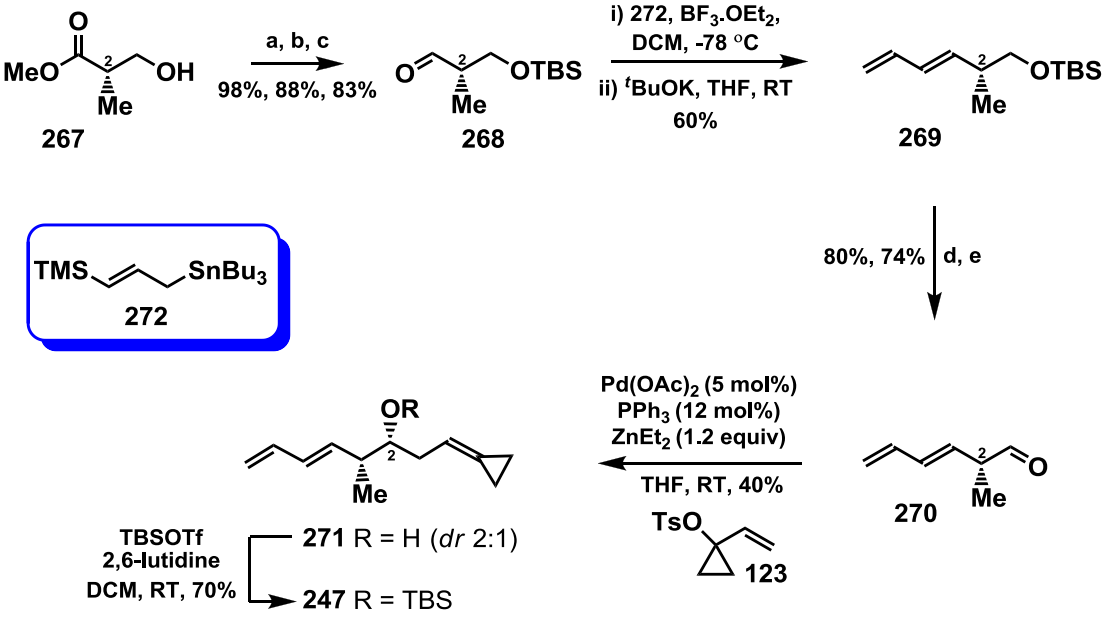
Compound **257** was converted to diene **258** using methyltriphenylphosphonium bromide salt and ^{n}BuLi in THF at –40 ˚C. The orthogonal deprotection of the primary TBS-ether in **258** was achieved by employing HF.pyridine complex in THF at 0 ˚C, producing primary alcohol **259**.

The oxidation of compound **259** using Dess-Martin periodinane (**261**) oxidation[24b] generated aldehyde **260**, and this underwent Wittig olefination with ylide **262** to produce ACP-diene **247**.[11a] Initially, the Wittig reaction proved problematic due to a poor yield, perhaps, due to the formation of **266** (**Scheme 70**). Surprisingly, commercially available ylide **264** was ineffective, since it led to decomposition.



Scheme 70: Formation of phosphorane **265**

The yield of ACP-diene **247** was improved by treating (3-bromopropyl)triphenylphosphonium bromide **262** with 2 equivalents of potassium *tert*-botuxde in THF at 70 ˚C for 2 h, generating the phosphorane **265** *in situ*. Subsequent addition of aldehyde **260** furnished the ACP-diene **247** in 90% yield. The purification of intermediate **247** was achieved by careful and slow column chromatography, using hexane only as eluent.



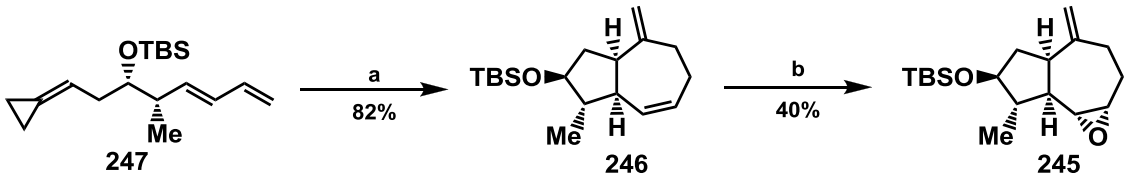
Scheme 71: Alternative route to ACP-Diene (*E*)-**247**; Reaction Conditions: a) DMAP (0.2 equiv), imidazole (1.5 equiv), TBS-Cl (1.3 equiv), DCM, rt, 98% (b) DIBAL-H (2.2 equiv), DCM, –78 ˚C, 88% (c) Dess-Martin Periodinane (1.2 equiv), DCM, 0 ˚C to rt, 83% (d) TBAF (1.5 equiv), THF, rt, 80% (e) Dess-Martin Periodinane (1.2 equiv), DCM, 0 ˚C to rt, 74%

An alternative route (**Scheme 71**) was explored for the construction of compound **247**. The synthesis commenced from chiral (*S*)-Roche ester **267**, which was synthetically transformed in nine linear steps to furnish compound **247**. However, this route proved to be expensive, and compound **247** was obtained as a mixture of diastereoisomers (2:1).

The TBS-ether protection of the primary alcohol in Roche ester **267**, followed by DIBAL-H reduction of the ester and Dess-Martin oxidation furnished aldehyde **268**. The Lewis acid mediated addition of TMS-crotyl stannane **272** to aldehyde **268** afforded a *β*-hydroxysilane,[25] which upon treatment with potassium *tert* butoxide produced the diene **269**.[26] Removal of the silyl ether and oxidation generated compound **270**. The diethylzinc mediated umpolung reaction[27] of **123** (see synthesis in chapter 2) with **270** furnished ACP-diene **271** in poor diastereoselectivity and yield. Subsequent protection of the resulting secondary alcohol gave compound **247** as a mixture of diastereoisomers (2:1).

3.7 Synthesis of Compound 245

The construction of compound **245** is delineated in Scheme **72**. The cationic rhodium(I)-catalysed [4+3] carbocyclisation reaction developed in chapter 2 was applied for the conversion of compound **247** to *cis*-fused 5,7-bicyclic compound **246**. Gratifyingly, the ACP-diene **247** successfully underwent cyclisation when exposed to 6 mol% of $[Rh(COD)_2]SbF_6$ and 6 mol% of $P(OCH_2CF_3)_3$ in PhMe at 110 ˚C to furnish *cis*-fused 5,7-bicyclic ring **246** with excellent diastereoselectivity (*dr* ≥19:1), albeit in 40% yield.



Scheme 72: Preparation of epoxide **245**: Reaction Conditions: a) 6 mol% of $[Rh(COD)_2]SbF_6$, 6 mol% of $P(OEt)_3$, PhMe, 110 ˚C, *dr* ≥19:1, 82% (b) *R*,*R*-Mn(III)-Salen **277** (10 mol%), mCPBA (3 equiv), NMO (5 equiv), DCM, –78 ˚C to rt, 40%

The replacement of $P(OCH_2CF_3)_3$ with $P(OEt)_3$ furnished the 5,7-bicyclic compound **246** in 82% yield without erosion of diastereoselectivity (*dr* ≥19:1). The corresponding 5,5-bicyclic ring was not observed.

This result showcases the successful application of the cationic rhodium(I)-catalysed [4+3] carbocyclisation reaction for the synthesis of a *cis*-fused 5,7-bicyclic core which are prevalent in natural products of interest. This compound, which possesses four contiguous stereogenic centres, was obtained in good yield and excellent diastereoselectivity.

With *cis*-fused 5,7-bicyclic compound **246** in hand, we initiated the process of installing the 5-membered γ-butyrolactone ring. Although numerous studies have been reported for the asymmetric epoxidation of allylic alcohols, the enantioselective epoxidation of unfunctionalised olefins remains limited. In 1986, Kochi and co-workers reported an achiral manganese salen complex **273** as a useful catalyst for the epoxidation of olefins.[28]

In 1990, Katsuki and co-workers reported the synthesis of a chiral manganese salen complex **274** (**Figure 19**). The introduction of the chiral centres closer to the metal centre resulted in stereochemical induction in epoxidation reactions.[29]

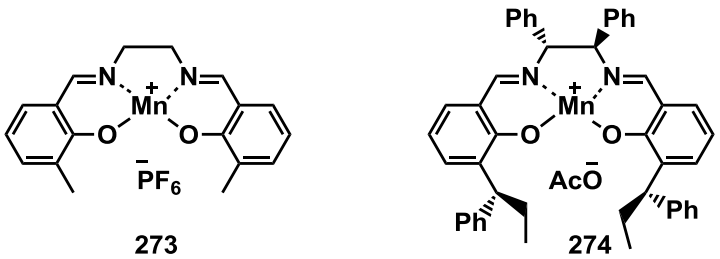
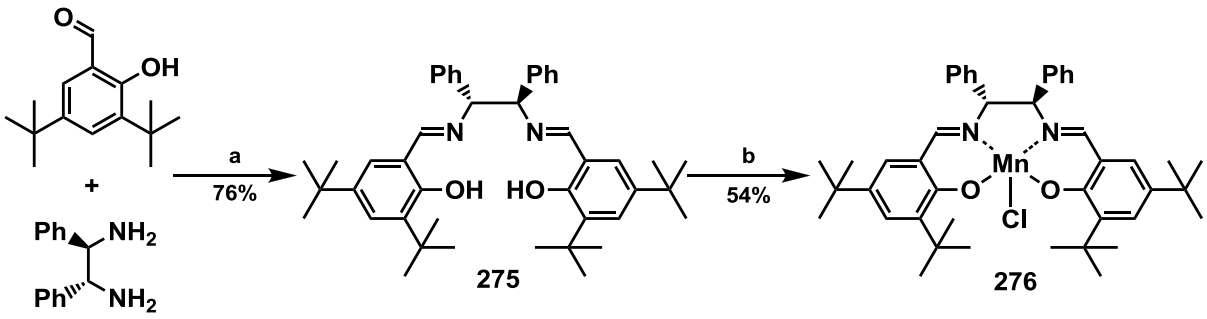


Figure 19: Achiral (**273**) and Chiral (**274**) — Mn(III)-Salen Complexes

In 1995, Jacobsen and co-workers disclosed the combination of *m*-chloroperbenzoic acid (mCPBA) and *N*-methylmorpholine-*N*-oxide (NMO) as an effective oxidant (and additive) system for Mn(III)-salen mediated enantioselective epoxidation of unfunctionalised olefins at low temperature (–78 ˚C).[30] Sodium hypochlorite has also been shown to be an effective and inexpensive oxidant with Mn(III)-salen complex.[31]

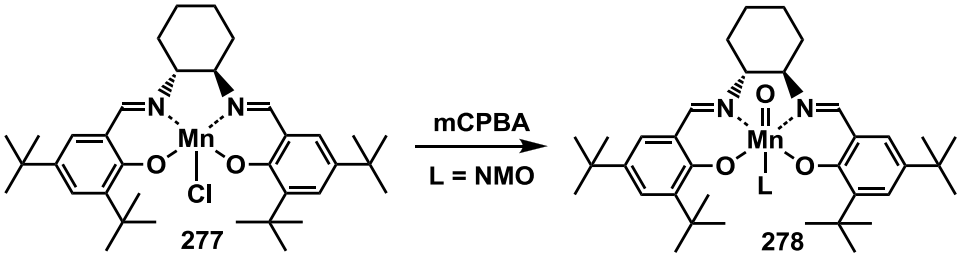
Mn(III)-salen complexes have been investigated in olefin asymmetric epoxidation with hydrogen peroxide as oxidant.[32] However, H_2O_2 causes catalyst deactivation in Mn(III)-salen mediated epoxidations due to radical formation *via* the homolytic cleavage of the weak O-O peroxide bond.[33a] Based on the knowledge of these complexes,[33b] we believed chiral Mn(III)-salen could mediate the epoxidation of compound **246** to produce compound **245** (**Scheme 72**).



Scheme 73: Preparation of Mn(III)-salen complex **276:** Reaction Conditions: a) EtOH, 100 ˚C, 76% (b) LiCl, $Mn(OAc)_2.4H_2O$, EtOH, 100 ˚C to 70 ˚C, 54%

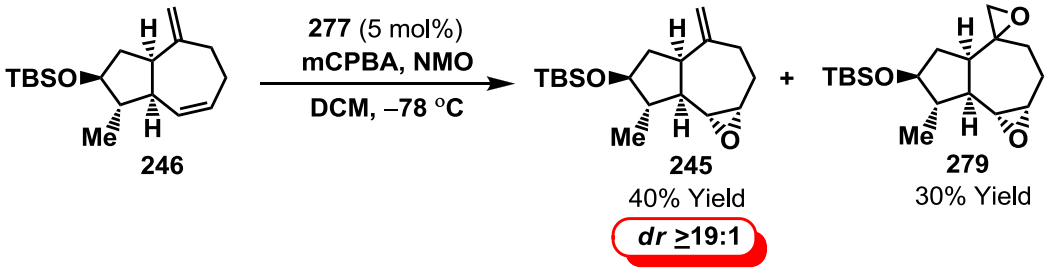
A previous report has shown that chiral Mn(III)-salen complexes are highly selective for *cis*-disubstituted alkenes.[34] Conversely, slow reaction rates and low enantioselectivities were obtained with *trans*-substituted olefins.[35] The aptitude of Mn(III)-salen complexes for *cis*-olefin is an attractive feature to us, given that compound **246** has a *cis* disubstituted endocyclic olefin. Our efforts begun with the synthesis of Mn(III)-salen complex **276** (**Scheme 73**). The chiral (*R*,*R*)-diamine was refluxed with 2 equiv of the aldehyde in ethanol which generated salen ligand **275** as a bright yellow powder in 76% yield.

A sample of $Mn(OAc)_2.4H_2O$ was added to a solution of **275** in ethanol, the resulting dark brown mixture was refluxed for 2 h, followed by the addition of lithium chloride at 70 ˚C. The mixture was diluted with water and cooled to 0 ˚C. The (*R*,*R*)-Mn(III)-salen complex **276** was obtained as a brown powder in 54% yield. Disappointingly, the epoxidation of compound **246** with complex **276**, mCPBA and NMO in DCM at –78 ˚C gave **245** in 20% yield (*50% conv.* over 12 h).



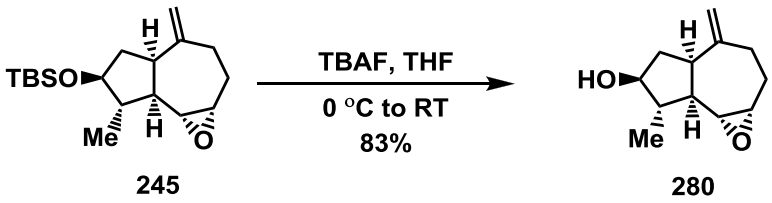
Scheme 74: Formation of Mn(V)-oxo species **278**

However, commercially available (*R*,*R*)-Mn(III) salen complex **277** (**Scheme 74**) was able to mediate the epoxidation of compound **246** to generate compound **245** in 40% yield and side-product **279** in 30% yield (*100% conv.;* 3 h) (**Scheme 75**). The Mn^{V}–oxo complex **278** is postulated to be the active species. A previous report has shown that this species can be detected by electron spray tandem mass spectrometry.[36] Other notable oxidants such as H_2O_2 or NaOCl or dimethyldioxirane (DMDO) or oxone gave no reaction, with most of the starting material being recovered in all cases.



Scheme 75: Mn(III)-salen epoxidation of **246**

We noticed that pyridine-*N*-oxide can be used as an alternative to NMO in this reaction. The over-epoxidation of compound **245** presumably led to the formation of compound **279**. The stereochemical model proposed by Jacobsen and co-workers suggested that (*R,R*)-Mn(III)salen complex **277** would deliver the oxygen atom from the Mn^{V}-oxo complex **278** to the least hindered face of hydroazulene structure of compound **246**.[37]



Scheme 76: Protodesilylation of compound **245**

It appears that a skewed side-on approach (Katsuki's model[33b], **Figure 20**) of **246** parallel to the salen-ligand is favoured. This approach will avoid the sterically demanding *tert*-butyl groups (side on approach) on the aryl rings.[38]

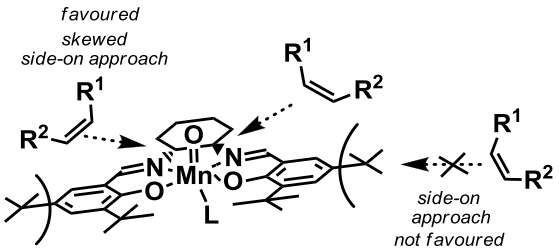


Figure 20: Skewed-side on approach (Katsuki's model)

2D NOESY analysis was used to provide evidence for the stereochemistry of compound **280** (**Figure 21**). The fifteen silyl hydrogen's interfere with the efficient interpretation of the 2D spectra of **246**. Deprotection of the silyl protecting group from compound **246** with TBAF gave **280** (**Scheme 76**). This allowed the efficient determination of the stereochemistry of compound **280**.

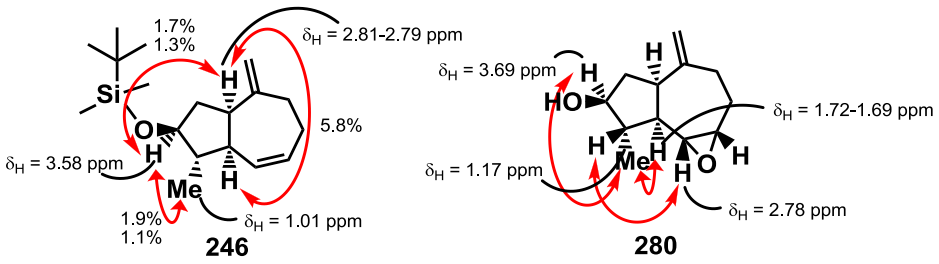


Figure 21: nOe analysis of **246**, 2D NOESY correlation of **280**

3.8 Epoxide Opening and Cyclisation

We envisaged that the *trans*-γ-butyrolactone could be introduced *via* an epoxide opening with an appropriate carbon nucleophile. The point of attack of the nucleophile on the epoxide would be expected to be from the least sterically congested direction. In a similar fashion, the regioselective epoxide opening by a nucleophile on a related system was described by Danishefsky[39] and Rigby[40] in their total synthesis of vernolepin, dehydrocostus lactone and estafiatin (**Figure 22**).

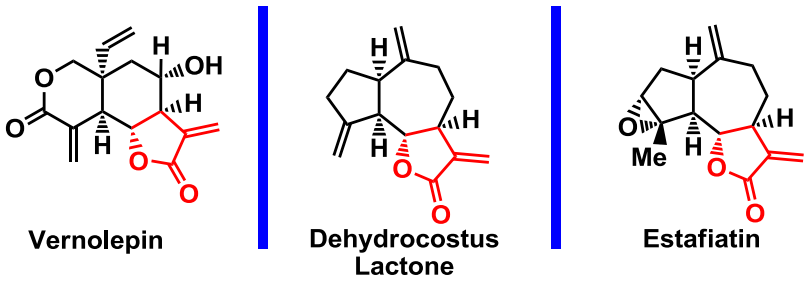
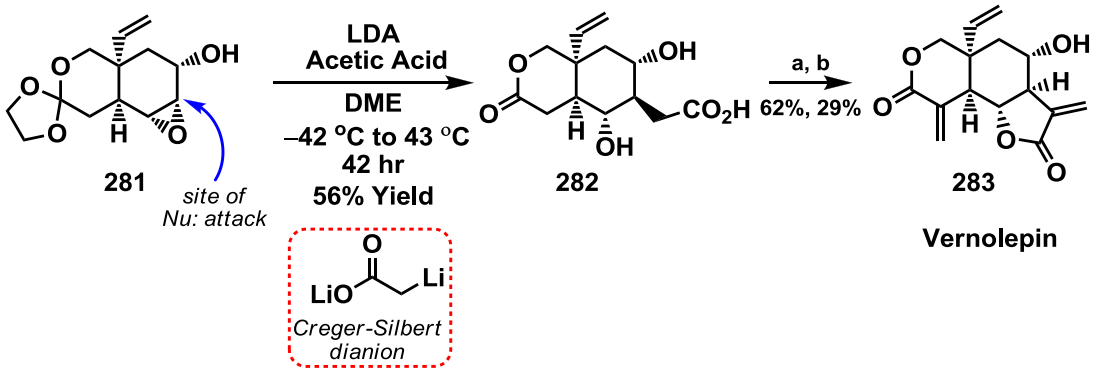


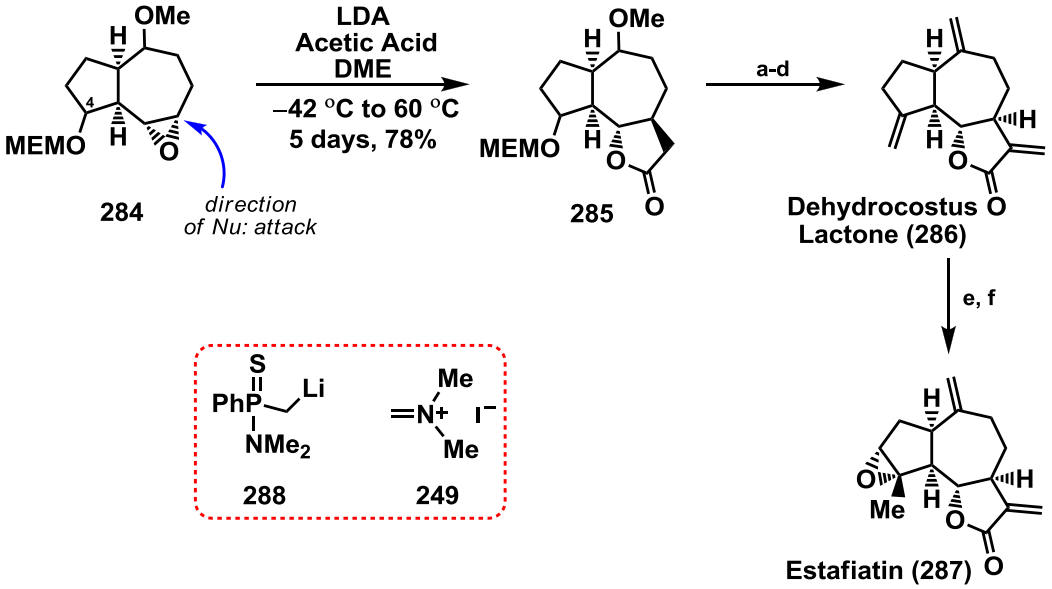
Figure 22: *Trans*-fused γ-butyrolactone in Natural Products

Danishefsky and co-workers employed Creger-Silbert dianion[41], $LiCH_2CO_2Li$, as the carbon nucleophile for the epoxide opening of **281** to give compound **282**. The direction of nucleophile attack on the epoxide was shown to be from the least hindered position (**Scheme 77**).



Scheme 77: Synthesis of Vernolepin **283**: Reaction Conditions: (a) *p*-TsOH, dean-stark, C_6H_6, 70 ˚C, (2:1 regioisomers), 62% (b) LDA, Eschenmoser salt[42a], HMPA, MeI, THF, -76 ˚C to -42 ˚C to RT, 29%

In a similar fashion, Rigby and co-workers[40] utilised the Creger-Silbert dianion[41], $LiCH_2CO_2Li$, as the carbon nucleophile for the epoxide opening of **284** (**Scheme 78**). The direction of nucleophile attack on the epoxide was shown to be from the least hindered position. Hence, exposing epoxide **284** to a large excess (14 equiv) of dilithioacetate in DME at 60 ˚C over 5 days, gave lactone **285** in 78% yield as one regio-isomer. It was noted that if the corresponding C4-alcohol was protected with a bulky *tert*-butyldimethylsilyl group, no reaction occurred under identical reaction conditions after 6 days.



Scheme 78: Synthesis of **286** and **287**: Reaction Conditions: (a) TMSCl, NaI, rt, MeCN (b) Oxalyl Chloride, DMSO, DCM, NEt_3, -78 ˚C to rt, 42% over two steps (c) ^{n}BuLi, **288**, THF, -78 ˚C to 0 ˚C, 15% (d) LDA, THF, **249**, -78 ˚C to RT, MeI, 71% (e) $BF_3.OEt_2$, C_6H_6, rt, 68% (f) mCPBA, DCM, 0 ˚C, 51%

Along the same lines, we exposed compound **245** to 14 equiv of dilithioacetate in DME at 60 °C for 7 days. Disappointingly, no reaction occurred, and the starting material was recovered (>80%). Extensive effort was undertaken to find a suitable carbon nucleophile that is able to open epoxide **245**. It is noteworthy that the required nucleophile for this epoxide opening reaction cannot consist of more than two carbon unit. To this end, glacial acetic acid (>99.99% purity) was treated with different bases such as LDA, LiHMDS (lithium hexamethyl disilazide) and ^{n}BuLi to generate the requisite dianion, using a fresh bottle of dry dimethoxyethane (DME). All these efforts were to no avail, as no reactions were ever observed. We switched our attention from dianions to enolates (**Figure 23**) as suitable nucleophile for the epoxide opening.

Unfortunately, no reaction occurred, starting materials were recovered and some β-keto ester products were observed. These results suggested that enolates are not suitable as nucleophiles for this reaction.

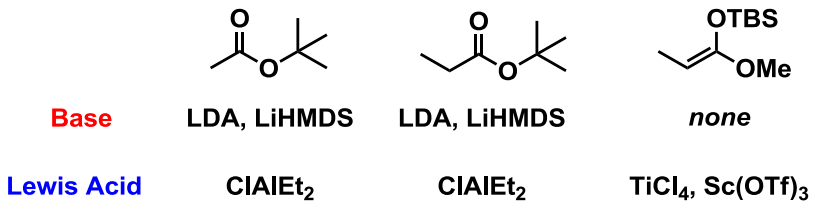
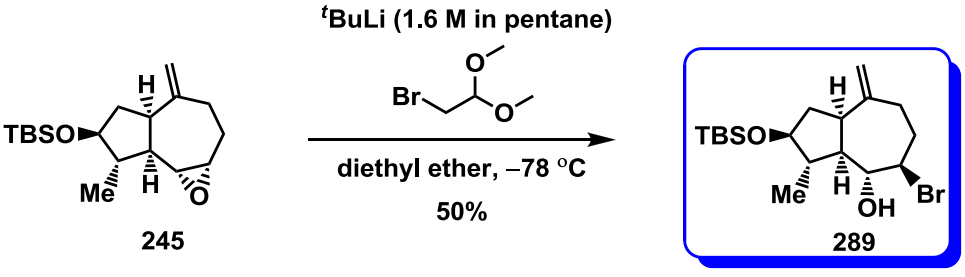


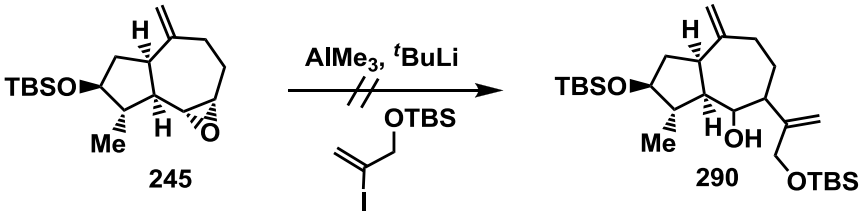
Figure 23: Enolate nucleophiles for epoxide opening

Next, we examined sp^3-hybridised carbon nucleophiles (**Scheme 79**). Unfortunately, the desired product was not observed. The structural elucidation of the isolated product corresponds to compound **289** (relative stereochemistry was not determined). A previous report has shown that lithium halides can be used for epoxide opening to generate halohydrins of type **289**.[42b]



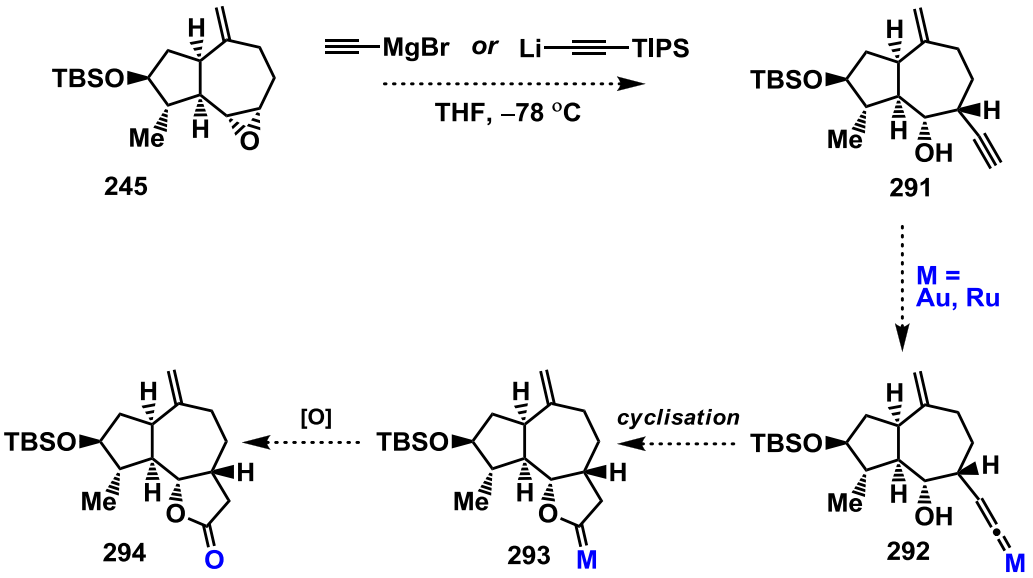
Scheme 79: Epoxide Opening with sp^3-hybridised carbon nucleophiles

Furthermore, we examined sp^2-hybridised carbon nucleophiles. Disappointingly, no reaction was observed, and the starting material was recovered (**Scheme 80**).



Scheme 80: Epoxide Opening with sp^2-hybridised carbon nucleophiles

Previous reports have shown alkynes as an ideal two carbon unit precursor for installing the γ-butyrolactone moiety.[43] We envisaged that by exposing epoxide **245** to ethynylmagnesium bromide or TIPS-protected lithium acetylene, in the hope that it would produce compound **291** (**Scheme 81**). The homopropagyl alcohol **291** can react with either gold or ruthenium complexes to form vinylidene carbene intermediate **292**. The intramolecular nucleophilic attack by the alcohol on vinylidene carbene **292** would generate an oxacarbene species **293**, and its oxidation should afford the 5-membered lactone in compound **294**. This tandem cycloisomerisation and oxidation reactions should provide access to the 5-membered lactone in **294** from the homoprogyl alcohol in **291** (**Scheme 81**).



Scheme 81: Au and Ru-catalysed tandem cycloisomerisation/oxidation of homopropagyl alcohols[43]

The epoxide **245** was exposed to ethynylmagnesium (0.5 M in THF) in THF at either –78 or 0 ˚C, but an undesired product, compound **289** in 46% yield (as shown in **Scheme 79**) was obtained. This is possibly due to the existence of Schlenk equilibrium between MgR_2, RMgBr, and $MgBr_2$ (**Figure 24**).[44]

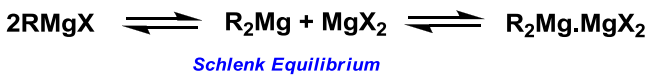
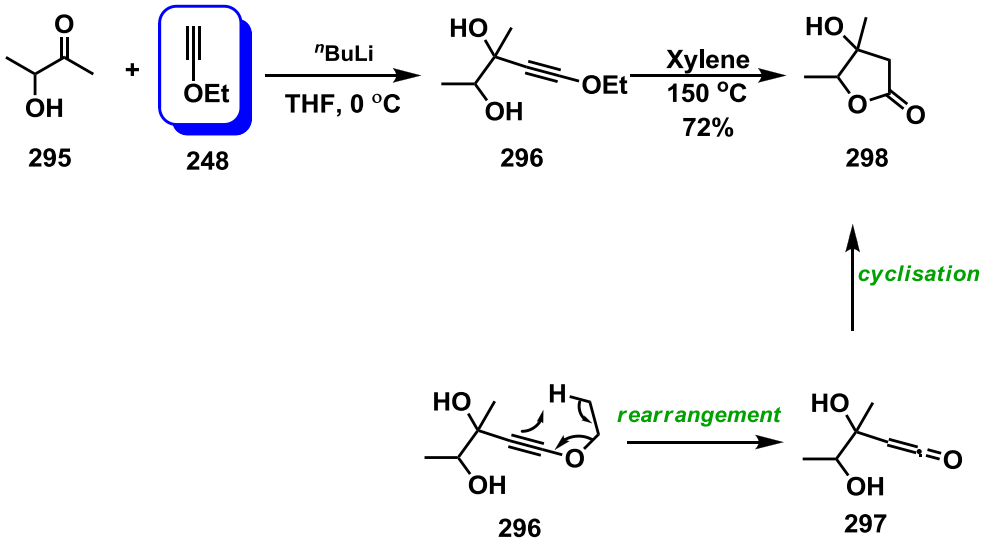


Figure 24: Schlenk equilibrium

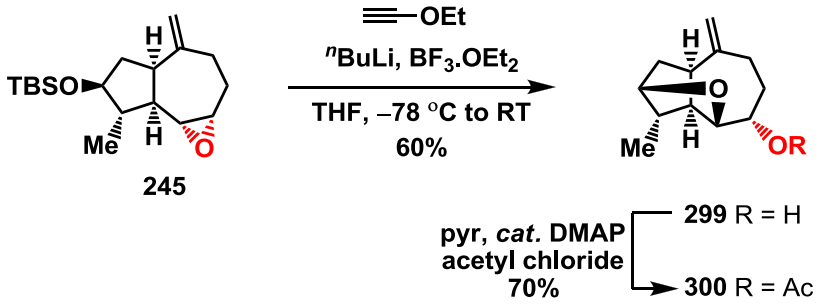
Switching to TIPS-protected lithium acetylene and $AlClMe_2$ or $BF_3.OEt_2$ (Lewis acids), no reaction occurred, and only the starting material was recovered. Previous reports have demonstrated that the nucleophilicity of lithium acetylene can be increased by introducing electron donating substituents on the alkyne, for the regioselective opening of vinyl epoxides.[45] A previous report has shown that ethoxy acetylene **248** is a suitable nucleophile for the synthesis of 5-membered lactone **298**.[46]

The nucleophilic (^{n}BuLi and ethoxyacetylene **248**) attack on compound **295** gave **296**. Subsequent rearrangement reaction generated ketene **297**, which was trapped by the secondary alcohol in an intramolecular fashion to produce 5-membered lactone **298** (**Scheme 82**).[46] The application of ethoxyacetylene **248** in total synthesis of natural products has been described.[47]



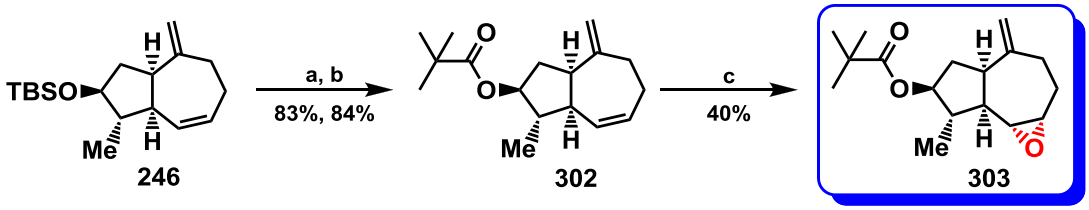
Scheme 82: Application of lithium ethoxyacetylene for the formation of butyrolactone **298**

The lithium ethoxyacetylide was generated by treating ethoxyacetylene **248** (50% weight in hexane) with ^{n}BuLi (1.6 M in hexane) at –78 ˚C in anhydrous THF. Subsequent addition of $BF_3.OEt_2$ and epoxide **245** at –78 ˚C, resulted in the formation of undesired product **299** (**Scheme 83**). This result suggests that, perhaps, the deprotection of TBS ether occurred, allowing the alcohol to attack the epoxide in an intramolecular fashion. Ball and stick molecular modelling showed the epoxide opening by the alcohol is feasible. Acetylation of the alcohol **299** gave compound **300** which allowed full characterisation of this proposed structure.



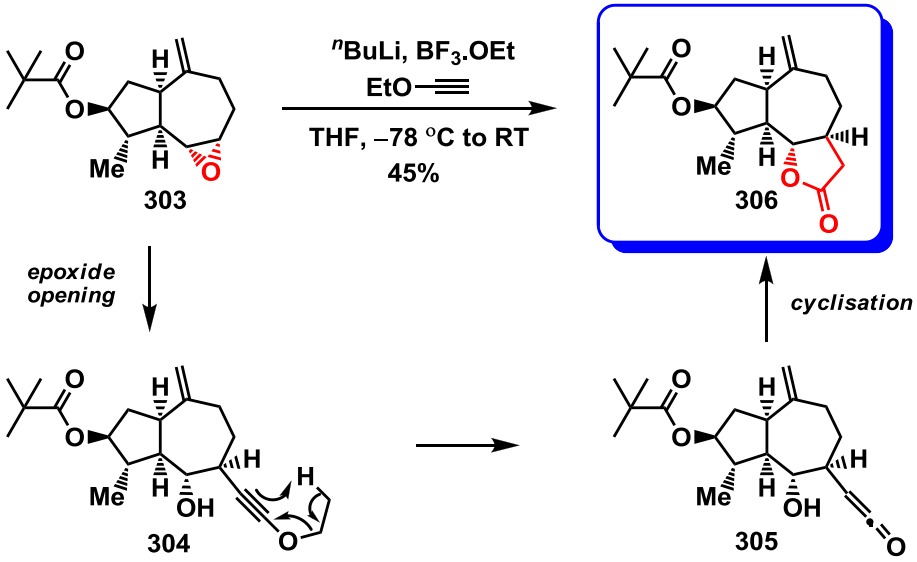
Scheme 83: Intramolecular epoxide opening

To prevent this side reaction from occurring, we examined the pivalate protecting group, in the hope that it could be less labile compared than the silyl ether. Compound **246** was de-silylated and then re-protected as a pivalate **298** using pivalolyl chloride in DMF and THF (1:1). Compound **298** was then subjected to Jacobsen-Katsuki asymmetric epoxidation reaction conditions and furnished compound **299** in 40% yield along with the bis-epoxide by-product obtained in 30% yield (**Scheme 84**).



Scheme 84: Preparation of **303**: Reaction Conditions: a) TBAF (3 equiv), THF, 0 ˚C to rt, 3Å MS, 83% (b) NaHMDS (2 equiv), Piv-Cl (2 equiv), 0 ˚C to rt, DMF/THF (1:1), 84% (c) 10 mol% of *R*, *R*-Mn(III)-Salen complex **277**, mCPBA (3 equiv), NMO (5 equiv), DCM, –78 ˚C to rt, 40%

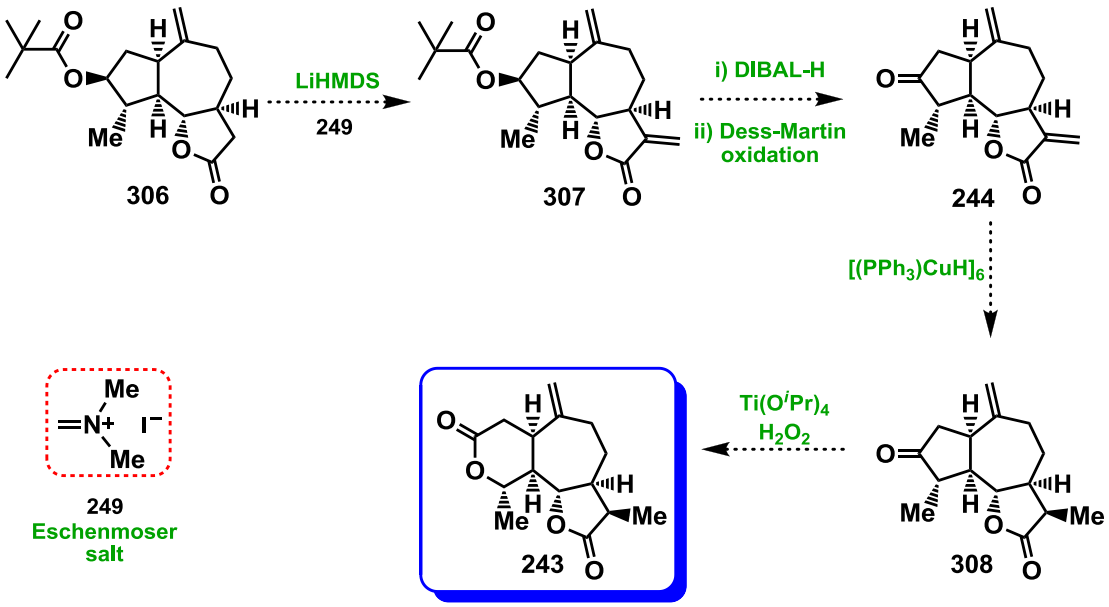
The addition of compound **303** to the yellow mixture of lithium ethoxyacetylene and $BF_3.OEt_2$ in THF at –78 ˚C, furnished compound **306** in 45% yield (**Scheme 85**). The poor yield could be due to the instability of the ketene **305** intermediate (not isolated). The undesired side product **299** was not observed.



Scheme 85: Synthesis of 5,7,5-tricyclic ring **306**

3.9 End Game Strategy for Zaluzanin E

The construction of zaluzanin E **243** could be completed in five additional steps (**Scheme 86**). The installation of the α-methylene group would produce compound **307**. DIBAL-H reduction of the pivalate protecting group and the 5-membered lactone could possibly be reduced to the corresponding lactol. However, Dess-Martin oxidation should oxidise both the secondary alcohol and the lactol to ketone and lactone respectively, to furnish estafiatone **244**. Stereoselective conjugate reduction of the α-methylene group can be effected by using a mild source of hydride such as Stryker's reagent to generate compound **308**. Baeyer-Villiger oxidation on the 5-membered ketone would then give 6-membered lactone to complete the synthesis of zaluzanin E **243**.



Scheme 86: End game strategy for zaluzanin E

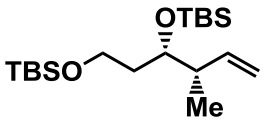
3.10 Conclusion

In conclusion, we have made considerable progress towards the first total synthesis of zaluzanin E. The 5,7,5-tricyclic core of zaluzanin E was synthesized in twelve steps from the commercially available aldehyde **251**. The highly diastereoselective Brown's crotylation, Jacobsen-Katsuki epoxidation, and cross metathesis were utilised in this synthetic study. Also, the diastereoselective cationic rhodium(I)-catalysed [4+3] carbocyclisation reaction was shown to be a reliable and effective methodology for the construction of a highly functionalised *cis*-fused 5,7-bicyclic compound which possess four stereogenic centres.

Overall, this chapter delineated the continuing importance of transition-metal catalysed carbocyclisation reaction as a powerful synthetic tool for assembling unique structures which are present as a core architectural motif in natural products.

3.11 Experimental Procedure and Spectra Data

A solution of compound **250**[14] (2.48 g, 10.16 mmol) in DCM (30 mL) was cooled to –78 °C, then 2,6-lutidine (3.55 mL, 30.50 mmol) was added at same temperature, followed by slow addition of TBSOTf (3.22 g, 10.16 mmol). The resulting reaction mixture was stirred for 2 h at –78 °C (t.l.c. control). Afterwards, the mixture was allowed to warm up to room temperature then quenched with saturated solution of $NaHCO_3$ (20 mL) and partitioned with DCM (25 mL). The organic layer was washed with water (25 mL), followed by brine (10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 2% diethyl ether/petroleum ether) afforded **254** as a colourless oil (3.60 g, 10.04 mmol, 99%).



(*S*)-5-((*S*)-but-3-en-2-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane 254.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 17.3, 11.5, 5.7 Hz, 1H), 5.01-4.98 (m, 2H), 3.72-3.60 (m, 3H), 2.31 (app q, *J* = 6.1 Hz, 1H), 1.65-1.55 (m, 2H), 0.95 (d, *J* = 6.95 Hz, 3H), 0.88 (s, 18H), 0.04-0.03 (m, 12H).

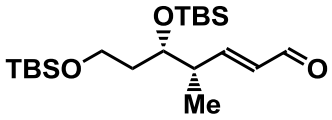
^{13}C NMR (125 MHz, $CDCl_3$) δ 141.24 (o), 114.14 (e), 72.97 (o), 60.14 (e), 43.09 (o), 36.68 (e), 26.10 (o), 26.09 (o), 18.42 (e), 18.30 (e), 14.87 (o), -4.19 (o), -4.35 (o), -5.09 (o), -5.13 (o).

IR (Neat) 2955 (m), 2929 (m), 2886 (m), 2857 (m), 1640 (w), 1470 (m), 1462 (m), 1252 (s), 1091 (vs) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{42}O_2Si_2Na$, 381.2621 found 381.2630.

[α]^{20} -41.68 (*c* = 1, $CHCl_3$)

The mixture of compound **254** (1.00 g, 2.79 mmol) and crotonaldehyde (0.45 mL, 5.58 mmol) in anhydrous DCM (25 mL) was heated to 60 °C for 10 min. In a separate vessel, HG-II (0.087 g, 0.13 mmol) was dissolved in anhydrous DCM (10 mL). The resulting green solution was transferred *via* Teflon® cannula into the vessel which contains **247** and crotonaldehyde. The resulting reaction mixture was left at 60 °C for 12 h (t.l.c. control). Afterwards, the reaction mixture was concentrated to dryness *in vacuo*. Purification by flash chromatography (silica gel, 10% diethyl ether/petroleum ether) afforded **257** as a light brown oil (0.87 g, 2.25 mmol, 81%).



(4*S*,5*S*,*E*)-5,7-bis(*tert*-butyldimethylsilyloxy)-4-methylhept-2-enal 257.

Stereochemistry: *E*/*Z*: ≥19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.8 Hz, 1H), 6.98 (dd, *J* = 15.8, 7.3 Hz, 1H), 6.11 (dddd, *J* = 15.8, 7.8, 6.4, 1.5 Hz, 1H), 3.89 (ddd, *J* = 16.2, 8.1, 4.1 Hz, 1H), 3.69-3.60 (m, 2H), 2.65 (ddq, *J* = 16.2, 8.1, 6.1 Hz, 1H), 1.64 (dddd, *J* = 17.6, 8.9, 4.6, 2.4 Hz, 1H), 1.53-1.47 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H).

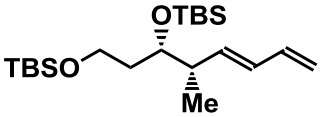
^{13}C NMR (125 MHz, $CDCl_3$) δ 194.27 (o), 161.28 (o), 132.64 (o), 72.12 (o), 59.63 (e), 42.55 (o), 36.58 (e), 26.03 (o), 25.98 (o), 18.35 (e), 18.21 (e), 13.86 (o), -4.28 (o), -4.43 (o), -5.19 (o).

IR (Neat) 2954 (m), 2885 (m), 2857 (m), 2929 (m), 1693 (s), 1635 (w), 1472 (m), 1462 (m), 1252 (s), 1090 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{20}H_{42}O_3Si_2Na$, 409.2570 found 409.2569.

[α]^{20} -39.63 (*c* = 1, $CHCl_3$)

A suspension of methyltriphenylphosphonium bromide salt (3.80 g, 10.64 mmol) in THF (30 mL) was cooled to –40 °C. ^{n}BuLi (4.25 mL, 2.5 M in hexane, 10.64 mmol) was slowly added to this suspension. The resulting yellow mixture was stirred at –40 °C for 2 h, followed by the slow addition of a solution of compound **257** (1.37 g, 3.55 mmol) in THF (10 mL). The resulting mixture was allowed to warm up to room temperature and stirred for further 1 h. Afterwards, the mixture was quenched with saturated solution of NH_4Cl (20 mL) and partitioned with diethyl ether (35 mL). The organic layer was washed with water (25 mL), followed by brine (15 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 1% diethyl ether/petroleum ether) afforded **258** as a colourless oil (1.20 g, 3.12 mmol, 89%).



(*S*)-5-((*S*,*E*)-hexa-3,5-dien-2-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane 258.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.03 (dd, *J* = 15.5, 10.3 Hz, 1H), 5.76 (dd, *J* = 15.4, 7.0 Hz, 1H), 5.09 (dd, *J* = 17.0, 1.1 Hz, 1H), 4.97 (d, *J* = 10.1 Hz, 1H), 3.73-3.60 (m, 3H), 2.36-2.34 (m, 1H), 1.66-1.52 (m, 2H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 18H), 0.03 (s, 12H).

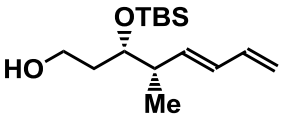
^{13}C NMR (125 MHz, $CDCl_3$) δ 137.86 (o), 137.70 (o), 130.58 (o), 115.03 (e), 73.10 (o), 60.09 (e), 42.08 (o), 36.91 (e), 26.10 (o), 26.07 (o), 18.43 (e), 18.28 (e), 15.07 (o), -4.21 (o), -4.35 (o), -5.11 (o), -5.14 (o).

IR (Neat) 2955 (m), 2929 (m), 2885 (m), 2857 (m), 1651 (w), 1603 (w), 1472 (m), 1462 (m), 1253 (s), 1090 (s), 1004 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{21}H_{44}O_2Si_2Na$, 407.2778 found 407.2766.

[α]^{20} -29.88 (*c* = 1, $CHCl_3$)

To a cooled solution of compound **258** (2.78 g, 7.23 mmol) in THF (35 mL) at 0 °C, a solution of HF.pyr complex (2.76 mL, 70% weight in pyridine, 21.70 mmol) in THF (15 mL) was slowly added. The resulting milky suspension was stirred at 0 °C for 2 h. The resulting mixture was allowed to warm up to room temperature and stirred for further 1 h. Afterwards, the mixture was quenched with saturated solution of $NaHCO_3$ (20 mL). The aqueous layer was washed with ethyl acetate (2 x 35 mL). The combined organic layers were washed with saturate solution of $CuSO_4$ (15 mL), water (25 mL), followed by brine (15 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10-20% ethyl acetate/petroleum ether) afforded **259** as a colourless oil (1.88 g, 6.95 mmol, 95%).



(3*S*,4*S*,*E*)-3-(*tert*-butyldimethylsilyloxy)-4-methylocta-5,7-dien-1-ol 259.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.05 (dd, *J* = 15.4, 10.3 Hz, 1H), 5.71 (dd, *J* = 15.4, 7.2 Hz, 1H), 5.11 (d, *J* = 16.8 Hz, 1H), 4.98 (d, *J* = 10.1 Hz, 1H), 3.80-3.67 (m, 3H), 2.46-2.44 (m, 1H), 2.08 (br s, 1H), 1.61-1.76 (m, 2H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

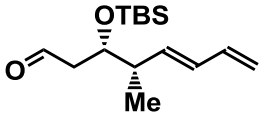
^{13}C NMR (125 MHz, $CDCl_3$) δ 137.45 (o), 136.76 (o), 131.10 (o), 115.50 (e), 75.07 (o), 60.34 (e), 41.93 (o), 35.28 (e), 26.02 (o), 18.18 (e), 16.11 (o), -4.21(o), -4.37 (o).

IR (Neat) 3328 (br), 2955 (m), 2929 (m), 2885 (m), 2857(m), 1650 (w), 1604 (w), 1472 (w), 1462 (w), 1377 (w), 1361 (w), 1252 (s), 1086 (s), 1003 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{30}O_2SiNa$, 293.1916 found 293.1904.

$[\alpha]^{20}$ -53.68 (*c* = 1, $CHCl_3$)

To a solution of Dess-Martin periodinane (2.92 g, 6.88 mmol) in DMSO (10 mL) and DCM (10 mL) at 0 °C, was added a solution of compound **259** (1.55 g, 5.73 mmol) in DCM (5 mL) slowly. The resulting reaction mixture was stirred at 0 °C for 1 h, then warmed to room temperature for a further 1 h. Afterwards, the mixture was quenched with saturated solutions of $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL) then partitioned with ethyl acetate (2 x 35 mL). The combined organic layers were washed with water (25 mL), followed by brine (15 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10-20% ethyl acetate/petroleum ether) afforded **260** as a colourless oil (1.40 g, 5.21 mmol, 91%).



(3*S*,4*S*,*E*)-3-(*tert*-butyldimethylsilyloxy)-4-methylocta-5,7-dienal 260.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 2.3 Hz, 1H), 6.31 (dt, *J* = 17.0, 10.2 Hz, 1H), 6.06 (dd, *J* = 15.4, 10.3 Hz, 1H), 5.67 (dd, *J* = 15.4, 7.3 Hz, 1H), 5.13 (d, *J* = 16.9 Hz, 1H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.09-4.07 (m, 1H), 2.56-2.39 (m, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H).

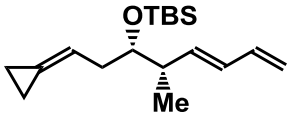
^{13}C NMR (125 MHz, $CDCl_3$) δ 202.21 (o), 137.17 (o), 135.96 (o), 131.85 (o), 116.09 (e), 72.01 (o), 48.41 (e), 43.00 (o), 25.93 (o), 18.17 (e), 15.74 (o), -4.30 (o), -4.45 (o).

IR (Neat) 2957 (m), 2930 (m), 2886 (m), 2857 (m), 1725 (s), 1650 (w), 1604 (w), 1472 (m), 1462 (m), 1253 (m), 1087 (s), 1004 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{15}H_{28}O_2SiNa$, 293.1759 found 291.1760.

[α]^{20} -37.30 (*c* = 1, $CHCl_3$)

Potassium *tert*-butoxide (1.00 g, 8.94 mmol) and ylide **262** (2.07 g, 4.47 mmol) were dissolved in THF (25 mL). The resulting light red suspension was heated to 70 °C for 2 h. Afterwards, the reaction mixture was left to stand at room temperature (*ca.* 10 min), then a solution of compound **260** (0.40 g, 1.49 mmol) in THF (5 mL) was added. The resulting reaction mixture was heated to 70 °C for 1 h. The reaction was quenched with water (10 mL) and partitioned with diethyl ether (2 x 35 mL). The combined organic layers were washed with water (25 mL), followed by brine (15 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 100% hexane) afforded **247** as a yellow oil (0.39 g, 1.33 mmol, 90%).



***tert*-butyl((3*S*,4*S*,*E*)-1-cyclopropylidene-4-methylocta-5,7-dien-3-yloxy)dimethylsilane 247.**

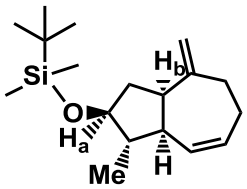
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (dt, *J* = 17.0, 10.1 Hz, 1H), 5.99 (dd, *J* = 15.3, 10.3 Hz, 1H), 5.76 (tquin, *J* = 6.2, 2.2 Hz, 1H), 5.70 (dd, *J* = 15.4, 7.6 Hz, 1H), 5.08 (d, *J* = 16.9 Hz, 1H), 4.96 (d, *J* = 10.1 Hz, 1H), 3.63 (q, *J* = 5.5 Hz, 1H), 2.28-2.37 (m, 3H), 1.06-0.96 (m, 7H), 0.88 (s, 9H), 0.02 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.62 (o), 137.71 (o), 130.41 (o), 123.42 (e), 115.02 (o), 115.00 (e), 76.01 (o), 41.71 (o), 37.43 (e), 26.04 (o), 18.28 (e), 14.90 (o), 2.72 (e), 1.86 (e), -4.16 (o), -4.40 (o).

IR (Neat) 2957 (m), 2929 (m), 2895 (m), 2857 (m), 1650 (w), 1603 (w), 1472 (m), 1462 (m), 1252 (s), 1082 (s), 1003 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{32}OSiNa$, 315.2133 found 315.2131.

$Rh(COD)_2SbF_6$ (0.017 g, 0.031 mmol) was inserted into a flamed dried reaction vessel, followed by the addition of toluene (2 mL). The vessel was placed under vacuum and backfilled with argon, $P(OEt)_3$ (0.0061 g, 0.037 mmol) was introduced, then heated to 110 ˚C for 10 min. The requisite ACP-diene (*E*)-**247** (0.13 g, 0.46 mmol) in toluene (3 mL) was added to the bright yellow solution *via* syringe pump over a period of 6 h (0.5 mL/h) at 110 ˚C. The reaction mixture was stirred for 1 h at the same temperature after the addition had completed (t.l.c. control), then cooled to room temperature, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 1% diethyl ether/petroleum ether) furnished bicycloheptadiene **246** as a yellow oil (0.11 g, 0.38 mmol, 82%).



***tert*-butyldimethyl((1*S*,2*S*,3a*R*,8a*R*)-1-methyl-4-methylene-1,2,3,3a,4,5,6,8a-octahydroazulen-2-yloxy)silane 246.**

Relative stereochemistry: *dr* ≥19:1 (^{1}H NMR analysis)

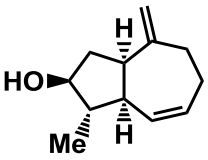
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58-5.56 (m, 1H), 5.48 (ddd, *J* = 11.0, 4.2, 1.5 Hz, 1H), 4.79 (s, 1H), 4.76 (s, 1H), 3.58 (dt, *J* = 9.1, 6.6 Hz, 1H, **H_a**), 2.81-2.79 (m, 1H, **H_b**), 2.39-2.21 (m, 4H), 2.18-2.12 (m, 1H), 1.99 (dt, *J* = 6.8, 7.3 Hz, 1H), 1.70-1.68 (m, 1H), 1.65-1.60 (m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.91 (e), 132.39 (o), 127.85 (o), 110.10 (e), 78.65 (o), 48.83 (o), 46.03 (o), 43.88 (o), 38.88 (e), 34.43 (e), 28.10 (e), 26.04 (o), 18.29 (e), 16.69 (o), -4.24 (o), -4.54 (o).

IR (Neat) 2953 (m), 2928 (m), 2885 (m), 2856 (m), 1641 (w), 1471 (m), 1461 (w), 1377 (w), 1360 (w), 1250 (m), 1112 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{32}OSiNa$, 315.2134 found 315.2132.

A solution of bicycloheptadiene **246** (0.43 g, 1.47 mmol) in THF (25 mL) with 3Å molecular sieves was cooled to 0 °C, then TBAF (4.43 mL, 1 M in THF, 4.43 mmol) was added. The resulting brown mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated solution of $NaHCO_3$ (5 mL) and partitioned with ethyl acetate (2 x 10 mL). The combined organic layers were washed with water (5 mL), followed by brine (5 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10% diethyl ether/petroleum ether) afforded **301** as a brown oil (0.22 g, 1.23 mmol, 83%).



(1*S*,2*S*,3a*R*,8a*R*)-1-methyl-4-methylene-1,2,3,3a,4,5,8a-octahydroazulen-2-ol 301.

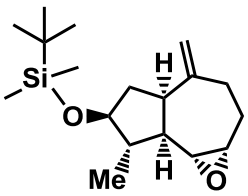
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57-5.62 (m, 1H), 5.46-5.49 (m, 1H), 4.79 (s, 1H), 3.68 (app q, *J* = 8.2 Hz, 1H), 2.85 (app q, *J* = 9.2 Hz, 1H), 2.22-2.43 (m, 4H), 2.11-2.19 (m, 2H), 1.72 (dt, *J* = 12.5, 9.6 Hz, 1H), 1.60-1.65 (m, 1H), 1.08 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.67 (e), 132.17 (o), 128.19 (o), 110.22 (e), 78.54 (o), 49.02 (o), 46.73 (o), 43.93 (o), 38.53 (e), 34.42 (e), 28.19 (e), 16.66 (e).

IR (Neat) 3323 (br), 2951 (s), 2884 (s), 1640 (m), 1454 (m), 1430 (m), 1373 (w), 1090 (s) cm^{-1}.

HRMS (ESI, $[(M-H_2O)+H]^+$) calcd for $C_{12}H_{18}O$, 161.1329 found 161.1326.

(*R,R*)-(−)-*N,N′*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride **277** (0.033 g, 0.051 mmol) and NMO (0.30 g, 2.56 mmol) were dissolved in DCM (2 mL), then cooled to –78 °C. A solution of bicycloheptadiene **246** (0.15 g, 0.51 mmol) in DCM (1 mL) was added at the same temperature. The resulting dark-red solution was stirred for 15 min, and then a solution of mCPBA (0.26 g, 70% weight, 1.54 mmol) in DCM (2 mL) was added in three portions over a 30 min period. The resulting black mixture was stirred at –78 °C for 3 h, then quenched with a saturated solution of $NaHCO_3$ (5 mL) and partitioned with DCM (3 x 5 mL). The combined organic layers were washed with water (5 mL), followed by brine (5 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10-20% ethyl acetate/petroleum ether) afforded **245** as a deep brown oil (0.065 g, 0.21 mmol, 40%). 50 mg of the *bis*-epoxide **279** was recovered.



tert-butyl((1a*S*,4a*R*,6*S*,7*S*,7a*R*,7b*R*)-7-methyl-4-methylenedecahydroazuleno[4,5-*b*]oxiren-6-yloxy) silane 245.

Relative stereochemistry: *dr* ≥19:1 (^{1}H NMR analysis)

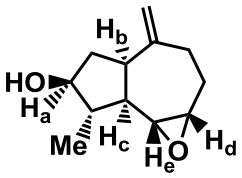
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (s, 2H), 3.59 (app q, *J* = 8.6 Hz, 1H), 2.98 (quin, *J* = 4.4 Hz, 1H), 2.77 (t, *J* = 4.2 Hz, 1H), 2.62 (app q, *J* = 9.6 Hz, 1H), 2.39-2.50 (m, 1H), 2.27-2.32 (m, 1H), 2.13-2.18 (m, 1H), 1.95 (quin, *J* = 6.5 Hz, 1H), 1.68-1.80 (m, 3H), 1.41-1.49 (m, 1H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.00 (dd, *J* = 6.5, 3.2 Hz, 1H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.32 (e), 110.48 (e), 78.24 (o), 58.17 (o), 54.15 (o), 47.49 (o), 46.66 (o), 40.04 (o), 38.12 (e), 34.19 (e), 26.96 (e), 26.01 (o), 18.29 (e), 16.29 (o), -4.29 (o), -4.57 (o).

IR (Neat) 2954 (m), 2928 (m), 2895 (m), 2856 (m), 1640 (w), 1471 (m), 1462 (m), 1380 (w), 1360 (w), 1250 (s), 1113 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{32}O_2SiNa$, 331.2072 found 331.2078.

A solution of compound **245** (0.05 g, 0.62 mmol) in THF (2 mL) with 3Å molecular sieves was cooled to 0 °C, then TBAF (0.81 mL, 1 M in THF, 0.81 mmol) was added. The resulting mixture was stirred at room temperature for 3 h, quenched with saturated solution of $NaHCO_3$ (3 mL) and partitioned with ethyl acetate (2 x 2 mL). The combined organic layers were washed with water (2 mL), followed by brine (2 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 30% ethyl acetate/petroleum ether) afforded **280** as a brown oil (0.026 g, 0.13 mmol, 83%).



(1a*S*, 4a*R*, 6*S*, 7*S*, 7a*R*, 7b*R*)-7-methyl-4-methylenedecahydroazuleno[4,5-*b*]oxiren-6-ol 280.

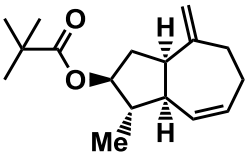
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.89 (s, 1H), 3.69 (dt, *J* = 9.2, 6.8 Hz, 1H, $\mathbf{H_a}$), 3.00 (quin, *J* = 4.4 Hz, 1H, $\mathbf{H_d}$), 2.78 (t, *J* = 4.6 Hz, 1H, $\mathbf{H_e}$), 2.66 (app q, *J* = 9.3 Hz, 1H, $\mathbf{H_b}$), 2.44 (dt, *J* = 12.5, 5.6 Hz, 1H), 2.35-2.31 (br m, 1H), 2.20-2.14 (m, 1H), 2.08 (tt, *J* = 12.5, 6.9 Hz, 1H), 1.84-1.78 (m, 3H), 1.72-1.67 (m, 1H, $\mathbf{H_c}$), 1.49-1.40 (m, 1H), 1.17 (d, *J* = 6.4 Hz, 3H, **Me**).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.18 (e), 110.53 (e), 78.03 (o), 58.02 (o), 54.10 (o), 47.54 (o), 47.36 (o), 39.98 (o), 37.74 (e), 34.12 (e), 29.86 (e), 26.91 (e), 16.13 (o).

IR (Neat) 3407 (br), 2953 (s), 1640 (m), 1441 (m), 1375 (w), 1070 (m) cm^{-1}.

HRMS (ESI, $[(M-H_2O)+H]^+$) calcd for $C_{12}H_{18}O_2$, 177.1279 found 177.1277.

NaHMDS (2.06 mL, 1 M in THF, 2.06 mmol) was added to a solution of compound **301** (0.18 g, 1.03 mmol) in THF (3 mL) and DMF (3 mL) at 0 °C. The resulting light yellow mixture was stirred for 1 h, followed by the addition of pivaloyl chloride (0.25 mL, 2.06 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h then quenched with saturated solution of NH_4Cl (10 mL) and partitioned with diethyl ethyl (15 mL). The organic layer was washed with water (10 mL), followed by brine (10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% diethyl ether/petroleum ether) afforded **302** as a colourless oil (0.026 g, 0.13 mmol, 83%).



(1*S*, 2*S*, 3a*R*, 8a*R*)-1-methyl-4-methylene-1,2,3,3a,4,5,6,8a-octahydroazulen-2-yl pivalate 302.

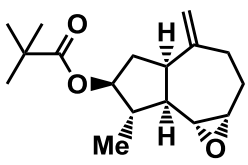
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57-5.62 (m, 1H), 5.46 (dd, *J* = 12.0, 3.1 Hz, 1H), 4.81 (s, 1H), 4.77 (s, 1H), 4.64 (q, *J* = 7.8 Hz, 1H), 2.93 (q, *J* = 8.5 Hz, 1H), 2.43 (app t, *J* = 8.9 Hz, 1H), 2.38-2.26 (m, 4H), 2.16-2.10 (m, 1H), 2.00-1.88 (m, 1H), 1.67 (dt, *J* = 13.3, 8.1 Hz, 1H), 1.20 (s, 9H), 1.03 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.83 (e), 150.84 (e), 131.68 (o), 128.35 (o), 110.35 (e), 79.76 (o), 46.66 (o), 45.82 (o), 44.67 (o), 38.82 (e), 35.44 (e), 34.81 (e), 28.41 (e), 27.40 (o), 16.79 (o).

IR (Neat) 2958 (m), 2931 (m), 2872 (m), 1725 (vs), 1641 (w), 1479 (w), 1458 (w), 1396 (w), 1364 (w), 1283 (s), 1157 (vs), 1118 (w), 1033 (w) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for $C_{17}H_{27}O_2$, 263.2014 found 263.2012.

(*R,R*)-(−)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride **277** (0.031 g, 0.049 mmol) and NMO (0.17 g, 1.47 mmol) were dissolved in DCM (1 mL), then cooled to –78 °C. A solution of bicycloheptadiene **302** (0.13 g, 0.51 mmol) in DCM (1 mL) was added at the same temperature. The resulting dark-red solution was stirred for 15 min, then a solution of mCPBA (0.24 g, 70% weight, 0.98 mmol) in DCM (1 mL) was added in three portions over 30 min period. The resulting black mixture was stirred at –78 °C for 3 h, then quenched with saturated solution of $NaHCO_3$ (5 mL) and partitioned with DCM (3 x 5 mL). The combined organic layers were washed with water (5 mL), followed by brine (5 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 10-20% ethyl acetate/petroleum ether 30-40) afforded **303** as a deep brown oil (0.055 g, 0.19 mmol, 40%).



(1*S*,2*S*,3a*R*,8a*R*)-1-methyl-4-methylene-1,2,3,3a,4,5,6,8a-octahydroazulen-2-yl pivalate 303.

Relative Stereochemistry: *dr* ≥19:1 (^{1}H NMR analysis)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (s, 1H), 4.89 (s, 1H), 4.65 (q, *J* = 7.7 Hz, 1H), 3.03 (dt, *J* = 8.3, 4.1 Hz, 1H), 2.83 (t, *J* = 4.3 Hz, 1H), 2.73 (q, *J* = 8.4 Hz, 1H), 2.40 (dq, *J* = 14.4, 5.5 Hz, 1H), 2.31-2.26 (m, 1H), 2.23 (tt, *J* = 13.4, 7.5 Hz, 1H), 2.15-2.13 (m, 1H), 2.03-1.95 (m, 1H), 1.91 (ddd, *J* = 14.6, 10.2, 4.3 Hz, 1H), 1.72 (tt, *J* = 13.3, 8.0 Hz, 1H), 1.64-1.56 (m, 1H), 1.21 (s, 9H), 1.12 (d, *J* = 6.5 Hz, 3H),

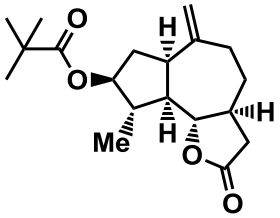
^{13}C NMR (125 MHz, $CDCl_3$) δ 178.76 (e), 148.58 (e), 110.76 (e), 79.11 (o), 57.79 (o), 54.61 (o), 46.89 (o), 43.95 (o), 41.14 (o), 38.85 (e), 34.68 (e), 33.77 (e), 27.38 (e), 27.31 (o), 16.24 (o).

IR (Neat) 2959 (m), 2873 (m), 1724 (vs), 1666(w), 1640 (w), 1479 (w), 1459 (w), 1396 (w), 1366 (w), 1283 (m), 1158 (vs), 1035 (w) cm^{-1}.

HRMS (ESI, $[M+H]^+$) calcd for calcd for $C_{17}H_{27}O_2$, 279.1964 found 279.1961.

^{n}BuLi (67.0 µL, 1.6 M in hexane, 0.10 mmol) was added to a solution of ethoxyacetylene **248** (15.1 mg, 50% weight in hexane, 0.108 mmol) in THF (20 µL) at –78 °C. The resulting light red solution was stirred for 10 min, followed by the addition of $BF_3.OEt_2$ (5.92 µL, 0.047 mmol), stirred for 5 min, then a solution of compound **303** (20 mg, 0.036 mmol) in THF (10 µL) was also added at –78 °C. The resulting mixture was stirred at –78 °C for 4 h, slowly warmed up to room temperature, then left to stir for a further 10 h. The reaction was quenched with saturated solution of NH_4Cl (5 mL) and partitioned with ethyl acetate (2 x 10 mL). The combined organic layers were washed with water (5 mL), followed by

brine (5 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5-10% ethyl acetate/petroleum ether 30-40) afforded **306** as a light brown oil (5.2 mg, 0.015 mmol, 45%).



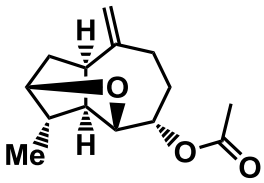
(3a*S*, 6a*R*, 8*S*, 9*S*, 9a*R*, 9b*S*)-9-methyl-6-methylene-2-oxododecahydroazuleno[4,5-*b*]furan-8-yl pivalate 306.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.88 (s, 1H), 4.65 (tt, *J* = 8.8, 6.6 Hz, 1H), 3.98 (t, *J* = 9.6 Hz, 1H), 2.85 (app q, *J* = 17.5, 9.6 Hz, 1H), 2.62 (d, *J* = 9.4 Hz, 1H), 2.55 (tt, *J* = 12.8, 4.1 Hz, 1H), 2.32 (tt, *J* = 12.8, 6.9 Hz, 1H), 2.27-2.22 (m, 2H), 2.16-2.09 (m, 2H), 1.86-1.96 (m, 2H), 1.68-1.63 (m, 2H), 1.20 (s, 9H), 1.13 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.82 (e), 176.12 (e), 149.19 (e), 112.96 (e), 88.20 (o), 79.51 (o), 50.33 (o), 45.07 (o), 43.93 (o), 42.89 (o), 37.31 (e), 36.83 (e), 35.52 (e), 33.69 (e), 29.86 (e), 27.31 (o), 18.06 (o).

IR (Neat) 2958 (m), 2930 (m), 1782 (s), 1726 (s), 1639 (w), 1480 (w), 1460 (w), 1369 (w), 1289 (m), 1162 (vs), 1039 (w) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{19}H_{28}O_4Na$, 343.1896 found 343.1894.



Compound 300.

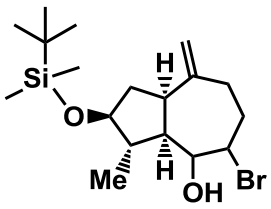
Colour and State: Colourless oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05-5.01 (m, 1H), 4.92 (s, 1H), 4.83 (s, 1H), 4.07 (tt, *J* = 5.2, 2.8 Hz, 1H), 4.01 (s, 1H), 2.99-2.97 (m, 1H), 2.45-2.31 (m, 3H), 2.28 (app t, *J* = 3.3 Hz, 1H), 2.20-2.15 (m, 1H), 2.01 (s, 3H), 2.00-1.95 (m, 1H), 1.73-1.66 (m, 2H), 1.01 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.35 (e), 150.50 (e), 112.88 (e), 84.25 (o), 80.44 (o), 76.00 (o), 45.93 (o), 45.40 (o), 39.88 (o), 36.67 (e), 29.87 (e), 25.88 (e), 21.46 (o), 11.11 (o).

IR (Neat) 2961 (m), 2933 (m), 2878 (m), 1732 (s), 1637 (w), 1460 (w), 1368 (m), 1237 (vs), 1028 (m), 1013 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{14}H_{20}O_3Na$, 259.1312 found 259.1310.



(2*S*, 3*S*, 3a*R*, 8a*R*)-5-bromo-2-(*tert*-butyldimethylsilyloxy)-3-methyl-8-methylenedecahydroazulen-4-ol 289.

Colour and State: Brown oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (s, 1H), 4.84 (s, 1H), 4.16-4.12 (m, 1H), 3.73 (dt, *J* = 11.4, 2.8 Hz, 1H), 3.59 (dt, *J* = 9.4, 5.6 Hz, 1H), 2.68-2.56 (m, 2H), 2.51-2.44 (m, 1H), 2.29 (d, *J* = 2.81 Hz, 1H), 2.11-2.07 (m, 1H), 2.05-1.98 (m, 1H), 1.95-1.85 (m, 2H), 1.75-1.65 (m, 2H), 1.12 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.50 (e), 110.95 (e), 78.55 (o), 77.25 (o), 66.17 (o), 49.19 (o), 46.91 (o), 40.74 (o), 38.12 (e), 35.43 (e), 35.52 (e), 26.03 (o), 19.44 (o), 18.28 (e), -4.22 (o), -4.54 (o).

IR (Neat) 3563 (br), 2952 (m), 2928 (m), 2890 (m), 2856 (m), 1639 (w), 1471 (w), 1462 (w), 1379 (m), 1250 (vs), 1114 (s), 1077 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calcd for $C_{18}H_{33}{}^{79}BrO_2SiNa$, 411.1413 found 411.1410.

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