Rhodium(I)-Catalysed Carbocyclisation Reactions of Alkylidene cyclopropane 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

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May 2014
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.
ACKNOWLEDGEMENT

I would like to 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.

Special thanks to my present and past research colleagues for their friendship and resourceful chemistry discussions. I am grateful for the financial support from EPSRC and The University of Liverpool.

Finally, I would like to thank Veronica Ojo for being a patient and abiding mother. Her moral support in moments of lack and difficulty will never be forgotten. I thank her for the faith and trust she has in my character and ability to achieve this difficult goal of being a Chemist. Special thanks to James Ojo for his fatherly love, loyalty, constant encouragement and support throughout the duration of my study. To all my siblings (Lanre, Segun, Ebenezer, Bukky and Tope), I thank you.

Lastly, I would like to thank Judith Braimah for her love, patience and financial support during the period of my PhD program.
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 alkylidene cyclopropane 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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<tr>
<td>9-BBN</td>
<td>9-borabicyclo(3.3.1)nonane</td>
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<td>2,2-DMP</td>
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<td>DIPEA</td>
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<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<td>Term</td>
<td>Definition</td>
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<tr>
<td>DMDO</td>
<td>dimethyldioxirane</td>
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<td>DME</td>
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<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
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<td>lithium diisopropylamide</td>
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Chapter 1

1. Transition Metal-Catalysed Carbocyclisation Reactions of Alkylidene cyclopropane, Methylene cyclopropane and Vinyl cyclopropane for the Construction of 5,5-Bicyclic Ring and 5,7-Bicyclic Ring Systems

1.1 Transition Metal Chemistry of MCP

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

![MCP, ACP and BCP](image)

**Figure 1**: MCP, ACP and BCP

The MCP 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).
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 acrylonitrile) 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 cyclobutanenickel 2.
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
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). 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.

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). 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. 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). 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)$_3$(η$^5$-C$_5$Me$_5$)]BF$_4$ produced [Mo-TMM]BF$_4$ 16 as a yellow crystalline complex in an unspecified yield (Scheme 8).$^8$a Complex 16 was isolated and characterised using $^1$H and $^{13}$C NMR analysis.

Scheme 8: The formation of [Mo-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$_2$SnMe$_3$)$_2$ 17 (Scheme 9).$^8$b X-ray crystallography was used to determine the structure of ruthenium-TMM and osmium-TMM complexes.$^8$b

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 pallacycloobutane. Subsequent rearrangement could provide the Pd-TMM complex 19 (Scheme 10). A complementary study has demonstrated that the same putative Pd-TMM complex 19 can be generated from compound 18.

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. The coordination of Rh(CO)$_2$Cl complex to the olefin of the VCP 20, followed by cyclopropane ring cleavage would produce σ-π-allylrhodium intermediate 21 (Scheme 11). 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, ruthenium, nickel, iron and palladium 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).

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(PPh₃)₄ complex was employed in place of Pd₂(dba)₃ complex. Substrates with R = H and OMe underwent efficient cyclisation in the presence of Pd₂(dba)₃ complex. Also, substrates with alkyynes 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 alkyynes and terminal alkyynes 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 alkyynes underwent successfully cyclisation in the presence of Pd₂(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 alkyynes
However, compound 29 with an electron-withdrawing group to the alkyne (R = CO$_2$Et) 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](image)

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\textsuperscript{i}Pr)\textsubscript{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**).

\[
\text{Scheme 15: Asymmetric Pd-catalysed [3+2] carbocyclisation reaction}
\]

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**). 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\textsubscript{2}(dba)\textsubscript{3}/P(O\textsuperscript{i}Pr)\textsubscript{3} system (**Scheme 13**).

\[
\text{Scheme 16: Ru-catalysed [3+2] carbocyclisation reactions of ACP tethered with alkynes}
\]
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).

**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).\textsuperscript{18}

![Diagram of reaction](Image)

\textbf{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 PPh3 for the cyclisation of substituted ACP olefin (R2) 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 diphenylmethylene cyclopropane tethered with enone 42 to 11 mol% of Pd(dba)$_2$ and 11 mol% of P(O\textsubscript{i}Pr)$_3$ 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).

![Scheme 19: Pd-catalysed [3+2] carbocyclisation reaction of MCP tethered with an alkene](image-url)
A related study investigated the tolerance of substitution on the alkene and at the C2 carbon.\textsuperscript{20b} Exposure of compound (Z)-\textbf{44} to 6 mol\% of \textit{Pd}\textsubscript{2}(dba)\textsubscript{3} and 20 mol\% of \textit{P(O\textsubscript{i}Pr)}\textsubscript{3} in toluene at 110 °C afforded \textit{trans}-fused 5,5-bicyclic rings \textbf{45} and \textbf{46} in 6:1 ratio and 43\% combined yield (\textbf{Scheme 20}). The critical feature of this reaction is that 5,5-bicyclic ring \textbf{45} was observed as the major product, possibly as a consequence of the inversion of the stereochemistry of the \textit{cis} double bond.

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

Interestingly, substrate (\textit{E})-\textbf{44} did not participate in this reaction. In contrast, (\textit{E}) and (Z)-ACP tethered with alkenes underwent successful cyclisation in the presence of \textit{Pd}\textsubscript{2}(dba)\textsubscript{3} and \textbf{L1} (\textbf{Scheme 21}).\textsuperscript{21} For example, both (\textit{E})-\textbf{47a} and (Z)-\textbf{47a} furnished the \textit{cis}-fused 5,5-bicyclic ring \textbf{48a} selectively as a single isomer in excellent yield, when \textit{L} = \textit{P(O\textsubscript{i}Pr)}\textsubscript{3}. The epimerisation of \textbf{49a} to \textbf{48a} was not detected and the observation of \textbf{48a} as the sole product was influenced by the reaction mechanism (\textbf{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.
The development of the scope of this reaction was achieved with two ligands, L1 and P(OiPr)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).

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

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 Alkylidene cyclopropane 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). In any case, three substrates (X = Y = O, R = CO₂Et 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 = CO₂Et) 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.
The palladium- and rhodium-catalysed \([3+2+2]\) carbocyclisation 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 \textit{via} the proximal ring opening of the ACP cyclopropane ring (Scheme 26).\textsuperscript{19}
In relation to the scope of this reaction, alkynes with methyl and CH$_2$OAc 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$_2$Et) 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$_2$OTBS 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 26: Ni-catalysed [3+2+2] carbocyclisation reaction of ACP with alkyne and activated alkenes
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). For example, subjecting ene-vinylcyclopropane 69 (X = C(CO₂Me)₂, R = R¹ = H) to RhCl(PPh₃)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'), 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). 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). 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 °C.

The ruthenium-catalysed [5+2] cycloaddition reaction is tolerant to substitution on the alkyne (R). However, substitution on the cyclopropane (R³) and C2-position (R¹) creates diastereoselectivity issues. Additionally, substrates with a methyl group on the olefin (R²) 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 \( \pi \)-systems can proceed via (a) the formation of metallacyclohexene A, which can rearrange to C. Carbometallation of the \( \pi \)-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 \( \pi \)-systems](image-url)
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). 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).

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). 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 $\sigma$-$\pi$-$\sigma$ 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 $\sigma$-$\pi$-$\sigma$ 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 $\sigma$-$\pi$-$\sigma$ 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

For examples of metal-catalysed reactions of MCP without the ring opening of the cyclopropane see:

Chapter 2

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. The intramolecular reaction of this putative palladacyclobutanes with an alkene, an alkyne or an allene in the [3+2] carbocyclisation reactions furnished 5,5-bicyclic rings exclusively. However, the intramolecular reaction of the palladacyclobutane with 1,3-diene led to the formation of a 5,5-bicyclic ring and a 5,7-bicyclic ring (Scheme 35 chapter 1 and Scheme 37).

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 \textbf{103} affected the selective formation of the 5,7-bicyclic ring \textbf{105}. This is due to the competition between reductive elimination and $\sigma$-$\pi$-$\sigma$ isomerisation of palladacycle \textbf{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 \textbf{106} and unsymmetrical alkynes for the construction of \textit{cis}-fused 5,7-bicyclic rings \textbf{110} which possesses an exocyclic methylene.\textsuperscript{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 \textbf{106} and CO furnished a \textit{cis}-fused 5,6-bicyclic ring with an $\alpha,\beta$-unsaturated system \textbf{111}.\textsuperscript{3b} Both studies proposed the insertion of a rhodium(I)-complex into the ACP distal bond. The later study\textsuperscript{3b} provided theoretical evidence for the \textit{cis}-fused $\pi$-allylrhodium complex \textbf{109} ($R = H$; \textbf{Scheme 38}).

\textbf{Scheme 38}: Rh(I)-catalysed carbocyclisation reactions of ACP (\textbf{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.\textsuperscript{3c}

Our main objective is to favour the $\sigma$-$\pi$-$\sigma$ 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, ancillary 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 $\sigma$-$\pi$-$\sigma$ 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).
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).

![Model substrates: ACP-Dienes (E)-127 and (E)-132](image)

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

Compound 123 is a useful synthetic synthon for the installation of the alkylidene cyclopropane moiety. The formation of chloroethyl cyclopropanol 121 was mediated by 20 mol% of Ti(OiPr)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. Elimination, promoted by potassium tert-butoxide at 0 °C, led to the formation of compound 123 (Scheme 40).
Scheme 40: Preparation of compound 123: Reaction Conditions: a) EtMgBr (2 equiv), 20 mol% Ti(O\text{OiPr})_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\text{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) Cs₂CO₃ (2 equiv), BocNHTs (1 equiv), TBAI (0.1 equiv), anhydrous acetone, rt, 60% (c) K₂CO₃ (5 equiv), MeOH, 80 °C, 99% (d) (i) NaH (1.2 equiv), DMF (ii) 1 mol% Pd₂(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 nBuLi 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 LiAlH₄ 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 PPh₃ and diisopropyl azodicarboxylate (DIAD) at room temperature, followed by deprotection of the Boc group using potassium carbonate (K₂CO₃) at 80 °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) nBuLi (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$_2$CO$_3$ (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 intermolecular [(3+2)+2] carbocyclisation reaction of ACP with activated alkyynes.²a

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>Rh:L</th>
<th>133:134:135</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>dppp</td>
<td>1:0.5</td>
<td>1:1:4</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>PPh₃</td>
<td>1:1</td>
<td>1:1:2</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>P(O₂Ph)₃</td>
<td>1:2</td>
<td>2:1:1</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>P(O₂Ph)₃</td>
<td>1:1</td>
<td>3:1:1</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>P(O₂-o-tolyl)₃</td>
<td>1:1</td>
<td>3:1:1</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>P(OEt)₃</td>
<td>1:1</td>
<td>3:1:1</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>P(OCH₂CF₃)₃</td>
<td>1:1</td>
<td>4:1:0</td>
<td>69</td>
</tr>
</tbody>
</table>

⁴All 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. Ratio of 133:134:135 was determined by HPLC on the crude reaction mixtures. ⁵HPLC yield of 133. ⁶70% 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. 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-o-tolyl)_3 and P(OEt)_3 furnished 133 as the major product, albeit in 3:1:1 selectivities (entries 5-7). Gratifyingly, 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 ($dr \geq 19:1$, 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](image)

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, we explored the effect of weakly coordinating 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$_2$CO$_3$ and Ag$_2$SO$_4$ 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.

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 preformed cationic rhodium(I)-complex, [Rh(COD)2]SbF6, 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.\textsuperscript{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)\textsubscript{2}]SbF\textsubscript{6} and 10 mol\% of P(OCH\textsubscript{2}CF\textsubscript{3})\textsubscript{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)\textsubscript{2}]SbF\textsubscript{6}, with a strongly electron deficient π-acceptor ligand, P(OCH\textsubscript{2}CF\textsubscript{3})\textsubscript{3} in toluene at 110 °C enabled the construction of a cis-fused 5,7-bicyclic ring 133 in \( \geq 99:1 \) (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 \( \sigma-\pi-\sigma \) 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. Carbometallation of the alkene should afford $\eta^3$ rhodacycle complex 138, which could undergo $\sigma$-$\pi$-$\sigma$ 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. Ancillary ligands and their electronic properties do have a huge impact on the rate of reductive elimination steps in organometallic chemistry. Based on this knowledge, we examined different ligands. $\text{P(OCH}_2\text{CF}_3)_3$, an electron withdrawing phosphite ligand favoured the [4+3] cycloadduct 133 (Table 3; entry 1, $R = \text{H}$).
Table 3: Effect of PPh$_3$ and Methyl Substitution, for the construction of 5,5-bicyclic ring 134 and 142

<table>
<thead>
<tr>
<th>Entry$^a$</th>
<th>L$^b$</th>
<th>R = H</th>
<th>Yield of</th>
<th>Entry$^a$</th>
<th>R = Me</th>
<th>Yield of</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$P(OCH$_2$CF$_3$)$_3$</td>
<td>&gt;19:1</td>
<td>88</td>
<td>7</td>
<td>3:1</td>
<td>70$^e$</td>
</tr>
<tr>
<td>2</td>
<td>$P(OEt)$_3</td>
<td>&gt;19:1</td>
<td>68</td>
<td>8</td>
<td>5:1</td>
<td>68$^e$</td>
</tr>
<tr>
<td>3</td>
<td>$P(OPh)$_3</td>
<td>&gt;19:1</td>
<td>60</td>
<td>9</td>
<td>3:1</td>
<td>72$^e$</td>
</tr>
<tr>
<td>4</td>
<td>$PCy$_3</td>
<td>&gt;19:1</td>
<td>60</td>
<td>10</td>
<td>3:1</td>
<td>55$^e$</td>
</tr>
<tr>
<td>5</td>
<td>PPh$_3$</td>
<td>1:8</td>
<td>71$^d$</td>
<td>11</td>
<td>&lt;1:19</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>P(p-OMe-Ph)$_3$</td>
<td>1:8</td>
<td>72$^d$</td>
<td>12</td>
<td>&lt;1:19</td>
<td>73</td>
</tr>
</tbody>
</table>

$^a$All reactions were carried out on a 0.25 mmol scale 8 h $^b$Ratios were determined by 500 MHz $^c$H NMR on the crude reaction mixtures $^d$Isolated yield of 133/125 $^e$Combined yield of 133 and 134 $^f$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.
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.\textsuperscript{22} A related study has also highlighted the destabilising effect of an alkyl substituted allyl moiety on the stability of π-allylmetal complexes.\textsuperscript{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 (\textbf{Figure 6}). The rotation around the carbon-carbon bond would possibly introduce A\textsuperscript{1,2} allylic strain. This could cause metallacycle intermediate 138a (or 138b) to undergo reductive elimination to produce a 5,5-bicyclic ring.
To test this hypothesis, ACP-diene \((E) \cdot 132\) 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 substituent 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).
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 PPh₃ could improve the selectivity of the 5,5-bicyclic compound 142. Gratifyingly, treatment of ACP-diene (E)-132 with 10 mol% of \([\text{Rh(COD)}_2]\text{SbF}_6\) and 10 mol% of PPh₃ 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](image)

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% \(\text{PdCl}_2\), 20 mol% \(\text{CuI}\) and diisopropylamine furnished the enyn-1-ol \(150\) in 63% yield. Reduction of \(150\) with \(\text{LiAlH}_4\) furnished \((E)\)-pentadienol \(151\) in 62% yield. Subsequent allylation reaction of \((E)-128\) with \(123\) furnished ACP-diene \((E)-143\) in 80% yield.
**Scheme 46:** Preparation of ACP-Diene (E)-**143**: Reaction Conditions: a) Pr$_2$NH (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). 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 furnished ACP-malonate 152 in 88% yield (Scheme 48). 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.

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.

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 ((vinyl oxymethyl) benzene 154 with \(t\)BuLi at \(-78\) °C in pentane/THF gave the corresponding \(\alpha\)-benzyloxy vinyl lithium.\(^{30}\) Subsequent addition of acrolein generated an allylic alcohol, which was treated \textit{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, \(\text{Ph}_3\text{P}^+\text{MeBr}\), 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.

\[
\begin{align*}
\text{BnO} & \xrightarrow{a} \text{OAc} \\
154 & \quad \xrightarrow{87\%} \quad 155 & \xrightarrow{b} \quad 156 & \xrightarrow{69\%} \quad 152 & \xrightarrow{66\%} \quad 147
\end{align*}
\]

\textbf{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) KHOBu (1.5 equiv), \(\text{Ph}_3\text{P}^+\text{MeBr}\) (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

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R</th>
<th>ACP-diene</th>
<th>5,7:5,5</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NTs</td>
<td>H</td>
<td>127</td>
<td>&gt;19:1</td>
<td>133</td>
</tr>
<tr>
<td>2</td>
<td>O</td>
<td>&quot;</td>
<td>143</td>
<td>&gt;19:1</td>
<td>158</td>
</tr>
<tr>
<td>3</td>
<td>C(CO₂Me)₂</td>
<td>&quot;</td>
<td>144</td>
<td>&gt;19:1</td>
<td>159</td>
</tr>
<tr>
<td>4</td>
<td>C[(CH₂O)₂C(Me)₂]</td>
<td>&quot;</td>
<td>145</td>
<td>&gt;19:1</td>
<td>160</td>
</tr>
<tr>
<td>5</td>
<td>NTs</td>
<td>Me</td>
<td>132</td>
<td>≤1:19</td>
<td>142</td>
</tr>
<tr>
<td>6</td>
<td>O</td>
<td>&quot;</td>
<td>146</td>
<td>≤1:19</td>
<td>162</td>
</tr>
<tr>
<td>7</td>
<td>C(CO₂Me)₂</td>
<td>&quot;</td>
<td>147</td>
<td>≤1:19</td>
<td>163</td>
</tr>
<tr>
<td>8</td>
<td>C[(CH₂O)₂C(Me)₂]</td>
<td>&quot;</td>
<td>148</td>
<td>≤1:19</td>
<td>164</td>
</tr>
</tbody>
</table>

*All reactions were carried out using 10 mol% [Rh(COD)]₂SbF₆, 10 mol% of ligand in PhMe at 110 °C on a 0.25 mmol scale 8 h. Ratio of 5,7/5,5 were determined by 500 MHz ¹H NMR on the crude reaction mixtures. Isolated yield Combined yield of regioisomers, 3:1 ratio.
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](image)

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 $^6$BuLi in THF at −78 °C generated the corresponding alkynyllithium, and quenching with acetaldehyde or benzaldehyde generated alcohols 178 or 179 in 96% and 89% yield, respectively. Compounds (E)-180 and (E)-181 were obtained by reduction of precursors 178 and 179 with LiAlH₄ in THF at 0 °C. 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.

![Scheme 50: Preparation of ACP-Dienes (E)-173 and (E)-174; Reaction Conditions (a) $^6$BuLi (1.2 equiv), THF, acetaldehyde (1 equiv) or benzaldehyde (1 equiv), −78 °C (96%; 178) (89%; 179) (b) LiAlH₄ (1.2 equiv), THF, 0 °C (78%; 180) (50%; 181) (c) NaH (1.2 equiv), THF (i) 10 mol% Pd₂(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 of alkynes 182 and 183 with vinyl bromide furnished enynes 184 and 185 in 54% and 80% yield, respectively. Subsequent LiAlH₄ reduction of the substituted propargyl alcohols 184 and 185 gave compounds (E)-186 and (E)-187 in 63% and 70% yield, respectively.
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) \(\text{Pr}_2\text{NH (2 equiv), 4 mol\% CuI, 5 mol\% Pd(PPh}_3\text{)}_4\) vinyl bromide (5 equiv), THF, rt (80%; 185) (54%; 184) (b) \(\text{LiAlH}_4 (1.2\text{equiv), THF, } 0^\circ\text{C (63\%; 186) (70\%; 187) (c) (i) NaH (1.2 equiv), THF (ii) 10 mol\% Pd}_2\text{(dba)}_3\text{, 20 mol\% dppe, 123 (1equiv), THF, rt (45\%; 167) (50\%; 168)}}\)

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,\(^3\) 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), PPh₃ (1.1 equiv), DEAD (1.1 equiv), THF, rt, 82% (b) K₂CO₃ (5 equiv), MeOH, 80 °C, 89% (c) LiAlH₄ (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) nBuLi (2 equiv), Ph₃P•MeBr (2 equiv), THF, -20 °C, (71%, 193; 83%, 194) (f) (i) NaH (1.1 equiv), DMF, 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 (H₂NTs) with commercially available benzaldehyde 196, mediated by 10 mol% of iron(III)-chloride (FeCl₃).

Compound 168 was subjected to a three step synthetic sequence consisting of; Grignard addition,⁵⁹ 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% FeCl₃, H₂NTs (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) nBuLi (2 equiv), Ph₃P·MeBr− (2 equiv), THF, −20 °C (72%, 200; 67%, 201)(e) (i) NaH (1.1 equiv), DMF, rt (ii) 1 mol% Pd₂(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 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 of 204 and 205 with dimethyl malonate furnished compounds 206 and 207 in 92% and 85% yield, respectively. Ozonolysis 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), Et₃N (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(PPh₃)₃, 20 mol% P(OMe)₃, rt, (85%; 207) (92%; 206) (c) Ozone, DCM, –78 °C (87%; 208) (88%; 209)

Two consecutive Wittig olefinations₄²ᵇ 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) Ph₃PCHCOME (2 equiv), toluene, 120 °C (65%; 211) (82%; 210) (b) nBuLi (2 equiv), Ph₃P-MeBr⁻ (2 equiv), THF, –20 °C (69%; 212) (68%; 213) (c) (i) NaH (1.1 equiv), THF, rt (ii) 1 mol% Pd₂(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. Stille cross coupling 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), CH$_3$I (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)](image)

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 $^1$H 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R</th>
<th>R¹</th>
<th>ACP-Diene</th>
<th>Ratio of 5,7:5,5</th>
<th>dr</th>
<th>Product</th>
<th>Yield of Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NTs</td>
<td>H</td>
<td>Me</td>
<td>165</td>
<td>≥19:1 ≥19:1</td>
<td>218</td>
<td>70</td>
<td></td>
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<tr>
<td>2</td>
<td>”</td>
<td>Ph</td>
<td></td>
<td>166</td>
<td>≥19:1 ≥19:1</td>
<td>219</td>
<td>80</td>
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</tr>
<tr>
<td>3</td>
<td>O</td>
<td>Me</td>
<td></td>
<td>167</td>
<td>≥19:1 ≥19:1</td>
<td>220</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>”</td>
<td>Ph</td>
<td></td>
<td>168</td>
<td>≥19:1 ≥19:1</td>
<td>221</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>C(CO₂Me)₂</td>
<td>Me</td>
<td></td>
<td>169</td>
<td>≥19:1 ≥19:1</td>
<td>222</td>
<td>78d</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>”</td>
<td>Ph</td>
<td></td>
<td>170</td>
<td>≥19:1 ≥19:1</td>
<td>223</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>NTs</td>
<td>Me</td>
<td>Me</td>
<td>171</td>
<td>≤1:19 ≥19:1</td>
<td>224</td>
<td>76</td>
<td></td>
</tr>
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<td>Ph</td>
<td></td>
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<td>≤1:19 ≥19:1</td>
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<td>72</td>
<td></td>
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<td>O</td>
<td>Me</td>
<td></td>
<td>173</td>
<td>≤1:19 ≥19:1</td>
<td>226</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>”</td>
<td>Ph</td>
<td></td>
<td>174</td>
<td>≤1:19 ≥19:1</td>
<td>227</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>C(CO₂Me)₂</td>
<td>Me</td>
<td></td>
<td>175</td>
<td>≤1:19 ≥19:1</td>
<td>228</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>”</td>
<td>Ph</td>
<td></td>
<td>176</td>
<td>≤1:19 ≥19:1</td>
<td>229</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

a All reactions were carried out using 10 mol% [Rh(COD)]₂SbF₆, 10 mol% of ligand in PhMe at 110 °C on a 0.25 mmol scale 8h. b Ratios of 5,7/5,5 and dr were determined by 500 MHz ¹H NMR analysis of the crude reaction mixtures. c Isolated yield d P(OEt)₃ was used as ligand.
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 $^3J$ $^1$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).
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 diastereoselective [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 (iPrMgCl) 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), iPrMgCl 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) Cul (1.3 equiv), 5 mol% Pd(PPh3)4, tributy(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 1H 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. The (E)-vinyl iodide was coupled with vinyllastannane 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.

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), iPrMgCl 2 M in THF (3 equiv), −20 °C to RT, THF, 65% (c) BuLi 1.6 M in pentane (1.2 equiv), 236 (1.2 equiv), 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 \((E)\text{-}234\) underwent the [4+3] carbocyclisation reaction successfully. Subjecting \((E)\text{-}234\) to the cationic rhodium catalytic system, \([\text{Rh(COD)}_2\text{SbF}_6\; (6\; \text{mol\%})]\) and triethylphosphite \( (6\; \text{mol\%})\), afforded the 5,7-bicyclic product \(237\) in 71% yield \((5,7\text{:}5,5 \geq 19\text{:}1)\) with excellent diastereocntrol \((\geq 19\text{:}1; \text{determined } ^1\text{H NMR analysis})\). Protodesilylation furnished \(1\text{-}\text{epi}\text{-}\text{dictamnol (\pm)\text{-}238}\) in 60% yield (Scheme 59).

![Scheme 59: Diastereoselective [4+3] carbocyclisation reaction of \((E)\text{-}234\)](image)

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

![Figure 12: 1D nOe of \(238\) (Proof of Stereochemistry)](image)
Further to our investigation, employing a strongly electron withdrawing phosphite \( \text{P(OCH}_2\text{CF}_3)\) as a ligand, 5,7-bicyclic products 237 and 237' was obtained as a mixture of inseparable diastereoisomers in 5:1 ratio (Scheme 60).

\[
\begin{array}{c}
\text{TMSO} \quad \text{Me} \\
(\text{E})-234
\end{array}
\quad \text{[Rh(COD)}_2\text{SbF}_6 \text{(6 mol\%)} \quad \text{P(OCH}_2\text{CF}_3)\text{3 (6 mol\%)} \\
\quad \text{PhMe, 110 °C} \quad \text{58\% Yield} \quad \text{dr 5:1}
\begin{array}{c}
\text{TMSO} \quad \text{Me} \\
(\pm)-237
\end{array}
\quad +
\begin{array}{c}
\text{TMSO} \quad \text{Me} \\
(\pm)-237'
\end{array}
\]

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

Additionally, subjecting substrate 233 to 6 mol\% [Rh(COD)\(_2\)]\text{SbF}_6 and 6 mol\% of P(OEt)\(_3\) furnished the corresponding inseparable diastereomeric mixtures of 5,7-cycloadducts 238 and 238\(_a\) in 7:1 ratio (Scheme 61).

\[
\begin{array}{c}
\text{HO} \quad \text{Me} \\
(\text{E})-233
\end{array}
\quad \text{[Rh(COD)}_2\text{SbF}_6 \text{(6 mol\%)} \quad \text{P(OEt)}_3 \text{(6 mol\%)} \\
\quad \text{PhMe, 110 °C} \quad \text{68\% Yield} \quad \text{dr 7:1}
\begin{array}{c}
\text{HO} \quad \text{Me} \\
(\pm)-238
\end{array}
\quad +
\begin{array}{c}
\text{HO} \quad \text{Me} \\
(\pm)-238a
\end{array}
\]

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.\(^{48,49}\)

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

A plausible mechanistic rationale for the excellent diastereoselectivity observed in scheme 59 is described in scheme 63. The O\(_{\text{Si}}\)(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 O\(_{\text{Si}}\)(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-F254 plates (Whatman PE SIL G/UV); Ultra-Violet light and by treatment with a KMnO4, p-anisaldehyde and Hanessian’s dip, followed by heating. The melting points (uncorrected) were obtained from a Griffin Melting Point Instrument. Optical rotations ([α]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 infrared) 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. 

1H NMR and 13C NMR spectra were recorded on a 

**Bruker Avance DRX-500** spectrometer in CDCl₃ at ambient temperature; chemical shifts (δ) are given in ppm and calibrated using the signal of residual undeuterated solvent as internal reference (δH = 7.26 ppm and δC = 77.16 ppm). 

1H 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. 

13C 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 hexane (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 selectivities 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

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\(_4\)Cl (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-(2-Chloroethyl)cyclopropyl 4-methylbenzenesulfonate 122.

**H NMR** (500 MHz, CDCl₃) 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).

**C NMR** (125 MHz, CDCl₃) 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 C₁₂H₁₅O₃ClNa 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 NaHCO₃ (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 MgSO₄, 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$_3$) $\delta$ 7.77 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.1$ Hz, 2H), 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$_3$) $\delta$ 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$_{16}$O$_3$NS 256.1002, found 256.1003.

A solution of compound 190 (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 (¹H NMR analysis)

¹H NMR (500 MHz, CDCl₃) 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),

¹³C NMR (125 MHz, CDCl₃) 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 C₁₃H₁₇NO₃NaS 290.0827, found 290.0825.

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

*Colour and State:* Yellow oil

Stereochemistry: \(E/Z = \geq 19:1\) (\(^1\)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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_3\)NaS 276.0671, found 276.0671.

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

*Colour and State:* Light brown oil

Stereochemistry: \(E/Z = \geq 19:1\) (\(^1\)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\(_3\)) \(\delta\) 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).
\( ^{13}\text{C NMR} \) (125 MHz, CDCl\(_3\)) \( \delta \) 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\(_3\)NaS 315.3872, found 315.3870.

\( (E)-4\text{-methyl-N-}(4\text{-oxo}-1\text{-phenylpent-2-}
\text{enyl})\text{benzenesulphonamide 199}. \)

\textit{Colour and State:} Yellow oil

Stereochemistry: \( E/Z = >19:1 \) (\(^1\text{H NMR analysis} \)

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

\(^1\text{H NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \) 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).

\(^{13}\text{C NMR} \) (125 MHz, CDCl\(_3\)) \( \delta \) 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\(_3\)S 329.4130 found 329.4128.
$^\text{t}^\text{BuLi}$ (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$_4$Cl (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$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$NaS 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.

**1H NMR** (500 MHz, CDCl₃) 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).

**13C NMR** (125 MHz, CDCl₃) 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 C₁₄H₁₉NO₂NaS 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.

**1H NMR** (500 MHz, CDCl₃) 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).
\[^{13}\text{C NMR}\ (125\ \text{MHz},\ \text{CDCl}_3)\ \delta\ \text{143.40 (e), 139.63 (e), 137.66 (e), 135.78 (o), 132.96 (o), 132.26 (o), 129.55 (o), 128.80 (o), 127.94 (o), 127.41 (o), 127.14 (o), 118.66 (e), 59.44 (o), 21.64 (o).}\]

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

\[\text{HRMS (ESI, [M+Na]\textsuperscript{+}) calcd for C}_{18}\text{H}_{19}\text{NO}_{2}\text{NaS 336.1034, found 336.1045.}\]

\[\text{(E)-4-methyl-N-(4-methyl-1-phenylpenta-2,4-dienyl)benzenesulfonamide 201.}\]

\[\text{Colour and State: Colourless oil}\]

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

\[^{1}\text{H NMR}\ (500\ \text{MHz},\ \text{CDCl}_3)\ \delta\ 7.63\ \text{(app. d, } J = 8.2\ \text{Hz, 2H)},\ 7.23-7.14\ \text{(m, 7H)},\ 6.06\ \text{(d, } J = 15.6\ \text{Hz, 1H)},\ 5.51\ \text{(dd, } J = 15.6,\ 7.5\ \text{Hz, 1H)},\ 5.39\ \text{(d, } J = 7.4\ \text{Hz, 1H)},\ 4.99\ \text{(app. t, } J = 7.1\ \text{Hz, 1H)},\ 4.92\ \text{(s, 1H)},\ 4.84\ \text{(s, 1H)},\ 2.36\ \text{(s, 3H)},\ 1.64\ \text{(s, 3H)}.\]

\[^{13}\text{C NMR}\ (125\ \text{MHz},\ \text{CDCl}_3)\ \delta\ 143.22\ \text{(e), 140.94 (e), 139.89 (e), 137.76 (e), 134.95 (o), 129.44 (o), 128.68 (o), 128.27 (o), 127.74 (o), 127.37 (o), 127.07 (o), 117.72 (e), 60.52 (o), 21.55 (o), 18.41 (o).}\]

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

\[\text{HRMS (ESI, [M+Na]\textsuperscript{+}) calcd for C}_{19}\text{H}_{21}\text{NO}_{2}\text{NaS 350.1191, found 350.1175.}\]
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, Pd₂(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 MgSO₄, 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.

**1H NMR** (500 MHz, CDCl$_3$) $\delta$ 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).

**13C NMR** (125 MHz, CDCl$_3$) $\delta$ 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$_2$NaS 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*.

**1H NMR** (500 MHz, CDCl$_3$) $\delta$ 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).
\textit{13C NMR} (125 MHz, CDCl$_3$) δ 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).

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


\textit{(E)-N-(2-Cyclopropylideneethyl)-N-(hexa-3,5-dien-2-yl)-4-methylbenzenesulfonamide} 165.

\textit{Colour and State}: Yellow oil.

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

\textit{1H NMR} (500 MHz, CDCl$_3$) δ 7.69 (d, \textit{J} = 8.3 Hz, 2H), 7.27 (d, \textit{J} = 8.4 Hz, 2H), 6.19 (dt, \textit{J} = 16.9, 10.2 Hz, 1H), 5.96 (dd, \textit{J} = 15.4, 10.3 Hz, 1H), 5.76 (tquin, \textit{J} = 6.6, 2.0 Hz, 1H), 5.49 (dd, \textit{J} = 15.5, 5.5 Hz, 1H), 5.12 (d, \textit{J} = 17.0 Hz, 1H), 5.05 (d, \textit{J} = 10.1 Hz, 1H), 4.61 (dq, \textit{J} = 6.9, 5.5 Hz, 1H), 3.93 (ddt, A of ABXY$_2$, \textit{J}_{AB} = 15.6 Hz, \textit{J}_{AX} = 6.6 Hz, \textit{J}_{AY} = 1.1 Hz, 1H), 3.84 (ddt, B of ABXY$_2$, \textit{J}_{AB} = 15.6, \textit{J}_{BX} = 6.6 Hz, \textit{J}_{BY} = 1.1 Hz, 1H), 2.41 (s, 3H), 1.21 (d, \textit{J} = 6.9 Hz, 3H), 1.05-0.98 (m, 4H).

\textit{13C 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).

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

\textit{HRMS} (ESI, [M+Na]$^+$) calcd for C$_{18}$H$_{23}$NO$_2$NaS 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\textsubscript{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).

^1^C NMR (125 MHz, CDCl\textsubscript{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\textsuperscript{-1}.

HRMS (ESI, [M+Na]\textsuperscript{+}) calcd for C\textsubscript{19}H\textsubscript{25}NO\textsubscript{2}NaS 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\textsubscript{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$_3$) $\delta$ 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$_2$Na 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$NaS 416.1665, found 416.1660.

A solution of \((E)\)-dien-ol \(\mathbf{151}\) (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, \(\text{Pd}_2(\text{dba})_3\) (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 \(\mathbf{123}\) (0.30 g, 1.25 mmol) in THF (5 mL) was added. The reaction was stirred until the dark red solution turned green \(\text{(ca. 30 min)}\). The electrophile (green solution) was then transferred \(via\) Teflon® cannula to the vessel containing the nucleophile (solution of \(\text{NaH}\) and \(\mathbf{151}\)). 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 \(\text{MgSO}_4\), filtered and concentrated \text{in vacuo}. Purification by flash chromatography (silica gel, 5% diethyl ether/ petroleum ether) afforded compound \((E)\)-\(\mathbf{143}\) 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.

**1H NMR** (500 MHz, CDCl₃) 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 (dd, J = 16.9 Hz, 1H), 5.09 (d, J = 10.0 Hz, 1H), 4.12 (ddquin, A of ABXY, 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).

**13C NMR** (125 MHz, CDCl₃) 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 C₁₁H₁₇O 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.

**1H NMR** (500 MHz, CDCl₃) 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).

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 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).

\(\text{IR}\) (Neat) 2924 (m), 2854 (m), 1680 (w), 1603 (w), 1492 (w), 1452 (m), 1452 (m), 1102 (m), 1107 (m), 1002 (s).

\(\text{HRMS}\) (ESI, [M+H]\(^+\)) calcd for C\(_{16}\)H\(_{19}\)O 227.1431, found 227.1431.

\[(E)-\text{(2-(Hexa-3,5-dien-2-yloxy)ethylidene)cyclopropane}\ 173\]

\(\text{Colour and State:}\) 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 \((E)-143\).

\(^{1}\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 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).

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 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).

\(\text{IR}\) (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).

\(\text{HRMS}\) (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.

^1H NMR (500 MHz, CDCl₃): δ 7.37-7.25 (m, 5H), 6.33 (d, J = 15.6 Hz, 1H), 5.99 (t, 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).

^13C NMR (125 MHz, CDCl₃): 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

\[
\begin{align*}
\text{DIBAL-H (11.22 mL, 1 M in hexane, 11.22 mmol) was slowly added to a solution of compound (E)-144} & \text{ (0.70 g, 2.67 mmol) in DCM (25 mL) at } -78 \degree C \text{ and then stirred for 2 h. After the reaction had reached completion (t.l.c. control), saturated aqueous solution of sodium potassium tartarate (30 mL) was added slowly until the precipitate turned to a suspension. The aqueous layer was extracted with DCM twice (20 mL). The combined organic layers were dried with MgSO}_4, \text{ filtered and concentrated in vacuo. The diol (0.55 g, 2.64 mmol, 99\%) was used without further purification.}
\end{align*}
\]

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-dimethoxypropane (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 (1H NMR analysis)

1H NMR (500 MHz, CDCl$_3$) $\delta$ 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).

13C 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), 1369 (m), 125 (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

(1H) 148 (73% yield on 1.13 mmol scale) was prepared according to the experimental procedure described for the synthesis of compound (E)-145.

1H NMR (500 MHz, CDCl$_3$) $\delta$ 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).

Colour and State: Colourless oil.

Compound (E)-148 was prepared according to the experimental procedure described for the synthesis of compound (E)-145.
**13C NMR** (125 MHz, CDCl₃) 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), 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.


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

A suspension of Ph₃PCHCOMe (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** (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%).

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(E)-dimethyl 2-(5-oxohex-3-en-2-yl)malonate 210.
Stereochemistry: $E/Z = \geq 19:1$ ($^1$H NMR analysis)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_5$Na 251.0895, found 251.0904.

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

Colour and State: Yellow oil

Stereochemistry: $E/Z = \geq 19:1$ ($^1$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 in DCM (20 mL) with acetic acid (0.012 mL, 0.0212 mmol) at room temperature.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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 (w), 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.

\(\text{\textsuperscript{a}BuLi}\) (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\(_4\)Cl (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 \textit{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%).

\[(E)-\text{dimethyl 2-(5-methylhexa-3,5-dien-2-yl)malonate 212.}\]

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 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).

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 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.


(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.

¹H NMR (500 MHz, CDCl₃) 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).

¹³C NMR (125 MHz, CDCl₃) 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.

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$_2$S$_2$O$_3$ (15 mL), 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 (1H 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$_9$H$_{14}$O$_4$I 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 (1H 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.

1H NMR (500 MHz, CDCl3) 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).

13C NMR (125 MHz, CDCl3) 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.


Pd2(dba)3 (0.18 g, 0.20 mmol) and PPh3 (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 NH4Cl 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 MgSO4, 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: $E/Z = 13:1$ (1H NMR analysis)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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), 48.24 (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 = \geq$19:1 (1H 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$_3$) $\delta$ 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$_3$) $\delta$ 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.


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, Pd₂(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 MgSO₄, 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.

**1H NMR** (500 MHz, CDCl₃) 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).

**13C NMR** (125 MHz, CDCl₃) 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.


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.

**1H NMR** (500 MHz, CDCl₃) 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 (ddquint, 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 (ddquint, A of ABXY₄, Jₐₐ = 14.2 Hz, Jₐₓ = 6.4 Hz, Jₐᵧ = 1.2 Hz, 1H), 2.63 (ddquint, B of ABXY₄, Jₐₐ = 14.3 Hz, Jₐₓ = 7.8 Hz, Jₐᵧ = 1.1 Hz, 1H), 1.83 (s, 3H), 1.03 (dt, J = 7.8, 1.2 Hz, 2H), 0.96-0.86 (m, 2H).
\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 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).

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

\(\text{HRMS}\) (ESI, [M+Na]\(^+\)) calcd for C\(_{22}\)H\(_{26}\)O\(_4\)Na 377.1741, found 377.1729.

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

\textit{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.

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 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).

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 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).

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

\(\text{HRMS}\) (ESI, [M+Na]\(^+\)) calcd for C\(_{16}\)H\(_{22}\)O\(_4\)Na 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, CDCl₃) 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, CDCl₃) 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_{4}Na 363.1580, found 363.1572.
2.8.6 Representative Experimental Procedure for the Rhodium(I)-Catalysed [4+3] Carbocyclisation Reaction

Rh(COD)$_2$SbF$_6$ (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$_2$CF$_3$)$_3$ (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%).
**(3aS,8aS)-4-methylene-2-tosyl-1,2,3,3a,4,5,6,8a-octahydrocyclohepta[c]pyrrole 133.**

Stereochemistry Assignment: \( dr \geq 19:1 \) (**1**H NMR analysis)

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

**1**H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 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).

**13C NMR** (125 MHz, CDCl\(_3\)) \( \delta \) 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\(_2\)NaS 326.1292, found 326.1191.

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**(3aS,8aS)-4-methylene-3,3a,4,5,6,8a-hexahydro-1H-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: \( dr \geq 19:1 \) (**1**H NMR analysis)

**1**H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 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.

(3aS, 8aS)-dimethyl-8methylene-3,3a,4,6,8,8a-hexahydroazulene-2,2- (1H)-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: $dr \geq 19:1$ ($^1$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$_4$Na 287.1362, found 287.1246.
Compound 160 (80% yield on 0.25 mmol scale) was prepared according to the representative [4+3] carbocyclisation reaction experimental procedure.

Stereochemistry Assignment: \( dr \geq 19:1 \) (\(^1\)H NMR analysis)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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.
(1R,3aS,8aS)-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\(_3\)) \( \delta \): 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\(_3\)) \( \delta \): 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\(_2\)NaS 340.1347, found 340.1347.
(1R,3aS,8aS)-1-methyl-4-methylene-3,3a,4,5,6,8a-hexahydro-
[1H]-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: $dr \geq 19:1$ ($^1$H NMR analysis)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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.
(3R,3aR,8aS)-dimethyl 3-methyl-8-methylene-3,3a,6,7,8,8a-hexahydroazulene-2,2 (1H)-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] carboxyclisation reaction experimental procedure.

Stereochemistry Assignment: $dr \geq 19:1$ ($^1$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$_3$) $\delta$ 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$_3$) $\delta$ 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$_4$Na 301.1425, found 301.1416.
(1S,3aS,8aS)-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: $dr \geq 19:1$ ($^1$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$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$NaS 402.1512, found 402.1504.
(1S,3aS,8aS)-4-methylene-1-phenyl-3,3a,4,5,6,8a-hexahydro-
1H-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 (1H NMR analysis)

**1H NMR** (500 MHz, CDCl₃) 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, Jₐₐ = 8.7 Hz, Jₐₓ = 7.0 Hz, 1H), 4.10 (dd, B of ABX, Jₐₐ = 8.7 Hz, Jₜₗₜ = 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).

**13C NMR** (125 MHz, CDCl₃) 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.
(35,3aS,8aS)-dimethyl 8-methylene-3-phenyl-3,3a,6,7,8,8a-hexahydroazulene-2,2(1H)-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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_4\)Na 363.1588, found 363.1572.
2.8.7 Representative Experimental Procedure for the Rhodium(I)-Catalysed [3+2] Carbocyclisation Reaction

Rh(COD)$_2$SbF$_6$ (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%).
(3aR,6aS)-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$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$NaS 340.1347 found, 340.1353.

(3aR,6aS)-6-methyl-4-(propan-2-ylidene)-3,3a,4,6a-tetrahydro-1H-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$_3$) $\delta$ 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).
\[ ^{13}\text{C NMR} \text{ (125 MHz, CDCl}_3 \text{) } \delta 144.70 \text{ (e), 142.18 \text{ (e), 127.59 \text{ (o), 120.52 \text{ (e), 74.93 \text{ (e), 70.83 \text{ (e), 54.03 \text{ (o), 46.49 \text{ (o), 21.39 \text{ (o), 20.84 \text{ (o), 16.04 \text{ (o).}}}}}}}}\]

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

\[ \text{HRMS (ESI, [M+H]^{+}) calcd for C}_{11}\text{H}_{17}\text{O 165.1201, found 165.1212}} \]

\[ (3aR,6aS)-\text{dimethyl 4-methyl-6-(propan-2-ylidene)-3,3a,6,6a-tetrahydropentalene-2,2(1H)-dicarboxylate} 163. \]

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

\[ \text{Stereochemistry Assignment: } dr \geq 19:1 \text{ (}^{1}\text{H NMR analysis)} \]

\[ ^{1}\text{H NMR (500 MHz, CDCl}_3 \text{) } \delta 5.85 \text{ (s, 1H), 3.73 \text{ (s, 3H), 3.65 \text{ (s, 3H), 3.25 (q, } J = 8.4 \text{ Hz, 1H), 3.16 (q, } J = 7.7 \text{ Hz, 1H), 2.64 (dd, A of ABX, } J_{AB} = 12.9 \text{ Hz, } J_{AX} = 8.7 \text{ Hz, 1H), 2.49 (dd, B of ABX, } J_{AB} = 13.0 \text{ Hz, } J_{BX} = 8.6 \text{ Hz, 1H), 1.99 (dd, A of ABX, } J_{AB} = 13.2 \text{ Hz, } J_{AX} = 6.6 \text{ Hz, 1H), 1.95 (dd, B of ABX, } J_{AB} = 13.1 \text{ Hz, } J_{BX} = 7.0 \text{ Hz, 1H), 1.77 (s, 3H), 1.70 (br s, 6H).} \]

\[ ^{13}\text{C NMR (125 MHz, CDCl}_3 \text{) } \delta 172.72 \text{ (e), 171.97 \text{ (e), 146.39 \text{ (e), 142.68 \text{ (e), 125.53 \text{ (o), 119.97 \text{ (e), 62.00 \text{ (e), 52.89 \text{ (o), 52.57 \text{ (o), 52.30 \text{ (o), 45.08 \text{ (o), 40.78 \text{ (e), 38.36 \text{ (e), 21.36 \text{ (o), 20.82 \text{ (o), 15.68 \text{ (o).}}}}}})}}}\]

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

\[ \text{HRMS (ESI, [M+Na]^{+}) calcd for C}_{16}\text{H}_{22}\text{O}_4\text{Na 301.1416, found 301.1429}}. \]
Compound 225 (72% yield on 0.25 mmol scale) was prepared according to the representative [3+2] carbocyclisation reaction experimental procedure.

Stereochemistry Assignment: $dr \geq 19:1$ ($^1$H NMR analysis)

Relative stereochemistry: $^1$H NMR analysis $^3$J$_{Ha-Hb} = 7.6$ 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$NaS 416.1656, found 416.1660.
(3S,3aR,6aS)-6-methyl-3-phenyl-4-(propan-2-ylidene)-3,3a,4,6a-tetrahydro-1H-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: $dr \geq 19:1$ ($^1$H NMR analysis)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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.

(1S,3aS,6aS)-dimethyl 4-methyl-1-phenyl-6-(propan-2-ylidene)-3,3a,6,6a-tetrahydropentalene-2,2 (1H)-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: $dr \geq 19:1$ ($^1$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$_4$Na 377.1727, found 377.1729.

$^{(3R,3aR,6aS)}$-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: $dr \geq 19:1$ ($^1$H NMR analysis)

Relative stereochemistry: $^1$H NMR analysis $^3$$J_{H_a-H_b} = 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).

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\[^{13}\text{C} \text{NMR}\] (125 MHz, CDCl\(_3\)) \(\delta\) 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).

\[\text{IR (Neat)}\] 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\(^{-1}\).

\[\text{HRMS (ESI, [M+Na]\(^+\})}\] calcd for C\(_{19}\)H\(_{25}\)NO\(_2\)NaS 354.1495, found 354.1504.

\((3\text{R},3\text{a}R,6\text{a}S)-3,6\text{-Dimethyl-4-(propan-2-ylidene)-3,3a,4,6a-tetrahydro-1H-cyclopenta[c]furan}\) 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: \(dr \geq 19:1\) (\(^1\text{H NMR analysis}\))

\[^1\text{H NMR}\] (500 MHz, CDCl\(_3\)) \(\delta\) 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).

\[^{13}\text{C NMR}\] (125 MHz, CDCl\(_3\)) \(\delta\) 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).

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

\[\text{HRMS (ESI, [M+H]\(^+\})}\] calcd for C\(_{12}\)H\(_9\)O 179.1358, found 179.1364
(1R,3aS,6aR)-dimethyl-1,4-dimethyl-6-(propan-2-ylidene)-3,3a,6,6a tetrahydropentalene-2,2(1H)-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 (_1H 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%).

**_1H 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, _J_ = 13.6 Hz, 1H), 2.11 (dd, _J_ = 7.2 Hz, 3H). 1.72 (s, 9H), 1.05 (d, _J_ = 7.2 Hz, 3H).

**_13C 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_{4}Na 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 MgSO₄, 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-cyclopropyldienebutanoate 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 \(-20^\circ C\), 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 \( \text{NH}_4\text{Cl} \) (20 mL) and partitioned with diethyl ether (50 mL). The organic layer was washed with brine (20 mL), dried with \( \text{MgSO}_4 \), filtered and concentrated \textit{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%).

\[
\text{4-Cyclopropyldiene-} N \text{-methoxy-} N \text{-methylbutanamide 235.}
\]

\textit{Colour and State:} Colourless oil

\( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \) 5.81 (tquin, \( J = 6.4, 1.9 \text{ Hz}, 1\text{H})\), 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).

\( ^{13}\text{C NMR} \) (125 MHz, CDCl\(_3\)) \( \delta \) 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).

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

\( \text{HRMS (ESI, [M+H]\(^+\))} \) calcd for C\(_9\)H\(_{16}\)O\(_2\)N 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, ethynylmagnesium 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 NaHCO₃ (25 mL) followed by brine (20 mL), dried over MgSO₄, 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

1H NMR (500 MHz, CDCl₃) δ 5.75 (tquint, 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).

13C NMR (125 MHz, CDCl₃) 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.

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 MgSO₄, 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 (1H NMR analysis)

^1H NMR (500 MHz, CDCl₃) 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).

^13C NMR (125 MHz, CDCl₃) 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 C₉H₁₂I0 262.9927, found 262.9933.
Pd(PPh$_3$)$_4$ (0.51 g, 0.44 mmol) and Cul (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$_4$Cl 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-butyl lithium (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 NH₄Cl (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 MgSO₄, 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:* ¹H NMR $E/Z > 19:1$

¹H NMR (500 MHz, CDCl₃) 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 (tq, $J = 6.0, 2.1$ 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).

¹³C NMR (125 MHz, CDCl₃) 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 C₁₁H₁₅O 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\(_4\)Cl (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 \textit{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%).

\(\text{Colour and State: Colourless oil}\)

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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-H\(_2\)O+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 NH₄Cl (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 MgSO₄, 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

**1H NMR** (500 MHz, CDCl₃) 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).

**13C NMR** (125 MHz, CDCl₃) 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.

Rh(COD)$_2$SbF$_6$ (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 ((1R,3aS,8aS)-1-methyl-4-methylene-1,2,3,3a,4,5,6,8a-octahydroazulen-1-yloxy)silane 237.

Stereochemistry assignment: dr > 19:1 (1H 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%).
\((1R,3aS,8aS)-1\text{-methyl-4-methylene-1,2,3,3a,4,5,6,8a-octahydroazulen-1-ol (1-epi-Dictamnol)}\) 238.

Relative Stereochemistry: nOe analysis, Me to H\textsubscript{b} (1.5%), H\textsubscript{a} to H\textsubscript{b} (1.7%), H\textsubscript{b} to H\textsubscript{a} (1.6%), H\textsubscript{b} to Me (0.9%). (Figure 12)

**\(^1\)H NMR** (500 MHz, CDCl\textsubscript{3}) \(\delta\) 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\textsubscript{a}), 2.67 (dd, \(J = 8.7, 7.4\) Hz, 1H, H\textsubscript{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\textsubscript{3}) \(\delta\) 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\textsubscript{3}]\(^+\)) calcd for C\textsubscript{12}H\textsubscript{22}ON 196.1696, found 196.1693.
2.9 References


18. Phosphoramidite ligands also favour the formation of a 5,7-bicyclic product but with 0% ee.

19. Tributylphosphine also gave >19:1 (5,7:5,5) in 60% yield. Tris(furyl)$_3$phosphine also gave >19:1 (5,7:5,5) in 63% yield, possibly due to furan being less aromatic than benzene ring.

20. For a study which showed that unsubstituted double bond in close proximity with Rh-C bond facilitated $\sigma$-$\pi$-$\sigma$ isomerisation, see; (a) Saito, A.; Mori, M.; Sato, Y. *Synthesis* **2009**, *6*, 969–979 (b) Sato, Y.; Oonishi, Y.; Mori, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 1218–1221.


24. Me-group on terminal double bond of the diene resulted to $\beta$-hydride elimination product. Substitution on other sites of the diene led to either decomposition or furnish 5,7-bicyclic rings selectively, albeit in poor yield.


51. Hardy, J. P.; Cumming, W. D. J. Am. Chem. Soc. 1971, 93, 928–932

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.
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. For example, salograviolide A inhibits the proliferation of a host of colon-derived cells. Rupicolin A-8-O-acetate possesses *in vitro* anti-plasmodial activity ($IC_{50} = 10.8–12.5 \, \mu g/mL$). Repin induces neurotoxicity in rodents and compound 239 exhibits toxicity towards liver and lung cancer cell lines (Figure 14).

![Figure 14: Biologically active guaianolides](image-url)
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](image)

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 \(\alpha\)-methylene \(\gamma\)-butyrolactone,\(^9c\) as well as the presence of the epoxide and the hydroxyl functional groups.
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 \( \text{244} \) can be installed through an enolate reaction with Eschenmoser salt \( \text{249} \) followed by elimination.\(^{39,41} \) Additionally, the ketone group in \( \text{244} \) can be obtained via deprotection followed by oxidation of the silyl protected alcohol in \( \text{245} \).

The epoxidation of the \( \text{cis} \)-fused 5,7-bicyclic compound \( \text{246} \) is expected to be possible under Jacobsen-Katsuki reaction condition,\(^ {30} \) using Mn(III)salen complex to produce compound \( \text{245} \). The intermediate \( \text{247} \) 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 \( \text{cis} \)-fused 5,7-bicyclic compound \( \text{246} \).
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.

\[
\text{Scheme 65: Retrosynthetic analysis of ACP-diene 247}
\]

### 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.

\[
\text{Scheme 66: Preparation of aldehyde 251; Reaction Conditions: a) NaH (1 equiv), TBS-Cl (1 equiv), THF, 0 °C to rt, 87% (b) Oxalyl chloride (2 equiv), DMSO (5 equiv), DIPEA (4 equiv), DCM, –78 °C, 88%}
\]
The aldehyde 251 was subjected to Brown’s crotylation using (+)-\((\text{Ipc})_2\text{B(OMe)}\) and \((Z)\)-\(\text{MeCH=CHCH}_2\text{Li}\), 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).

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, \textit{tert}-potassium butoxide, \textit{cis}-2-butene and enantiopure borane \((+)-(\text{Ipc})_{2}\text{B(OMe)}\). Additionally, the crotylborane reagent 256 can be prepared in 2 h without employing an organocatalyst or a transition metal. \textbf{Scheme 68} explains the mechanism of the crotylation reaction and the rationale for the excellent diastereoselectivity observed in this reaction.

\textbf{Scheme 68}: Proposed mechanism of the crotylation reaction
Allylic deprotonation of the cis-2-butene by Schlosser base\textsuperscript{21} provided a cis-allyllithium species 255, which reacts with (+)-(1pc)\textsubscript{2}B(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.\textsuperscript{10b}

**Scheme 69** shows the complete synthesis of key intermediate ACP-diene 247. The cross-metathesis\textsuperscript{11b} of compound 254 with crotonaldehyde, mediated by 5 mol\% of Hoveyda Grubbs 2\textsuperscript{nd} 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) Ph₃PMeBr (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 PCy₃ 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 PCy₃. 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.²⁴α
Compound 257 was converted to diene 258 using methyltriphenylphosphonium bromide salt and "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\textsuperscript{24b} generated aldehyde 260, and this underwent Wittig olefination with ylide 262 to produce ACP-diene 247.\textsuperscript{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.
The yield of ACP-diene 247 was improved by treating (3-bromopropyl)triphenylphosphonium bromide 262 with 2 equivalents of potassium tert-butoxide 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 $\beta$-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)]_2SbF_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)]_2SbF_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.

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.

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\(_2\)O, EtOH, 100 °C to 70 °C, 54%
A previous report has shown that chiral Mn(III)-salen complexes are highly selective for \textit{cis}-disubstituted alkenes.\textsuperscript{34} Conversely, slow reaction rates and low enantioselectivities were obtained with \textit{trans}-substituted olefins.\textsuperscript{35} The aptitude of Mn(III)-salen complexes for \textit{cis}-olefin is an attractive feature to us, given that compound 246 has a \textit{cis} disubstituted endocyclic olefin. Our efforts begun with the synthesis of Mn(III)-salen complex 276 (Scheme 73). The chiral (\textit{R},\textit{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$_2$O 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 (\textit{R},\textit{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).

\textbf{Scheme 74: Formation of Mn(V)-oxo species 278}

![](image.png)
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\(_2\)O\(_2\) 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](image)

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.\(^{37}\)
It appears that a skewed side-on approach (Katsuki’s model\textsuperscript{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.\textsuperscript{38}

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.
3.8 Epoxide Opening and Cyclisation

We envisaged that the $\text{trans-}\gamma$-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 $\gamma$-butyrolactone in Natural Products](image)

Danishefsky and co-workers employed Creger-Silbert dianion$^{41}$, LiCH$_2$CO$_2$Li, 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, C₆H₆, 70 °C, (2:1 regioisomers), 62% (b) LDA, Eschenmoser salt, HMPA, MeI, THF, -76 °C to -42 °C to RT, 29%

In a similar fashion, Rigby and co-workers utilised the Creger-Silbert dianion, LiCH₂CO₂Li, 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, NEt₃, -78 °C to rt, 42% over two steps (c) nBuLi, 288, THF, -78 °C to 0 °C, 15% (d) LDA, THF, 249, -78 °C to RT, Mel, 71% (e) BF₃·OEt₂, C₆H₆, 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 nBuLi 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 $\beta$-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](image)

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](image)
Furthermore, we examined sp\textsuperscript{2}-hybridised carbon nucleophiles. Disappointingly, no reaction was observed, and the starting material was recovered (Scheme 80).

![Scheme 80: Epoxide Opening with sp\textsuperscript{2}-hybridised carbon nucleophiles](image)

Previous reports have shown alkynes as an ideal two carbon unit precursor for installing the γ-butyrolactone moiety.\textsuperscript{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 homopropyl alcohol in 291 (Scheme 81).
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 MgR₂, RMgBr, and MgBr₂ (Figure 24).
Switching to TIPS-protected lithium acetylene and AlClMe₂ or BF₃·OEt₂ (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 (⁰BuLi 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 \( { }^{n} \text{BuLi} \) (1.6 M in hexane) at \(-78^\circ\text{C}\) in anhydrous THF. Subsequent addition of BF\(_3\).OEt\(_2\) and epoxide 245 at \(-78^\circ\text{C}\), 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 to 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 (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 NaHCO₃ (20 mL) and partitioned with DCM (25 mL). The organic layer was washed with water (25 mL), followed by brine (10 mL), dried with MgSO₄, 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%).

\[(S)-5-(\textit{S})\text{-but-3-en-2-yl})\text{-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxo-3,9-disilaundecane} \ 254.\]

\(^{1}H\text{ NMR}\ (500 \text{ MHz, CDCl}_3) \delta 5.83 (\text{ddd}, J = 17.3, 11.5, 5.7 \text{ Hz, 1H}), \ 5.01-4.98 (\text{m, 2H}), \ 3.72-3.60 (\text{m, 3H}), \ 2.31 (\text{app q, } J = 6.1 \text{ Hz, 1H}), \ 1.65-1.55 (\text{m, 2H}), \ 0.95 (\text{d, } J = 6.95 \text{ Hz, 3H}), \ 0.88 (\text{s, 18H}), \ 0.04-0.03 (\text{m, 12H}).\]

\(^{13}C\text{ NMR}\ (125 \text{ MHz, CDCl}_3) \delta 141.24 (\text{o}), \ 114.14 (\text{e}), \ 72.97 (\text{o}), \ 60.14 (\text{e}), \ 43.09 (\text{o}), \ 36.68 (\text{e}), \ 26.10 (\text{o}), \ 26.09 (\text{o}), \ 18.42 (\text{e}), \ 18.30 (\text{e}), \ 14.87 (\text{o}), \ -4.19 (\text{o}), \ -4.35 (\text{o}), \ -5.09 (\text{o}), \ -5.13 (\text{o}).\]

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

\textbf{HRMS}\ (ESI, [M+Na]^+) calcd for C\textsubscript{19}H\textsubscript{42}O\textsubscript{2}Si\textsubscript{2}Na, 381.2621 found 381.2630.

[\(\alpha\)]\textsubscript{20} ^20 -41.68 (c = 1, CHCl\textsubscript{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%).

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

Stereochemistry: E/Z: ≥19:1 (1H NMR analysis)

1H NMR (500 MHz, CDCl3) 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 (dddd, 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).

13C NMR (125 MHz, CDCl3) 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.


[α]20 -39.63 (c = 1, CHCl3)
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$_4$Cl (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%).

\[
\text{(S)-5-((S,E)-hexa-3,5-dien-2-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane 258.}
\]

$^1$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$_2$Si$_2$Na, 407.2778 found 407.2766.

$[\alpha]^{20}$ -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 NaHCO₃ (20 mL). The aqueous layer was washed with ethyl acetate (2 x 35 mL). The combined organic layers were washed with saturate solution of CuSO₄ (15 mL), water (25 mL), followed by brine (15 mL), dried with MgSO₄, 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%).

\[
(3S,4S,E)-3-(\text{tert-butylimethylsilyloxy})-4\text{-methylocta-5,7-dien-1-ol} \text{ 259.}
\]

\[
\text{^1H NMR (500 MHz, CDCl₃) } \delta \text{ 6.31 (dt, } J = 17.0, 10.2 \text{ Hz, 1H), 6.05 (dd, } J = 15.4, 10.3 \text{ Hz, 1H), 5.71 (dd, } J = 15.4, 7.2 \text{ Hz, 1H), 5.11 (d, } J = 16.8 \text{ Hz, 1H), 4.98 (d, } J = 10.1 \text{ Hz, 1H), 3.80-3.67 (m, 3H), 2.46-2.44 (m, 1H), 2.08 (br s, 1H), 1.61-1.76 (m, 2H), 1.01 (d, } J = 6.8 \text{ Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).}
\]

\[
\text{^13C NMR (125 MHz, CDCl₃) } \delta \text{ 137.45 (o), 136.76 (o), 131.10 (o), 115.50 (e), 75.07 (o), 60.34 (e), 41.93 (o), 35.28 (e), 26.02 (o), 18.18 (e), 16.11 (o), -4.21(o), -4.37 (o).}
\]

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

\[
\text{HRMS (ESI, [M+Na]⁺) calcd for } \text{C}_{15}\text{H}_{36}\text{O}_{2}\text{SiNa, 293.1916 found 293.1904.}
\]

\[
[\alpha]^{20}_D \text{ -53.68 (c = 1, CHCl₃)}
\]
To a solution of Dess-Martin periodinan (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 NaHCO₃ (10 mL) and Na₂S₂O₃ (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 MgSO₄, 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%).

\[
(3S,4S,E)\cdot 3\text{-}(\text{tert-butyldimethylsilyloxy})\cdot 4\text{-methylocta-5,7-dienal 260.}
\]

\[\text{H NMR}\ (500\ MHz, \text{CDCl}_3)\delta 9.79\ (t, J = 2.3\ Hz, 1H),\ 6.31\ (dt, J = 17.0, 10.2\ Hz, 1H),\ 6.06\ (dd, J = 15.4, 10.3\ Hz, 1H),\ 5.67\ (dd, J = 15.4, 7.3\ Hz, 1H),\ 5.13\ (d, J = 16.9\ Hz, 1H),\ 5.01\ (d, J = 10.4\ Hz, 1H),\ 4.09\text{-}4.07\ (m, 1H),\ 2.56\text{-}2.39\ (m, 3H),\ 1.02\ (d, J = 6.8\ Hz, 3H),\ 0.87\ (s, 9H),\ 0.07\ (s, 3H),\ 0.04\ (s, 3H).
\]

\[\text{C NMR}\ (125\ MHz, \text{CDCl}_3)\delta 202.21\ (o),\ 137.17\ (o),\ 135.96\ (o),\ 131.85\ (o),\ 116.09\ (e),\ 72.01\ (o),\ 48.41\ (e),\ 43.00\ (o),\ 25.93\ (o),\ 18.17\ (e),\ 15.74\ (o), -4.30\ (o), -4.45\ (o).
\]

\[\text{IR}\ (\text{Neat})\ 2957\ (m),\ 2930\ (m),\ 2886\ (m),\ 2857\ (m),\ 1725\ (s),\ 1650\ (w),\ 1604\ (w),\ 1472\ (m),\ 1462\ (m),\ 1253\ (m),\ 1087\ (s),\ 1004\ (s)\ \text{cm}^{-1}.
\]

\[\text{HRMS (ESI, [M+Na]^+) calcd for}\ C_{15}H_{28}O_2SiNa, 293.1759\ \text{found} 291.1760.
\]

\[\left[\alpha\right]_D^{20} -37.30\ (c = 1, \text{CHCl}_3)
\]
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 MgSO₄, 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((3S,4S,E)-1-cyclopropylidene-4-methylocta-5,7-dien-3-yloxy)dimethylsilane 247.**

1H NMR (500 MHz, CDCl₃) 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).

13C NMR (125 MHz, CDCl₃) 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 C₁₈H₃₂OSiNa, 315.2133 found 315.2131.
Rh(COD)$_2$SbF$_6$ (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-butylidimethyl((1S,2S,3aR,8aR)-1-methyl-4-methylene-1,2,3,3a,4,5,6,8a-octahydroazulen-2-yloxy)silane 246.**

Relative stereochemistry: $dr \geq 19:1$ ($^1$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 NaHCO₃ (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 MgSO₄, 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%).

![Chemical Structure](image)

(1S,2S,3aR,8aR)-1-methyl-4-methylene-1,2,3,3a,4,5,8a-octahydroazulen-2-ol 301.

**1H NMR** (500 MHz, CDCl₃) 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).

**13C NMR** (125 MHz, CDCl₃) 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.

(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.

![Molecule structure](image)

Relative stereochemistry: $dr > 19:1$ (1H 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).
\[ ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \ \delta \ 148.32 \ (e), \ 110.48 \ (e), \ 78.24 \ (o), \ 58.17 \ (o), \ 54.15 \ (o), \ 47.49 \ (o), \ 46.66 \ (o), \ 40.04 \ (o), \ 38.12 \ (e), \ 34.19 \ (e), \ 26.96 \ (e), \ 26.01 \ (o), \ 18.29 \ (e), \ 16.29 \ (o), \ -4.29 \ (o), \ -4.57 \ (o). \]

\[ \text{IR} \ (\text{Neat}) \ 2954 \ (m), \ 2928 \ (m), \ 2895 \ (m), \ 2856 \ (m), \ 1640 \ (w), \ 1471 \ (m), \ 1462 \ (m), \ 1380 \ (w), \ 1360 \ (w), \ 1250 \ (s), \ 1113 \ (s) \ \text{cm}^{-1}. \]

\[ \text{HRMS} \ (\text{ESI, [M+Na]^+}) \ \text{calcd for C}_{18}\text{H}_{32}\text{O}_{2}\text{SiNa, 331.2072 found 331.2078}. \]

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 \textit{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%).

\[ \ (1\text{aS, 4aR, 6S, 7S, 7aR, 7bR})\text{-7-methyl-4-methylenedecahydroazuleno[4,5-b]oxiren-6-ol 280}. \]

\[ ^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \ \delta \ 4.93 \ (s, 1\text{H}), \ 4.89 \ (s, 1\text{H}), \ 3.69 \ (dt, J = 9.2, 6.8 \text{ Hz, 1H, H}_a), \ 3.00 \ (\text{quin, } J = 4.4 \text{ Hz, 1H, H}_d), \ 2.78 \ (t, J = 4.6 \text{ Hz, 1H, H}_e), \ 2.66 \ (\text{app q, } J = 9.3 \text{ Hz, 1H, H}_b), \ 2.44 \ (dt, J = 12.5, 5.6 \text{ Hz, 1H}), \ 2.35-2.31 \ (\text{br m, 1H}), \ 2.20-2.14 \ (\text{m, 1H}), \ 2.08 \ (tt, J = 12.5, 6.9 \text{ Hz, 1H}), \ 1.84-1.78 \ (\text{m, 3H}), \ 1.72-1.67 \ (\text{m, 1H, H}_c), \ 1.49-1.40 \ (\text{m, 1H}), \ 1.17 \ (d, J = 6.4 \text{ Hz, 3H, Me}). \]
$^{13}$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$_2$O)+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$_4$Cl (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%).

(1S, 2S, 3aR, 8aR)-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).
\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 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).

\(\text{IR}\) (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\(^{-1}\).

\(\text{HRMS}\) (ESI, [M+H]\(^+\)) calcd for C\(_{17}\)H\(_{27}\)O\(_2\), 263.2014 found 263.2012.

\((R,R)-(\sim)\cdot N,N'\)-Bis(3,5-di-tert-butylnsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride \(\text{277}\) (0.031 g, 0.049 mmol) and NMO (0.17 g, 1.47 mmol) were dissolved in DCM (1 mL), then cooled to \(-78^\circ\text{C}\). A solution of bicycloheptadiene \(\text{302}\) (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 \(-78^\circ\text{C}\) 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 \(\text{in vacuo}\). Purification by flash chromatography (silica gel, 10-20% ethyl acetate/petroleum ether 30-40) afforded \(\text{303}\) as a deep brown oil (0.055 g, 0.19 mmol, 40%).
Relative Stereochemistry: $dr \geq 19:1$ ($^1$H NMR analysis)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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 C$_{17}$H$_{27}$O$_2$, 279.1964 found 279.1961.

$n$BuLi (67.0 $\mu$L, 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 $\mu$L) at $-78$ °C. The resulting light red solution was stirred for 10 min, followed by the addition of BF$_3$.OEt$_2$ (5.92 $\mu$L, 0.047 mmol), stirred for 5 min, then a solution of compound 303 (20 mg, 0.036 mmol) in THF (10 $\mu$L) 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$_4$Cl (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%).

![Chemical Structure of 306](image)

$^{(3aS, 6aR, 8S, 9S, 9aR, 9bS)}$-9-methyl-6-methylene-2-oxododecahydroazuleno[4,5-b]furan-8-yl pivalate 306.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_4$Na, 343.1896 found 343.1894.
Compound 300.

*Colour and State:* Colourless oil

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$Na, 259.1312 found 259.1310.

(2S, 3S, 3aR, 8aR)-5-bromo-2-((tert-butyldimethylsilyloxy)-3-methyl-8-methylenedecahydroazulen-4-ol 289.

*Colour and State:* Brown oil

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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).
$^{13}\text{C NMR}$ (125 MHz, CDCl$_3$) $\delta$ 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).

$\text{IR}$ (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$^{-1}$.

$\text{HRMS (ESI, [M+Na]$^+$) calcd for}\ C_{18}H_{33}^{79}\text{BrO}_2\text{SiNa}, 411.1413 \text{ found} 411.1410.$
3.12 References


47. (a) Alkoxy acetylene was used as a mechanistic probe for macrolactonisation, see; Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Synlett.* **1989**, 36–37. (b) Lithium ethoxyacetylene was employed as a lynchpin to close a marocycle, see; Moslin, R. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106–15107. (c) For the synthesis of lactams, see; Mak, X. Y.; Ciccolini, R. P.; Robinson, J. M.; Tester, J. W.; Danheiser, R. L. *J. Org. Chem.* **2009**, *74*, 9381–9387 (d) For the