Synthetic Studies towards Sesquiterpenoids



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Jiarui Zong

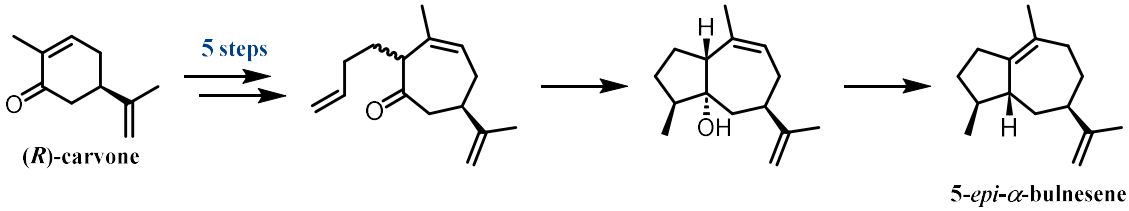
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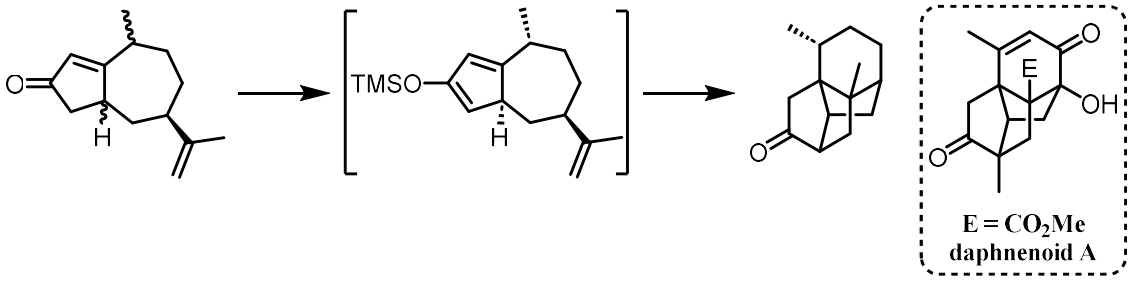
Trinity Term 2023

Abstract

Chapter 1 explores synthetic efforts carried out during this project towards α-bulnesene. Several radical cyclisation methods are discussed for constructing the 5,7-fused bicyclic framework. A concise and enantiospecific route to 5-*epi*-α-bulnesene, combining a new reductive rearrangement method, is presented.



Chapter 2 focuses on the total synthesis of daphnenoid A. A unique strategy towards this cage-like tetracyclic structure is developed via an intramolecular Diels–Alder reaction and a 20-step synthesis leading to an advanced intermediate to daphnenoid A is presented.



Acknowledgments

Firstly, I would like to thank my supervisor Professor Jeremy Robertson for his countless help and guidance both in and out of lab. Thank you for solving my problems even when they're difficult or idiotic and helping me revise my paper and thesis despite how much Chinglish there is. Without your boundless knowledge in theoretical and experimental chemistry, I could never have achieved success in my projects! Thank you for your suggestions in my future career, which has greatly released my pain. You are the nicest and most reliable supervisor I've ever met.

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Abbreviations

δ	NMR chemical shift
ν_{max}	Infrared absorption maximum
μ	Micro
Ac	Acetyl
AIBN	Azobis*iso*butyronitrile
Ar	Aryl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
cat	Catalyst
d	Doublet
DCE	1,2-Dichloroethane
DIBAL-H	Di*iso*butylaluminum hydride
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMPU	*N*,*N*′-Dimethylpropyleneurea
DMSO	Dimethylsulfoxide
EI	Electron ionisation
ESI	Electrospray ionisation
eq.	equivalents
et al.	*et alia*
FID	Flame ionisation detector
FT	Fourier transform
g	Gram

GC	Gas chromatography
h	Hour
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant
LDA	Lithium di*iso*propylamide
m	Multiplet
m	Medium
M	Molar
MCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligram
MHz	Megahertz
mL	Millilitre
mmol	Millimole
M.p.	Melting point
MS	Mass spectrometry
Ms	Methanesulfonyl
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMR	Nuclear Magnetic Resonance
n.O.e	Nuclear Overhauser effect
o	*Ortho*
p	*Para*

R	Unspecified alkyl group
RCM	Ring-closing metathesis
R_f	Retention factor
RT	Room temperature
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TCDI	Thiocarbonyldiimidazole
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSCl	Chlorotrimethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
$TMSNTf_2$	*N*-(Trimethylsilyl)bis(trifluoromethanesulfonyl)imide
Ts	*p*-Toluenesulfonyl
UV	Ultraviolet

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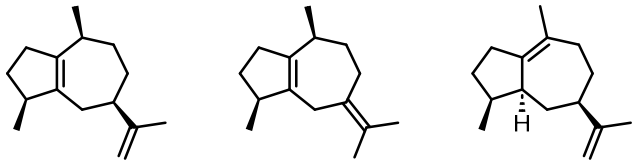
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Project I: Synthetic Studies towards α-Bulnesene

1. Introduction

1.1 Guaiene sesquiterpenes

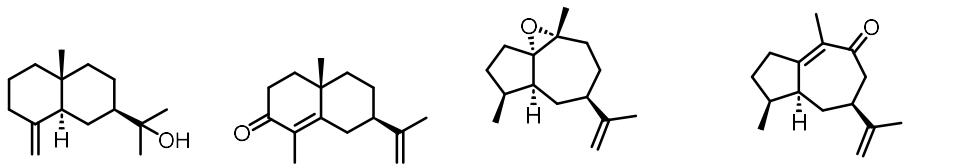
Sesquiterpenes are C15-terpenoids built from three isoprene units.[1] Guaienes are sesquiterpenes containing a 5,7-fused ring structure, which were first characterised by Takeda and coworkers from the elimination mixture of guaiol in 1961.[2] Three major alkene regioisomers were originally classified (*Scheme 1*) as α-guaiene, β-guaiene and δ-guaiene (also called α-bulnesene).



1.01 α-guaiene | **1.02** β-guaiene | **1.03** δ-guaiene (α-bulnesene)

Scheme 1 Guaiene sesquiterpenes.

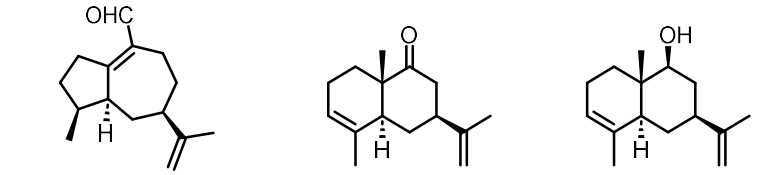
These compounds can be found, among many other secondary metabolites, in a variety of tree species including *Cedrelopsis grevei*, the cocklebur *Xanthium strumarium*, and the Japanese musk maple *Premna microphylla*. [3] Most of these sesquiterpenes and their oxidised derivatives (sesquiterpenoids) have pleasant smells and are widely used in the perfume and fragrance industries (*Scheme 2*).[4] In addition to their high industrial value, guaienes and their derivatives have a wide range of biological activities including antibacterial, anti-inflammatory, antioxidant and antimalarial activities.[5]



1.04 β-eudesmol | **1.05** α-cyperone | **1.06** (−)-epoxyguai-11-ene | **1.07** (+)-guaia-1(10),11-dien-9-one

Scheme 2 Examples of sesquiterpenoids used in the perfume industry.

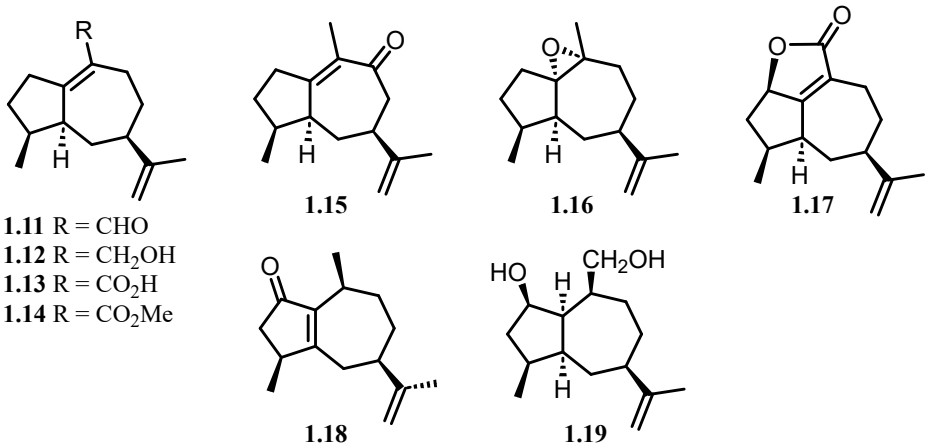
In 1991, the Ishihara group isolated three sesquiterpenoids (*Scheme 3*) from Kanankoh,[6] which is one of the highest quality traded agarwoods. Agarwood is the resinous heartwood of the *Aquilaria* tree that has been damaged in some way, often by fungal infection[6] and commands a high price because of its prized medicinal and aromatic properties, and religious value.[7] Characterisation of these compounds revealed one guaiene structure and two bicyclic[4.4.0]decenes which together contribute to the 'gorgeous and elegant aroma' of Kanankoh.[8]



1.08 (–)-Guaia-1(10),11-dien-15-al **1.09** (–)-Selina-3,11-dien-9-one **1.10** (+)-Selina-3,11-dien-9-ol

Scheme 3 Three sesquiterpenoids isolated from Kanankoh.

The Ishihara group subsequently reported the isolation of additional sesquiterpenoids from agarwood (*Scheme 4*),[6] all of which contain the guaiene core and are considered to be generated from α-bulnesene and α-guaiene by enzymatic oxidation.

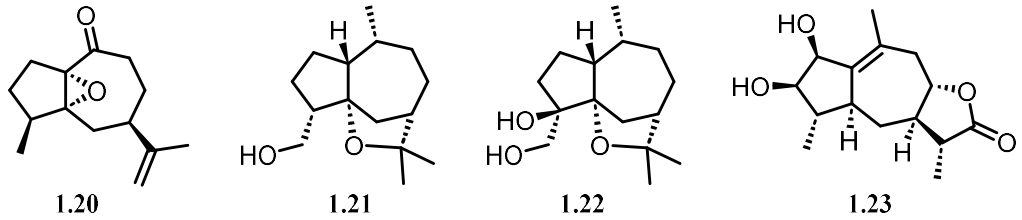


1.11 R = CHO
1.12 R = CH_2OH
1.13 R = CO_2H
1.14 R = CO_2Me

1.15 **1.16** **1.17** **1.18** **1.19**

Scheme 4 Further agarwood sesquiterpenoids.

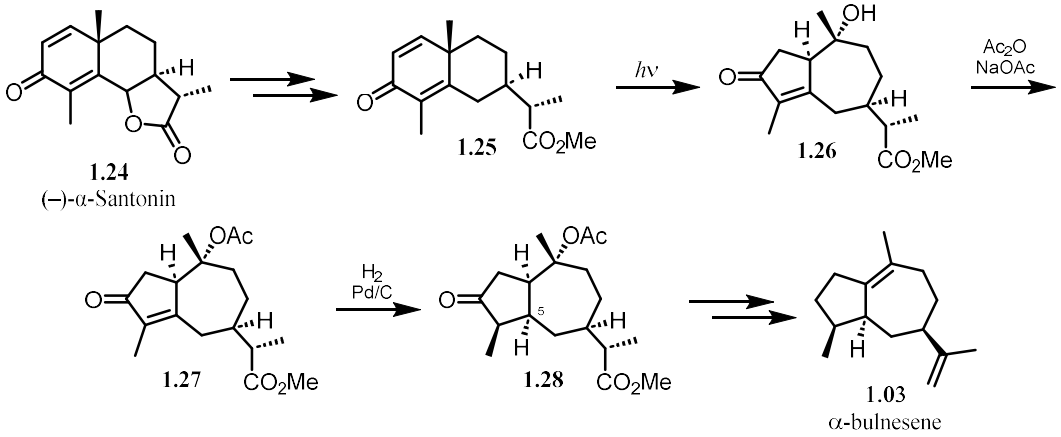
In 2021, the Mei and Dai groups isolated and characterised a series of sesquiterpenoids from 'Qi-Nan' agarwood (*Scheme 5*). In addition to the known compounds previously isolated, many new highly oxidised compounds with fresh woody fragrances were identified.[9]



Scheme 5 New sesquiterpenoids isolated from 'Qi-Nan'.

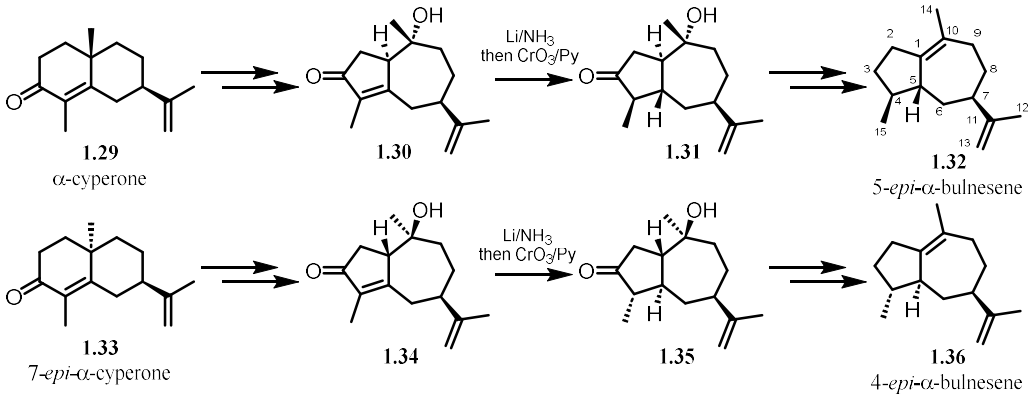
1.2 Synthesis of guaiene-type structures

The first synthesis of α-bulnesene was reported in 1969 by the Piers group (*Scheme 6*),[10] starting from compound **1.25**, accessible from santonin in three steps.[11] Upon irradiation, compound **1.25** rearranged to give substrate **1.26** stereoselectively. After acetylation of the tertiary alcohol, the enone was reduced with Pd/C hydrogenation, giving the desired configuration at the bridgehead (C-5) position. Further manipulation completed the α-bulnesene synthesis in nine steps, although the final step, an acetate pyrolysis at 400 °C, gave a mixture of olefins from which the desired sesquiterpene was isolated in unspecified yield.



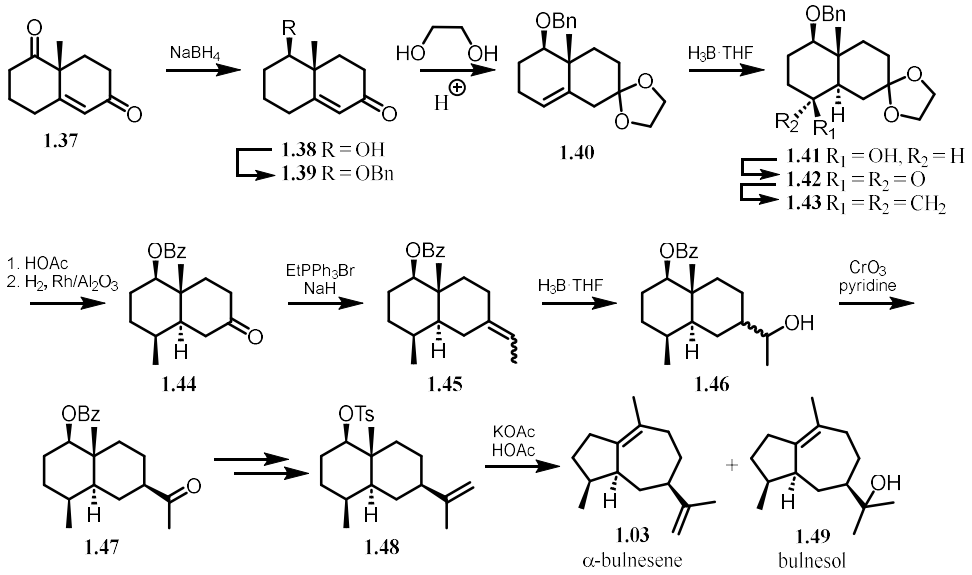
Scheme 6 Piers' synthetic route to α-bulnesene.

The Piers group further reported the synthesis of 4-*epi*-α-bulnesene and 5-*epi*-α-bulnesene using the same strategy (*Scheme 7*), this time using α-cyperone and 7-*epi*-α-cyperone as starting materials, and carrying out a similar photochemical rearrangement to access the 5,7-fused bicyclic products **1.30** and **1.34**, respectively. Stereoselective Birch reduction was reported to give the depicted configuration at the Me- and H-bearing C-4 and C-5 centres, assigned on the basis of optical rotatory dispersion curves. Removal of the ketone group by Wolff–Kishner reduction, and elimination gave the two α-bulnesene epimers in six steps.[12]



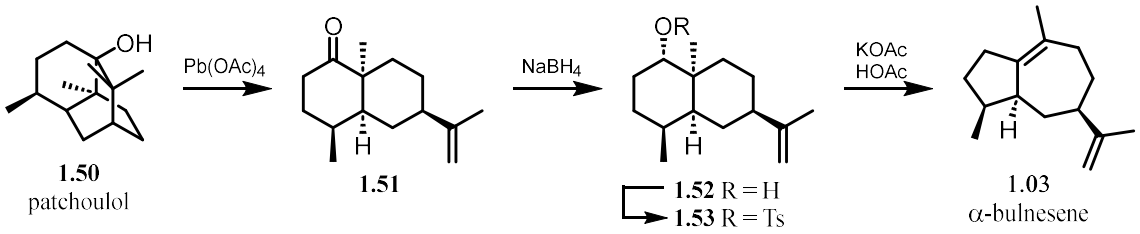
Scheme 7 Piers' synthetic route to 4-*epi*-α-bulnesene and 5-*epi*-α-bulnesene.

In 1971 the Heathcock group reported a new strategy towards α-bulnesene based on carbocation rearrangement of the 6,6-fused bicyclic ring system (*Scheme 8*). Starting with (racemic) Wieland–Miescher ketone and, using the method of Boyce,[13] regio- and stereo-selective reduction gave the keto-alcohol **1.38**, which was protected as its benzyl ether. Ketone protection led to alkene isomerisation, then a five-step sequence installed the C15- methyl group. Wittig reaction of the ketone and functional group manipulation of the ethylidene group led to the *iso*propenyl side-chain. The synthesis was completed by solvolytic carbocation rearrangement, furnishing racemic α-bulnesene and bulnesol in 17 steps.[14]



Scheme 8 Heathcock's synthetic route to racemic α-bulnesene and bulnesol.

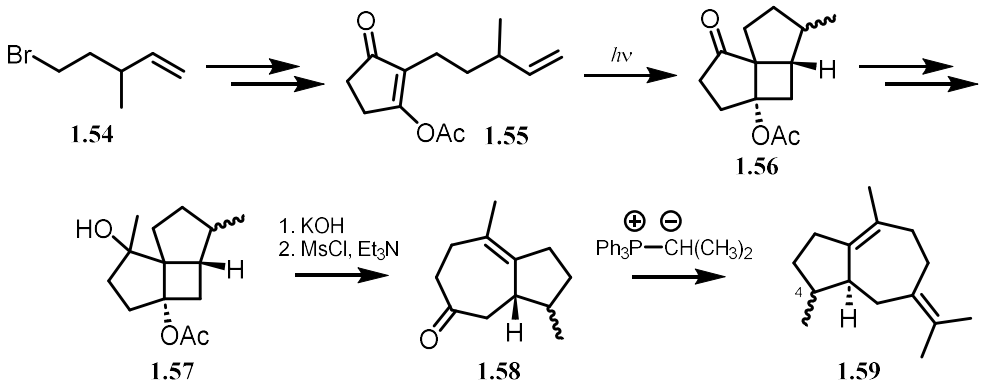
Four years later, a short synthetic route towards α-bulnesene was achieved by Mehta's group based on Heathcock's rearrangement strategic final step but here beginning with the oxidative rearrangement of naturally abundant patchoulol to give the 6,6-fused bicyclic compound **1.51** with the correct configuration at C-4, C-5, and C-7. Reduction with $NaBH_4$ gave the *cis*-relationship between the hydroxy and methyl groups required for successful solvolytic rearrangement via the chair-chair *cis*-decalin conformation having an equatorial *iso*propenyl substituent. Overall, this synthesis provided α-bulnesene in just four steps from patchoulol (*Scheme 9*).[15]



Scheme 9 Mehta's synthesis of α-bulnesene.

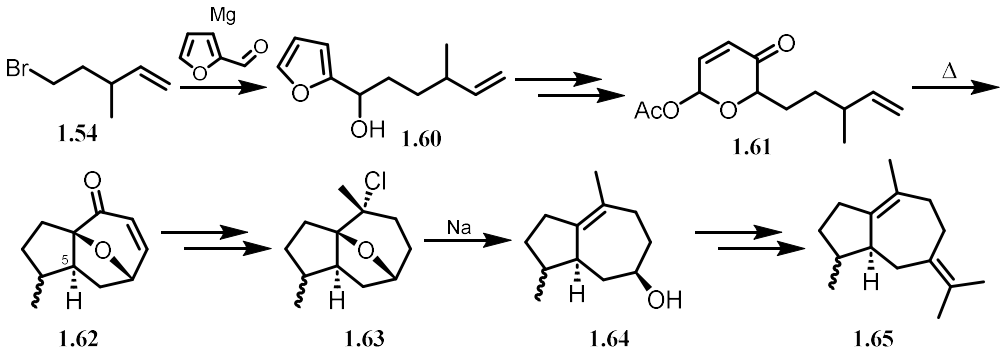
The total synthesis of β-bulnesene started in 1980. Oppolzer and Wylie reported the synthesis of racemic β-bulnesene and 4-*epi*-β-bulnesene using intramolecular photoaddition as the key step. Starting with 5-

bromo-3-methyl-1-pentene, the cyclopentenone ring was installed in five steps, then intramolecular [2+2]-cycloaddition gave the cyclobutane ring as a pair of epimers. Methyl addition to the ketone and subsequent carbocation rearrangement gave the 5,7-fused bicyclic core and a final Wittig olefination installed the fully-substituted alkene to provide β-bulnesene in ten steps.[16] (*Scheme 10*)



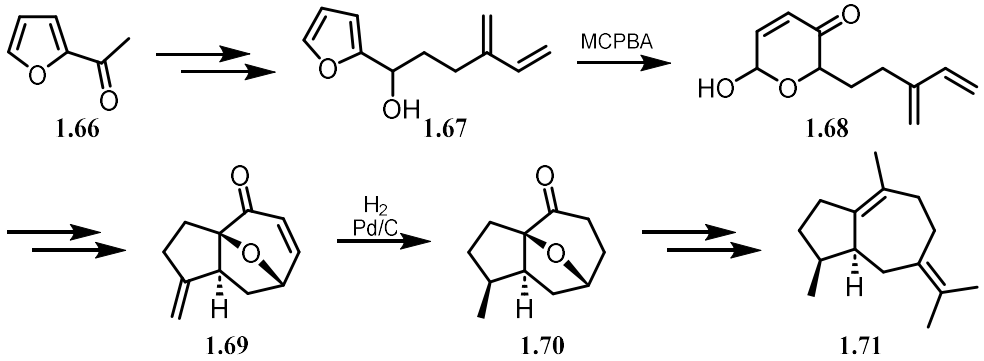
Scheme 10 Oppolzer and Wylie's synthesis of β-bulnesene and its 4-epimer.

In 1983, Sammes and Street reported an oxidopyrylium (5+2)-cycloaddition strategy applied to the synthesis of a series of natural products, including β-bulnesene, cryptofauronol, fauronyl acetate and valeranone.[17] The Grignard reagent derived from 5-bromo-3-methyl-1-pentene was added to furfural to give a substrate for Achmatowicz rearrangement, the product of which was acetylated and heated. The ensuing (5+2)-cycloaddition delivered the desired configuration at C(5), and reductive elimination of the epoxy bridge installed the endocyclic alkene. Again, a Wittig reaction was used to install the side chain, delivering β-bulnesene and its 4-*epi*-diastereomer in ten steps (*Scheme 11*).



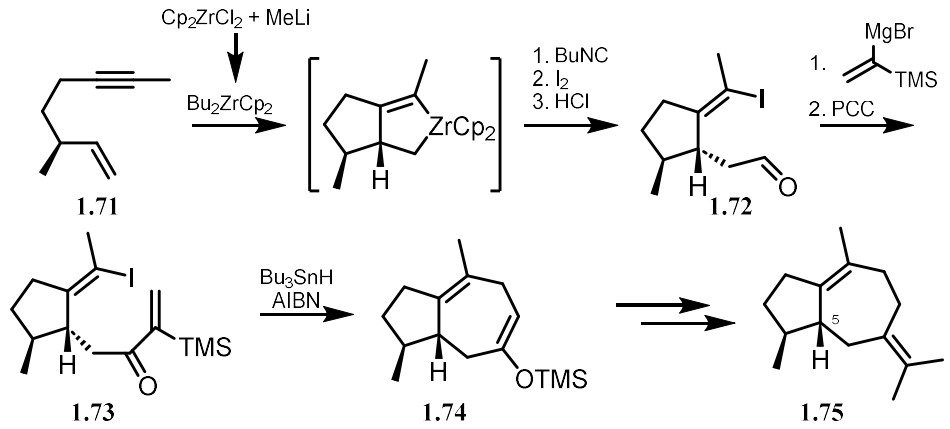
Scheme 11 Sammes' and Street's synthesis of β-bulnesene and its 4-epimer.

The same group later (1985) refined their route by using a diene substrate in the cycloaddition reaction.[18] The enolate of 2-acetylfuran was alkylated with 2-(bromomethyl)-1,3-butadiene then $NaBH_4$ reduction gave furyl alcohol **1.67**. After Achmatowicz rearrangement, (5+2)-cycloaddition proceeded smoothly to afford the product as a single diastereomer. Hydrogenation reduced both alkenes in a single step, supplying the correct configuration at the methyl group. The same final steps gave β-bulnesene free from other diastereomers in nine steps overall (*Scheme 12*).



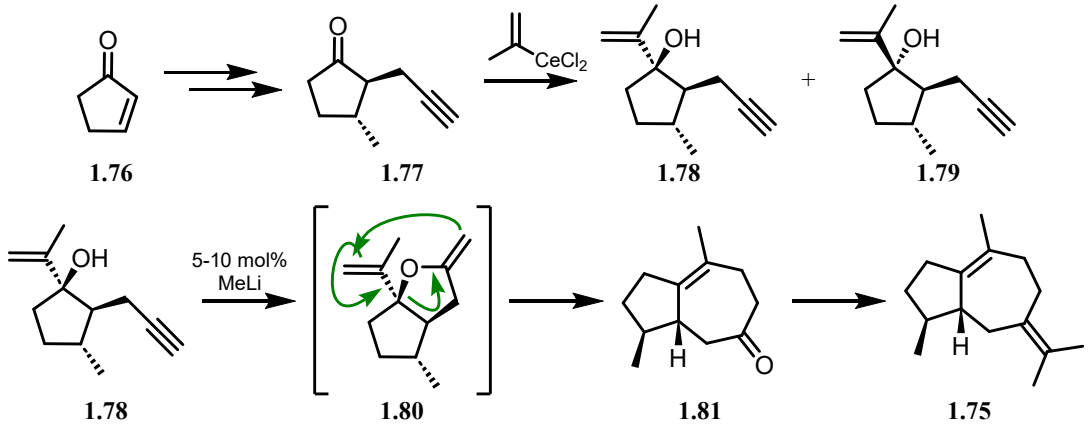
Scheme 12 Sammes' and Street's second route to β-bulnesene.

More recently (1997), the Negishi group developed a general method for the synthesis of hydrazulenes based on Zr-promoted enyne cyclisation.[19] Enyne substrates, such as that shown in *Scheme 13* are readily prepared, in this case from (*E*)-crotyl bromide in four steps.[20] Zr-promoted cyclisation and treatment with butyl *iso*cyanide and iodine afforded aldehyde **1.72**. A vinyl-trimethylsilyl group was installed by Grignard reaction and then, following PCC oxidation, 7-*endo-trig* radical cyclisation furnished the 5,7-fused ring system. Deprotection and Wittig reaction completed the synthesis of (±)-5-*epi*-β-bulnesene in six steps from enyne **1.71**.



Scheme 13 Negishi's synthesis of 5-*epi*-β-bulnesene.

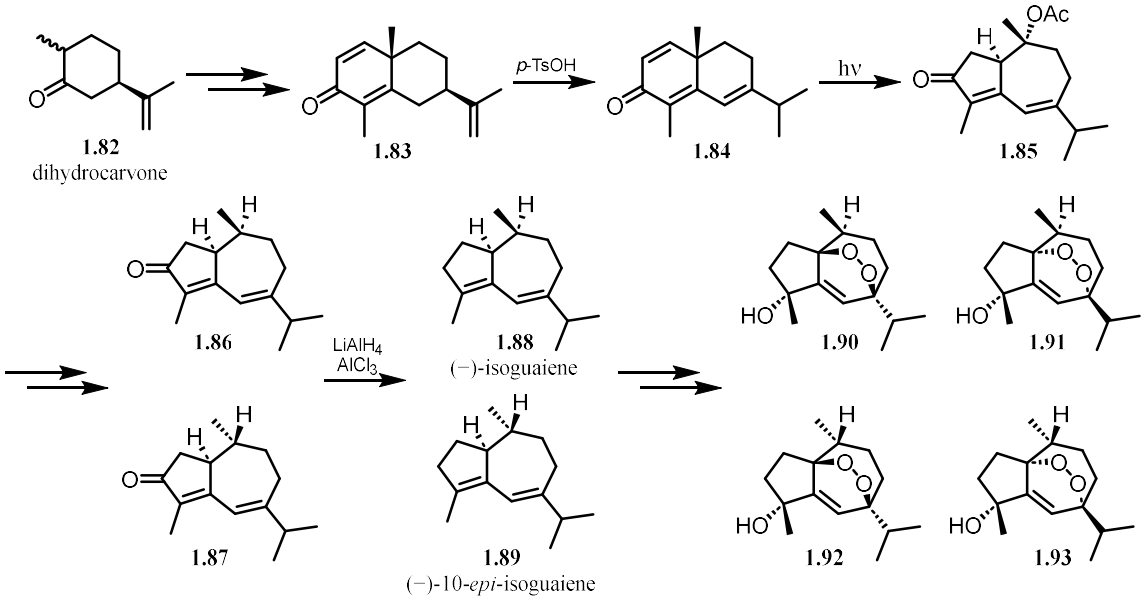
Finally, a new strategy towards the bicyclo[5.3.0]decane ring was reported by Ovaska's group in 2002.[21] Here, a tandem 5-*exo-dig* cyclisation/Claisen rearrangement sequence was initiated from diastereomer **1.78** (*Scheme 14*), prepared in three steps from cyclopentenone. The tandem rearrangement sequence progressed smoothly upon addition of 5-10 mol% methyllithium to produce ketone **1.81**. 5-*epi*-β-Bulnesene was then obtained following earlier precedent, overall just five steps from cyclopentenone.



Scheme 14 Ovaska's five-step synthesis of 5-epi-β-bulnesene.

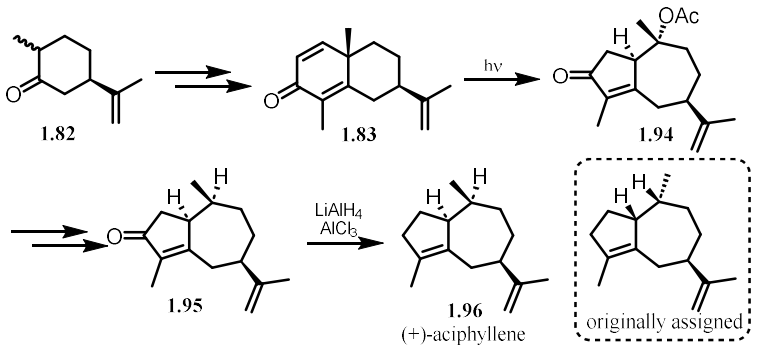
Related bicyclo[5.3.0]decanes have been prepared either as targets in their own right or as intermediates in syntheses of sesquiterpenoids. For example, the Pedro group synthesised four diastereomers of the natural product 4α-hydroxy-1β,7β-peroxy-1βH-guaia-5-ene **1.92** (*Scheme 15*) via two naturally-

occurring guaiene isomers (−)-isoguaiene and (−)-10-*epi*-isoguaiene. In this work, (5*R*)-dihydrocarvone was converted into 1,2-dehydro-α-cyperone **1.83** using de Groot's method.[22] The terminal alkene was equilibrated into the conjugated position, and then photochemical rearrangement[23] gave the guaiane skeleton. Reduction of the hydroxyl and ketone groups gave (−)-isoguaiene and its 10-*epi* isomer.



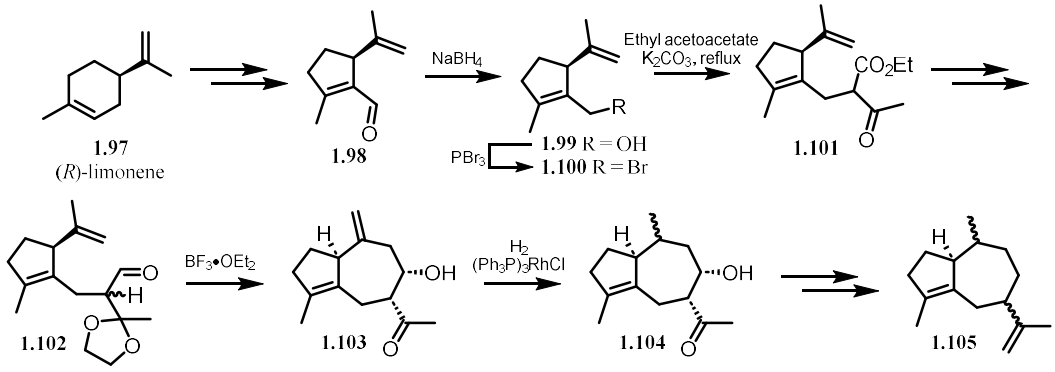
Scheme 15 The Pedro group's synthesis of 4α-hydroxy-1β,7β-peroxy-1βH-guaia-5-ene and its diastereomers.

Two years later, in 2007, the same group reported the semi-synthesis and structural revision of (+)-aciphyllene using a similar strategy (*Scheme 16*). Photochemical rearrangement of 1,2-dehydro-α-cyperone[22] furnished the guaiene skeleton. Reduction of the acetate group and epimerisation at the bridgehead methine were accomplished in one step by reduction with Li in di*iso*propylamine.[24] Deoxygenation using $AlCl_3$-$LiAlH_4$ gave compound **1.96** which, by NMR comparison, was confirmed to be the natural compound (+)-aciphyllene.[25]



Scheme 16 The Pedro group's synthesis of (+)-aciphyllene.

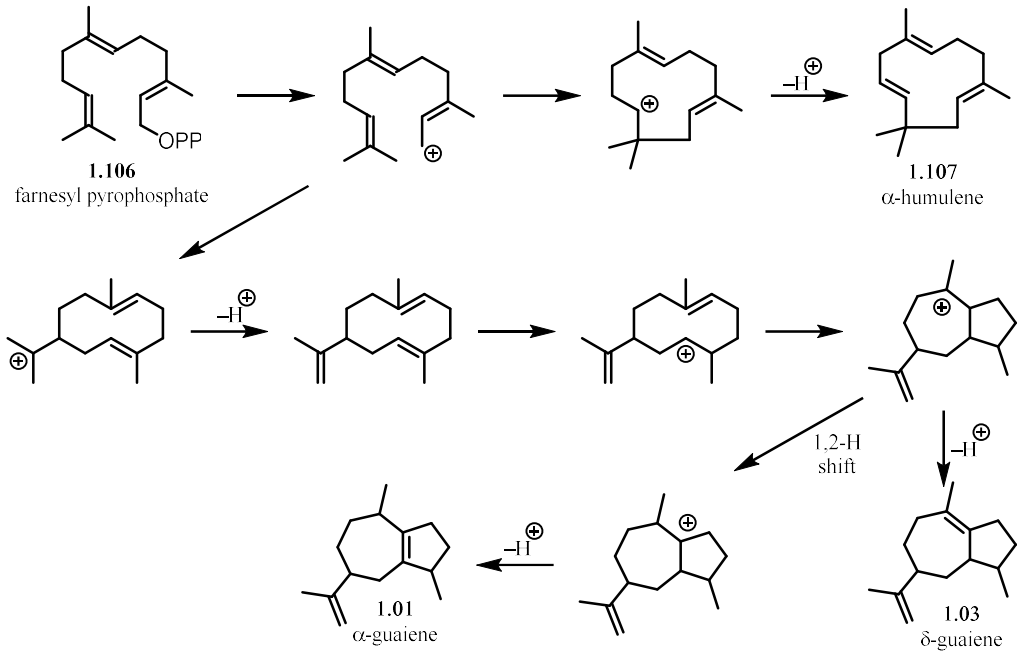
In 2010, Srikrishna and Pardeshi reported the enantiospecific total synthesis of aciphyllene and its three diastereomers using a Type II intramolecular carbonyl ene reaction (*Scheme 17*). (*R*)-Limonene was converted into aldehyde **1.98** using the group's previously reported method,[26] then reduction and alkylation supplied ketoester **1.101**. The ketone carbonyl was protected and the ester group reduced to an aldehyde to give key intermediate **1.102**. The key carbonyl ene reaction afforded the bicyclo[5.3.0]decane structure stereoselectively from which the different diastereomers were generated in 12 steps overall by varying the subsequent reductive transformations.[27]



Scheme 17 Srikrishna's and Pardeshi's synthesis of aciphyllene and its diastereomers.

A study of the biosynthesis of the guaienes was disclosed in the same year by the Ito group. Three sesquiterpene synthases were characterised for the first time from cultured cells of *Aquilaria crassna* leaves treated with methyl jasmonate. From the isolated genes, the encoded enzymes yielded three

major products: α-humulene, α-guaiene and δ-guaiene, based on which the authors proposed a biosynthetic pathway (*Scheme 18*).[28] These genes and their encoded enzymes are the first sesquiterpene synthases reported to yield guaiane-type sesquiterpenes as their major products.



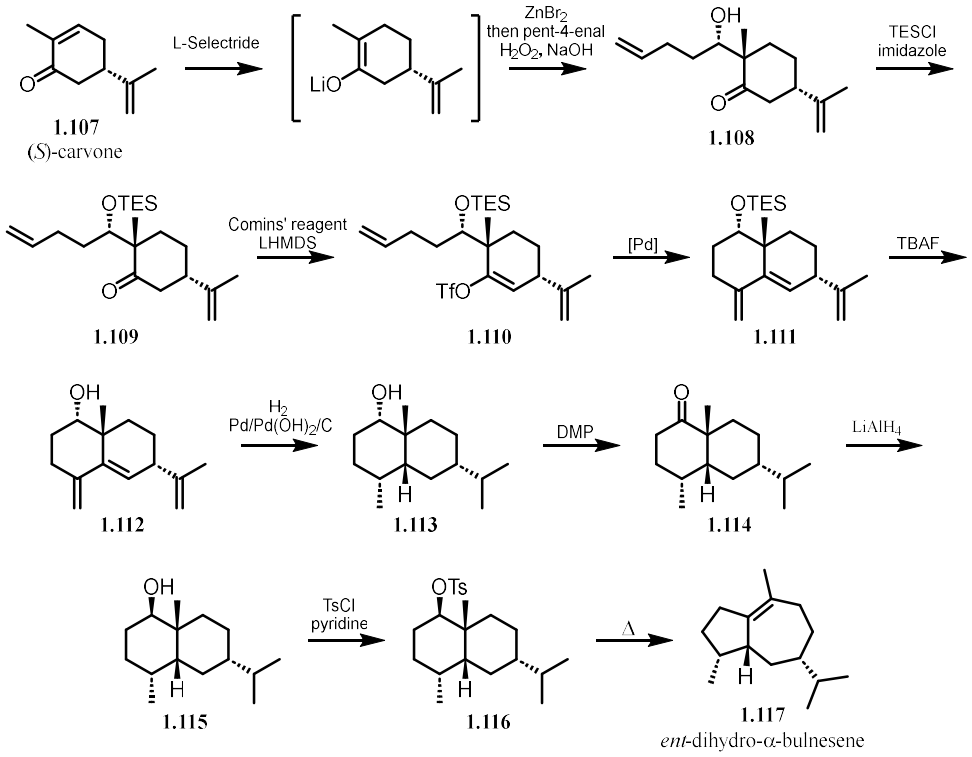
Scheme 18 Proposed biosynthesis pathways leading to α- and δ-guaiene.

1.3 Previous studies towards α-bulnesene in the Robertson group

$P450_{BM3}$ was the third cytochrome P450 enzyme to be identified from the bacterium *Bacillus megaterium*; the wild-type enzyme's role is thought to be to catalyse the hydroxylation of long chain fatty acids. Collaborative work between the Robertson and Wong groups discovered that $P450_{BM3}$ enzymes can recognise enantiomers as entirely different substrates and thus give different oxidation products.[29] To further this study, the enzymatic oxidation of α-bulnesene and its stereoisomers, particularly its enantiomer, was initiated in order to provide further insight into $P450_{BM3}$-mediated kinetic resolutions and to understand the structure-aroma relationships of these sesquiterpenes and their oxidation products.

Of the few total syntheses of α-bulnesene, Piers'[10, 12] and Mehta's[15] routes are short but can only produce the natural α-bulnesene enantiomer. Heathcock's route[14] led to the racemate and could be adapted to provide either enantiomer but the synthesis is unwieldy at 18 steps. Our group's aim was to develop a short, efficient synthesis equally amenable to both α-bulnesene and its enantiomer.

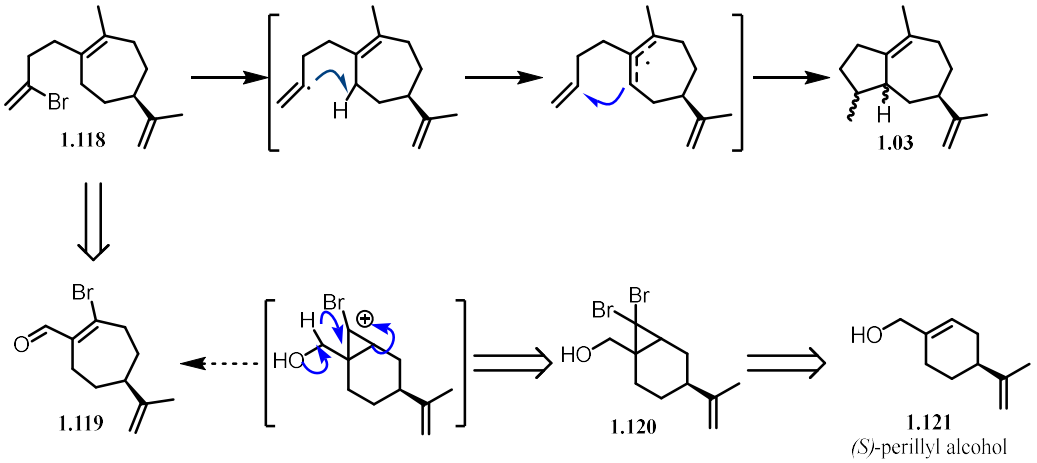
The study was initiated by previous group member Zhang,[30] culminating in a ten-step synthesis of *ent*-dihydro-α-bulnesene from (*S*)-carvone (*Scheme 19*). Conjugate reduction and aldol reaction installed the side chain and gave the keto-alcohol **1.108** which, in turn, generated the six-membered ring by intramolecular Heck coupling. Regioselective alkene reduction proved difficult and ultimately all the alkenes were reduced. The configuration of alcohol **1.113** was inverted by an oxidation-reduction sequence to allow the ring-rearrangement step to proceed without complication, furnishing *ent*-dihydrobulnesene **1.117**.



Scheme 19 Zhang's route towards *ent*-dihydro-α-bulnesene.

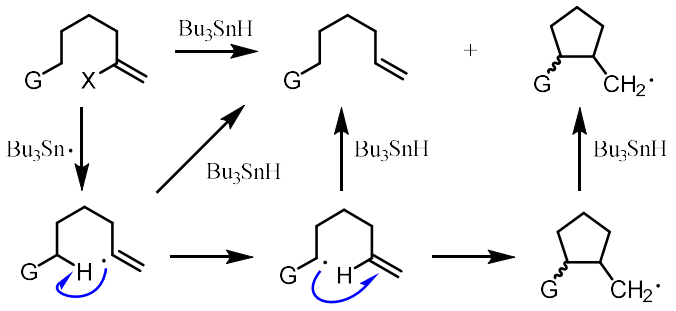
1.4 Project aims

Continuing Zhang's work, a strategy was envisaged based on a tandem 1,5-H atom transfer (HAT)/5-*exo-trig* radical reaction[27, 29] to construct the key (5,7)-fused ring system (*Scheme 20*). Initially, the vinyl halide precursor **1.118** was to be constructed from the aldehyde **1.119**, while the methyl group would be derived from the vinyl bromide. A tandem ring expansion and [1,2]-H shift was planned for substrate **1.120** to construct the β-bromo-enal, which, in turn, could be achievable from commercially available (*S*)-perillyl alcohol.



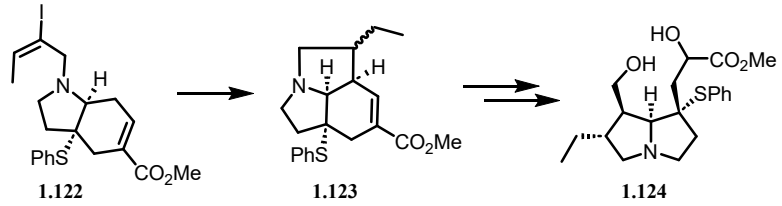
Scheme 20 An initial plan towards α-bulnesene and its stereoisomers.

The key step, the tandem radical transfer cyclisation, has been widely used in synthetic chemistry following Curran's first report of the method in 1988 using trialkyltin hydride chemistry.[31] The initial 1,5-H atom transfer to a reactive sp^2-centred radical results in translocation of the radical site, made productive using a radical stabilising group (G) to weaken the target C-H bond (*Scheme 21*). The new radical is then either reduced or can participate in further radical chain reactions by suitable substrate design.



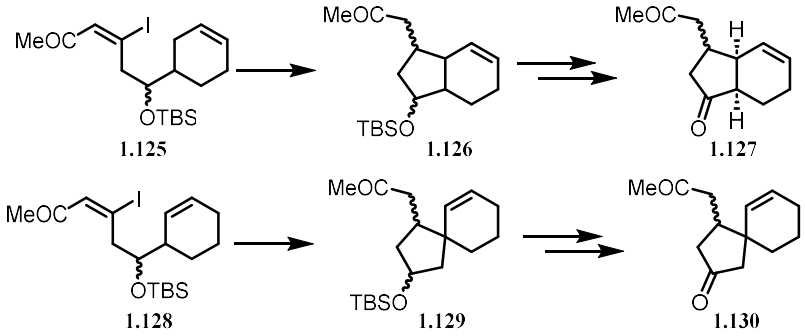
Scheme 21 Curran's method for 1,5-H atom transfer and 5-*exo-trig* cyclisation.

In the same year, Parsons' group reported an efficient route towards a pyrrolizidine ring system using the same approach to form the target product as a 4:1 mixture of diastereomers (*Scheme 22*).[32]



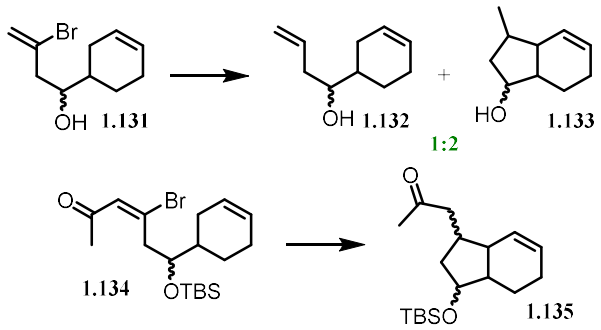
Scheme 22 Parsons' synthesis of the pyrrolizidine ring system using tandem 1,5-H atom transfer and 5-*exo-trig* cyclisation.

The Parsons group elaborated this radical process further over the following few years. In 1990, they reported that this method was suitable for the construction of highly functionalised cyclopentanoid ring systems (*Scheme 23*).[33]



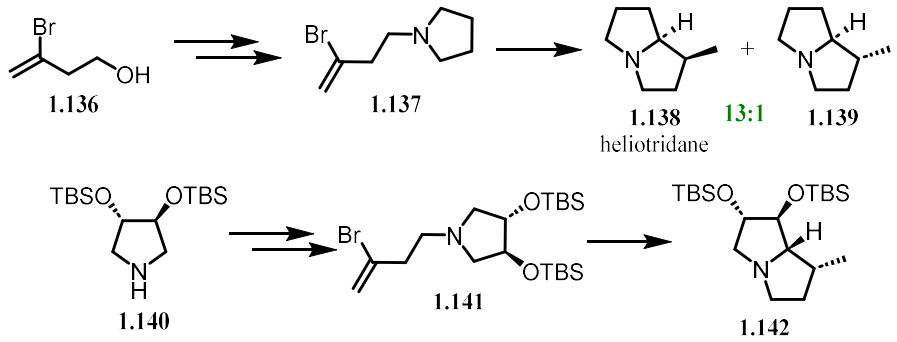
Scheme 23 Construction of cyclopentanoid rings using tandem 1,5-H atom transfer and 5-*exo-trig* cyclisation.

Then, in 1992, the group showed that this tandem radical process reaction is more favoured when the vinyl halide is situated on an alkene activated by an electron withdrawing group. Without this activation, the translocated radical suffers competing reduction (*Scheme 24*).[34]



Scheme 24 Efficient 5-*exo-trig* cyclisation of the translocated allylic radical requires an activated alkene.

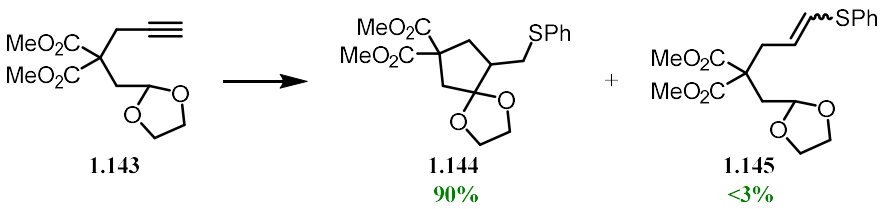
In 1996, our group used this strategy to synthesise heliotridane and (6*S*,7*S*)-dihydroxyheliotridane (*Scheme 25*). The substrates were prepared by *N*-alkylation of pyrrolidine and its 3,4-dioxygenated derivative and the tandem 1,5-H transfer/5-*exo-trig* cyclisations proceeded stereoselectivity. An effective work-up procedure was developed which employed thiophenol to convert the tributyltin bromide by-product into the corresponding sulfide, easily removed by chromatography. [35]



Scheme 25 The Robertson group's synthesis of heliotridane and (6*S*,7*S*)-dihydroxyheliotridane.

This tandem radical cyclisation can also proceed following addition to an alkyne, [36] as developed in 2005 by the Renaud group (*Scheme 26*), here using thiophenol to generate the vinyl radical intermediate.

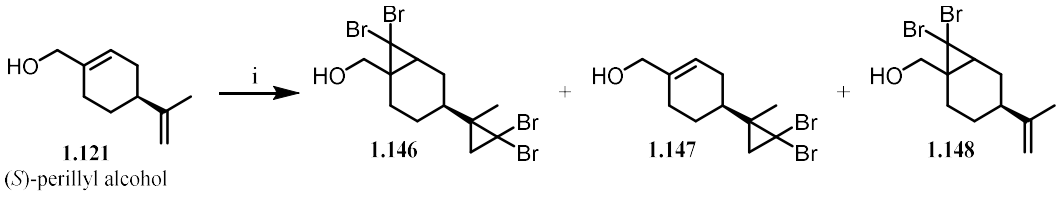
This method requires no tributyltin hydride and is suitable for the construction of complex bicyclic ring systems.[37]



Scheme 26 Renaud's development by using alkyne substrate.

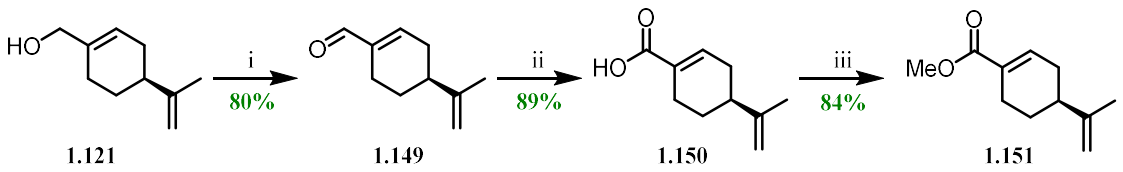
2. Results and discussion

Following the plan outlined in *Scheme 20*, the dibromocyclopropanation step was attempted on (*S*)-perillyl alcohol **1.121** (*Scheme 27*); however, this method showed poor regioselectivity, with just one equivalent of bromoform leading to three cyclopropanation products mixed with starting material which were difficult to separate.



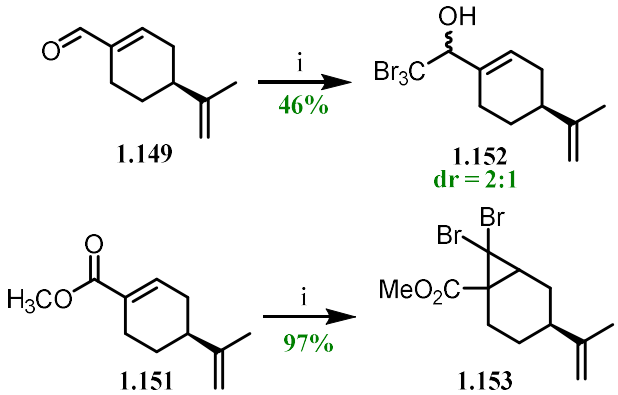
Scheme 27 Dibromocyclopropanation of **1.121**. **Reagents and conditions: i)** BTEAC, $CHBr_3$, NaOH, H_2O, DCM, RT, 2 h.

It has been reported that dibromocyclopropanation can occur selectively by conjugate addition to an α,β-unsaturated ester,[38] and so (*S*)-perillyl methyl ester was prepared by DMP oxidation, oxidation with Tollen's reagent, and esterification (*Scheme 28*). Some attempts to shorten the route included using activated MnO_2[39] or $Fe(NO_3)_3{\bullet}9H_2O$/TEMPO/KCl[40] to oxidise the alcohol into the acid, or alternatively MnO_2/KCN/MeOH[41] or MnO_2/NHC/DBU/MeOH[42] to oxidise the alcohol into the ester. All these methods stalled upon reaching aldehyde **1.149**, and so an additional oxidation step was necessary.



Scheme 28 Conversion of alcohol **1.121** into ester **1.151**. **Reagents and conditions: i)** DMP, DCM, RT, 1 h; **ii)** $AgNO_3$, NaOH, H_2O, EtOH, RT, 3 h; **iii)** CH_3I, K_2CO_3, acetone, 60 °C, 18 h.

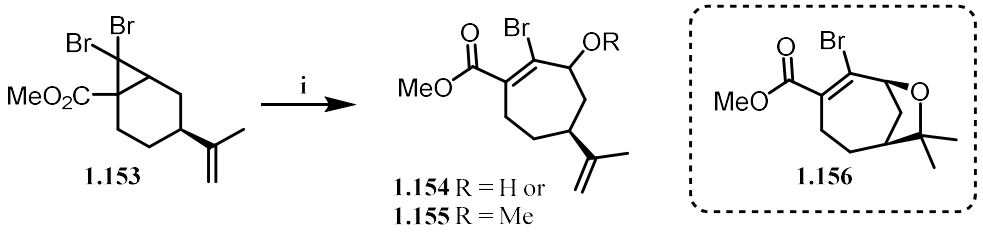
Aldehyde **1.149** and ester **1.151** were both tested in the dibromocyclopropanation reaction (*Scheme 29*); however, for aldehyde **1.149**, the 1,2-adduct **1.152** was the only product. When the aldehyde was replaced with the less reactive ester carbonyl, the target product dibromocyclopropane **1.153** was obtained in high yield as a single diastereomer.



Scheme 29 Dibromocyclopropanation of aldehyde **1.149** and ester **1.151**. **Reagents and conditions: i)** $CHBr_3$, NaHMDS, THF, –78 °C, 5 h.

With this key intermediate **1.153** in hand, the ring expansion step was tested. Although the ring expansion mediated by Ag(I) salts had been widely reported,[43] substrate **1.153** was resistant to a variety of conditions with different silver salts, solvents and temperatures (*Appendix 01*). Several trialled conditions are listed in *Table 1*. Protic solvents such as water or methanol were required to improve the solubility of the silver salts, which resulted in quenching of the carbocation intermediate (*Entries 1,3 and 4*). Freshly-prepared $AgBF_4$ gave a detectable yield for the ring expansion product **1.156** (*Entry 2*). Other conditions gave no productive reaction, or decomposition under more harsh conditions.

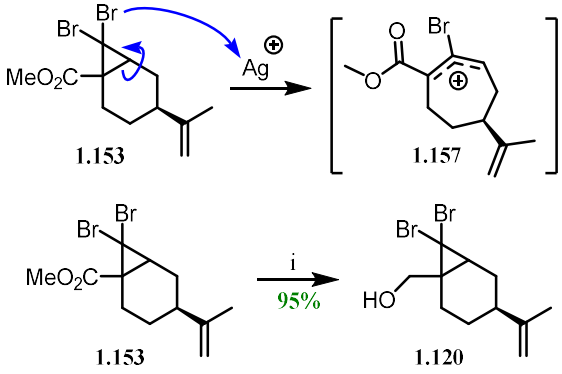
Table 1 Attempted ring expansion of ester **1.153** into **1.154** or **1.155**.



Entry	[Ag] (eq.)	Solvent	Temperature (°C)	Result
1	$AgBF_4$ (1.3)	DME:H_2O = 5:1	80	n.r.
2	Ag_2O+HBF_4 (1.2)	DME:H_2O = 4:1	80	3% **1.156**
3[a]	$AgBF_4$ (2)	acetone:H_2O = 1:1	130	n.r.
4	$AgNO_3$ (1.5)	MeOH	65	n.r.

[a] In a sealed tube.

The failure of the ring expansion is attributed to the developing positive charge being destabilised by the adjacent ester, raising the energy of the transition state leading to intermediate **1.157** (*Scheme 30*). Accordingly, the ester group was reduced back to the alcohol, giving intermediate **1.120** after five steps.

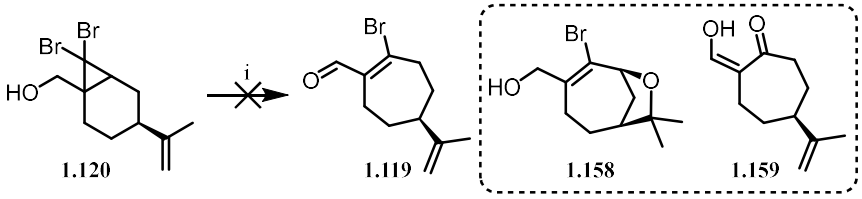


Scheme 30 High energy intermediate in the ring expansion of substrate **1.153** and preparation of **1.120**. **Reagents and conditions: i)** DIBAL-H, DCM, –78 °C, 3 h.

Ring expansion of substrate **1.120** was tested using similar conditions to those explored with the corresponding ester (*Appendix 02*). As expected, the ring expansion step proceeded more easily; however, the desired product **1.119** was still not detected. A selection of the key conditions is

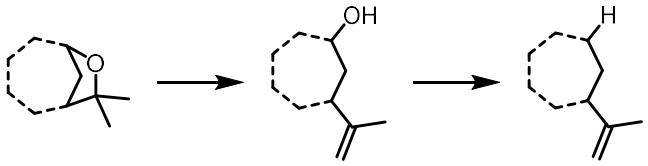
summarised in *Table 2*. A combination of protic and polar aprotic solvents was necessary for ring expansion to occur, generating cyclic ether **1.158** as the main isolated product in most cases. Optimisation of silver salt and solvent ratio gave a reproducible moderate yield (*Entries 1–3*). Using $AgBF_4$ in supposedly dry DMF afforded the formyl ketone product **1.159**, resulting from the planned ring expansion-carbocation rearrangement with additional hydrolysis of the vinyl bromide by an unknown water source (*Entry 5*). Deliberate inclusion of water in this reaction prevented the reaction completely (*Entry 4*).

Table 2 Attempted ring expansion of alcohol **1.120** into **1.119**.



Entry	[Ag] (eq.)	Solvent	Temperature (°C)	Result
1	$AgBF_4$ (2)	acetone:H_2O = 9:1	100	14% **1.158**
2	$AgClO_4$ (1.5)	acetone:H_2O = 9:1	100	18% **1.158**
3	$AgClO_4$ (1.5)	acetone:H_2O = 7:3	100	32% **1.158**
4	$AgBF_4$ (2)	DMF:H_2O = 10:1	100	n.r.
5	$AgBF_4$ (1.5)	DMF	100	19% **1.159**

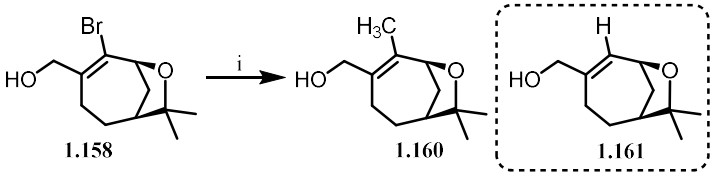
Bicyclic ether **1.158** was selected for further exploration as the primary alcohol and vinyl bromide groups were deemed suitable for elaboration, and the ether linkage could allow regeneration of the terminal alkene (*Scheme 31*).



Scheme 31 Plan to regenerate terminal alkene.

Various methods were explored to convert the vinyl bromide into a methyl group (*Table 3*). Methods were chosen based on their expected compatibility with the free hydroxyl group present in substrate **1.158**. Narcyzk's work,[44] using Negishi coupling, had proven compatibility with a free alcohol; however, no reaction occurred for substrate **1.158** under these reported conditions (*Entries 1–3*). The more reactive species dimethylzinc was able to be used at higher temperatures, but gave no change (*Entries 4–6*). Suzuki coupling[45] was also tested but only trace amounts of the reduced product **1.161** were obtained (*Entry 7*). Finally, the Gilman reagent lithium dimethylcuprate[46] supplied the target product **1.160** in 51% yield, along with 38% recovered starting material, which could be recycled (*Entry 8*).

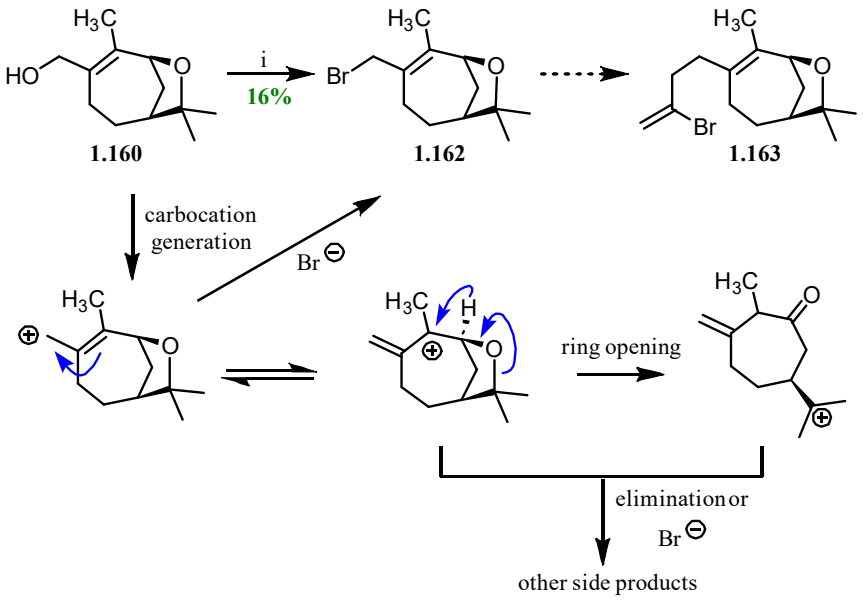
Table 3 Methylation of vinyl bromide **1.158** leading to **1.160**.



1.158 **1.160** **1.161**

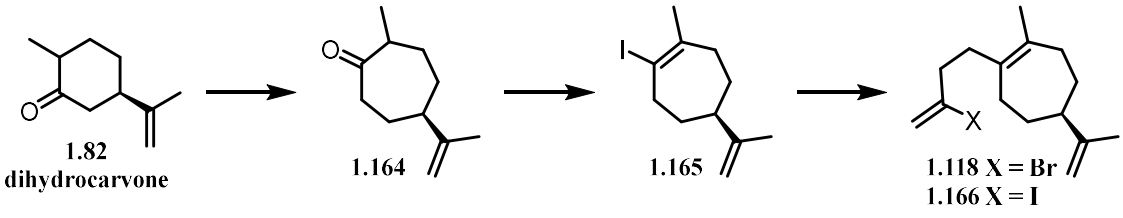
Entry	Conditions (i)	Result
1	5% $Pd(PPh_3)_4$, 3 eq. MeMgBr, 3 eq. $ZnCl_2$, THF, 0 °C	n.r.
2	5% $Pd(dppf)Cl_2$, 3 eq. MeLi, 3 eq. $ZnCl_2$, THF, 0 °C	n.r.
3	5% $Pd(PPh_3)_4$, 3 eq. MeMgBr, 3 eq. $ZnBr_2$, THF, –78 °C	n.r.
4	5% $Pd(dppf)Cl_2$, 2 eq. $Zn(CH_3)_2$, dioxane, RT	n.r.
5	10% $Pd(dppf)Cl_2$, 3 eq. $Zn(CH_3)_2$ (freshly prepared), THF, RT	n.r.
6	10% $Pd(dppf)Cl_2$, 3 eq. $Zn(CH_3)_2$ (freshly prepared), dioxane, 60 °C	n.r.
7	$Pd(PPh_3)_4$, $CH_3B(OH)_2$, K_3PO_4, THF, 80 °C	trace of **1.161**
8	MeLi, CuI, Et_2O, –78 °C	51% of **1.160**

An attempt to convert the alcohol into a halogen leaving group for cross-coupling using an Appel reaction gave a complex mixture. The target product **1.162** was isolated in 16% yield along with many uncharacterised minor products. It was speculated that activated allylic intermediates equivalent to the allylic carbocation could undergo uncontrolled rearrangements as exemplified in (*Scheme 32*).



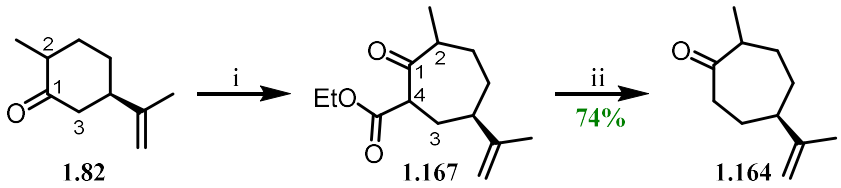
Scheme 32 Appel reaction of alcohol **1.160** into bromide **1.162** and proposed plans. **Reagents and conditions: i)** PPh_3, CBr_4, DCM, 0 °C, 1 h.

At this point, the route was becoming lengthy and prevalent low yields limited ready access to substrate **1.163**; as a result, a new plan towards radical cyclisation substrate **1.118** was proposed based on another ring expansion strategy. The combination of ethyl diazoacetate and a Lewis acid has been reported as a reagent for the one-carbon ring-expansion of cyclic ketones.[47] If applied to dihydrocarvone **1.82**, subsequent decarboxylation was expected to give a simple cycloheptanone **1.164** (*Scheme 33*). This ketone could then be elaborated via, for example, vinyl halide **1.165** to target substrate **1.118** or iodide substrate **1.166**.



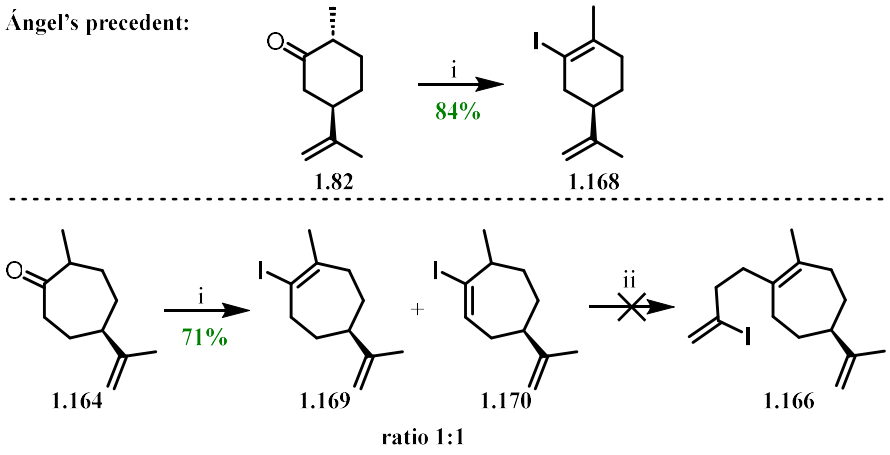
Scheme 33 Second synthetic plan towards radical reaction substrate **1.118** from dihydrocarvone **1.82**.

The ring expansion with ethyl diazoacetate proceeded smoothly, giving ketone ester **1.167** in nearly quantitative yield (*Scheme 34*). The product was confirmed by the coupling between inserted H(4) and H(3), and this regioselectivity is proposed to arise by migration via the less sterically-crowded transition state.[47a] Decarboxylation under basic conditions afforded the desired ketone **1.164** in 74% yield over two steps.



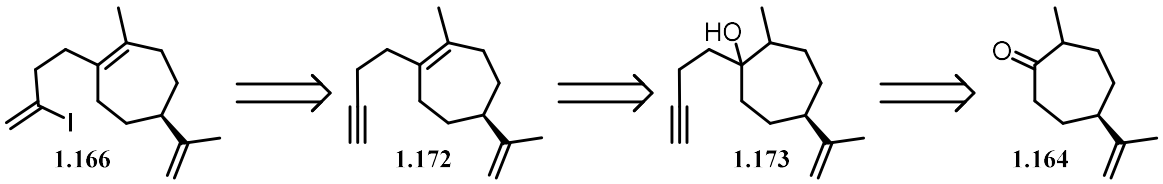
Scheme 34 Ring expansion of dihydrocarvone **1.82** and decarboxylation of ketone ester **1.167** into ketone **1.164**. **Reagents and conditions: i)** ethyl diazoacetate, BF_3•OEt_2, Et_2O, RT, 3 h; **ii)** NaOH, MeOH, H_2O, reflux, 3 h.

Angel reported the application to dihydrocarvone of Barton's general method for converting ketones into vinyl iodides and showed the tetrasubstituted alkene to be generated regioselectively in 84% yield (*Scheme 35*);[48] however, the analogous reaction of ketone **1.164** resulted in an inseparable 1:1 mixture of regioisomers **1.169** and **1.170**. Attempts to use this vinyl iodide mixture for Grignard or vinyllithium alkylations with tosylate **1.171** were unsuccessful and this route was not developed further.



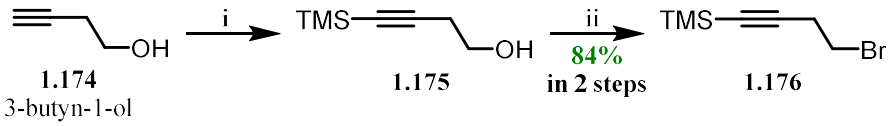
Scheme 35 Iodination of ketone **1.164** into **1.169** and further reaction of the mixture **1.169** and **1.170**. **Reagents and conditions: i)** a) N_2H_4, Et_3N, EtOH, reflux, 24 h; b) DBN, I_2, Et_2O; c) DBU, benzene, reflux, 3 h; **ii)** H_2C=C(I)CH_2CH_2OTs (**1.171**), Mg or *t*-BuLi, THF, –78 °C or RT, 2 h.

Another approach towards substrate **1.166** was proposed which involved Grignard addition to ketone **1.164** then dehydration of the resulting alcohol (*Scheme 36*) from which the vinyl iodide would be accessed from the alkyne according to Hoveyda and Gao's method.[49]



Scheme 36 Retrosynthetic plan towards vinyl iodide **1.166** by Grignard reaction.

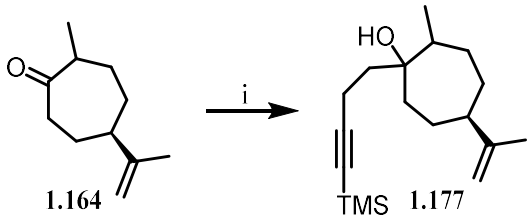
The side-chain Grignard precursor was synthesised from commercially available 3-butyn-1-ol (*Scheme 37*).*[105]*



Scheme 37 Synthesis of side-chain bromide **1.176**. **Reagents and conditions: i)** BuLi, TMSCl, THF, –78 °C, 3 h; **ii)** CBr_4, PPh_3, DCM, –40 °C to 0 °C, 4 h.

The addition of the Grignard derived from bromide **1.176** to ketone **1.164** proved more difficult than expected and some optimisation was necessary (*Table 4*). Direct reaction between the two reagents yielded only 7% of the target product **1.177**, otherwise returning the starting material which indicated that the Grignard reagent was probably deprotonating the ketone (*Entry 1*). According to Knochel's research,[50] lanthanide metal salts such as $CeCl_3$ and $LaCl_3$ can activate the ketone and significantly improve the yield of 1,2-Grignard addition. Addition of $CeCl_3$ provided a slight increase in yield while $LaCl_3$•2LiCl, commercially available as a THF solution, completed this Grignard reaction perfectly with 88% yield (*Entries 2,3*).

Table 4 Grignard addition converting ketone **1.164** into alcohol **1.177**.

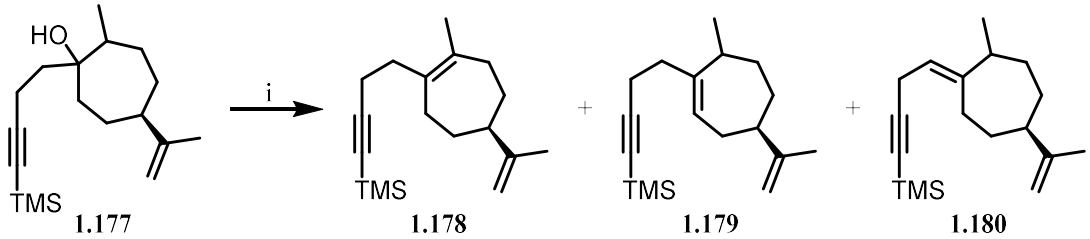


1.164 **1.177**

Entry	Conditions (i)	Yield of **1.38**
1	**1.176**, Mg, LiCl, THF	7%
2	dry $CeCl_3$, **1.176**, Mg, LiCl, THF	13%
3	$LaCl_3$•2LiCl, **1.176**, Mg, LiCl, THF	88%

Dehydration of alcohol **1.177** was then conducted with the classic dehydration method $SOCl_2$/pyridine (*Table 5*). Previous studies suggested that this method should generate mainly the fully substituted alkene product **1.178**;[51] however, the unique mobility of cycloheptyl substrate **1.177** led to poor regioselectivity under these conditions. The three possible products were generated as an inseparable mixture with a 1:1:1 ratio (*Entry 1*). Changing the reaction solvent, temperature and time gave no meaningful improvement (*Appendix 03*). Some protic acid catalysed conditions were also tested but the mixture of products was similar to the $SOCl_2$/pyridine conditions (*Entry 2,3*) and further work on this approach was suspended.

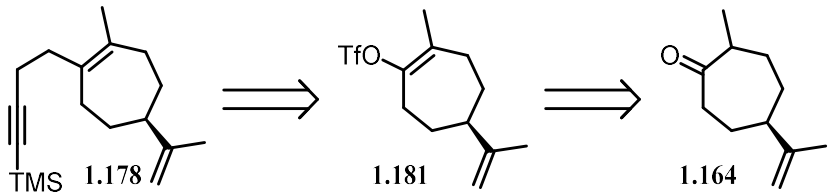
Table 5 Dehydration of alcohol **1.177** into substrate **1.178**.[52]



1.177 **1.178** **1.179** **1.180**

Entry	Conditions (i)	**178**:**179**:**180**
1	1.1 eq. $SOCl_2$, 1.2 eq. pyridine, DCM, –30 °C, 20 h	33:40:26
2	1.1 eq. PPTS, DCM, RT, 20 h	32:42:25
3	1.1 eq. PPTS, DCM, 40 °C, 20 h	30:43:26

Regioselective enol triflation then transition metal catalysed cross-coupling was proposed, with the expectation that conditions would be found to form the enol triflate regioselectively (*Scheme 38*).

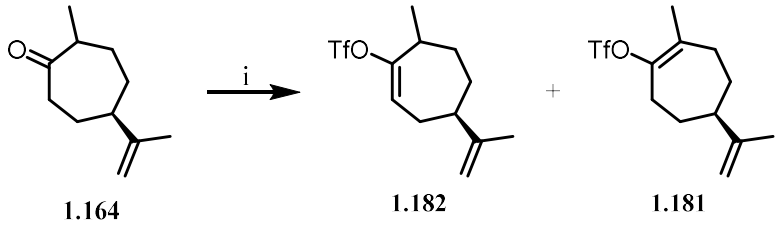


Scheme 38 Second strategy towards alkyne **1.178** by metal catalysed coupling.

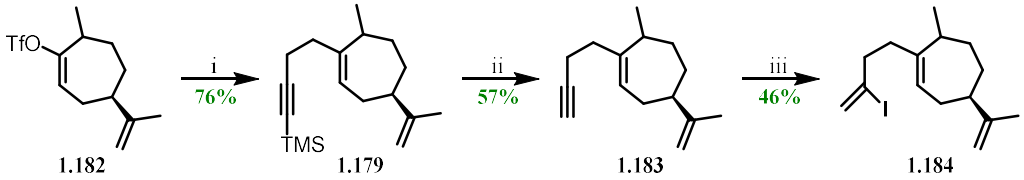
The reactivity of ketone **1.164** was tested under various enol triflation conditions (*Table 6*). Combinations of a potassium hydride or amide base with triflating reagents *N*-phenyl-bis(trifluoromethanesulfonimide) or Comins' reagent resulted in low yields as well as poor regioselectivity (*Entries 1–4*). LHMDS showed a stronger preference for the unwanted regioisomer **1.182**, and changing the triflation reagent to Comins' reagent gave a satisfactory yield for **1.182** (*Entries 5,6*). According to Stille's work, the Hauser base *i*-Pr_2NMgBr was able to generate the more substituted enolate with very good selectivity;[53] however, for ketone **1.164** the reaction proceeded very slowly although it did give the desired isomer **1.181** (*Entry 7*).

The subsequent steps were tested with enol triflate **1.182** (*Scheme 39*). According to Fürstner's work, $[Fe(MgX)_2]_n$ complexes, generated *in situ* by the reduction of Grignard reagents, can catalyse cross-coupling reactions of Grignard reagents and triflates.[54] Application of this method to compound **1.182** with bromide **1.176** gave a 76% yield of product **1.179**. TBAF deprotection gave terminal alkyne **1.183** which in turn was converted into the vinyl iodide **1.184** via a vinyl aluminium intermediate then displacement with iodine. The moderate yields for these two steps were attributed to the volatility of the hydrocarbon compound. By this overall route, a suitable substrate for radical cyclisation was obtained in six steps from dihydrocarvone.

Table 6 Enol triflate formation from ketone **1.164**.



Entry	Conditions (i)	Result
1	2 eq. KHMDS, 0.8 eq. $PhNTf_2$, THF, 0 °C, 3.5 h	10% **182**:**181** (1:1)
2	KH (excessive), 0.9 eq. $PhNTf_2$, THF, RT, 3 h	24% **182:181** (26:74)
3	1.4 eq. KHMDS, 1.6 eq. Comins' reagent, THF, –78 °C, 20 h	26% **182:181** (72:28)
4	1.2 eq. KO*t*-Bu, 1.4 eq. Comins' reagent, THF, RT, 20 h	23% **182:181** (22:78)
5	1.5 eq. LHMDS, 0.9 eq. $PhNTf_2$, THF, 0 °C, 3 h	37% **182**
6	1.2 eq. LHMDS, 1.4 eq. Comins' reagent, THF, RT, 20 h	81% **182**
7	1.2 eq. *i*-Pr_2NMgBr, 0.9 eq. $PhNTf_2$, ether, 0 °C, 60 h	3% **181**

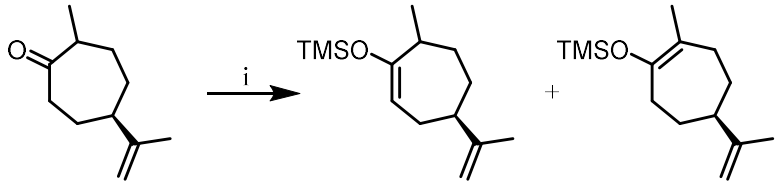


Scheme 39 Conversion of triflate **1.182** into vinyl iodide **1.184** for radical reaction. **Reagents and conditions: i) 1.176**, Mg, $Fe(acac)_3$, NMP, THF, –30 °C, 0.5 h; **ii)** TBAF, THF, RT, 2 h; **iii)** $Ni(dppp)Cl_2$, DIBAL-H, THF, 0 °C, 4 h then NIS, RT, 18 h.

The other regioisomer was reconsidered since regioselective ketone silylation has been widely explored and the resulting silyl enol ether can be converted into the corresponding triflate.[55] Accordingly, the regioselective silylation of ketone **1.164** was investigated (*Table 7*). Excess triethylamine and trimethylsilyl triflate were first tested at –78 °C; the conversion was good but the product was formed as a pair of inseparable regioisomers **1.185** and **1.186** (*Entry 1*). Considering that the target product **1.186** was expected to be the more stable isomer, trimethylsilyl triflate was replaced by the milder trimethylsilyl chloride and the reaction was heated at 160 °C in DMF; however, these conditions gave

surprisingly no reaction (*Entry 2*). This indicated that the chlorosilane was insufficiently electrophilic to activate the ketone, and NaI was added to generate the corresponding iodosilane *in situ* which led to full conversion of ketone **1.164** into both regioisomers (*Entry 3*). When the temperature was higher, the reaction showed a preference for the more substituted isomer **1.186**, but the undesired isomer **1.185** was still formed (*Entry 4*). Finally, according to Holton and Krafft's work, the Fe(0) cluster generated from $FeCl_3$ and methyl Grignard reagent has been shown to generate the more stable enolate in certain cases.[56] This method was tested on ketone **1.164** and, gratifyingly, it gave the pure isomer **1.186** with full conversion (Entry 5).

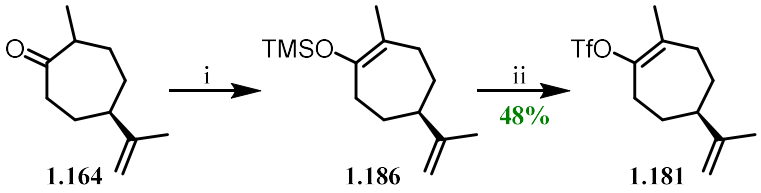
Table 7 Silylation of ketone **1.164** into enol ether **1.186**.



1.164 **1.185** **1.186**

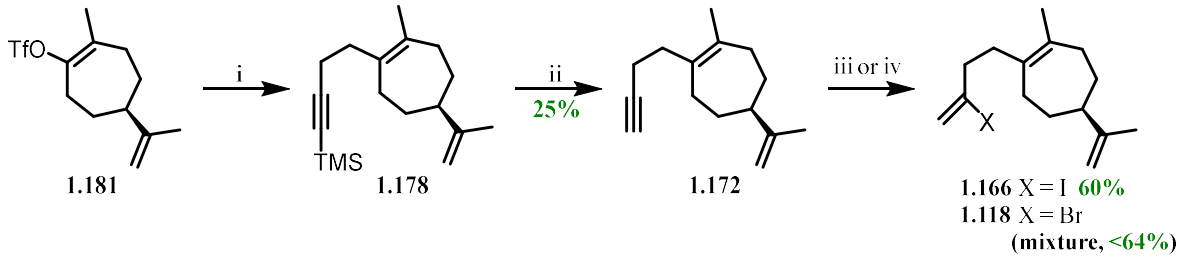
Entry	Conditions (i)	Result
1	12 eq. Et_3N, 4 eq. TMSOTf, DCM, –78 °C, 2 h	78% **1.185**:**1.186** (2:1)
2	2.4 eq. Et_3N, 1.2 eq. TMSCl, DMF, 160 °C, 20 h	n.r.
3	1.8 eq. Et_3N, 1.8 eq. TMSCl, 1.8 eq. NaI, CH_3CN, 0 °C, 3 h	**1.185:1.186** (2:1)
4	1.8 eq. Et_3N, 1.8 eq. TMSCl, 1.8 eq. NaI, CH_3CN, 70 °C, 3	**1.185:1.186** (1:1)
5	6 eq. MeMgBr, 2 eq. $FeCl_3$, Et_2O then 3 eq. TMSCl, 3 eq. Et_3N, 1 eq. HMPA, RT, 20 h	90% **1.186**

As expected, trimethylsilyl enol ether **1.186** could be converted into triflate **1.181** via the lithium enolate and the desired pure isomer **1.181** was finally achieved in 48% yield by this two-step strategy (*Scheme 40*).



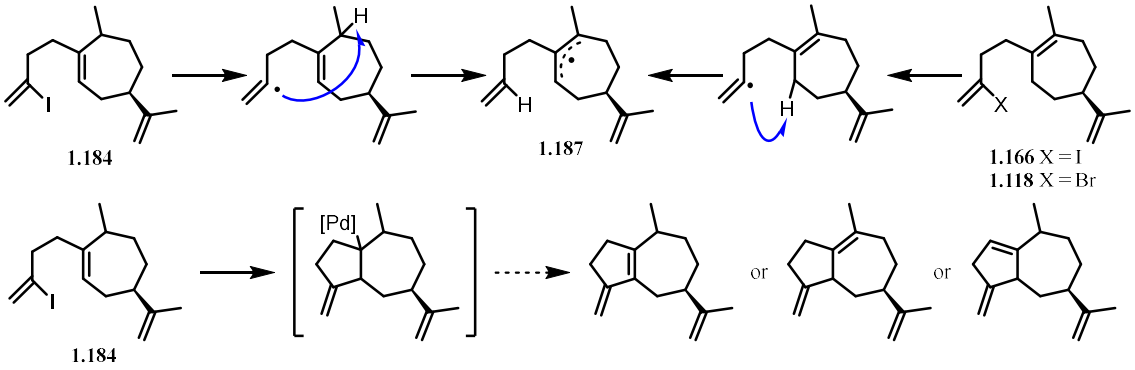
Scheme 40 Regioselective conversion of ketone **1.164** into triflate **1.181**. **Reagents and conditions: i)** MeMgBr, $FeCl_3$, Et_2O, then TMSCl, Et_3N, HMPA, RT, 20 h; **ii)** MeLi, THF, RT, 0.5 h then Comins' reagent, –78 °C to RT, 2 h.

Triflate **1.181** was then converted into the corresponding vinyl iodide radical precursor using the same method as for triflate **1.178** (*Scheme 41*). The Kumuda coupling of **1.181** into **1.178** gave a surprisingly low yield, perhaps because of slow palladium insertion into the C-OTf bond due to the co-planar (and hence crowded) sulfonyl and methyl groups. Careful TBAF deprotection gave alkyne **1.172** in 25% yield after two steps then hydroalumination-iodination gave the target vinyl iodide substrate **1.166** in 60% yield. The corresponding bromide **1.118** was also be prepared by replacing NIS with purified NBS as an inseparable mixture in which the bromide **1.118** was the major component.



Scheme 41 Conversion of triflate **1.181** into vinyl iodide **1.166** and bromide **1.118** for radical reaction. **Reagents and conditions: i) 1.176**, Mg, $Fe(acac)_3$, NMP, THF, –30 °C, 0.5 h; **ii)** TBAF, THF, RT, 2 h; **iii)** $Ni(dppp)Cl_2$, DIBAL-H, THF, 0 °C, 4 h then NIS, RT, 18 h; **iv)** $Ni(dppp)Cl_2$, DIBAL-H, THF, 0 °C, 4 h then NBS, RT, 18 h.

Substrates **1.118**, **1.166** and **1.184** were all potentially suitable for cyclisation because after the 1,5-hydrogen shift all three compounds would produce intermediate **1.187** (*Scheme 42*). Substrate **1.184** was also considered to be potentially capable of reacting by an intramolecular Heck coupling to give the five-membered ring.

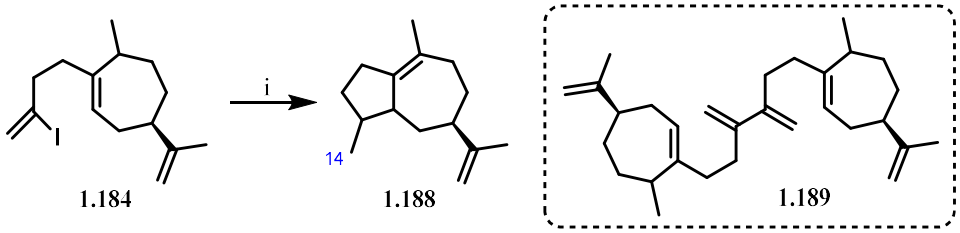


Scheme 42 Possible intermediates for 1,5-HAT/5-*exo-trig* cyclisation.

Standard conditions for the radical cyclisation were first tested with substrate **1.184** (*Table 8*). Use of tributyltin hydride with AIBN as the radical initiator gave a complex mixture, and no sign of a new methyl doublet for C14 in target product **1.188** could be detected in the ^{1}H NMR spectrum of the crude product. This result was not improved by diluting the solution and adding tin hydride slowly with a syringe pump to control the concentration of the radical-terminating reagent (*Entries 1,2*). Pd-catalysed Heck reaction conditions were also tested with high reaction temperatures resulting in a complex while milder conditions gave the dimer **1.189** preferentially (similar side reactions have been reported[57]); no cyclisation product **1.188** could be identified in these reactions (*Entries 3–5*).

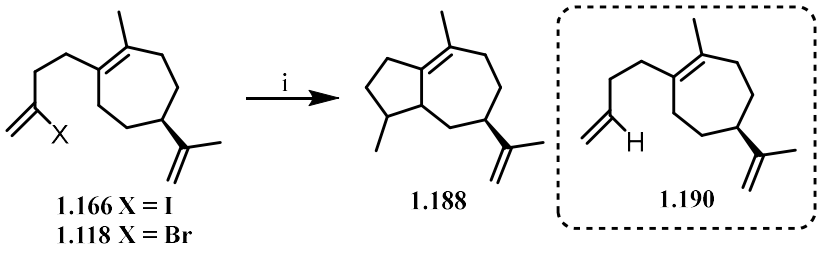
Test reactions with regioisomer **1.166** and bromide **1.118** gave similar results (*Table 9*). The low-temperature initiation conditions using triethylborane[58] reported by Oshima and co-workers were used to avoid mass loss from decomposition at high temperatures; however, these conditions, as well as the classic thernal conditions with AIBN, only led to direct reduction product **1.190** (*Entries 1–3*). A reaction with bromide **1.118** resulted in a complex mixture (*Entry 4*).

Table 8 Attempted cyclisations of **1.184** into **1.188**.



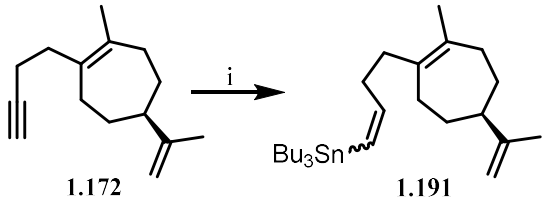
Entry	Conditions (i)	Result
1	1.2 eq. Bu_3SnH, 10 mol% AIBN, benzene, 90 °C, 2.5 h	complex
2	1.2 eq. Bu_3SnH, 10 mol% AIBN, benzene, 90 °C, 18 h	complex
3	10 mol% $Pd(OAc)_2$, 40 mol% PPh_3, 4 eq. K_2CO_3, DMF, 120 °C, 18 h	complex
4	10 mol% $Pd(OAc)_2$, 40 mol% PPh_3,1 eq. Ag_2CO_3, 4 eq. K_2CO_3, DMF, 80 °C, 2.5 h	**1.189**
5	10 mol% $Pd(OAc)_2$, 40 mol% PPh_3, 4 eq. K_2CO_3, DMF, 80 °C, 18 h	**1.189**

Table 9 Attempted radical cyclisations of **1.166** or **1.118** into **1.188**.



Entry	Conditions (i)	Result
1	**1.166**, 5 eq. Bu_3SnH, 30 mol% Et_3B, air, THF, RT, 4 h	**1.190**
2	**1.166**, 1.2 eq. Bu_3SnH, 30 mol% AIBN, benzene, reflux, 2.5 h	**1.190**
3	**1.166**, 0.58 eq. Bu_3SnH, 30 mol% AIBN, benzene, reflux, 2.5 h	**1.190**
4	**1.118**, 1.2 eq. Bu_3SnH, 30 mol% AIBN, toluene, 90 °C, 2.5 h	complex

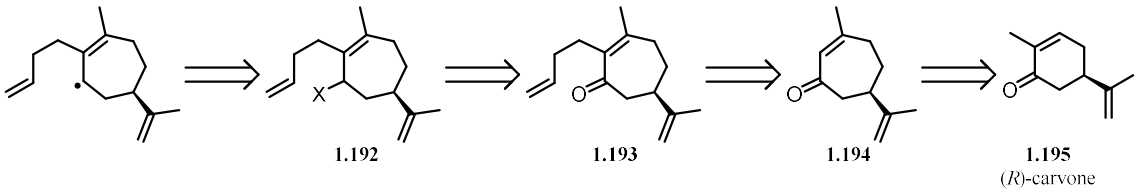
Alkyne **1.172** was also trialled as a radical cyclisation substrate (*Scheme 43*), with the vinyl radical being potentially generated by tributylstannyl radical addition onto the alkyne.[59] This addition took place but the resulting vinyl radical did not engage in further productive reactions and vinyl stannane **1.191** was achieved as the major product.



Scheme 43 Radical cyclisation of alkyne **1.172**. **Reagents and conditions: i)** 1.2 eq. Bu_3SnH, 10 mol% AIBN, benzene, 90 °C, 2.5 h or 1.3 eq. Bu_3SnH, 24 mol% AIBN, toluene, 110 °C, 2.5 h.

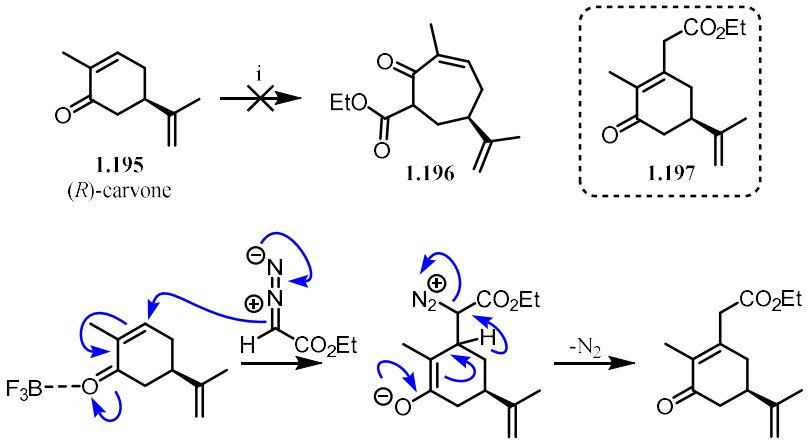
In summary, the planned radical translocation and cyclisation sequence merely gave the reduction product and, since it was not obvious which of the two steps was at fault, a plan was proposed to form the 'translocated' radical directly to probe the 5-*exo-trig* cyclisation step.

Substrate **1.192** was designed to generate the cycloheptenyl radical directly; successful cyclisation from this intermediate would then implicate the 1,5-H atom transfer step as problematic. Projecting towards a xanthate or similar radical precursor group led back via ketone **1.193** to enone **1.194** which is a known ring-expansion product of (*R*)-carvone **1.195** (*Scheme 44*).



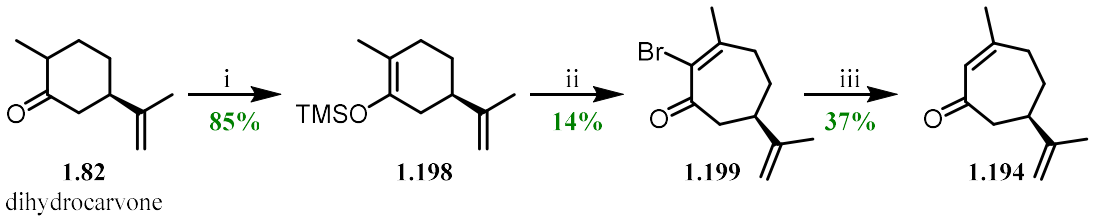
Scheme 44 Proposed substrate **1.192** for radical cyclisation (X = OR or halides).

In an attempt to shorten the published route (see below) to enone **1.194**, the direct ring expansion method with ethyl diazoacetate was tested on (*R*)-carvone; however, the only identified product was the 1,4-addition product **1.197** (*Scheme 45*), mechanistically related to a vicarious nucleophilic substitution in aromatic systems.



Scheme 45 Attempted ring expansion of (R)-carvone **1.195** into ketone **1.196**. **Reagents and conditions: i)** ethyl diazoacetate, BF_3•OEt_2, ether, RT, 3 h.

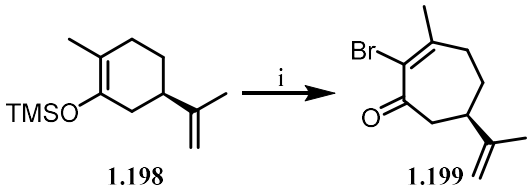
Wenkert reported the dibromocyclopropanation and ring expansion of a trimethylsilyl enol ether derived from a ketone similar to dihydrocarvone.[60] Regioselective silylation of dihydrocarvone **1.82** was achieved smoothly under standard 'thermodynamic' conditions (*Scheme 46*). Reaction between the so-formed silyl enol ether and dibromocarbene gave the target compound **1.199** in just 14% yield. Further reduction of the bromide with Zn/AcOH[61] gave the ring-expanded carvone homologue **1.194** in just three steps but an overall unacceptable yield of under 5%.



Scheme 46 Ring expansion of dihydrocarvone **1.82** leading to enone **1.194**. **Reagents and conditions: i)** Et_3N, NaI, TMSCl, CH_3CN, 80 °C, 18 h; **ii)** $CHBr_3$, *t*-BuOK, hexane, –30 °C to RT, 18 h; **iii)** Zn, AcOH, 90 °C, 1.5 h.

A brief optimisation of the ring expansion step was tried (*Appendix 04; Table 10*). Although a slightly higher yield (25%) was obtained by decreasing the quantity of the reagents (*Entry 2*), the reaction failed at a larger scale (*Entry 3*) and an alternative method was sought.

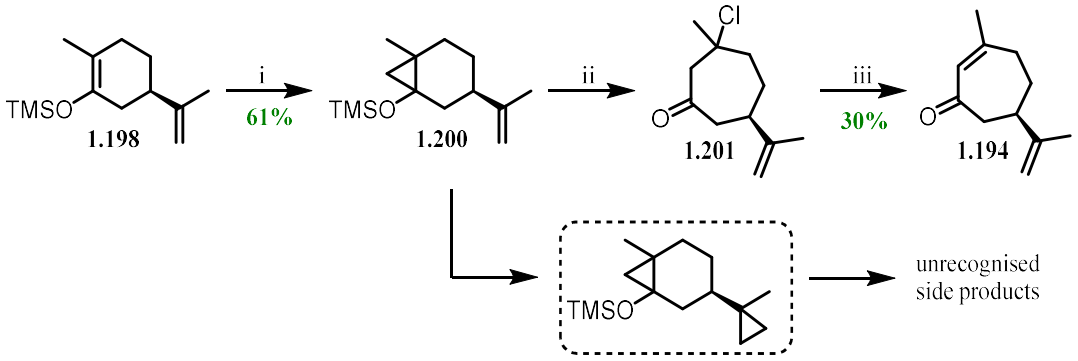
Table 10 Study of the ring expansion step (**1.198** to **1.199**).



Entry	Conditions (i)	Yield
1[a]	5 eq. $CHBr_3$, 6 eq. *t*-BuOK, hexane, –30 °C to RT, 18 h	14%
2[a]	1.2 eq. $CHBr_3$, 3 eq. *t*-BuOK, hexane, –30 °C to RT, 18 h	25%
3[b]	1.2 eq. $CHBr_3$, 3 eq. *t*-BuOK, hexane, –30 °C to RT, 18 h	decomposed

[a] 1.0 mmol; [b] 8.0 mmol.

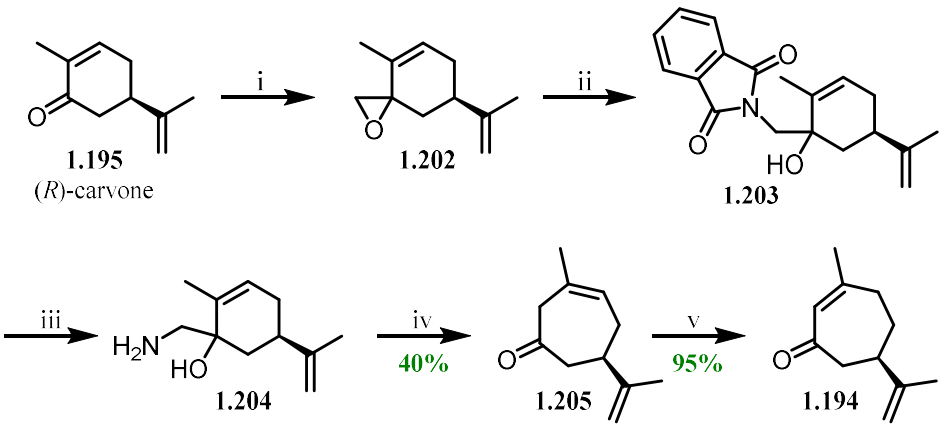
Another three-step method, as reported by Brocksom and co-workers, was also examined.[62] Furakawa modified Simmons–Smith cyclopropanation of trimethylsilyl enol ether **1.198** formed cyclopropane **1.200** (*Scheme 47*) with poor regioselectivity and the product contained over-reacted dicyclopropane product. Ring expansion of the desired product **1.200** gave intermediate chloroketone **1.201** which could be easily eliminated into the target product **1.194**. This method, whilst successful, also suffered from low yielding steps and the product **1.194** could not be obtained free from minor impurities.



Scheme 47 Brocksom's method for ring expansion of **1.198** into **1.194**. **Reagents and conditions: i)** Et_2Zn, diiodomethane, toluene/DCM; **ii)** $FeCl_3$, silica gel, THF/DCM, 0 °C to RT, 3 h; **iii)** NaOAc, MeOH, reflux, 2 h.

Eventually, a reliable method was found in the publication by Ley and Brocksom.[63] This overall five-step route (*Scheme 48*) from (*R*)-carvone **1.195**, proceeded via Corey–Chaykovsky epoxidation then Tiffeneau–Demjanov ring-expansion of the derived 1,2-aminoalcohol. These first four steps gave enone

1.205 with 40% overall yield in four steps and the product could be prepared on multigram scale. Base-catalysed isomerisation of enone **1.205** into **1.194** proceeded with near-quantitative yield.

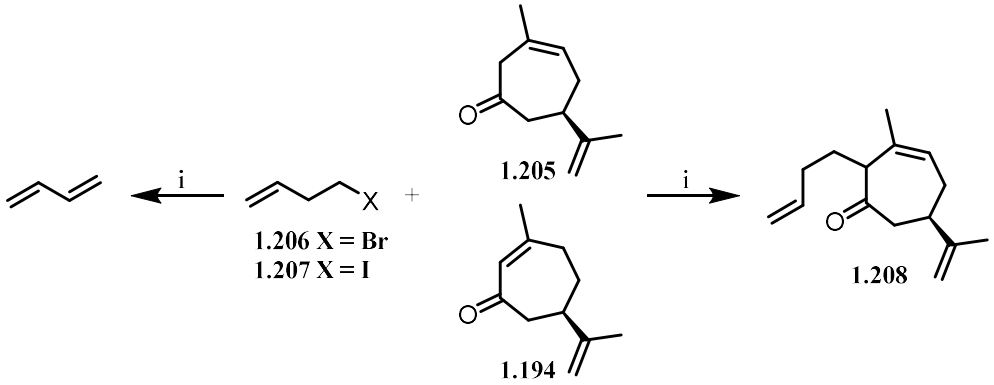


Scheme 48 Ley's and Brocksom's method for the preparation of enone **1.205**, and its isomerisation into ketone **1.194**. **Reagents and conditions: i)** $Me_3S^+I^-$, BuLi, DMSO, THF, 0 °C, 3 h; **ii)** K-phthalimide, DMF, 155–160 °C, 3 h; **iii)** $NH_2NH_2 \bullet H_2O$, EtOH, 80–85 °C, 2 h; iv) $NaNO_2$, AcOH 10% (v/v), 0 °C, 4 h; v) DBU, DCM, RT, 18 h.

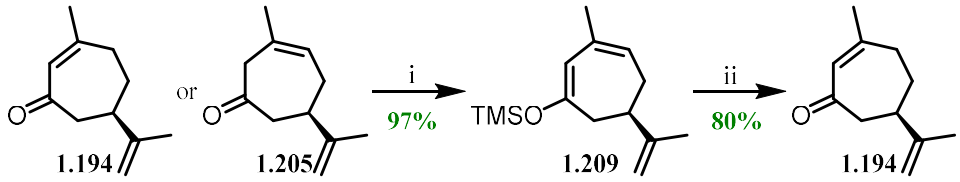
Direct alkylation of ketones **1.194** or **1.205** with either 4-bromo-1-butene **1.206** or 4-iodo-1-butene **1.207** suffered from low conversion and yield due to the competitive elimination of the halide (*Appendix 05*). Some relatively successful conditions are listed in *Table 11*; other bases (LHMDS, KHMDS, *t*-BuONa), solvents (DMF, DMPU, *t*-BuOH) and temperatures only gave trace yields.

Both ketones **1.194** and **1.205** gave the same trimethylsilyl enol ether under silylation conditions (*Scheme 49*) but an attempt to regenerate and alkylate the enolate with iodoalkene **1.207** resulted in recovery of ketone **1.194**.

Table 11 Direct butenylation of enones **1.194** and **1.205**.

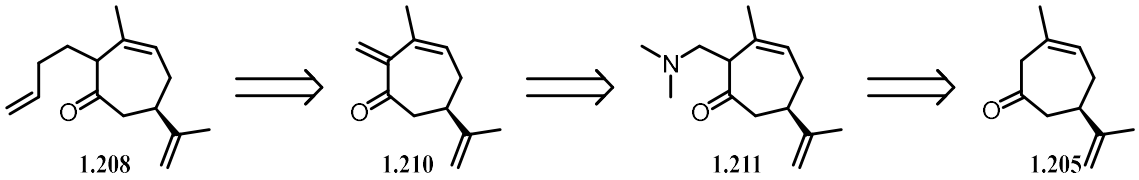


Entry	Conditions (i)	Yield
1	**1.205**, 1.5 eq. **1.207**, 1.4 eq. *t*-BuOK, THF, RT, 18 h	25%
2	**1.205**, 1.3 eq. **1.207**, 1.1 eq. *t*-BuOK, 12 eq. DMPU, DMF, RT, 18 h	21%
3	**1.194**, 1.5 eq. **1.207**, 1.2 eq. *t*-BuOK, 30 eq. HMPA, THF, RT, 18 h	25%



Scheme 49 Trimethylsilylation and then alkylation of ketones **1.194** and **1.205**. **Reagents and conditions: i)** KHMDS, TMSCl, DMF, RT, 3 h; **ii)** MeLi, THF, 0 °C, 1 h then **1.207**, HMPA, –78 °C to RT, 18 h.

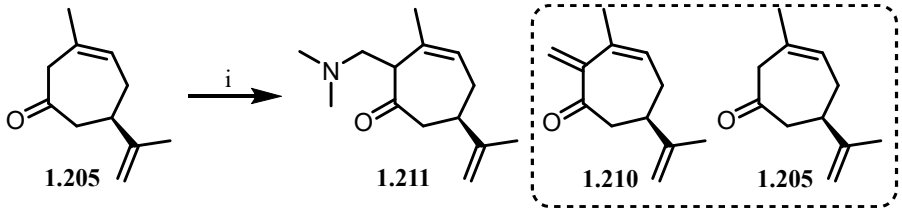
An alternative plan was based on conjugate allylation of methylene ketone **1.210** (*Scheme 50*) which would be obtained by elimination of Mannich addition product **1.211**.



Scheme 50 A conjugate allylation approach to ketone **1.208**.

Enolate dimethylaminomethylation with Eschenmoser's salt[64] led to a complex crude product mixture in which three compounds – target product **1.211**, starting material **1.205** and elimination product **1.210** – were detected in a ratio of 1:1:2.5 (*Table 12, Entries 1–2*). A clean crude product and an acceptable yield of the aminoketone **1.211** was obtained by reacting silyl enol ether **1.209** with Eschenmoser's salt without any other additives (*Entry 3*). Direct aldol condensation[65] to form the enone directly led to alkene isomerisation and a complex product mixture (*Entry 4*).

Table 12 Dimethylaminomethylation of ketone **1.205** into ketone **1.211**.

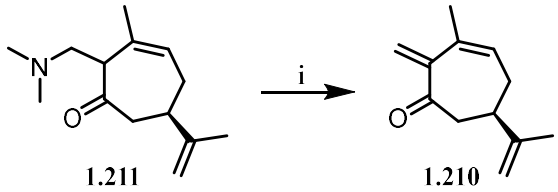


Entry	Conditions (i)	Result
1	1.2 eq. KHMDS, THF, –78 °C, then 1.5 eq. Eschenmoser's salt, 4 eq. HMPA, 1.5h	complex
2	1.2 eq. KHMDS, THF, –78 °C, then 3.5 eq. Eschenmoser's salt, 4 eq. HMPA, 1.5h	complex
3	**1.209** as substrate, 1.5 eq. Eschenmoser's salt, DCM, RT, 1 h	**67%**
4	1.2 eq. CH_2O, 10 mol% piperidine, 10 mol% AcOH, MeOH, 60 °C, 10 h	complex

Hofmann elimination from amine **1.211** gave recovered starting material (*Table 13; Entry 1*) but with more methyl iodide added and an extended reaction time the target product **1.210** was isolated in trace yield from a complex product mixture (*Entry 2*). Cope elimination with MCPBA gave a slightly better result but over-oxidation of the *iso*propenyl side-chain made the reaction unreliable (*Entry 3*).

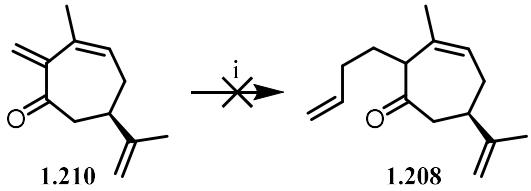
The 1,4-allylation was attempted just once with no sign of the target product **1.208** detectable (*Scheme 51*) and this approach was terminated.

Table 13 Elimination of amine side chain on ketone **1.211** into ketone **1.210**.



1.211 **1.210**

Entry	Conditions (i)	Result
1	6.6 eq. MeI, ether, RT, 1 h then 30 eq. NaOAc(aq), RT, 1 h	n.r.
2	13 eq. MeI, ether, RT, 18 h then 10 eq. $NaHCO_3$(aq), RT, 1 h	**2%**
3	1.5 eq. MCPBA, DCM, RT, 0.5 h	**12%**



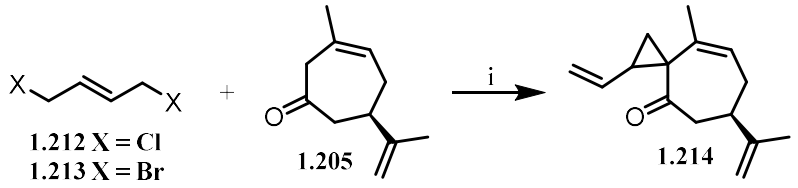
1.210 **1.208**

Scheme 51 Attempted conjugate allylation of ketone **1.208**. **Reagents and conditions: i)** 4 eq. allylmagnesium chloride, 2 eq. CuBr•Sme_2, THF, –50 °C, 1 h then **1.210**, –40 °C, 2 h.

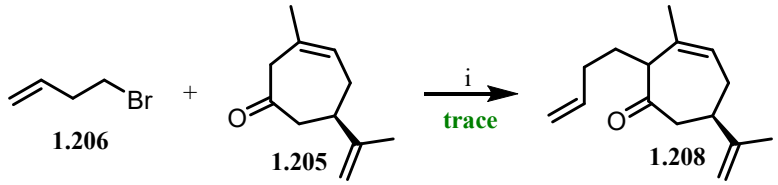
Lautens and co-workers reported the two step butenylation of ketones using 1,4-dichloro-2-butene as the electrophile for enolate alkylation then Pd-catalysed reduction of the intermediate vinylcyclopropane.[66] Both steps of the reported conditions applied to ketone **1.205** worked poorly and needed significant optimisation (*Table 14*). Following various unsuccessful modifications to the conditions reported for the alkylation step (Entries 2–5), the use of a base combination (NaH and KO*t*-Bu)[67] led to a reasonable outcome (Entry 6); increasing the quantity of electrophile **1.213** and reducing the alkylation temperature finally gave the target product **1.214** in satisfactory yield (*Entry 7*).

The same conditions using bromide **1.206** as electrophile gave just traces of the butenylated product (*Scheme 52*).

Table 14 Double alkylation of ketone **1.205** to generate cyclopropane **1.214**.



Entry	Conditions (i)	Yield
1	1.2 eq. KHMDS, 1.5 eq. **1.212**, THF, –78 °C to RT, 2 h	trace
2	1.2 eq. KHMDS, 1.5 eq. **1.212**, 4 eq. HMPA, THF, –78 °C to RT, 2 h	25%
3	1.2 eq. KHMDS, 2 eq. **1.212**, 10 eq. DMPU, THF, –78 °C to RT, 6 h	trace
4	1.3 eq. LDA, 4 eq. **1.212**, 1.1 eq. DMPU, THF, –78 °C, 18 h	trace
5	1.2 eq. KHMDS, 5 eq. **1.213**, THF, –78 °C to RT, 18 h	complex
6	1.2 eq. KO*t*-Bu, 2 eq. NaH, 1.5 eq. **1.213**, toluene, RT, 2 h	33%
7	1.2 eq. KO*t*-Bu, 2 eq. NaH, toluene, RT, 1 h then 4 eq. **1.213**, –78 °C to RT, 2 h	73%

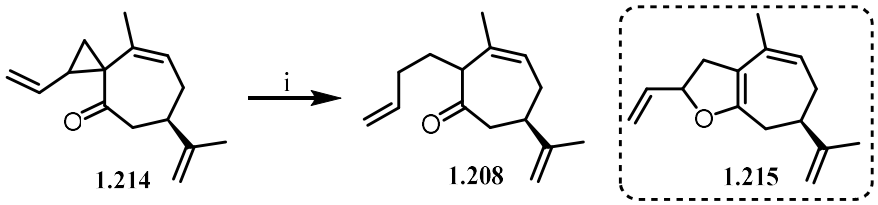


Scheme 52 Direct alkylation of **1.205** with bromide **1.206** using the conditions optimised for the formation of vinyl cyclopropane **1.208**. **Reagents and conditions: i)** KO*t*-Bu, NaH, toluene, RT, 1 h then **1.206**, –78 °C to RT, 2 h.

The Pd-catalysed reductive ring cleavage also needed optimisation (*Table 15*). Deviations from the reported procedure (*Entry 1*) included: omitting the ligand tributylphosphine, which led to no reaction (*Entry 2*); decreasing the loading of catalyst formed dihydrofuran **1.215** as the major product (*Entry 3*) whilst changing the reducing reagent to diethylzinc gave only **1.215** (*Entry 4*); adding water improved selectivity but only up to a certain point (*Entries 5,6*); adding formic acid improved the ratio further (*Entry 7*); replacing the ammonium formate with formic acid and triethylamine enhanced the ratio to 4:1 but additional formic acid alone made little difference (*Entries 8,9*); finally, increasing the loading of both acid and base gave the target compound **1.208** efficiently, free from side-product **1.215** (*Entry*

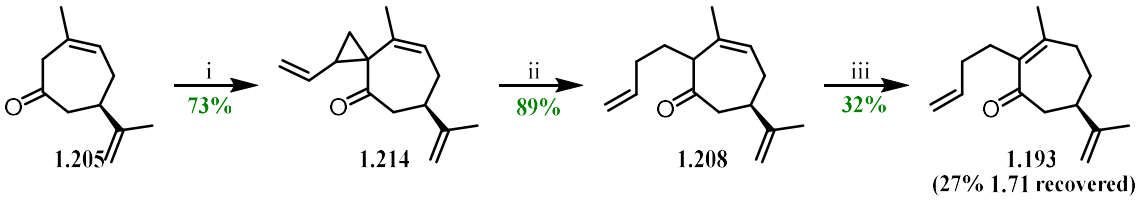
10). This interesting outcome may arise from the base increasing the rate of hydride transfer and the acid quenching the ring-opened enolate quickly preventing *O*-cyclisation to dihydrofuran **1.215**.

Table 15 Reduction of cyclopropane **1.214** into alkylation product **1.208**.



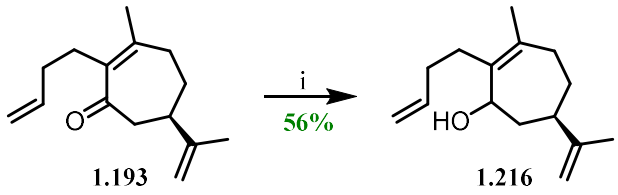
Conditions (i) in toluene, 105 °C, 2 h					
Entry	Pd_2dba_3 mol%	PBu_3 mol%	Reducing agent (eq.)	Modifications	Result
1	10	80	HCO_2NH_4 (2.2)		complex
2	2	–	HCO_2NH_4 (2.2)		n.r.
3	2	16	HCO_2NH_4 (2.2)		**1.208** /**1.215** = 1:4.8
4	2	16	Et_2Zn (3.0)	75 °C	**1.215**
5	2	16	HCO_2NH_4 (2.2)	+ H_2O (2.0 eq.)	**1.208** /**1.215** = 1:2.7
6	2	16	HCO_2NH_4 (2.2)	+ H_2O (55 eq.)	**1.208** /**1.215** = 1:2.7
7	2	16	HCO_2NH_4 (2.2), HCO_2H		**1.208** /**1.215** = 1:1
8	2	16	HCO_2H (5.0)	+ Et_3N (2.0 eq.)	**1.208** /**1.215** = 4:1
9	2	16	HCO_2H (7.0)	+ Et_3N (2.0 eq.)	**1.208** /**1.215** = 4:1
10	2	16	HCO_2H (14.0)	+ Et_3N (4.0 eq.)	**1.208** (89%)

Based on this two-step procedure, the alkylation product could be achieved in large scale and high yield and enone isomerisation furnished conjugated ketone **1.193** (*Scheme 53*).



Scheme 53 Alkylation of ketone **1.205** and formation of enone **1.193**. **Reagents and conditions: i)** KO*t*-Bu, NaH, toluene, RT, 1 h then **1.213**, –78 °C to RT, 2 h; **ii)** Pd_2dba_3, PBu_3, HCO_2H, Et_3N, toluene, 105 °C, 2 h; **iii)** KO*t*-Bu, THF, 70 °C, 4 h.

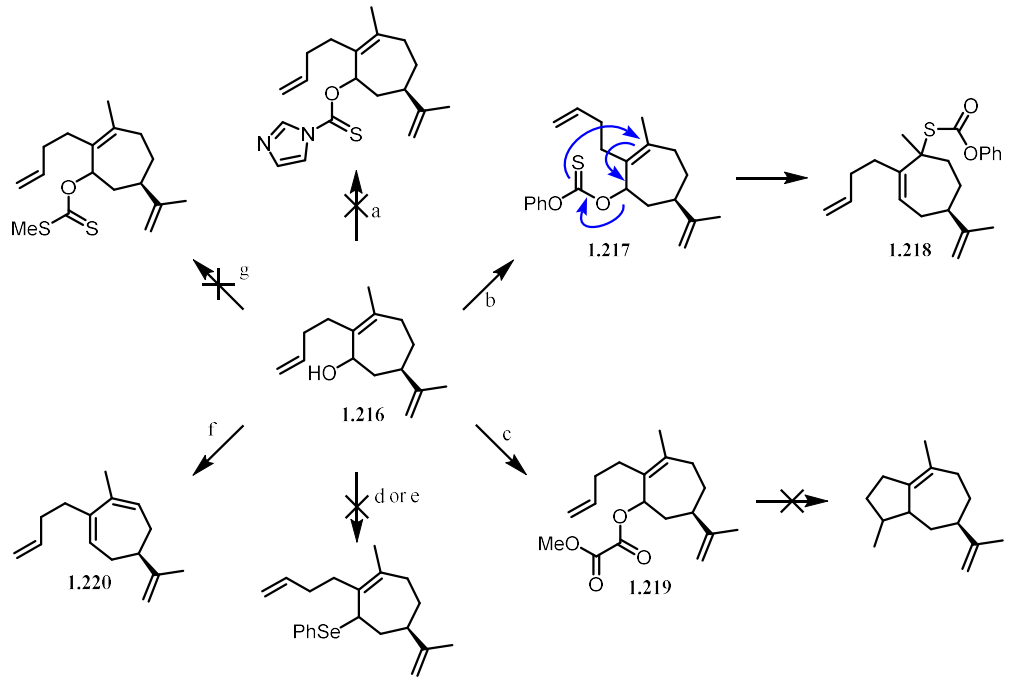
Selective reduction of enone **1.193** under Luche conditions gave alcohol **1.216** as a pair of unassigned diastereomers with ratio 6:1 (*Scheme 54*).



Scheme 54 Luche reduction of enone **1.193**. **Reagents and conditions: i)** $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 1 h.

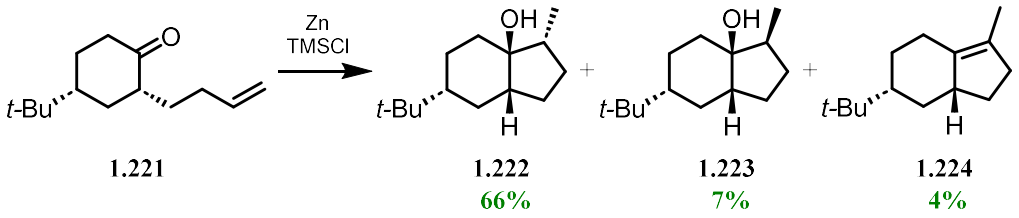
Various substitution methods were then tested on allylic alcohol **1.216** to make a precursor for Barton–McCombie radical generation;[68] (*Scheme 55*). The sterically-hindered alcohol proved unreactive towards the mild reagent TCDI and classical xanthate formation. The phenoxythionocarbonate derivative **1.217** was formed but underwent [3,3]-sigmatropic rearrangement leading to compound **1.218**, of no value as a radical precursor. Selenylation attempts also gave no reaction while halogenation gave primarily diene **1.220**. The only promising result came from the methyl oxalyl ester derivative **1.219**[69] which was the major component in an inseparable mixture; however, this mixture was unreactive or led to decomposition with no sign for cyclisation under a variety of radical reaction conditions (*Appendix 06*).

The failure of radical cyclisation could be attributed to the low reactivity of the allylic radical. As Parsons mentioned in his work,[34] allylic radicals generally need an activated alkene partner for efficient cyclisation. Regardless, in order to complete the ring construction, another cyclisation method was proposed.



Scheme 55 Different methods for generation of radical precursors. **Reagents and conditions:** a) TCDI, DMAP, DCM, RT; b) *O*-phenyl chlorothionoformate, pyridine, DCM, 0 °C to RT, 18 h; c) methyl chlorooxoacetate, pyridine, DCM, RT, 1 h; d) MsCl, TMPDA, toluene, RT, 1 h then $(PhSe)_2$, $NaBH_4$, EtOH, 0 °C to RT, 18 h; e) NPSP, PBu_3, THF or DCM, 0 °C to RT, 1 h ; f) PPh_3, CBr_4, DCM, –46 °C to RT, 2 h; g) BuLi, THF, –78 °C, 0.5 h, then CS_2, 0.5 h, then MeI, 1 h.

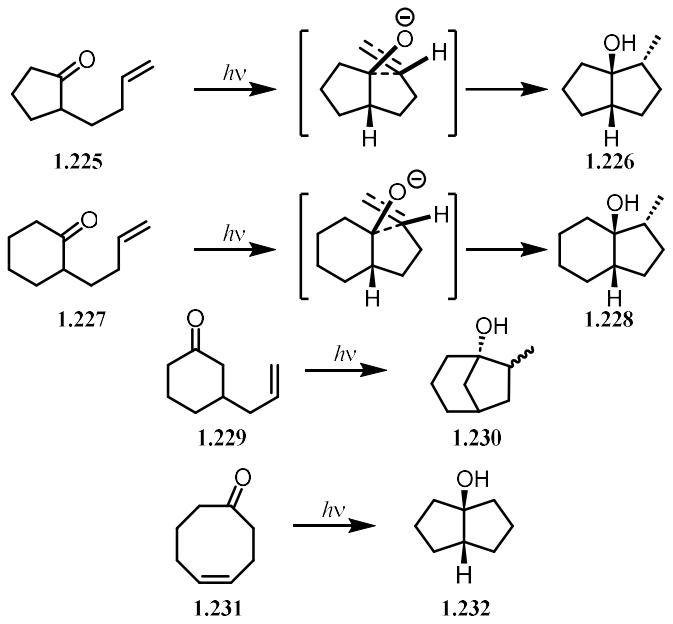
In 1983, Corey and Pyne reported the first cyclisation of δ,ε-unsaturated ketones using Zn and TMSCl[70] (*Scheme 56*) with 2,6-lutidine added to prevent the elimination of the tertiary alcohol in the product.[71] This stereoselective method was shown to be compatible with numerous functional groups.



Scheme 56 Corey and Pyne's method of ketyl radical cyclisation with Zn/TMSCl.

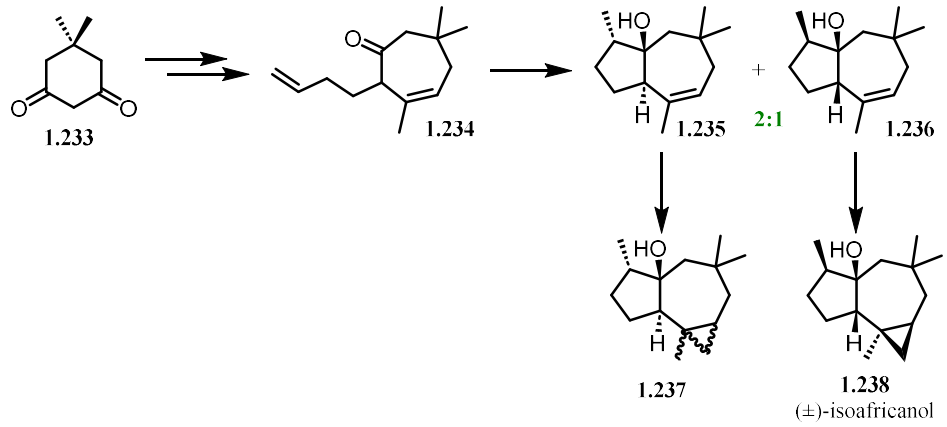
The Portella group, in 1985, further established the alkene-ketone coupling by a radical anion mechanism (*Scheme 57*), using UV irradiation in the presence of HMPA or a tertiary amine such as triethylamine to cyclise δ,ε-unsaturated cycloketones.[72] The stereoselectivity likely derives from a

repulsive electrostatic interaction between the oxygen anion and the approaching alkene π-system which would favour the transition state with the larger dihedral angle between these two groups, resulting in the observed *anti*-relationship of OH and CH_3 in the products.[73]



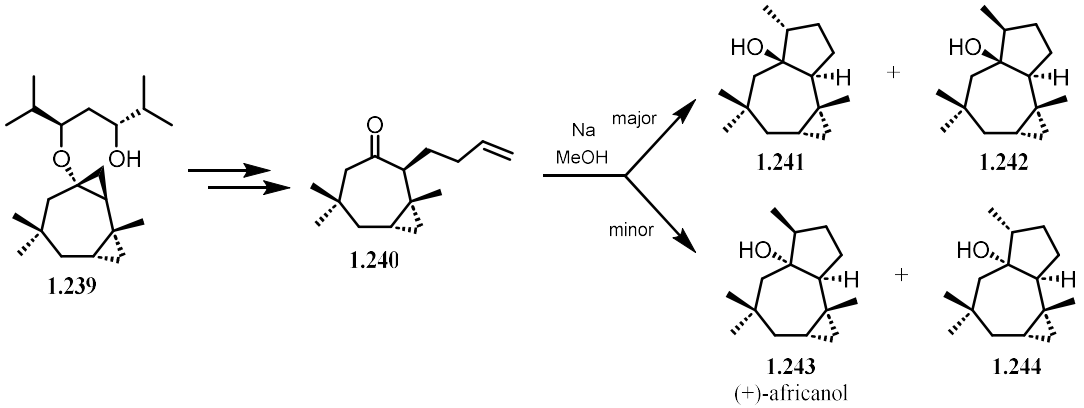
Scheme 57 Alkene-ketone coupling under UV irradiation.

This photoreductive coupling method was used as a key step in the total synthesis of (±)-isoafricanol and its diastereomers, as reported by Cossy in 1998 (*Scheme 58*). UV irradiation of δ,ε-unsaturated ketone **1.234** generated a pair of cyclised tertiary alcohol diastereomers in a ratio of 2:1.[74]



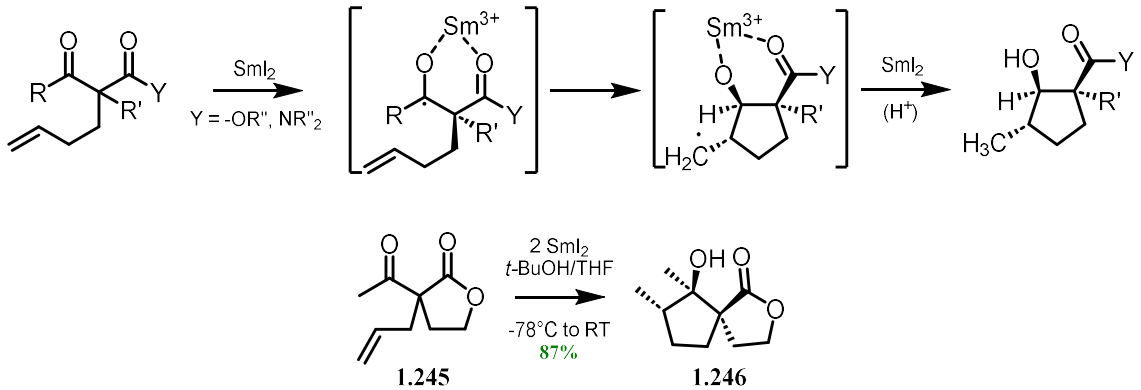
Scheme 58 Isoafricanol synthesis by photoreductive coupling.

Other studies focused on cyclisations mediated by metals and low-valent metal salts. For example, in 1990 Tai's group reported a short synthetic route to (+)-africanol using Na-mediated reductive ketone-alkene coupling as the key step (*Scheme 59*). Prior to this report, the Na-mediated reductive cyclisation had been studied for γ-ethynyl ketones to form *exo*-alkylidenyl cyclic alcohols.[75] In Tai's route, the enantiomerically enriched substrate **1.240** was cyclised using Na in methanol, delivering four diastereomers with preference for a *trans* disposition of the bridgehead hydroxyl group and proton.[76]



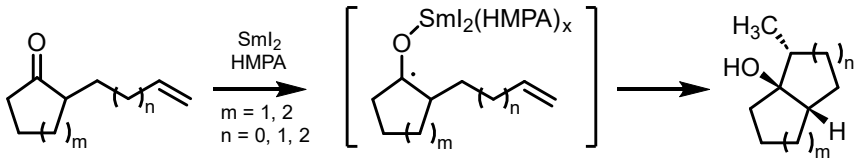
Scheme 59 The Tai group's synthesis of (+)-africanol.

Since Kagan's first use of samarium(II) iodide (SmI_2) in an organic reaction in 1977,[77] the reagent has become one of the most versatile for initiating single electron transfer.[78] In 1987, after their successful stereoselective cyclisation of 2-(ω-haloalkyl)-β-keto-esters and -amides using SmI_2,[79] the Molander group reported a ketone-alkene coupling mediated by SmI_2 (*Scheme 60*).[80]



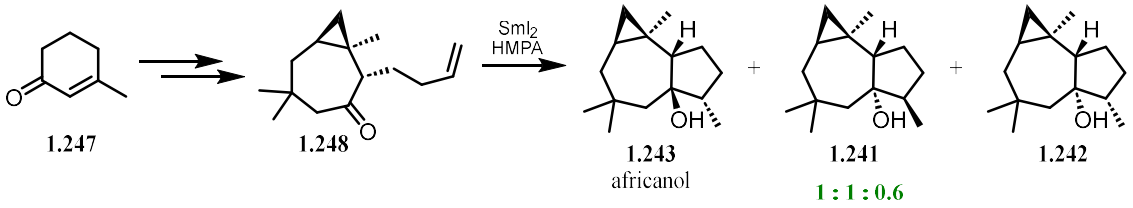
Scheme 60 Molander's SmI_2-mediated alkene-ketone coupling.

The group found that adding the polar solvent HMPA activates SmI_2, improving both reactivity and stereoselectivity (*Scheme 61*).[81] The authors postulated that $SmI_2(HMPA)_x$ species were responsible for effecting the reaction rather than simple SmI_2 due to the ligand field influence of the strong electron donor HMPA. The improved stereoselectivity was proposed to arise from the increased steric demand of the HMPA complex in the cyclisation transition states.



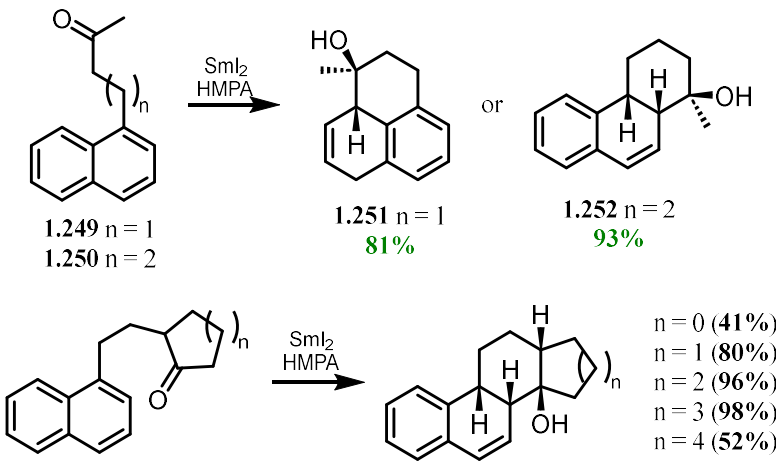
Scheme 61 SmI_2-mediated cyclisation promoted by HMPA.

Later, in 2000, Piers reported another synthesis of (±)-africanol using this method, giving the natural product and two diastereomers (*Scheme 62*).[82] In this process, the general preference for the production of a *trans* relationship of hydroxyl and methyl substituents was maintained (*trans/cis* = 3.3:1) but, in contrast to Tai's Na-mediated variant of this reaction, the desired *cis*-fused bicyclic product was the minor (*cis*-fused/*trans*-fused = 1:1.6).



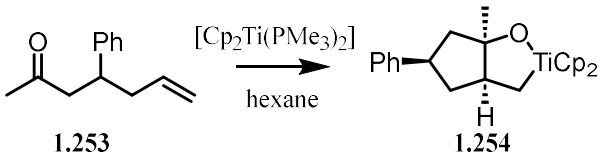
Scheme 62 Piers' synthesis of (±)-africanol.

Then, in 2007, Reissig reported a strategy towards steroid-like skeletons using SmI_2-mediated reductive cyclisation of 1-(ω-oxoalkyl)naphthalene derivatives (*Scheme 63*). The radical-anion generated was shown to be sufficiently reactive to disrupt the aromatic system to form a six-membered ring, the preference for six-membered ring formation directing the cyclisation regioselectivity. Tricyclic and tetracyclic compounds were prepared with high stereoselectivity (up to single diastereomer product).[83]



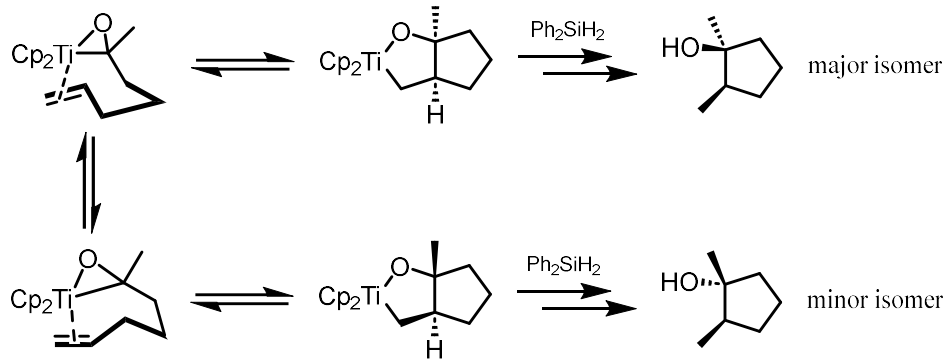
Scheme 63 Reissig's SmI_2-mediated ketone-naphthalene reductive coupling.

Titanium-reagents have also been used to mediate this type of cyclisation. In 1990, the Whitby group isolated an organotitanium intermediate in the reaction of an enone with the low-valent organotitanium reagent $Cp_2Ti(PMe_3)_2$ (*Scheme 64*).[84] The authors proposed that this first example of an intramolecular heteroalkene coupling involving both titanium and a carbonyl group might find useful application in organic synthesis.



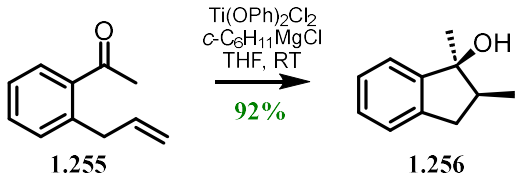
Scheme 64 An oxatitanacyclic intermediate isolated from a titanium-mediated alkene-ketone coupling.

Indeed, the Buchwald group elaborated on this idea in 1995. They showed how the inclusion of a silyl reducing reagent such as diphenylsilane could release the Ti species such that a stoichiometric quantity of the titanium reagent was not necessary (*Scheme 65*). With this modification, $Cp_2Ti(PMe_3)_2$ loadings as low as 10 mol% could be used effectively. In contrast to the SmI_2-mediated cyclisations, the 'titanium method' has a preference for the production of a *cis* disposition between the hydroxyl and methyl groups as a result of the preferential formation of a *cis*-fused bicyclic titanacycle.[85]



Scheme 65 Buchwald's method of coupling with the titanium reagent as catalyst.

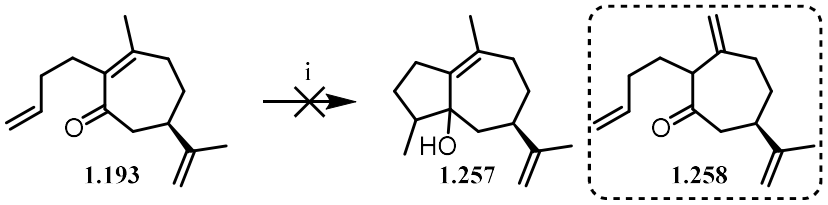
This method was further developed by Cha and Quan, as reported in 2001 (*Scheme 66*). In this work, the reagent combination $Cp_2Ti(PMe_3)_2/Ph_2SiH_2$ was replaced with the more stable Kulinkovich reagent system that uses titanium(IV) alkoxides/phenoxides along with a Grignard reagent. After optimisation, the authors discovered that the combination of $Ti(OPh)_2Cl_2$ and cyclohexylmagnesium chloride gave the same yield and stereoselectivity as $Cp_2Ti(PMe_3)_2/Ph_2SiH_2$.[86]



Scheme 66 Cha and Quan's titanium-mediated cyclisation.

Based on substrates already achieved, application of such a reductive cyclisation to ketones **1.193** and **1.208** was proposed. Several reported coupling methods were tested initially with enone **1.193** (*Table 16*). Bonjoch and Bradshaw's method using $Fe(acac)_3$/triethylsilane[87] gave over-reduction (*Entry 1*), proceeding through proton transfer and thus having no selectivity between the two terminal double bonds. A more classical SmI_2-mediated coupling[80] gave no reaction (*Entry 2*) but when the proton source was changed from *tert*-butanol to methanol, regioisomer **1.258** was observed as a major product (*Entry 3*) within a multi-component product mixture.

Table 16 Attempted ketone-alkene coupling of enone **1.193** leading to alcohol **1.257**.

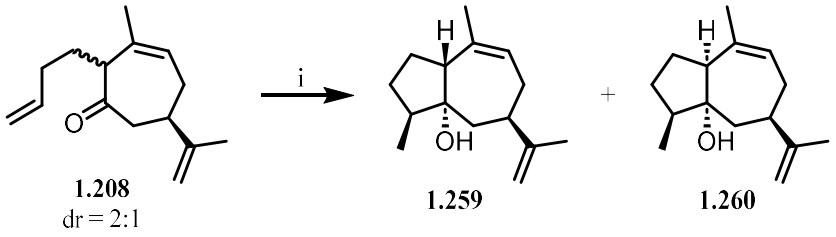


Entry	Conditions (i)	Result
1	2.5 eq. $PhSiH_3$, 0.2 eq. $Fe(acac)_3$, EtOH, 60 °C, 24 h	complex
2	4 eq. SmI_2, 2 eq. *t*-BuOH, 25 eq. HMPA, THF, RT, 3 h	n.r.
3	4 eq. SmI_2, 2 eq. MeOH, 25 eq. HMPA, THF, RT, 3 h	complex with **1.258**

The unconjugated enone isomer **1.208** was then tested in alkene-ketone coupling reactions (*Table 17*). Corey's Zn and trimethylsilyl chloride method[70] gave no reaction (*Entry 1*) and the $Fe(acac)_3$/triethylsilane method gave over-reduction (*Entry 2*). The SmI_2-mediated reaction proceeded smoothly, and stereospecifically, to give the desired alcohol products **1.259** and **1.260** (*Entry 3*) from the α- and β- butenyl diasteromers of **1.208**, respectively. The relative configuration in these compounds was supported by extensive NMR spectroscopic analysis including the key n.O.e correlations shown (*Appendix 07, Scheme 67*). In both cases, the hydroxyl group was *anti* disposed with respect to the newly-formed methyl group, in keeping with the reported mechanism.[78]

With the 5,7-fused bicyclic ring system in hand, the idea arose of converting the alcohols **1.259** and **1.260** directly into α-bulnesene diastereomers. The plan was to use a combination of a Lewis acid – to encourage the departure of the 3°-hydroxyl group – and a hydride reducing agent – to quench the allylic cation formed following [1,2]-H shift (*Scheme 68*). Since alcohols **1.259** and **1.260** both contain the methyl group in the correct β-orientation, the bridgehead configuration in **1.261** would determine whether this approach could lead to α-bulnesene itself (from **1.260**) or the 5-epimer (from **1.259**).

Table 17 Ketone-alkene coupling of ketone **1.208**.

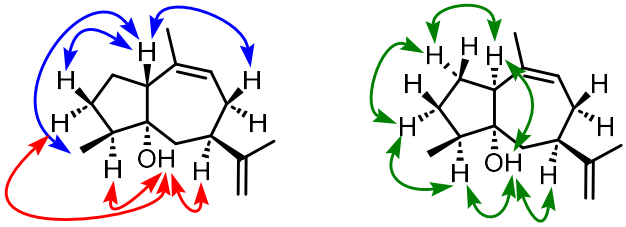


1.208
dr = 2:1

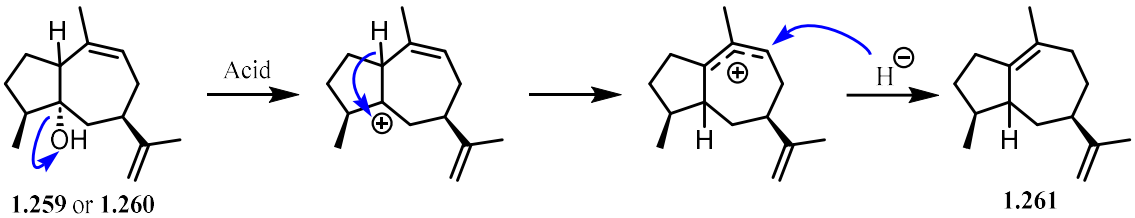
1.259

1.260

Entry	Conditions (i)	Result
1	20 eq. Zn, 6 eq. TMSCl, 2 eq. pyridine, THF, reflux, 24 h	n.r.
2	2.5 eq. $PhSiH_3$, 1 eq. $Fe(acac)_3$, EtOH, 60 °C, 24 h	complex
3	2.5 eq. SmI_2, 2 eq. *t*-BuOH, 10 eq. HMPA, THF, RT, 0.5 h	**1.259** (35%), **1.260** (27%)



Scheme 67 Key n.O.e correlations for characterising cyclised products **1.259** and **1.260**.

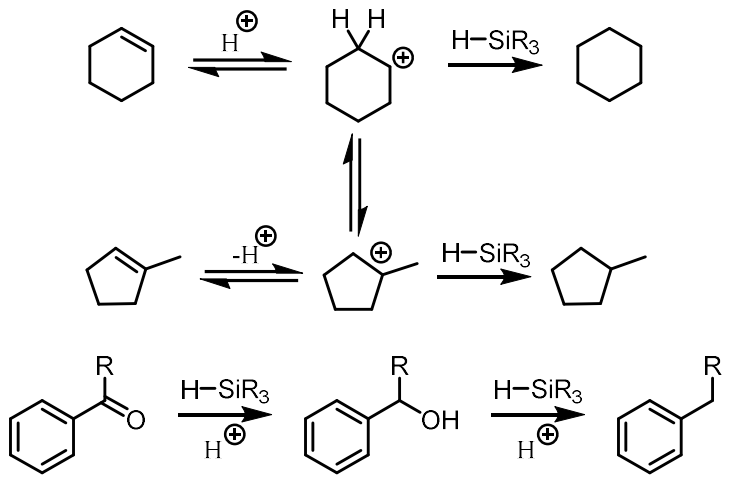


1.259 or **1.260**

1.261

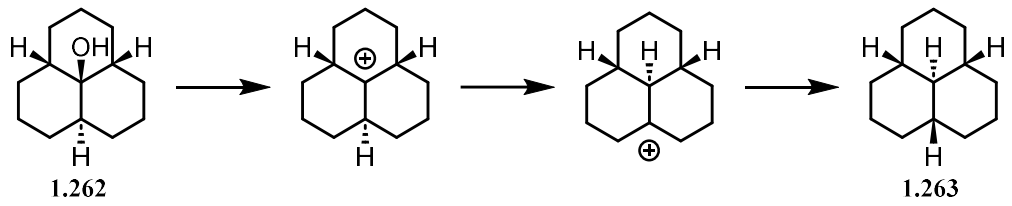
Scheme 68 Proposed strategy for converting alcohol **1.259** or **1.260** into bulnesene type **1.261**.

By way of brief background, the Zdanovich group first reported the ionic hydrogenation of alkene and carbonyl double bonds under protic acid conditions in 1967, using silanes, cycloheptatriene, or saturated branched hydrocarbons as hydride-ion donors (*Scheme 69*). Rearranged reduction products could be formed by this method and, when the ketone is adjacent to a phenyl group, the hydrogenation was followed by further reduction.[88]



Scheme 69 Zdanovich's ionic hydrogenation using silanes as hydride donors.

Variants of this silane hydride reduction were then studied systematically by Carey and Tremper, as reported, for example, in 1968. These authors proposed that this reduction is suitable for a wide range of carbocations with stability over a range of pK_R^+ from –17.4 to +24. From a comparison of the reagents' activities, triethylsilane was identified as the strongest.[89] In further development of this method, reported in 1971, 3°-alcohols were tested under trifluoroacetic acid/triethylsilane conditions, showing that carbocation rearrangements occurred faster than triethylsilane hydride transfer (*Scheme 70*).[90]

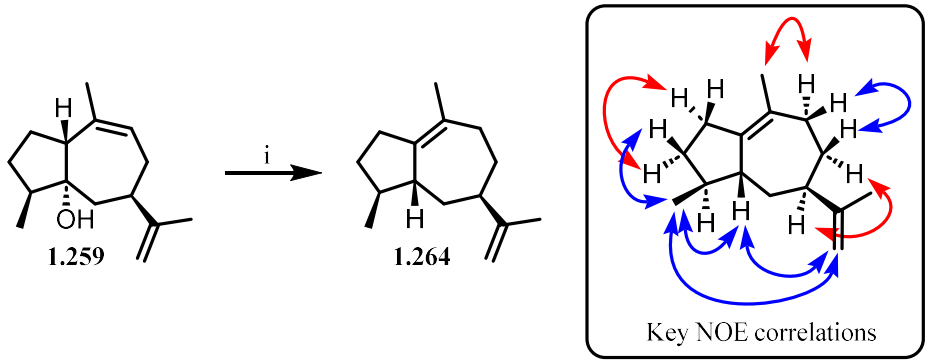


Scheme 70 Reduction of a 3°-alcohol with carbocation rearrangement by suprafacial [1,2]-H shift.

This method was further developed by replacing the strong protic acid with a milder Lewis acid and in 1976 Doyle reported that the BF_3/triethylsilane system could reduce ketones and aldehydes selectively into alcohols. The process involves hydrosilylation of the BF_3-activated carbonyl and desilylation with BF_3 to form a borate ester intermediate.[91] In the same year, these conditions were also shown to remove alcohol groups selectively[92] and also proved to be useful for the reduction of hemiacetals to ethers.[93]

This idea was tested with *trans*-fused isomer **1.259** (*Table 18*). A test reaction without reducing reagent gave a complex mixture of elimination products (*Entry 1*); however, when the reaction temperature was lowered to –78 °C the reaction shut down completely. Triethylsilane was selected as the reducing agent based on its reported reactivity in hydride donation (see above) and its wide use in natural product synthesis.[91] Mixing this with the Lewis acid and substrate at low temperature and slowly warming the mixture gave a relatively clean product, from which the target compound **1.264** was isolated as the major product (*Entry 2*). The configuration was assigned on the basis of a full NMR spectroscopic analysis including the key n.O.e correlations shown (*Appendix 08*). Further optimisation of reagent loading, solvent and temperature gave this product in 54% yield (*Appendix 09*). Use of diphenylchlorosilane and a catalytic amount of $InCl_3$ to reduce the alcohol, as reported by Baba,[94] led to many unrecognisable products (*Entry 4*).

Table 18 Reductive rearrangement of alcohol **1.259** into product **1.264**.

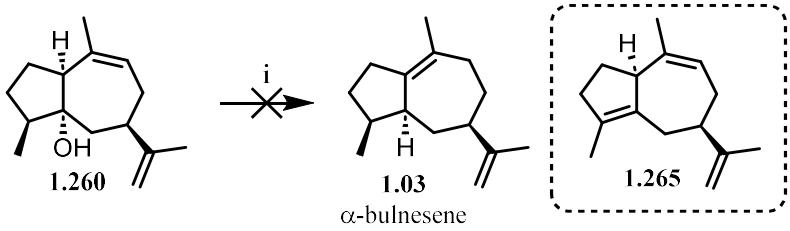


Entry	Conditions (i)	Result
1	1 eq. BF_3•OEt_2, DCM, –78 °C, 2.5 h then 0 °C, 1 h	complex
2	1 eq. BF_3•OEt_2, 1 eq. Et_3SiH, DCM, –78 °C to 0 °C, 1 h	**17%**
3	0.7 eq. BF_3•OEt_2, 6 eq. Et_3SiH, DCM, –78 °C to –10 °C, 1 h	**54%**
4	5 mol% $InCl_3$, 2 eq. Ph_2SiHCl, DCM, RT, 1 h	complex

As substrate **1.259** gave product **1.264** by suprafacial hydrogen transfer, diastereomer **1.260** was predicted to give the natural product α-bulnesene **1.03**; however, **1.260** did not give the target product after testing various conditions (*Appendix 10*; *Table 19*). The conditions used successfully for substrate

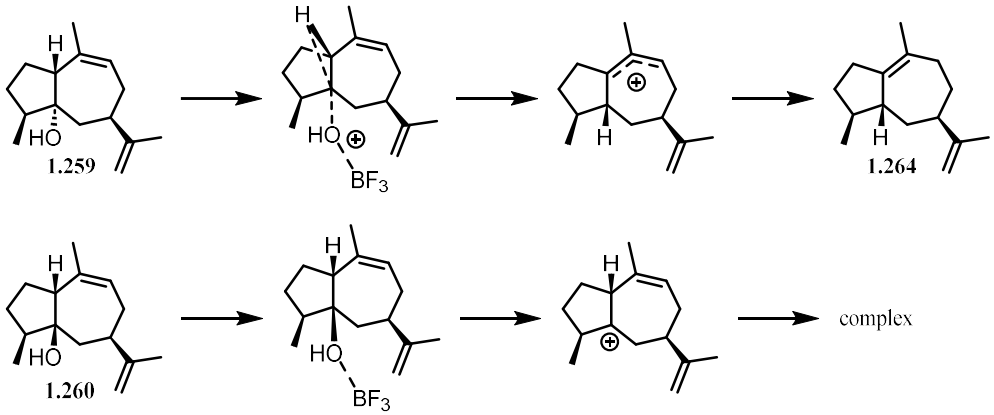
1.259 (*Entry 1*) gave only a complex mixture with substrate **1.260**. Clean elimination product **1.265** was obtained using acetonitrile as the solvent. Other acids (TfOH, $InCl_3$, $B(C_6F_5)_3$) and solvents (methanol, acetonitrile, DMPU, toluene) were also tested but no clear results were obtained.

Table 19 Attempted reductive rearrangement of alcohol **1.260** into product **1.03**.



Entry	Conditions (i)	Result
1	1 eq. BF_3•OEt_2, 2 eq. Et_3SiH, DCM, –78 °C to 0 °C, 1 h	complex
2	1 eq. BF_3•OEt_2, 2 eq. Et_3SiH, CH_3CN, –40 °C to RT, 1 h	**1.265** (23%)
3	1 eq. TfOH, 4 eq. Et_3SiH, CH_3CN, –35 °C, 1 h	**1.265**

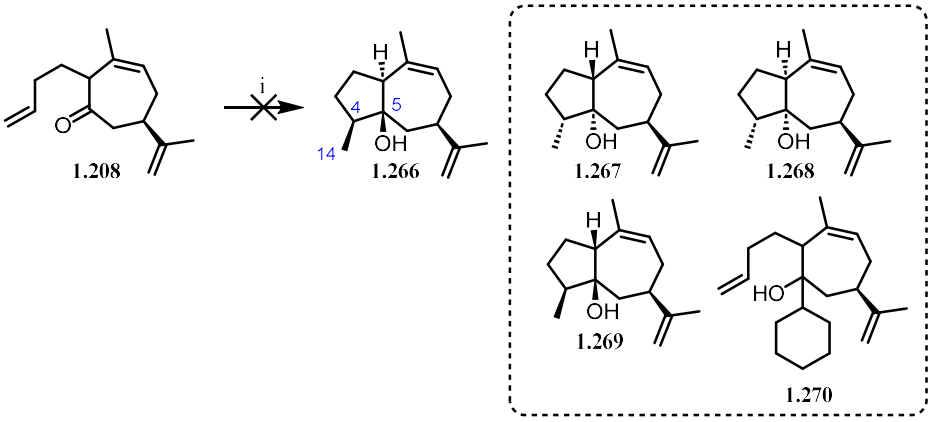
The different results between diastereoisomers **1.259** and **1.260** reflected a mechanism controlling the formation of product **1.264** (*Scheme 71*). For *trans*-fused isomer **1.259**, the departure of the BF_3-activated hydroxyl group probably benefits from participation of the antiperiplanar C-H bond leading directly to a relatively long-lived allylic cation; while for *cis*-fused isomer **1.260**, the carbocation must form fully which leads to a variety of uncontrolled reactions that compete to the exclusion of a clean [1,2]-H shift.



Scheme 71 Different mechanisms for diastereomers **1.259** and **1.260**.

Considering this, diastereomer **1.266** (*Table 20*), with a *cis* relationship between C(4)Me and C(5)OH, was targeted to give α-bulnesene in this reductive rearrangement reaction. The titanium-mediated coupling, as discussed earlier, should result in the desired *cis* relative configuration of methyl and hydroxyl groups;[85] accordingly, some reported conditions were tested for substrate **1.208**. With the combination of Mg(Hg)/$TiCl_4$, multiple types of cyclised products were formed along with simple ketone reduction products (*Entry 1*). Using a larger excess of Mg(Hg) decreased the proportion of unwanted side products and gave three types of cyclisation products, *trans*-fused isomer **1.267**, and *cis*-fused isomers **1.268** and **1.269**, in low yields; however the target diastereomer **1.266** could not be detected in the reaction (*Entry 2*). Cha and Quan's method[86] using different Ti(IV)/Grignard combinations was tested but only Ti(O*i*-Pr)$_3$Cl led to cyclisation; others such as Cp_2TiCl_2 had no noticeable effect and instead the Grignard addition product **1.270** was detected from the crude mixture (*Entries 3–6*). The Ti(O*i*Pr)$_3$Cl reagent gave the same types of products as *Entry 2* but with a stronger preference for *trans*-fused isomer **1.267** (*Entry 6*).

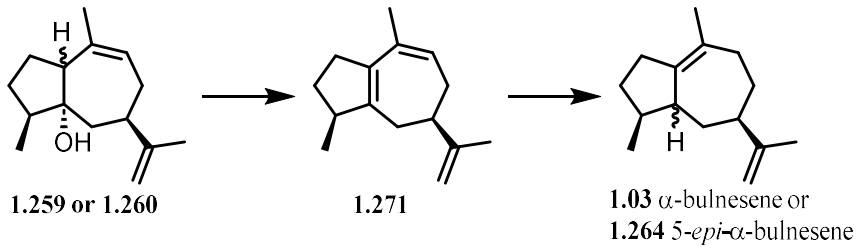
Table 20 Titanium-mediated alkene-ketone coupling of ketone **1.208**.



Entry	Conditions (i)	**266, 267, 268, 269**
1	3 eq. Mg(Hg), 8 mol% $HgCl_2$, 1.5 eq. $TiCl_4$, THF, 0 °C, 1.5 h	complex
2	6.7 eq. Mg(Hg), 8 mol% $HgCl_2$, 1.5 eq. $TiCl_4$, THF, 0 °C, 1.5 h	0, 5.2%, 8.3%, 2.2%
3	1 eq. Ti(O*i*-Pr)$_4$, 2.5 eq. CyMgCl, THF, 0 °C, 1.5 h	complex
4	1 eq. Cp_2TiCl_2, 2.5 eq. CyMgCl, THF, 0 °C, 1.5 h	42% **1.270**
5	1 eq. Ti(Oph)$_2$Cl$_2$, 2.5 eq. CyMgCl, THF, 0 °C, 1.5 h	n.r.
6	1 eq. Ti(O*i*-Pr)$_3$Cl, 5 eq. CyMgCl, THF, 0 °C, 1.5 h	0%, 32%, 6.4%, 9.2%

These three isomers were tested in the reductive rearrangement reaction described previously, but none led to clean products. The *cis*-fused diastereomers **1.268** and **1.269** led to multiple products uncontrollably, while the diastereomer **1.267** also gave a complex result even with the *trans*-disposition of bridgehead substituents. It is possible that the different orientation of the methyl group in diastereomer **1.267** altered the conformation of the molecule unhelpfully, raising the energy barrier for the [1,2]-hydrogen shift and making other reactions competitive.

Some final efforts were undertaken to elaborate alcohols **1.259** or **1.271** to natural α-bulnesene. For example, dehydration of either would give conjugated diene **1.271** which could, in principle, be reduced to α-bulnesene or its 5-epimer via Birch reduction (*Scheme 72*).[95]



1.259 or 1.260 **1.271** **1.03** α-bulnesene or **1.264** 5-*epi*-α-bulnesene

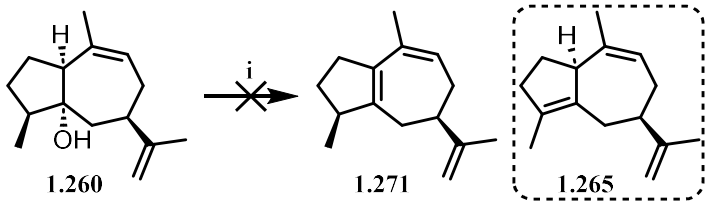
Scheme 72 Another plan for converting alcohol **1.259** or **1.260** into α-bulnesene.

The *cis*-fused isomer **1.260** was considered to be more appropriate as there are reagents, such as the Burgess reagent,[96] which are *syn* selective and might lead to controlled formation of the conjugated diene; however, Burgess reagent gave no reaction after mixing with substrate at 0 °C (*Table 21, Entry 1*). The elimination could be effected with this reagent at higher temperature but only to give compound **1.265**, also a *syn* elimination product with, presumably, a more accessible transition state (*Entry 2*). An Appel reaction was also attempted in order to activate the alcohol group but the sterically-hindered alcohol was unreactive to these conditions (*Entry 3*). In contrast to the analogous reaction of diastereomer **1.259**, dehydration with $SOCl_2$ in pyridine as solvent gave a relatively clean crude product from which 1,4-diene **1.265** was isolated in 45% yield (*Entry 4*).

The *trans*-fused isomer **1.259** was also tested (*Appendix 11*). Burgess reagent and $SOCl_2$ both gave good selectivity towards the 1,4-diene product **1.272** (*Table 22, Entries 1,2*). Application of Martin's

sulfurane,[97] which has been reported to have a strong *anti*-elimination selectivity, gave no reaction (*Entry 3*). Esterification methods (TFAA, acetic anhydride, mesyl chloride) were tested in order to activate the alcohol but most did not lead to any reaction (e.g. *Entry 4*).

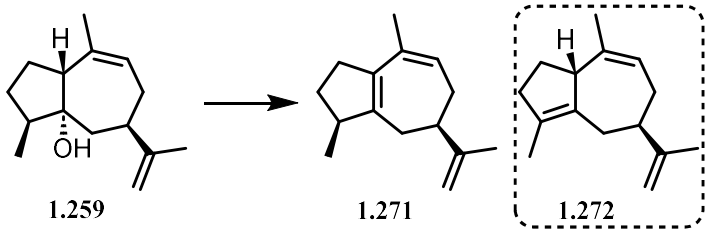
Table 21 Attempted dehydration of alcohol **1.260** into diene **1.271**.



1.260 **1.271** **1.265**

Entry	Method (i)	Result
1	2 eq. Burgess reagent, THF, 0 °C, 2 h	n.r.
2	2 eq. Burgess reagent, THF, RT, 2 h	53% **1.265**
3	1.1 eq. PPh_3, 1.1 eq. CBr_4, DCM, –46 °C to RT, 3 h	n.r.
4	2.5 eq. $SOCl_2$, pyridine, 0 °C, 0.5 h	45% **1.265**

Table 22 Attempted dehydration of alcohol **1.259** into diene **1.271**.

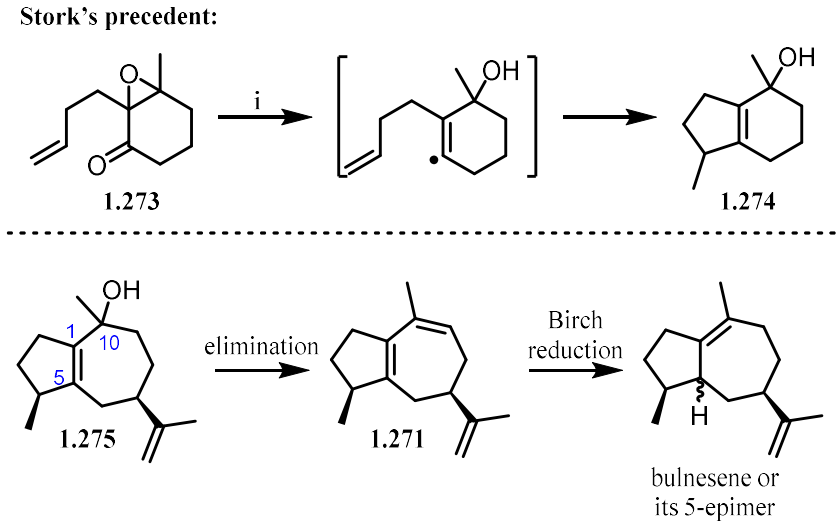


1.259 **1.271** **1.272**

Entry	Method	Result
1	2 eq. Burgess reagent, THF, RT, 2 h	87% **1.272**
2	3 eq. $SOCl_2$, 5 eq. 2,4,6-collidine, 5eq. pyridine, DCM, –78 °C, 2 h	**1.272**
3	1 eq. Martin's sulfurane, DCM, RT, 2 h	n.r.
4	2 eq. MsCl, 3 eq. KHMDS, THF, –78 °C to 0 °C, 1 h	n.r.

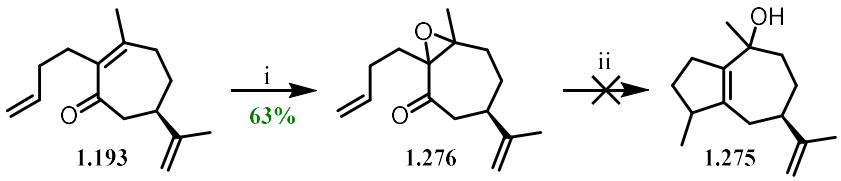
Stork reported an alkene-ketone coupling reaction as a side reaction in the well-known Wharton reaction (*Scheme 73*). Thus, in the reaction of epoxyketone **1.273**, the unexpected cyclisation product **1.274** was isolated as the major product, proposed to arise via a vinyl radical intermediate and a rapid 5-*exo-trig*

cyclisation.[98] Applied to an analogous cycloheptenone derivative, this method would generate the product **1.275** containing the desired C1-C5 alkene from which dehydration and Birch reduction could lead to α-bulnesene or its 5-epimer.



Scheme 73 Attempted alkene-ketone coupling under Wharton rearrangement conditions. **Reagents and conditions: i)** N_2H_4•H_2O, MeOH, 0 °C

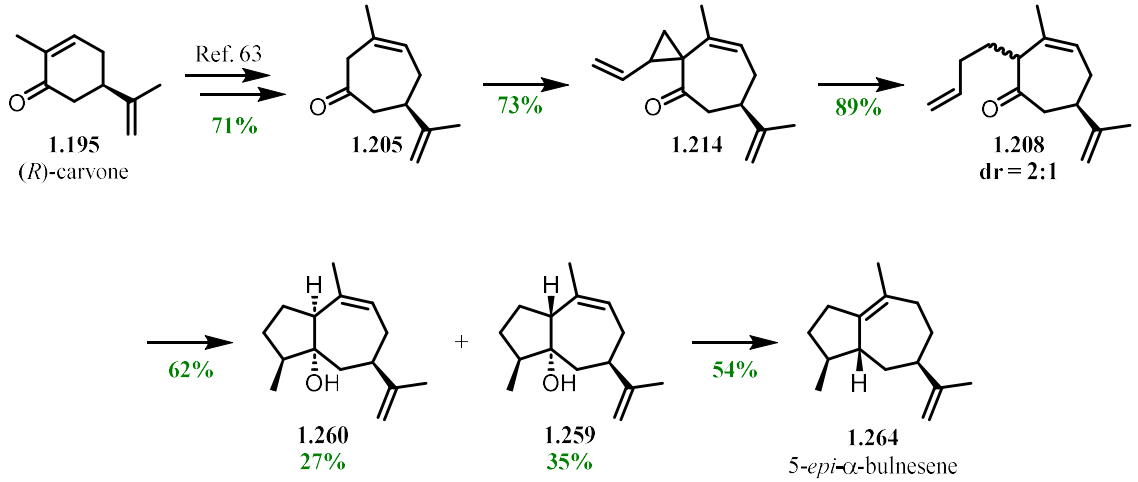
This method was evaluated for accessing diene **1.271** from enone **1.193** (*Scheme 74*). To avoid epoxidation of the isolated alkenes, nucleophilic epoxidation with NaOH/H_2O_2 was conducted, but the fully substituted C=C bond made this reaction proceed very slowly. The product **1.276** was subjected to Stork's conditions for the Wharton variant but substrate **1.276** was found to be minimally soluble in the solvent (methanol) which was presumed to hinder its reaction with hydrazine. Acetic acid was added to accelerate the reaction but this led to substrate decomposition and, with time on the project running out, no further approaches were explored.



Scheme 74 Alkene-ketone coupling for enone **1.193**. **Reagents and conditions: i)** H_2O_2, NaOH, MeOH, 0 °C, 18 h; **ii)** N_2H_4•H_2O, MeOH, 0 °C

3. Conclusions and future work

The original target of this project was the development of a new synthetic strategy towards the enantiomers of α-bulnesene. The planned tandem 1,5-H atom transfer /5-*exo*-*trig* radical cyclisation proved unsuccessful, leading to the exploration of ketyl radical cyclisation methods. A modified reductive cyclisation method afforded the 5,7-fused bicyclic ring system stereoselectively and a newly-developed reductive rearrangement step completed the synthesis of 5-*epi*-α-bulnesene. This route is short (seven steps) and efficient with 15% overall yield (*Scheme 75*). Future study will focus on the exploration of cyclisation methods towards the missing diastereomer **1.266** which is expected to lead to natural α-bulnesene.



Scheme 75 Summary of the completed synthesis of 5-*epi*-α-bulnesene.

References

[1] M. D. Awouafack, P. Tane, V. Kuete and J. N. Eloff in *2 - Sesquiterpenes from the Medicinal Plants of Africa*, (Ed. V. Kuete), Elsevier, Oxford, **2013**, pp. 33–103.

[2] K. i. Takeda, H. Minato and S. Nosaka, *Tetrahedron* **1961**, *13*, 308–318.

[3] a) S. Afoulous, H. Ferhout, E. G. Raoelison, A. Valentin, B. Moukarzel, F. Couderc and J. Bouajila, *Food Chem. Toxicol.* **2013**, *56*, 352–362; b) J. Sharifi-Rad, S. Hoseini-Alfatemi, M. Sharifi-Rad, M. Sharifi-Rad, M. Iriti, M. Sharifi-Rad, R. Sharifi-Rad and S. Raeisi, *Molecules* **2015**, *20*, 7034–7047; c) H.-Y. Zhang, Y. Gao and P.-X. Lai, *Molecules* **2017**, *22*, 381; d) A. Zardi-Bergaoui, A. Jelassi, M. Daami-Remadi, F. Harzallah-Skhiri, G. Flamini, R. Ascrizzi and H. Ben Jannet, *J. Essent. Oil Res.* **2020**, *32*, 111–120.

[4] H. Ansari and A. Curtis, *J. Soc. Cosmet. Chem* **1974**, *25*, 203–231.

[5] a) J. S. Rad, M. H. Alfatemi, M. S. Rad and D. J. Sen, *Am. J. Adv. Drug Deliv.* **2013**, *1*, 001–010; b) J. S. Rad, S. M. H. Alfatemi and M. S. Rad, *Int. J. Biosci.* **2014**, *4*, 217–222; c) J. Sharifi-Rad, S. Hoseini-Alfatemi, M. Sharifi-Rad and A. Miri, *Minerva Biotechnol.* **2014**, *26*, 287–293.

[6] M. Ishihara, T. Tsuneya and K. Uneyama, *Phytochemistry* **1991**, *30*, 3343–3347.

[7] P. S. Naziz, R. Das and S. Sen, *Front. Plant Sci.* **2019**, *10*, 840.

[8] M. Ishihara, T. Tsuneya, M. Shiga and K. Uneyama, *Phytochemistry* **1991**, *30*, 563–566.

[9] L. Yang, J.-L. Yang, W.-H. Dong, Y.-L. Wang, J. Zeng, J.-Z. Yuan, H. Wang, W.-L. Mei and H.-F. Dai, *Molecules* **2021**, *26*, 436.

[10] E. Piers and K. F. Cheng, *J. Chem. Soc. D* **1969**, 562–563.

[11] E. Piers and K. F. Cheng, *Can. J. Chem.* **1968**, *46*, 377–383.

[12] E. Piers and K. F. Cheng, *Can. J. Chem.* **1970**, *48*, 2234–2245.

[13] C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.* **1960**, *0*, 2680–2686.

[14] C. H. Heathcock and R. Ratcliffe, *J. Am. Chem. Soc.* **1971**, *93*, 1746–1757.

[15] G. Mehta and B. P. Singh, *Tetrahedron Lett.* **1975**, *16*, 4495–4498.

[16] W. Oppolzer and R. D. Wylie, *Helv. Chim. Acta* **1980**, *63*, 1198–1203.

[17] P. G. Sammes and L. J. Street, *J. Chem. Soc., Chem. Commun.* **1983**, 666–668.

[18] S. M. Bromidge, P. G. Sammes and L. J. Street, *J. Chem. Soc., Perkin Trans. 1* **1985**, 1725–1730.

[19] E.-I. Negishi, S. Ma, T. Sugihara and Y. Noda, *J. Org. Chem.* **1997**, *62*, 1922–1923.

[20] a) R. C. Gadwood, R. M. Lett and J. E. Wissinger, *J. Am. Chem. Soc.* **1986**, *108*, 6343–6350; b) S. Y. Lee, Y. S. Kulkarni, B. W. Burbaum, M. I. Johnston and B. B. Snider, *J. Org. Chem.* **1988**, *53*, 1848–1855.

[21] J. S. R. Kumar, M. F. O'Sullivan, S. E. Reisman, C. A. Hulford and T. V. Ovaska, *Tetrahedron Lett.* **2002**, *43*, 1939–1941.

[22] V. N. Zhabinskii, A. J. Minnaard, J. B. P. A. Wijnberg and A. De Groot, *J. Org. Chem.* **1996**, *61*, 4022–4027.

[23] G. Blay, V. Bargues, L. Cardona, A. M. Collado, B. García, Muñoz and J. R. Pedro, *J. Org. Chem.* **2000**, *65*, 2138–2144.

[24] G. Blay, B. Garcia, E. Molina and J. R. Pedro, *Tetrahedron* **2005**, *61*, 11156–11162.

[25] G. Blay, B. Garcia, E. Molina and J. R. Pedro, *Tetrahedron* **2007**, *63*, 9621–9626.

[26] A. Srikrishna and N. C. Babu, *Tetrahedron Lett.* **2001**, *42*, 4913–4914.

[27] A. Srikrishna and V. H. Pardeshi, *Tetrahedron* **2010**, *66*, 8160–8168.

[28] Y. Kumeta and M. Ito, *Plant Physiol.***2010**, *154*, 1998–2007.

[29] J. G. Moloney in *Evolved P450 mutants as general oxidation catalysts for target synthesis via C–H activation*, DPhil thesis, University of Oxford, **2022**.

[30] X. Zhang in *Evolved P450 mutants as general oxidation catalysts for target synthesis via early-/late-stage hydroxylation*, DPhil thesis, University of Oxford, **2022**.

[31] D. P. Curran, D. Kim, H. T. Liu and W. Shen, *J. Am. Chem. Soc.* **1988**, *110*, 5900–5902.

[32] D. C. Lathbury, P. J. Parsons and I. Pinto, *J. Chem. Soc., Chem. Commun.* **1988**, 81.

[33] A. D. Borthwick, S. Caddick and P. J. Parsons, *Tetrahedron Lett.* **1990**, *31*, 6911–6914.

[34] A. D. Borthwick, S. Caddick and P. J. Parsons, *Tetrahedron* **1992**, *48*, 10655–10666.

[35] J. Robertson, M. A. Peplow and J. Pillai, *Tetrahedron Lett.* **1996**, *37*, 5825–5828.

[36] S. D. Burke and K. Woon Jung, *Tetrahedron Lett.* **1994**, *35*, 5837–5840.

[37] F. Beaufils, F. Dénès, B. Becattini, P. Renaud and K. Schenk, *Adv. Synth. Catal.* **2005**, *347*, 1587–1594.

[38] M. P. Cooke and J. Y. Jaw, *J. Org. Chem.* **1993**, *58*, 267–269.

[39] R. J. Gritter and T. J. Wallace, *J. Org. Chem.* **1959**, *24*, 1051–1056.

[40] X. Jiang, J. Liu and S. Ma, *Org. Process Res. Dev.* **2019**, *23*, 825–835.

[41] E. J. Corey, N. W. Gilman and B. E. Ganem, *J. Am. Chem. Soc.* **1968**, *90*, 5616–5617.

[42] A. Chan and K. A. Scheidt, *Org. Lett.***2005**, *7*, 905–908.

[43] a) M. Sato, T. Tanaka, J. Tsunetsugu and S. Ebine, *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2395–2396; b) R. B. Miller and C. G. Gutierrez, *J. Org. Chem.* **1978**, *43*, 1569–1573; c) F. J. Manganiello, S. M. Oon, M. D. Radcliffe and W. M. Jones, *Organometallics* **1985**, *4*, 1069–1072; d) J. E. McMurry and R. Swenson, *Tetrahedron Lett.* **1987**, *28*, 3209–3212; e) T. J. Brocksom, E. T. C. Pesquero and F. T. Lopes, *Synth. Commun.* **1990**, *20*, 1181–1191.

[44] A. Narczyk and S. Stecko, *Org. Biomol. Chem.* **2020**, *18*, 1204–1213.

[45] N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437–3440.

[46] H. Gilman, R. G. Jones and L. A. Woods, *J. Org. Chem.* **1952**, *17*, 1630–1634.

[47] a) H. J. Liu and S. P. Majumdar, *Synth. Commun.* **1975**, *5*, 125–130; b) W. L. Mock and M. E. Hartman, *J. Org. Chem.* **1977**, *42*, 459–465; c) W. L. Mock and M. E. Hartman, *J. Org. Chem.* **1977**, *42*, 466–472; d) S. W. Baldwin and N. G. Landmesser, *Synth. Commun.* **1978**, *8*, 413–419.

[48] S. Álvarez, Y. Pazos-Randulfe, H. Khanwalkar, P. Germain, R. Álvarez, H. Gronemeyer and Á. R. de Lera, *Bioorg. Med. Chem.* **2008**, *16*, 9719–9728.

[49] F. Gao and A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10961–10963.

[50] A. Krasovskiy, F. Kopp and P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 497–500.

[51] a) H. Hagiwara and H. Uda, *J. Chem. Soc., Chem. Commun.* **1988**, 815; b) H. Hagiwara and H. Uda, *J. Chem. Soc., Perkin Trans. 1* **1991**, 1803.

[52] A. J. Minnaard, J. B.P.A. Wijnberg and A. d. Groot, *Tetrahedron* **1994**, *50*, 4755–4764.

[53] G. T. Crisp, W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.* **1984**, *106*, 7500–7506.

[54] B. Scheiper, M. Bonnekessel, H. Krause and A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943–3949.

[55] J. E. Mc Murry and W. J. Scott, *Tetrahedron Lett.* **1983**, *24*, 979–982.

[56] M. E. Krafft and R. A. Holton, *J. Org. Chem.* **1984**, *49*, 3669–3670.

[57] D. E. Ames and A. Opalko, *Tetrahedron* **1984**, *40*, 1919–1925.

[58] K. Nozaki, K. Oshima and K. Uchimoto, *J. Am. Chem. Soc.* **1987**, *109*, 2547–2549.

[59] A. Srikrishna, D. Vijaykumar and G. V. R. Sharma, *Tetrahedron Lett.* **1997**, *38*, 2003–2004.

[60] E. Wenkert, T. S. Arrhenius, B. Bookser, M. Guo and P. Mancini, *J. Org. Chem.* **1990**, *55*, 1185–1193.

[61] M. Leiva de Faria, R. de A. Magalhães, F. C. Silva, L. G. de O. Matias, M. A. Ceschi, U. Brocksom and T. J. Brocksom, *Tetrahedron: Asymmetry* **2000**, *11*, 4093–4103.

[62] T. J. Brocksom, U. Brocksom and F. P. Barbosa, *J. Braz. Chem. Soc.* **2006**, *17*, 792–796.

[63] C. Alves Lde, A. L. Desidera, K. T. de Oliveira, S. Newton, S. V. Ley and T. J. Brocksom, *Org. Biomol. Chem.* **2015**, *13*, 7633–7642.

[64] J. Schreiber, H. Maag, N. Hashimoto and A. Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 330–331.

[65] S. Albrecht, E. Salomon, A. Defoin and C. Tarnus, *Bioorg. Med. Chem.* **2012**, *20*, 4942–4953.

[66] G. Hughes, M. Lautens and J. Wu. *Synlett* **2000**, *2000*, 0835–0837.

[67] R. Chahboun, J. M. Botubol-Ares, M. J. Duran-Pena, F. Jimenez, R. Alvarez-Manzaneda and E. Alvarez-Manzaneda, *J. Org. Chem.* **2021**, *86*, 8742–8754.

[68] D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

[69] S. C. Dolan and J. Macmillan, *J. Chem. Soc., Chem. Commun.* **1985**, 1588.

[70] E. J. Corey and S. G. Pyne, *Tetrahedron Lett.* **1983**, *24*, 2821–2824.

[71] A. L. J. Beckwith, *Tetrahedron* **1981**, *37*, 3073–3100.

[72] D. Belotti, J. Cossy, J. P. Pete and C. Portella, *Tetrahedron Lett.* **1985**, *26*, 4591–4594.

[73] D. Belotti, J. Cossy, J. P. Pete and C. Portella, *J. Org. Chem.* **1986**, *51*, 4196–4200.

[74] J. Cossy, S. Bouzbouz and C. Mouza, *Synlett* **1998**, *1998*, 621–622.

[75] a) G. Stork, S. Malhotra, H. Thompson and M. Uchibayashi, *J. Am. Chem. Soc.* **1965**, *87*, 1148–1149; b) S. K. Pradhan, S. R. Kadam, J. N. Kolhe, T. V. Radhakrishnan, S. V. Sohani and V. B. Thaker, *J. Org. Chem.* **1981**, *46*, 2622–2633.

[76] S. Takashi, F. Tohru and T. Akira, *Chem. Lett.* **1990**, *19*, 2295–2298.

[77] P. Girard, J. L. Namy and H. B. Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.

[78] M. Szostak, N. J. Fazakerley, D. Parmar and D. J. Procter, *Chem. Rev.* **2014**, *114*, 5959–6039.

[79] G. A. Molander, J. B. Etter and P. W. Zinke, *J. Am. Chem. Soc.* **1987**, *109*, 453–463.

[80] G. A. Molander and C. Kenny, *Tetrahedron Lett.* **1987**, *28*, 4367–4370.

[81] G. A. Molander and J. A. McKie, *J. Org. Chem.* **1992**, *57*, 3132–3139.

[82] F. D. A. Marques, J. T. B. Ferreira and E. Piers, *J. Braz. Chem. Soc.* **2000**, *11*, 502–511.

[83] F. Aulenta, M. Berndt, I. Brudgam, H. Hartl, S. Sorgel and H. U. Reissig, *Chemistry* **2007**, *13*, 6047–6062.

[84] D. F. Hewlett and R. J. Whitby, *J. Chem. Soc., Chem. Commun.* **1990**, 1684.

[85] N. M. Kablaoui and S. L. Buchwald, *J. Am. Chem. Soc.* **1995**, *117*, 6785–6786.

[86] L. G. Quan and J. K. Cha, *Tetrahedron Lett.* **2001**, *42*, 8567–8569.

[87] M. Saladrigas, C. Bosch, G. V. Saborit, J. Bonjoch and B. Bradshaw, *Angew. Chem. Int. Ed.* **2018**, *57*, 182–186.

[88] D. N. Kursanov, Z. N. Parnes, G. I. Bassova, N. M. Loim and V. I. Zdanovich, *Tetrahedron* **1967**, *23*, 2235–2242.

[89] F. A. Carey and H. S. Tremper, *J. Am. Chem. Soc.* **1968**, *90*, 2578–2583.

[90] F. A. Carey and H. S. Tremper, *J. Org. Chem.* **1971**, *36*, 758–761.

[91] M. P. Doyle, C. T. West, S. J. Donnelly and C. C. McOsker, *J. Organomet. Chem.***1976**, *117*, 129–140.

[92] M. G. Adlington, M. Orfanopoulos and J. L. Fry, *Tetrahedron Lett.* **1976**, *17*, 2955–2958.

[93] a) G. A. Kraus, K. A. Frazier, B. D. Roth, M. J. Taschner and K. Neuenschwander, *J. Org. Chem.* **1981**, *46*, 2417–2419; b) C. Brueckner, H. Holzinger and H. U. Reissig, *J. Org. Chem.* **1988**, *53*, 2450–2456.

[94] M. Yasuda, Y. Onishi, M. Ueba, T. Miyai and A. Baba, *J. Org. Chem.* **2001**, *66*, 7741–7744.

[95] P. W. Rabideau and Z. Marcinow, *Org. React.* **2004**, *42*, 1–334.

[96] G. M. Atkins and E. M. Burgess, *J. Am. Chem. Soc.* **1968**, *90*, 4744–4745.

[97] B. A. Roden, *Encyclopedia of Reagents for Organic Synthesis* **2001**.

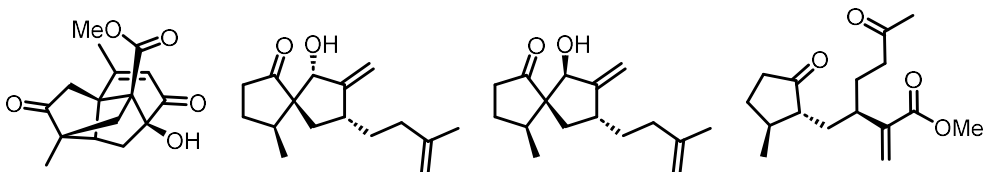
[98] G. Stork and P. G. Williard, *J. Am. Chem. Soc.* **1977**, *99*, 7067–7068.

Project II: Synthetic Studies towards Daphnenoid A

1. Introduction

1.1 Daphnenoid A

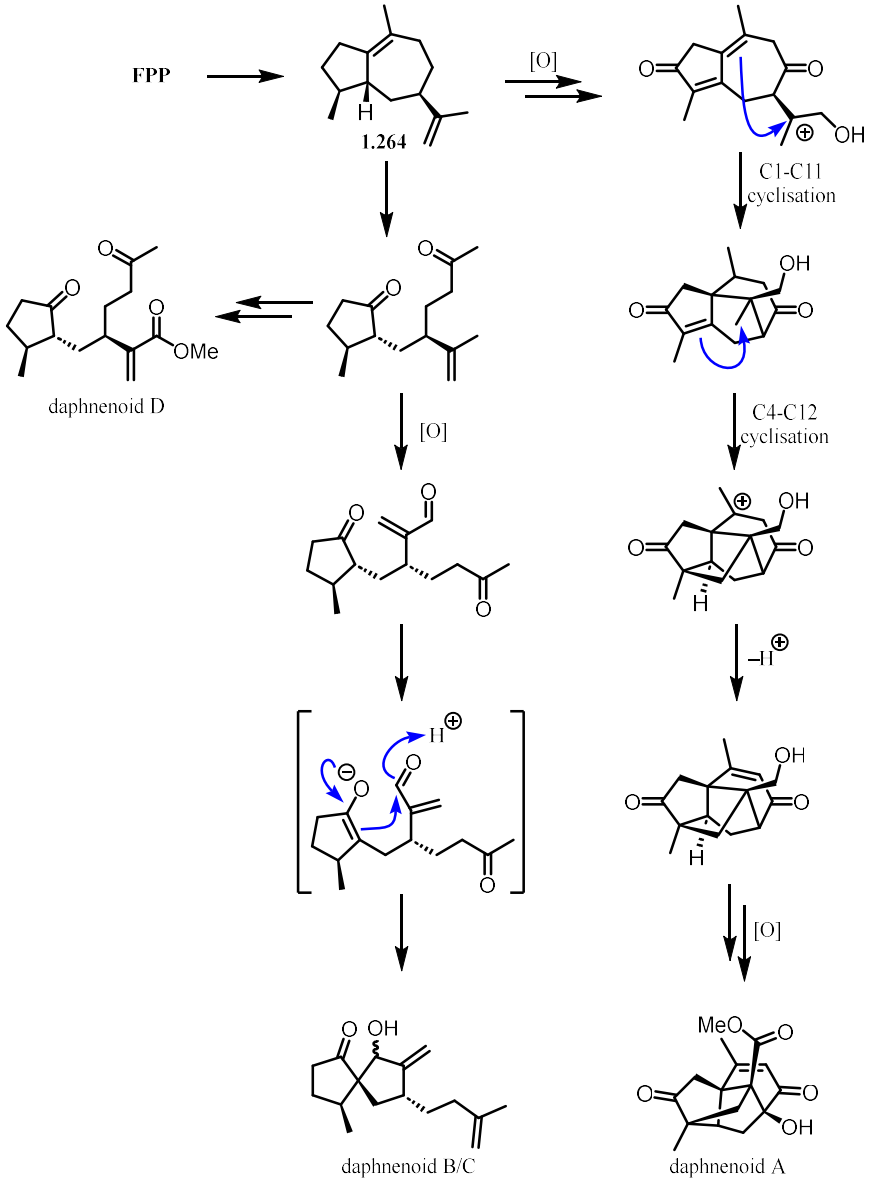
Song and Huang recently (2021) reported the isolation and characterisation of four new sesquiterpenes, named daphnenoids A–D, from the herb *Daphne penicillata* (*Scheme 76*).[1] Among these new compounds, daphnenoid A was the most interesting, being based on a unique caged tetracyclo[5.3.2.$0^{1,6}$.$0^{4,11}$]dodecane scaffold, confirmed by X-ray crystallography. All four daphnenoids exhibited potent anti-inflammatory activity.



2.01 daphnenoid A | **2.02** daphnenoid B | **2.03** daphnenoid C | **2.04** daphnenoid D

Scheme 76 Structures of daphnenoids A–D as depicted in ref. 1.

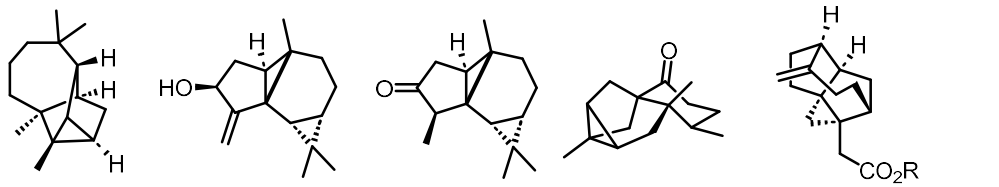
The authors proposed an outline biosynthetic pathway in which 5-*epi*-α-bulnesene (*Scheme 77*) – itself formed by the usual terpenoid pathway from farnesyl pyrophosphate (FPP) – is the common precursor for all these compounds. On the one hand, oxidative cleavage of the endocyclic alkene then allylic oxidation into an ester would result in daphnenoid D. An intramolecular aldol reaction between the cyclopentanone and aldehyde would instead result in spirocyclic daphnenoids B and C. On the other hand, double allylic oxidation of 5-*epi*-α-bulnesene then a multistep sequence initiated by epoxidation of the *iso*propenyl substituent would give the tetracyclic ring system from which further oxidation would generate daphnenoid A. In this process, the nature of the C4-C12 cyclisation onto a bare methyl group was not specified, and there are inconsistencies in the proposed mechanistic course.



Scheme 77 Biosynthetic pathways towards daphnenoids A–D as proposed by Song and Huang and as depicted in ref. 1.

1.2 Other tetracyclic sesquiterpenes/sesquiterpenoids

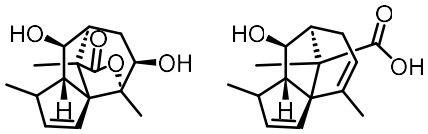
The unprecedented tetracyclic cage structure of daphnenoid A and its proposed biosynthetic link with α-bulnesene or its diastereomers, along with consideration of how the C4-C12 bond could be formed, attracted our attention. Tetracyclic, meaning tetracarbocyclic, sesquiterpenes are rare structures in natural products and most of them include at least one three-membered ring as the following examples illustrate (*Scheme 78*).[2]



2.05 longicyclene **2.06** (–)-myliol **2.07** (–)-dihydromylione **2.08** ishwarone **2.09** R = H (echinopine A) **2.10** R = Me (echinopine B)

Scheme 78 Other tetracarbocyclic sesquiterpenoids.

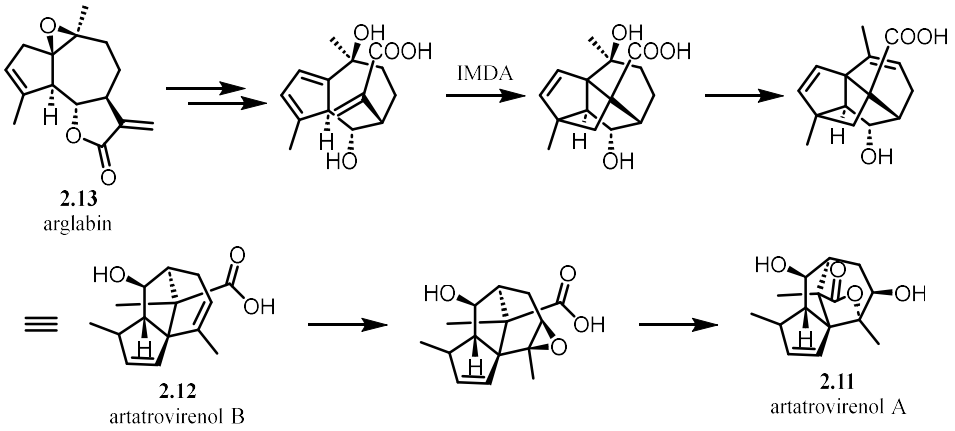
Despite the 'unique' structure of daphnenoid A, further literature searching showed that Chen's group had reported two novel cagelike sesquiterpenoids in 2020, named artatrovirenols A and B, isolated from *Artemisia atrovirens* (*Scheme 79*). These two compounds were described as containing an unprecedented tetracyclo[5.3.1.1.^{4,11}0^{1,5}]dodecane scaffold which, although not obvious from the way the respective authors depict the molecules in their papers, share the same carbocyclic skeleton as daphnenoid A. Artatrovirenol A was shown to be cytotoxic against some human hepatoma cell lines.[3]



2.11 artatrovirenol A **2.12** artatrovirenol B

Scheme 79 Structures of artatrovirenols A and B as depicted in ref. 3.

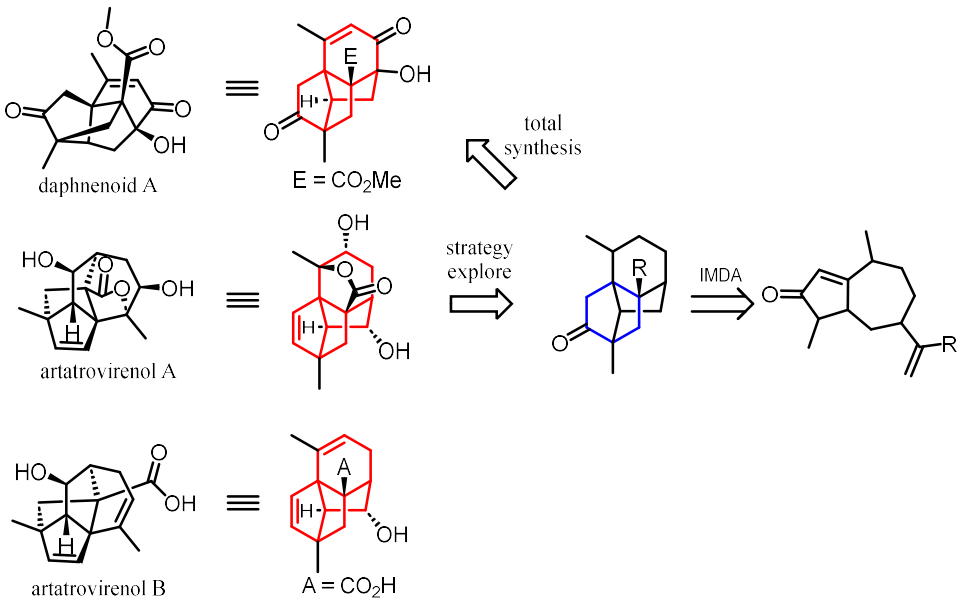
To date, there has been no reported synthetic study towards artatrovirenols A and B but the authors proposed a biosynthetic route (*Scheme 80*) from arglabin, a sesquiterpenoid lactone isolated from the same plant. Epoxide isomerisation and lactone hydrolysis afford a key intermediate enoic acid from which the tetracycle could be constructed by intramolecular Diels–Alder reaction, regioselective dehydration then giving artatrovirenol B. Artatrovirenol A is considered to be obtained from artatrovirenol B by epoxidation and ring opening to form the hydroxylactone.[3]



Scheme 80 Chen's proposed biosynthetic pathways to artatrovirenols A and B.

1.3 Project aims

Chen's proposal of a biosynthetic IMDA reaction attracted our attention as there is no precedent of such a Diels–Alder reaction to construct this caged tetracyclic structure (see *Chapter 1.4*). Redrawing the structures of daphnenoid A and artatrovirenols A and B highlights the common ring system, so the proposed IMDA reaction could provide an effective synthetic strategy towards them. This project set out to verify the possibility of the IMDA reaction and, if the IMDA reaction were to give the desired caged carbon skeleton, a total synthesis of daphnenoid A would be developed (*Scheme 81*).



Scheme 81 Project aims to explore an IMDA approach to the daphnenoid A and artatrovirenol ring systems.

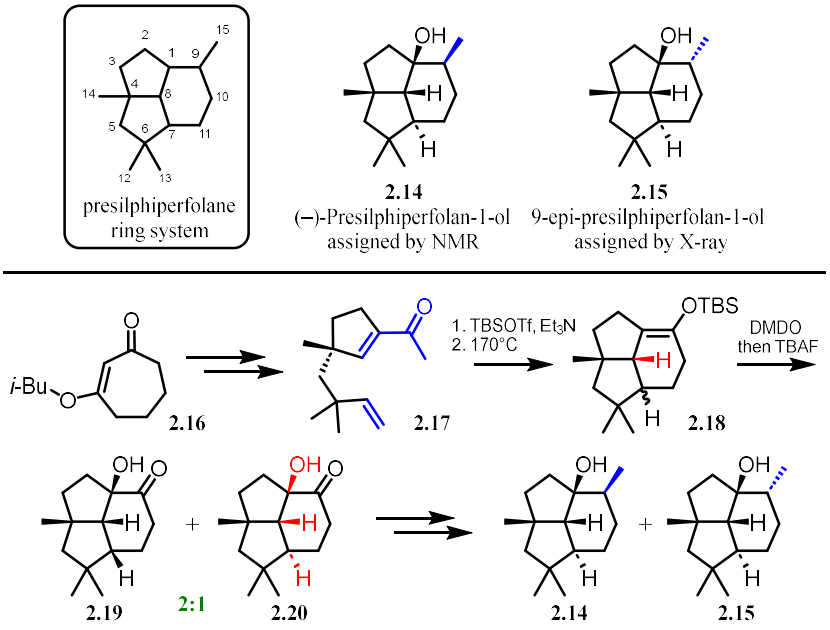
1.4 The IMDA reaction and equivalent double Michael addition

Since its first report by Otto Diels and Kurt Alder in 1928, the Diels–Alder [4+2]-cycloaddition has become recognised as the most general and versatile of the pericyclic reactions for building six-membered carbocyclic (and certain heterocyclic) compounds. The intramolecular version – the IMDA reaction – further extends its applications within complex natural products synthesis.[4] The area has been extensively reviewed;[4-5] therefore, just two examples are given to highlight applications of IMDA reactions in sesquiterpenoid total synthesis.

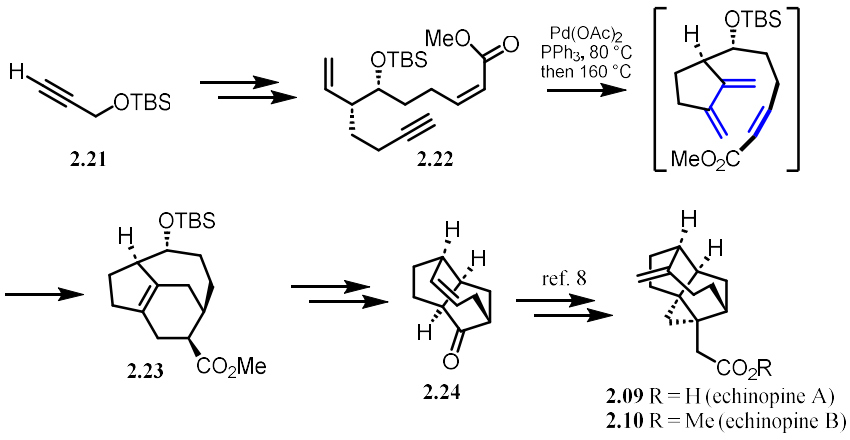
For example, the tricyclic presilphiperfolanols are important biosynthetic precursors to a diverse range of other sesquiterpenoids.[6] König's group assigned the first isolated (–)-presilphiperfolan-1-ol **2.14** by NMR spectroscopic analysis in 1999[6b] and ten years later another natural product with very similar NMR data was characterised by crystallographic analysis as 9-*epi*-presilphiperfolan-1-ol **2.15** by Joseph-Nathan and co-workers (*Scheme 82*). [6c, d] The Stoltz group then conducted the total synthesis of both epimers in 2012.[7] In that synthesis, commercially-available 3-*iso*butoxycycloheptenone was elaborated to IMDA substrate **2.17** in eight steps, then IMDA reaction acted as the key step to construct the tricyclic structure and control the C(8) configuration. Further ketone α-hydroxylation and deprotection gave a pair of diastereomers in a 2:1 ratio. Isomer **2.20** was converted into presilphiperfolan-1-ol and its 9-epimer stereoselectively via two pathways and the authors found that while the 9-epimer has the same NMR data as those reported, the data for the synthesised presilphiperfolan-1-ol **2.14** were very different from those reported for (–)-presilphiperfolan-1-ol which led the group to conclude that König's structural assignment of presilphiperfolan-1-ol is incorrect.

Echinopines A and B were first isolated in 2008 by Shi, Kiyota and co-workers and were characterised by NMR spectroscopic analysis as an unprecedented tetracyclic skeleton.[2c] This challenging skeleton raised the interest of the synthetic community and total synthesis efforts were soon reported by Magauer[8] (2009) and Nicolaou and Chen[9] (2010). In the following year, Chen's group completed the formal asymmetric synthesis of these compounds using a cycloisomerisation/IMDA cascade reaction (*Scheme 83*).[10] Here, from *O*-protected propargyl acohol, substrate **2.22** was reached in ten steps. Treatment of this compound with $Pd(OAc)_2/PPh_3$ gave a cycloisomerised diene intermediate that, upon

heating further, led to the desired 5,6,7-tricyclic system **2.23** stereoselectively in a single step. A further eight steps were required to convert this compound into a reported intermediate[8] towards echinopine.



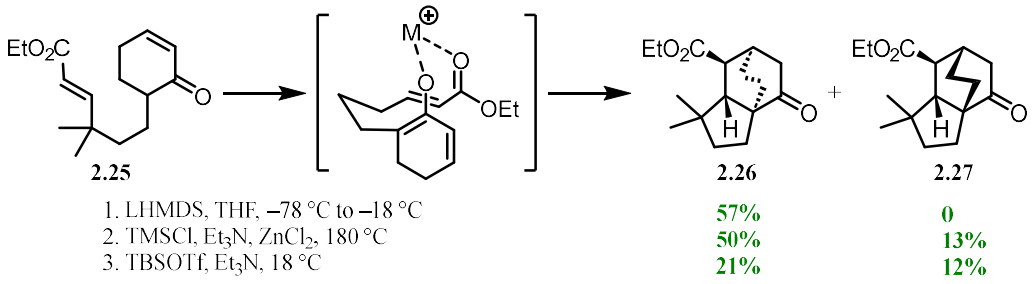
Scheme 82 Stoltz's total synthesis of presilphiperfolan-1-ol and its 9-*epi* isomer.



Scheme 83 Chen's formal asymmetric synthesis of echinopines A and B.

When the dienophile component in a Diels–Alder reaction is adjacent to a carbonyl group and the connected diene component is formed from an enolate of an α,β-unsaturated enone, the reaction can, and usually does, proceed by double Michael addition, achieving the same bond connections as the

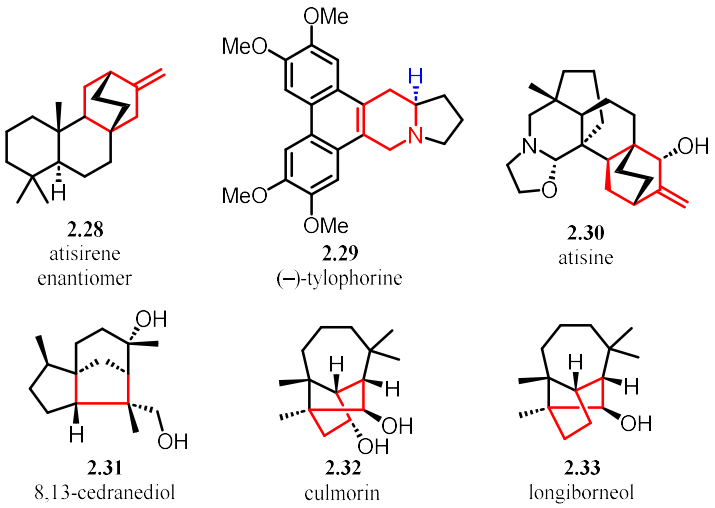
IMDA reaction. Ihara's group made important developments for this general method.[11] In their first report of this process in 1981 (*Scheme 84*), IMDA reaction of an unactivated diene failed to construct a bicyclo[2.2.2]octane framework stereoselectively, while the double Michael addition afforded the product as single isomer.[12] The authors suggested that the high stereoselectivity arose through coordination of the two carbonyl oxygens with the metal cation. Also in this work, various conditions were explored and, besides the effective basic conditions (LHMDS/–78 °C), two acidic conditions (TMSCl/Et_3N/$ZnCl_2$/180 °C or TBSOTf/Et_3N/RT) were also identified as general for effecting double Michael addition.



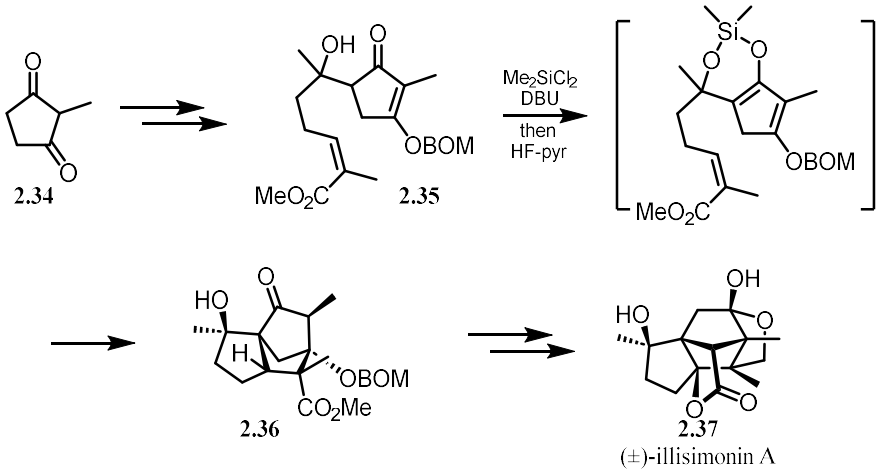
Scheme 84 Ihara's first report of double Michael addition resulting in overall IMDA cycloaddition.

Subsequently, the group deployed this strategy in a series of natural product syntheses; for example, of the enantiomer of the diterpene (–)-atisirene[13] (1984), of (–)-tylophorine[14] (1988), the first enantioselective total synthesis of atisine[15] (1990), and of cedranediol and longiborneol type compounds[16] (1996–2000) (*Scheme 85*).

More recently (2019), Rychnovsky and Burns reported a further development of this IMDA-equivalent reaction using a dimethylsilyl tethering group to constrain the conformation whilst simultaneously activating the enone as a silyloxydiene. This method was used in the synthesis of illisimonin A (*Scheme 86*), the formal cycloaddition affording the tricyclic intermediate efficiently as a single diastereomer.[17] Rychnovsky's 2021 report of a systematic study of this silacycle-templated reaction showed that this method proceeds with impressive stereoselectivity and is able to construct up to seven stereocentres in a single reaction.[18]



Scheme 85 Natural products synthesised by Ihara's group using double Michael addition.



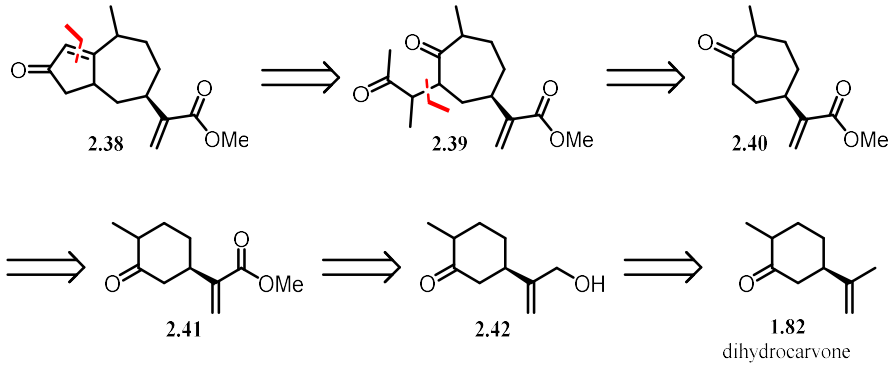
Scheme 86 Total synthesis of illisimonin A by silacycle-templated IMDA reaction.

2. Model study of IMDA reaction

2.1 Retrosynthesis plan

To test whether an IMDA reaction could construct the cage-like daphenoid A structure, compound **2.38** was proposed as a reasonable model substrate (*Scheme 87*), to be obtained by aldol condensation from compound **2.39** which could derive from ketone α-alkylation of compound **2.40**. In this overall plan,

ketoester **2.40** would be generated by ring expansion of precursor **2.41**, the ester group of which would be achieved by oxidation of allylic alcohol **2.42**, from commercially-available dihydrocarvone **1.82**.



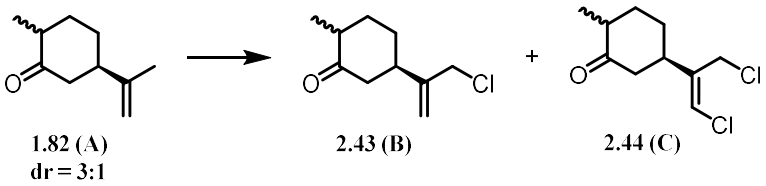
Scheme 87 Retrosynthetic plan for an IMDA model substrate **2.38**.

2.2 Synthesis of IMDA precursor

The regioselective oxidative chlorination of dihydrocarvone **1.82** is published but use of the reported conditions failed to deliver satisfactory yields due to uncontrollable over-oxidation.[19] Another reported method used trimethylsilyl chloride and Oxone® to control the chlorine concentration by the slow oxidation of trimethylsilyl chloride; with these conditions the literature yield was repeatable (*Table 23*).[20] Over-oxidation occurred with excess reagent (*Entry 1*), but 1.5 equivalents proved most successful with 91% conversion to the target product (*Entries 2–4*). On larger scales, further optimisation found 1.3 equivalents gave 80% conversion (*Entries 5–7*).

Basic hydrolysis of allylic chloride **2.43** gave the desired alcohol **2.42** smoothly which was then protected as its *tert*-butyldiphenylsilyl derivative (*Scheme 88*). The diastereomers were able to be isolated after protection.

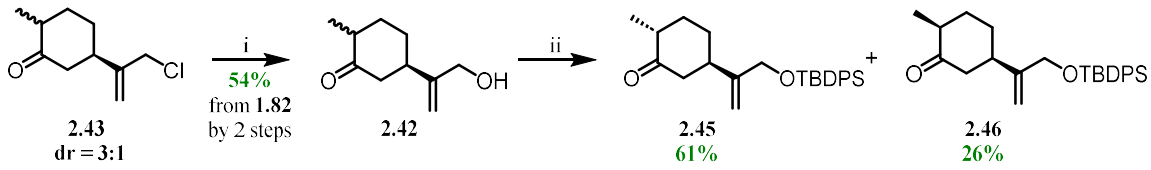
Table 23 Oxidation of dihydrocarvone into chloro-dihydrocarvone **2.43**.



1.82 (A) dr = 3:1 | **2.43 (B)** | **2.44 (C)**

Entry	TMSCl + Oxone® (eq.)	Time (h)	Ratio (A:B:C)
1	3	0.5	0:0:100
2	1.1	0.5	83:17:0
3	1.5	0.5	9:91:0
4	2	0.5	0:50:50
5[a]	1.6	2	0:55:45
6[a]	1.1	2	33:67:0
7[b]	1.3	2	20:80:0

Reagents and conditions: 0.2 mmol of **1.82**, 4 eq. $NaHCO_3$ then TMSCl and Oxone®, DCM/H_2O (1:1) then adding dry ice for 2 h. [a] 5.0 mmol **2.13**. [b] 25.0 mmol of **2.13**.



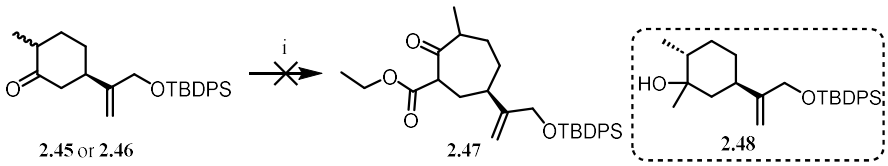
2.43 dr = 3:1 | **2.42** | **2.45** 61% | **2.46** 26%

Scheme 88 Hydrolysis of **2.43** and protection of the alcohol product. **Reagents and conditions: i)** $NaHCO_3$, dioxane, H_2O, 105 °C, 2h; **ii)** TBDPSCl, DMAP, imidazole, DMF, RT, 2 h.

The ring expansion with ethyl diazoacetate that had previously been used successfully for the conversion of dihydrocarvone **1.82** into homo-dihydrocarvone **1.167** was unsuccessful with oxidised dihydrocarvone **2.45** or **2.46** (*Table 24*). No reaction occurred with BF_3 mediation (*Entries 1,2*) and it was speculated that the substrate is generally hindered by the bulky TBDPS group and which may interfere with complexation to the Lewis acid or hinder the addition of the diazo species to the complexed ketone. Changing to $SbCl_5$ led to a complex crude product mixture with no trace of the silyl group remaining (*Entry 3*). Trimethylaluminium has also been reported as an effective Lewis catalyst

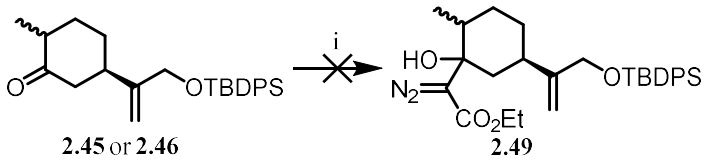
for this type of process; however, for substrate **2.45**, only the methyl addition product **2.48** could be isolated (*Entry 4*).

Table 24 Attempted ring expansion of **2.45** or **2.46** into seven-membered ring **2.47**.



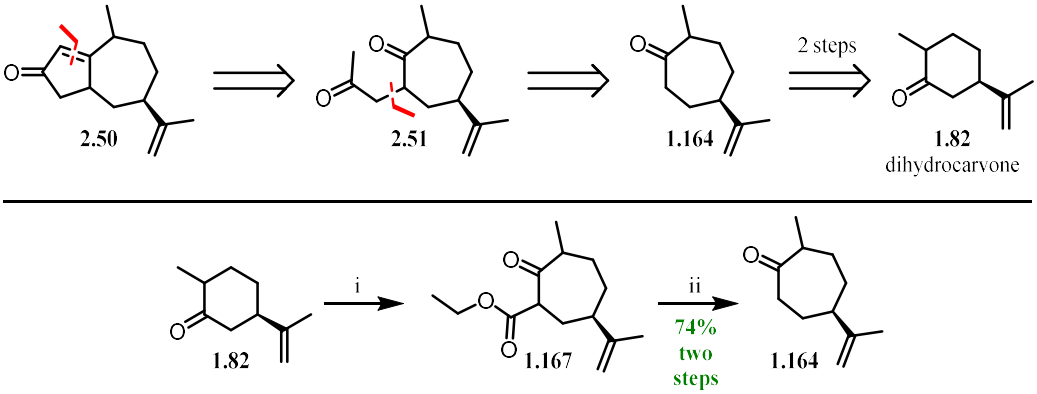
Conditions (i) with ethyl diazoacetate in DCM, 3 h			
Entry	Lewis acid	Temperature (°C)	Result
1	BF_3•OEt_2	0	n.r.
2	BF_3•OEt_2	RT	n.r.
3	$SbCl_5$	–78	complex
4	$AlMe_3$	–78	62% **2.48**

It has also been reported that ethyl diazoacetate could be deprotonated by strong base and then added to a ketone;[21] however, with LDA or LHMDS as base, no reaction occurred (*Scheme 89*), which also suggested that the carbonyl site is hindered by the large silyl group.



Scheme 89 Attempted ethyl diazoacetate addition with ketone **2.45** or **2.46**. **Reagents and conditions: i)** LDA or LHMDS, ethyl diazoacetate, THF, –78 °C to RT, 2 h.

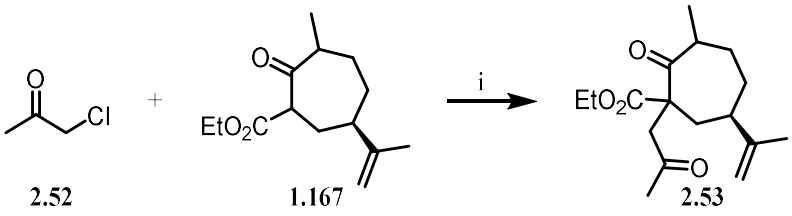
As the ring expansion of dihydrocarvone had proceeded smoothly with high yield, a simpler model substrate **2.50** for the IMDA reaction was proposed (*Scheme 90*). This substrate would be achieved by a similar route from intermediate **1.164** which, as discussed in Project I, can be obtained from dihydrocarvone **1.82** in two steps.



Scheme 90 Planned route to a simplified IMDA model substrate **2.50**. **Reagents and conditions: i)** BF_3•OEt_2, ethyl diazoacetate, DCM, 0 °C, 3 h; **ii)** NaOH, MeOH, H_2O, 70 °C, 3 h.

The α-alkylation step was first tested with ketone **1.167** due to its expected ease and predictable regioselectivty of deprotonation (*Table 25*). Using potassium *tert*-butoxide in *tert*-butanol solution gave no reaction, while irreversible deprotonation with NaH led to a complex mixture (*Entries 1,2*). These results indicated that chloroacetone **2.52**, though widely used as an alkylation partner, was not sufficiently active for this reaction. Activation with NaI, using Cs_2CO_3 as a base gave the target product **2.53** in 28 % yield, with 45% of starting material **1.167** recovered (*Entry 3*). Further optimisation by increasing the base loading improved the yield to 55% (*Entries 4,5*).

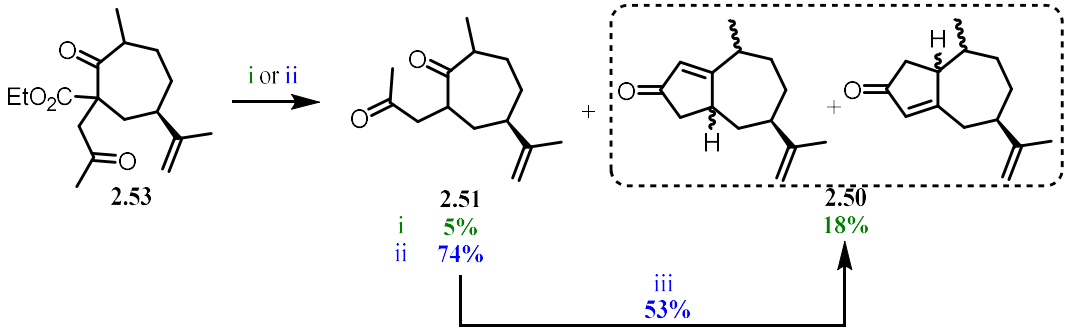
Table 25 α-Alkylation of **1.167** leading to diketone **2.53**.



Entry	Base	Solvent	Temperature (°C)	Result
1	KO*t*-Bu	*t*-BuOH	80	n.r.
2	NaH	DMF	RT	complex
3	Cs_2CO_3, NaI	DMF	RT	28% of **2.20**
4[a]	Cs_2CO_3, NaI	DMF	RT	50% of **2.20**
5[a,b]	Cs_2CO_3, NaI	DMF	RT	55% of **2.20**

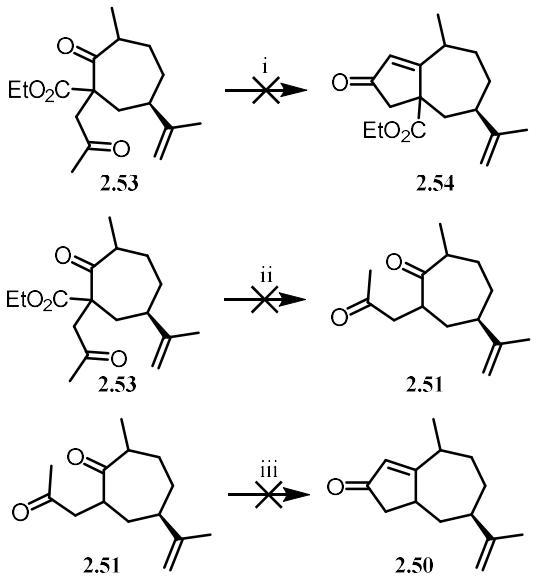
Reagents and conditions: i) 0.2 mmol **1.167** and 1.2 eq. base in solvent then 1 eq. **2.52**, 18 h. [a] 1.6 eq. base. [b] 1 mmol scale.

It was considered that diketo-ester **2.53** could undergo decarboxylation and aldol condensation in one step under base catalysis; however, this one-pot method was plagued by incomplete conversions and very low yields. The transformation was therefore divided into two steps: reaction with NaOH in aqueous methanol at lower temperature gave decarboxylation product **2.51** in good yield, then cyclisation with KOH furnished enone **2.50** as a mixture of regio- and diastereo-isomers in 53% yield (*Scheme 91, Appendix 12*).



Scheme 91 Decarboxylation and aldol condensation of **2.53**. **Reagents and conditions: i)** KOH, H_2O, 100 °C, 2 h; **ii)** NaOH, H_2O, MeOH, 70 °C, 2 h; **iii)** KOH, H_2O, 100 °C, 2 h.

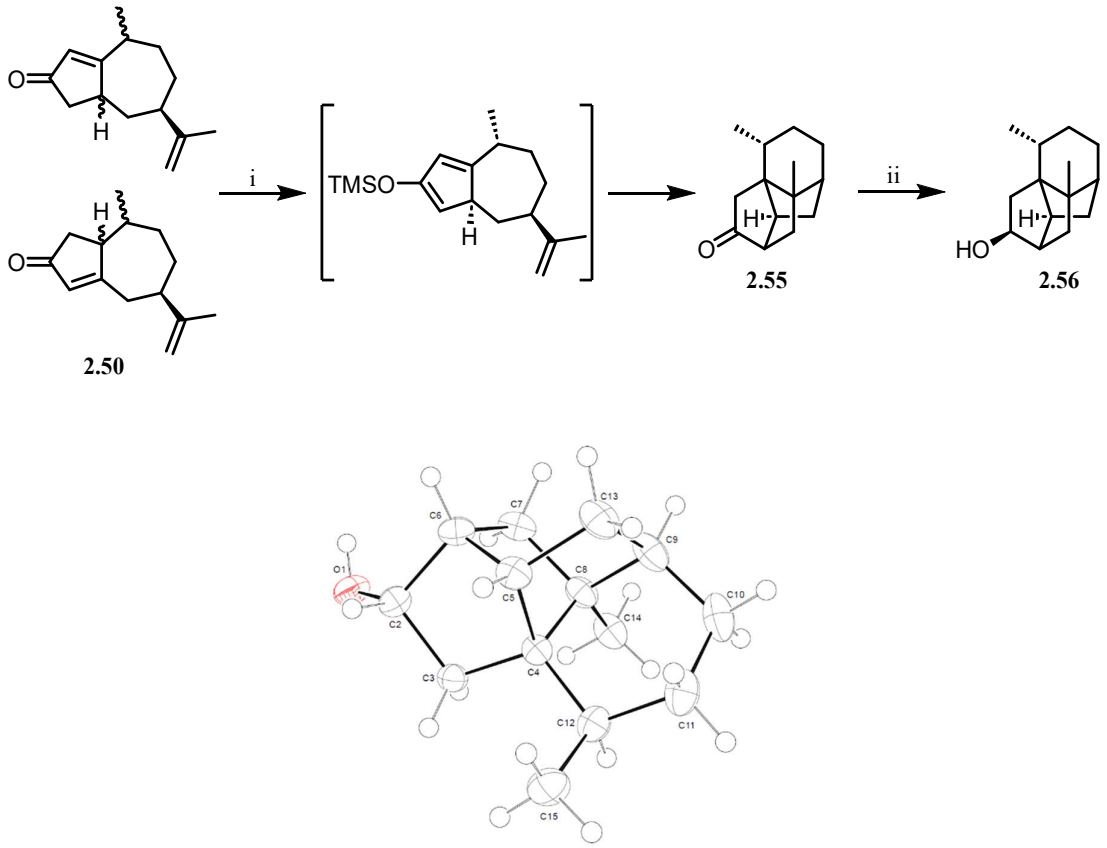
Some other methods towards enone **2.50** were also tested unsuccessfully (*Scheme 92*). To prevent the cyclopentenone isomerisation, aldol cyclisation before decarboxylation was tested with K_3PO_4, which has been reported by the Irie group;[22] however, K_3PO_4 had a very low solubility in *iso*propanol and the reaction proceeded very slowly. Krapcho decarboxylation[23] was tested because it may give fewer isomers than the basic decarboxylation method, but this reaction did not proceed, probably due to the steric hindrance of the ester group. Intramolecular aldol reaction of diketone **2.51** with NaHMDS under kinetic conditions also gave no reaction.



Scheme 92 Failed alternatives for the decarboxylation and aldol steps towards compound **2.50**. **Reagents and conditions: i)** K_3PO_4, *i*-PrOH, 45 °C, 40 h; **ii)** LiCl, H_2O, DMSO, 175 °C, 3 h; **iii)** NaHMDS, HMPA, THF, –78 °C to 50 °C, 1 h.

2.3 IMDA reaction of substrate 2.50

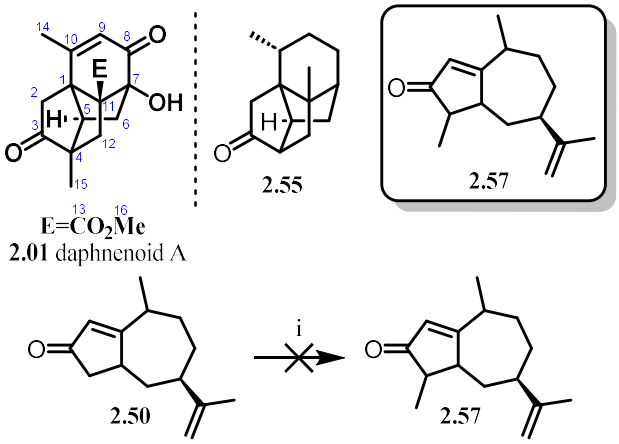
A remarkable and satisfying result was achieved when substrate **2.50** was heated in the presence of trimethylsilyl chloride, triethylamine, and $ZnCl_2$ (Ihara's 'acidic' conditions for the double Michael process); despite being a complex mixture of isomers, under these reaction conditions all isomers equilibrated, with the only isomer capable of cyclising then leading to cyclised product **2.55** (*Scheme 93*). A control experiment without trimethylsilyl chloride gave a complex mixture, indicating that enone **2.50** needs to form the silyl enol ether first in order to initiate the Diels–Alder reaction. Ketone **2.55** decomposed upon attempted purification by silica gel chromatography but reduction with $NaBH_4$ afforded the stable alcohol **2.56**, obtained as a crystalline solid suitable for structural confirmation by X-ray diffraction.



Scheme 93 IMDA reaction of **2.50** and single-crystal molecular structure of tetracycle **2.56. Reagents and conditions: i)** TMSCl, Et_3N, $ZnCl_2$, toluene, 160 °C in a pressure tube, 18 h; **ii)** $NaBH_4$, MeOH, 0 °C, 2 h.

2.4 Synthesis of model substrate with full carbon skeleton

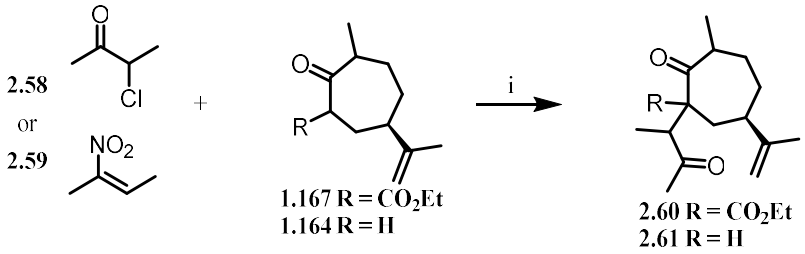
Comparing the model system to daphnenoid A and the artatrovirenols, the model cycloadduct **2.55** is missing the C15 methyl group (*Scheme 94*). To achieve the full carbon skeleton of the sesquiterpenoid, direct methylation was considered but the tertiary and bridgehead nature of C(4) makes this difficult. Methylation of enone **2.50** gave a complex mixture of inseparable products, in which the methylation product could not be detected (NMR). Therefore, enone **2.57** needed to be fashioned using an alternative route.



Scheme 94 Second model substrate **2.57** for IMDA reaction. **Reagents and conditions: i)** LHMDS, MeI, THF, –78 °C, 2 h.

Attempts to achieve α-alkylation with a 2-oxobut-3-yl equivalent electrophile commenced with ketone **1.167** and 3-chloro-2-butanone **2.58** but no reaction occurred between these reactants (*Table 26, Entry 1*). It was concluded from this that in **2.58** the 2°-chloride is too hindered to be an effective electrophile for enolate alkylation. Nitro-alkene **2.59**, easily synthesised by the elimination of commercially available 3-nitro-2-butanol,[24] was considered as a potentially more active alkylation partner. In the event, Michael addition between **1.167** and **2.59** gave no reaction while the less hindered decarboxylated substrate **1.164** gave the target diketone in 37% yield product **2.61** after Nef reaction.[25] (*Entries 2,3*).

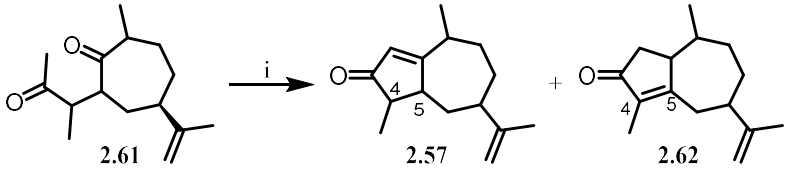
Table 26 Attempts to achieve α-alkylation of **1.164** leading to diketone **2.61**.



Entry	Conditions (i)	Result
1	**1.167**, 1.5 eq. **2.58**, 1.2 eq. LHMDS, THF, –78 °C, 2 h	n.r.
2	**1.167**, 1 eq. **2.59**, 1.4 eq. Cs_2CO_3, DMF, RT, 1 h	n.r.
3	**1.164**, 1.5 eq. **2.59**, 1.2 eq. LHMDS, THF, –78 °C, 2 h, then HCl, RT, 2 h	37% **2.61**

Compared with the reaction of diketone **2.51**, the aldol condensation of diketone **2.61** was also more complicated (*Table 27, Entry 1*). The product enone, here and in the simpler substrate, isomerises readily and the extra methyl group in isomer **2.62** stabilises the undesired tetrasubstituted alkene form. Irie's method[22] promised a solution, but no reaction occurred for substrate **2.61** (*Entry 1*). Reversible base NaOMe also gave no reaction even at 60 °C (*Entries 2,3*); however, irreversible base NaH gave the cyclised product as an inseparable mixture, the major component being decided by the amount of NaH. Using exactly 1.0 equivalent of NaH afforded the desired enone **2.57** as the major component (*Entries 4,5*; *Appendix 13*).

Table 27 Aldol condensation of **2.61** into enone **2.57** and **2.62**.

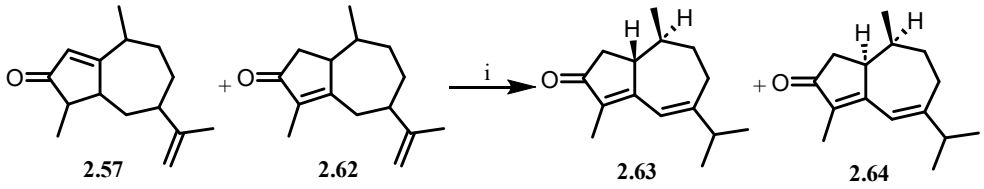


Entry	Conditions (i)	Result
1	1 eq. K_3PO_4, *i*-PrOH, 45 °C, 32 h	n.r.
2	1 eq. NaOMe, MeOH, RT, 18 h	n.r.
3	1 eq. NaOMe, MeOH, 60 °C, 3 h	n.r.
4	5 eq. NaH, 6 mol% *t*-BuOH, benzene, 85 °C, 0.5 h	**2.57** and **2.62** (major)
5	1 eq. NaH, 6 mol% *t*-BuOH, benzene, 85 °C, 0.5 h	**2.57** (major) and **2.62**

The IMDA reaction was then tested on the inseparable mixture of enones **2.57** and **2.62** (also including their different diastereomers); however the proposed reaction did not occur under various trialled conditions (*Appendix 14, Table 28*). The previously applied Ihara conditions led merely to decomposition of starting material (*Entry 1*). A control experiment showed that removing $ZnCl_2$ could prevent the substrate from decomposing but other reactions were also stopped (*Entry 2*). Based on this, it was assumed that the enone decomposed before it could even form the silyl enol ether. Several enolisation conditions were tested but none afforded the diene intermediate (*Entry 3*). Trimethylsilyl triflimide has been reported trimethylsilylation-enolation of acid-sensitive substrates;[26] with this

reagent an interesting rearrangement occurred, resulting in two previously-reported conjugated dienone diastereomers[27] **2.63** and **2.64** (*Entry 4*). By reduction with $LiAlH_4$-$AlCl_3$, these two isomers can be converted into two natural products, (–)-isoguaiene and (–)-10-*epi*-isoguaiene and the current route constitutes a more efficient formal synthesis of these sesquiterpenes.

Table 28 Attempted IMDA reaction of regioisomers **2.57** and **2.62**.



2.57 **2.62** **2.63** **2.64**

Entry	Conditions (i)	Result
1[a]	10 eq. TMSCl, 10 eq. Et_3N, 10 eq. $ZnCl_2$, toluene, 160 °C, 18 h	complex
2[a]	10 eq. TMSCl, 10 eq. Et_3N, toluene, 120 °C, 5 h	n.r.
3	5 eq. TESCl, 2 eq. LHMDS, THF, –78 °C, 1 h	n.r.
4[a]	5 eq. $TMSNTf_2$, 4.5 eq. Et_3N, toluene, 110 °C, 1 h	21% **2.63**, 12% **2.64**

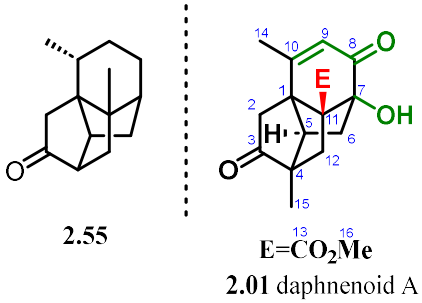
[a] In a sealed tube.

In summary, enone **2.57** failed to cyclise, with its substituted C4-position perhaps proving harder to deprotonate and providing steric hindrance towards reaction with the dienophile. In daphnenoid A, however, the dienophile is activated by a methyl ester group which may be sufficient to enable the IMDA to occur; therefore, a total synthesis route towards daphnenoid A was proposed.

3. First generation synthetic routes towards daphnenoid A

Compared with the IMDA product **2.55**, there are three major structural differences in daphnenoid A: (1) a methyl ester in place of the C(13) methyl group; (2) an α-hydroxy enone in the six-membered ring; and (3) the C(15) methyl group (*Scheme 95*). With no obvious methods available to introduce the extra methyl group after the IMDA reaction, it was necessary to incorporate the α-methyl within the cyclopentenone-derived diene component. Based on the failed IMDA model study of enone mixture

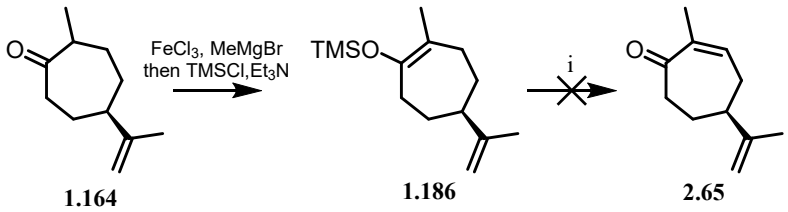
2.57 and **2.62**, the presence of the dienophile-activating methyl ester group was expected to be a key factor. Separately, the high oxidation state of the six-membered ring could potentially be reached by late-stage oxidation, provided that a functional group handle could be incorporated within that ring prior to the IMDA reaction.



Scheme 95 Comparison between model cycloadduct **2.55** and daphnenoid A.

Ketone **1.164** was selected as a possible substrate for functionalisation (*Table 29*). Regioselective silyl enol ether formation was achieved using Holton's method in preparation for Saegusa–Ito oxidation to install the enone; [28] however, several conditions were tried without success.

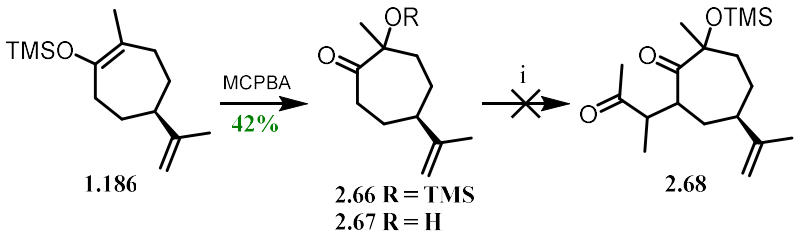
Table 29 Attempted oxidation of ketone **1.164** into enone **2.65**.



Entry	Conditions (i)	Result
1	$Pd(OAc)_2$ (1 eq.), MeCN	complex
2	$Pd(OAc)_2$ (5 mol%), O_2, Na_2HPO_4, Oxone®, MeCN	complex
3	DDQ, $NaHCO_3$, DCM	n.r.
4	DDQ, collidine, benzene	n.r.

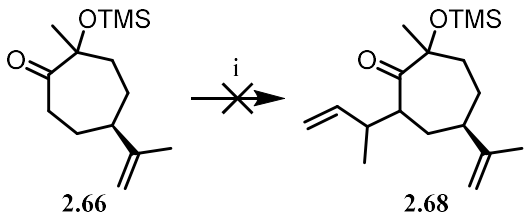
As an alternative, Rubottom oxidation of enol ether **1.186** gave α-silyloxy ketone **2.66** (*Table 30*) which was tested as a substrate for α-alkylation. With 3-chloro-2-butanone as electrophile, no alkylation product was detected by NMR analysis of the crude product, even when NaI was included as a nucleophilic catalyst; instead, simple desilylation occurred leading to hydroxy ketone **2.67** (*Entry 1*). Other bases gave no reaction (*Entry 2–4*) and an attempted Lewis acid-catalysed Michael addition gave only a complicated reaction mixture (*Entry 5*), assumed to result from side-reactions of the fragile 3° α-silyloxy group.

Table 30 Attempted α-alkylation of hydroxy ketone **2.66**.



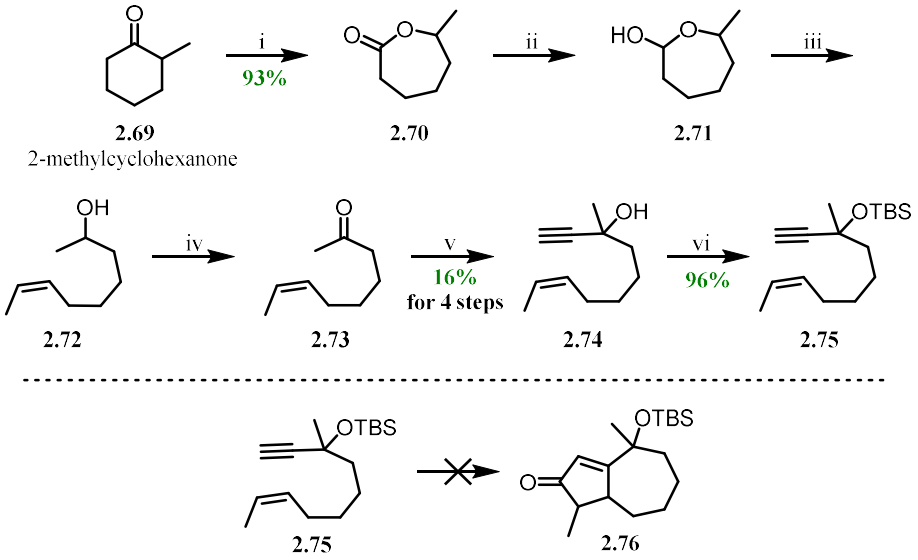
Entry	Conditions (i)	Result
1	KHMDS then 3-chloro-2-butanone, NaI	**2.67**
2	NaH, KO*t*-Bu then 3-chloro-2-butanone	n.r.
3	LHMDS then 2-nitro-2-butene	n.r.
4	NaH then 2-nitro-2-butene	n.r.
5	LHMDS, TMSCl then 2-nitro-2-butene, $SnCl_4$	decomposition

In principle, Claisen rearrangement of an intermediate *O*-crotyl enol ether would deliver terminal alkene **2.68** (*Scheme 96*) which could then be subjected to Wacker oxidation to give the desired methyl ketone. In retrospect, conditions appropriate for an isolated ketone should have been tested; those provided in Jacobsen's precedent[29] were, unsurprisingly, not successful. Future work could revisit this idea.



Scheme 96 Mitsunobu conditions failed to couple ketone **2.66** and crotyl alcohol in an attempted Claisen approach to ketone **2.68**. **Reagents and conditions: i)** crotyl alcohol, PPh_3, DEAD, THF, –20 °C to RT, 5 h.

Another plan to introduce oxygen functional groups was envisaged based on Pauson–Khand reaction to construct the bicyclic ring system. A model substrate **2.75** was easily achieved with satisfying yield from 2-methylcyclohexanone (*Scheme 97*); however, the Pauson–Khand reaction failed to construct the ring and this approach was soon abandoned.



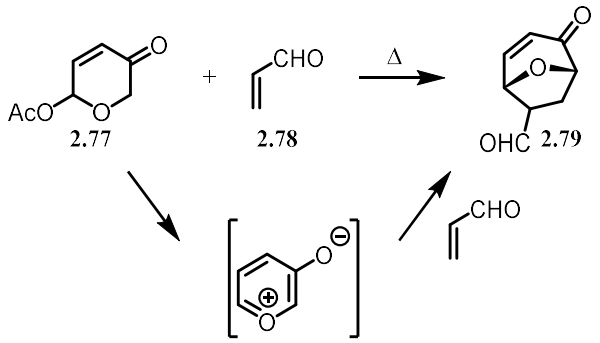
Scheme 97 Conversion of ketone **2.69** into enyne **2.75** and unsuccessful Pauson–Khand reaction. **Reagents and conditions: i)** MCPBA, DCM, 0 °C, 2 h; **ii)** DIBAL-H, THF, –78 °C, 1 h; **iii)** KHMDS, $EtPPh_3Br$, THF, –78 °C, 2 h; **iv)** DMP, DCM, RT, 1 h; **v)** Ethynylmagnesium bromide, THF, 0 °C, 2 h; **vi)** TBSOTf, Et_3N, DCM, 0 °C to RT, 1 h.

4. Second generation synthetic route using oxidopyrylium (5+2) cycloaddition

4.1 Introduction to oxidopyrylium (5+2) cycloadditions

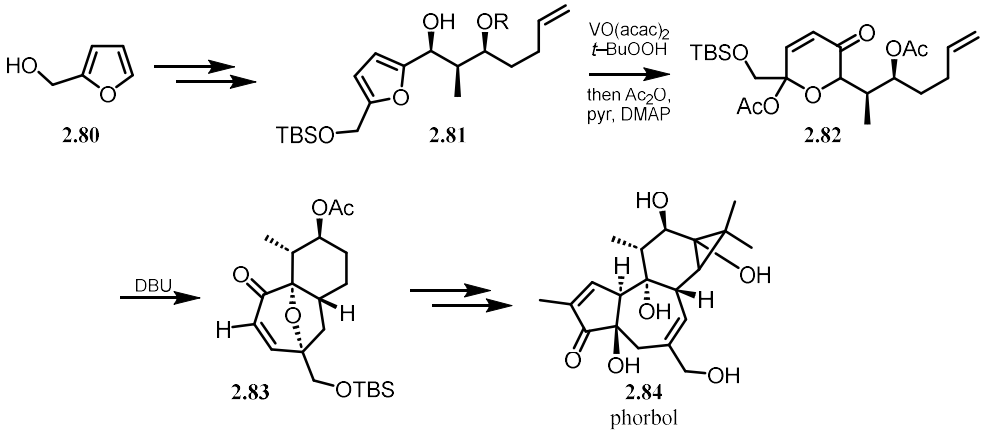
Pericyclic cycloaddition reactions are invaluable for the synthesis of complex cyclic skeletons as a result of their high efficiency in generating C-C bonds and multiple stereogenic centres in a single step but,

in comparison with the formation of five- and six-membered rings, cycloadditions that form seven-membered rings are not as extensively developed. The general methods may be classified as (4+3) and (5+2) cycloaddition reactions;[30] within these, the (5+2) cycloaddition of oxidopyrylium ions, first developed in 1980 by Hendrickson and Farina (*Scheme 98*),[31] was quickly adopted as an important method for the synthesis of oxa-bridged cycloheptanoid fragments, with many subsequent applications in total synthesis.[32]



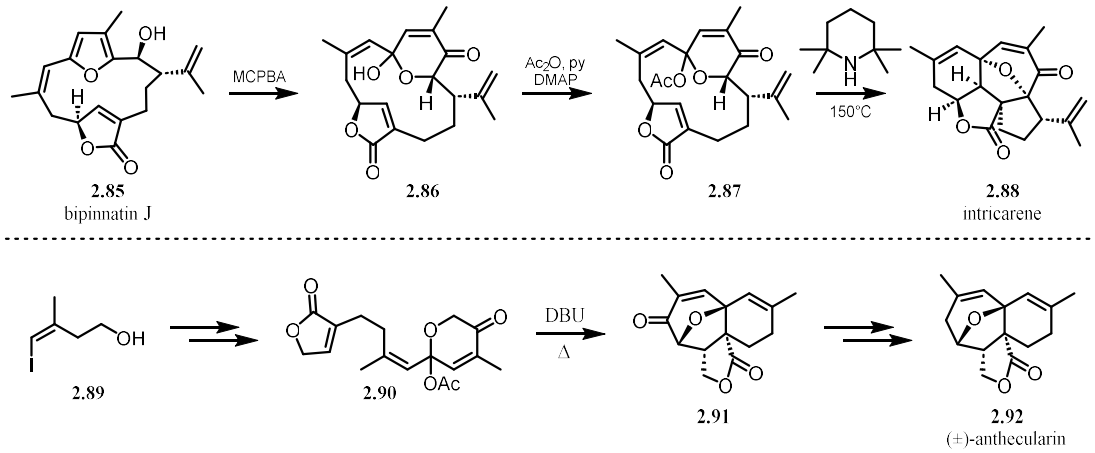
Scheme 98 Hendrickson and Farina's first reported (5+2) cycloaddition.

For example, focusing on the intramolecular variant, see below, in the series of synthetic work towards the diterpenoid phorbol reported by the Wender group (*Scheme 99*), the (5+2) cycloaddition was always central to their construction of the 5,7,6-tricyclic carbon skeleton, in which acetoxypyranone **2.82** was simply treated with base to afford the desired (5+2) cycloaddition product as a single diastereomer.[33]



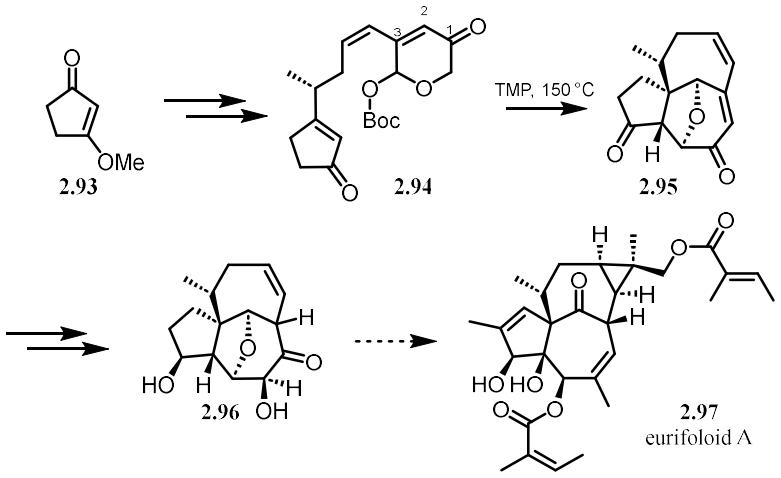
Scheme 99 The (5+2) oxidopyrylium cycloaddition employed to form the B and C rings of phorbol in Wender's asymmetric total synthesis.[33a]

Some years later, in 2006, Trauner's group reported the asymmetric synthesis of (–)-bipinnatin J **2.85**, and its further conversion into (+)-intricarene **2.88**, (+)-rubifolide and (+)-isoepilophodione B (*Scheme 100*). Direct oxidation of the furyl alcohol of (–)-bipinnatin J was followed by an impressive intramolecular (5+2) cycloaddition of the oxidopyrylium zwitterion, giving intricarene stereoselectively.[34] A similar cycloaddition strategy was also used in the synthesis of (±)-anthecularin **2.92**, as reported by Pattenden in 2009, the key step proceeding in 15–20% yield.[35]



Scheme 100 Synthesis of intricarene and anthecularin by intramolecular (5+2) cycloaddition reactions.

The Li group developed the Type II intramolecular (5+2) cycloaddition to construct bridged ring systems[36] as exemplified by their 2017 study of the synthesis of eurifoloid A **2.97** (*Scheme 101*). Similar to the Type II IMDA reaction, the dienophile is tethered to an internal (C3) position of the acetoxypyranone thus the reaction energy is higher due to the strain inherent in the formation of a relatively strained bridgehead double bond. The reactions require a high temperature (160 °C) but high yields (60–90%) and stereoselectivities (dr = 1.3–20:1) can be maintained. In the synthesis of eurifoloid A, the highly functionalised 5,7,7-tricyclic structure **2.95** was obtained in 30% yield as a single diastereomer.[37]

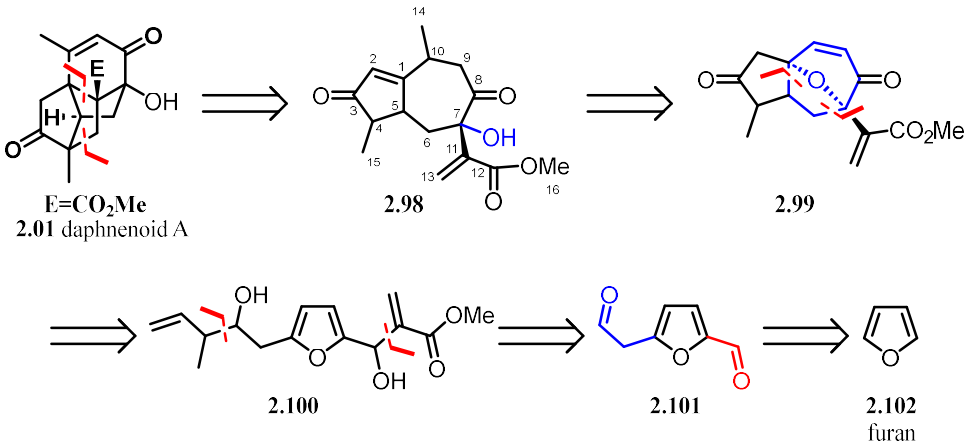


Scheme 101 A 'Type II' intramolecular (5+2) cycloaddition applied to the core of the diterpenoid erifoloid A.

Related intramolecular oxidopyrylium cycloadditions have been used in many other natural product synthetic studies, including Sammes's synthesis of β-bulnesene[38] building from the group's initial development of the intramolecular reaction,[39] the cyathin diterpene skeleton,[40] guanacastepenes,[41] cordytropolone,[42] and arteminolides A–D.[43] All these works indicate that the intramolecular oxidopyrylium (5+2) cycloaddition is a reliable method for constructing the highly functionalised seven-membered ring systems in natural products stereoselectively.

4.2 Retrosynthetic plan

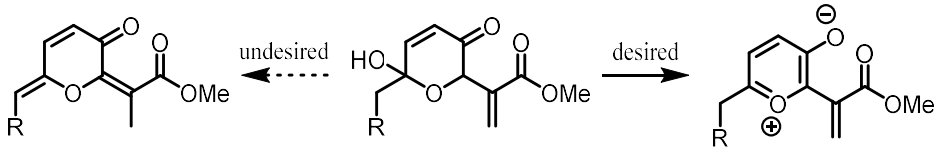
The product from an oxidopyrylium (5+2) cycloaddition contains an enone and an oxa-bridge across a seven-membered ring, appropriate for a daphnenoid A synthesis, and so a new stereoselective plan, accounting for all functional groups, was proposed (*Scheme 102*). The final key step remained the IMDA reaction with some late-stage oxidations required to reach the natural product. The C7 3°-alcohol in precursor **2.98** would be released by the cleavage of the C1-C7 oxa-bridge. The methyl group at C10 would be added to the enone of **2.99** which would, in turn, be generated by oxidopyrylium (5+2) cycloaddition from furan derivative **2.100**, achieved by coupling reactions to an intermediate of overall reactivity equivalent to dialdehyde **2.101**.



Scheme 102 Proposed route towards daphnenoid A **2.01**.

4.3 Model study of oxidopyrylium (5+2) cycloaddition

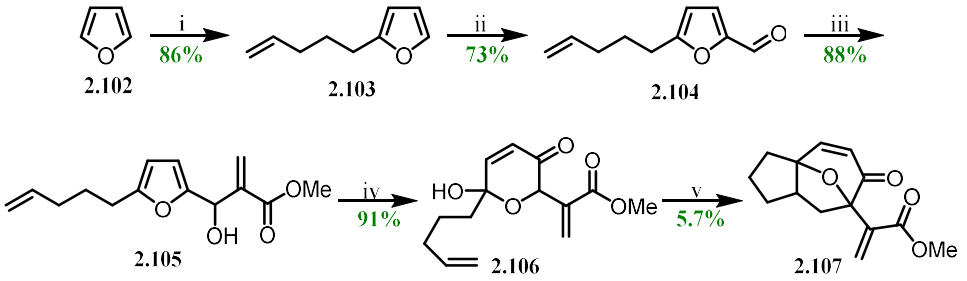
Before starting this synthesis route, a model study was commenced to create precedent for (5+2) cycloaddition with the potentially labile methylene ester adjacent to the pyranone. It was important to test whether simple elimination and other reactions would outcompete the formation and cycloaddition of the oxidopyrylium intermediate (*Scheme 103*).



Scheme 103 Possible pathways for dihydropyran elimination.

To this end, precursor **2.106** was synthesised from furan (*Scheme 104*). α-Alkylation with 5-bromo-1-pentene installed the desired side chain[44] then Vilsmeier–Haack formylation[45] gave aldehyde **2.104** which was then transformed into alcohol **2.105** by addition of the hydroalumination adduct of DIBAL-H and methyl propiolate.[46] Lefebvre oxidation of furyl alcohol **2.105** gave the desired dihydropyran **2.106** in good yield. The first step leading to the (5+2) cycloaddition was successful on substrate **2.106**, giving the unstable acetate derivative (not shown) with full conversion; however, the cycloaddition itself gave the target product in only 5.7% yield among other unrecognisable products. This indicated

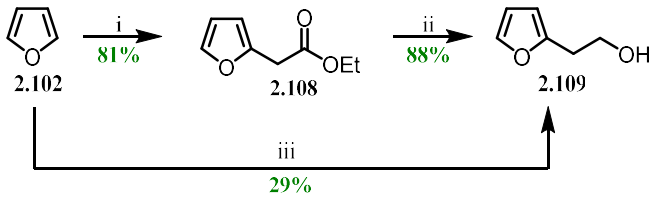
that the electron withdrawing group does complicate the process but, recognising that optimisation in the real system would inevitably be necessary, the strategy was deemed sufficiently viable to proceed.



Scheme 104 Model study of the oxidopyrylium (5+2) cycloaddition towards enone **2.107**. **Reagents and conditions: i)** BuLi, 5-bromo-1-pentene, 0 °C, 18 h; **ii)** $POCl_3$, DMF, 0 °C, 1 h; **iii)** DIBAL-H, methylpropiolate, HMPA, THF, 0 °C, 1 h then **2.104**, RT, 4 h; **iv)** MCPBA, DCM, 0 °C, 1.5 h; **v)** Ac_2O, pyridine, DMAP, DCM, 0 °C, 2 h, then DBU, CH_3CN, 60 °C, 18 h.

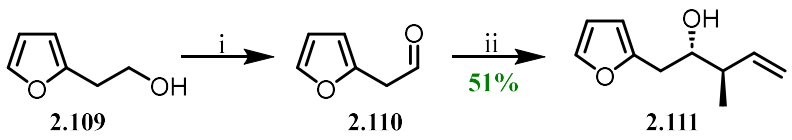
4.4 Oxidopyrylium (5+2) cycloaddition on substrate 2.100

Furan alcohol **2.109** was prepared efficiently in two steps from furan based on the Baciocchi[47] radical addition of ethyl iodoacetate to furan then $LiAlH_4$ reduction of ester **2.108** (*Scheme 105*). This overall conversion was also achieved in one step by alkylation of 2-furyllithium with ethylene oxide gas; however, this reaction was difficult to scale up and the yield was lower than the two-step method.



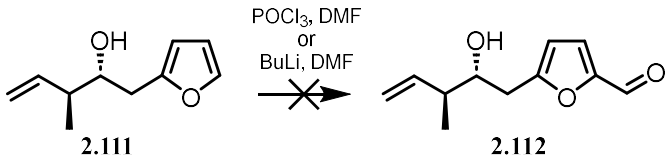
Scheme 105 Elaboration of furan **2.102** into furyl ethanol **2.109**. **Reagents and conditions: i)** ethyl iodoacetate, $FeSO_4 \bullet H_2O$, H_2O_2, furan, DMSO, 0 °C to RT, 18 h; **ii)** $LiAlH_4$, THF, 0 °C, 1 h; **iii)** BuLi, ethylene oxide, THF, 0 °C, 18 h.

Aldehyde **2.110**, obtained from alcohol **2.109** by DMP oxidation (*Scheme 106*) was very unstable to silica so the diluted reaction crude product was just washed with $NaHCO_3/Na_2S_2O_3$ solution to remove any residual reagent and its by-products to give crude aldehyde that was sufficiently pure for the next step. Allylation was performed according to Fürstner's procedure[48] to give the *anti*-diastereomer **2.111** of the crotylation product as a single isomer.



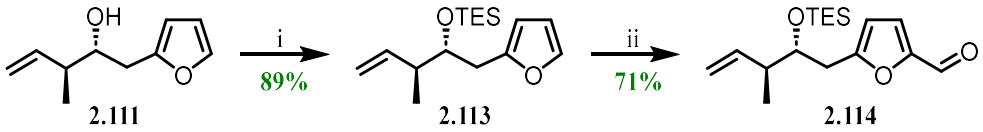
Scheme 106 Oxidation then crotylation of furyl ethanol **2.109** into **2.111**. **Reagents and conditions: i)** DMP, DCM, RT, 2 h; **ii)** crotyl bromide, $CrCl_2$, Mn, TMSCl, THF, 4 h.

To keep the route as concise as possible, an attempt was made to avoid protecting the alcohol during the formylation reaction; however, use of either the Vilsmeier–Haack conditions or treating the derived furyllithium with DMF led to no productive outcome beyond slow decomposition of the starting material (*Scheme 107*).



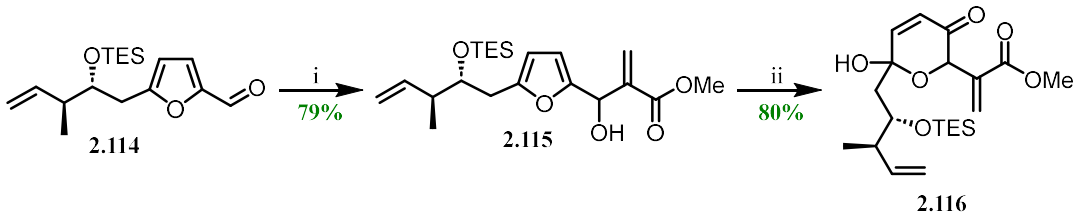
Scheme 107 Direct formylation of alcohol **2.111** into aldehyde **2.112.**

Since alcohol protection seemed necessary, bulky groups such as TBS or TBDPS were considered to hinder the (5+2) reaction so TES was chosen as a compromise, leading to furan derivative **2.113** which was deprotonated and formylated smoothly with DMF (*Scheme 108*).



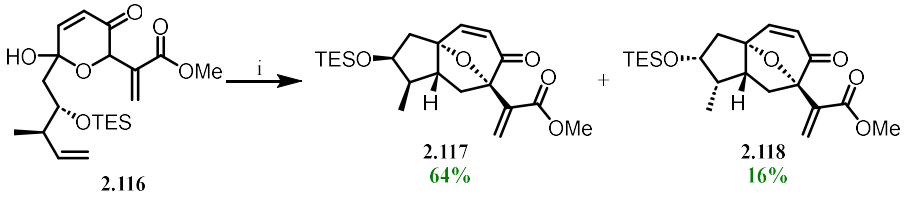
Scheme 108 Protection of the alcohol **2.111** and formylation into aldehyde **2.114**. **Reagents and conditions: i)** TESCl, imidazole, DMF, 0 °C, 1 h; **ii)** BuLi, DMF, THF, –78 °C to 0 °C, 1.5 h.

The next two steps were accomplished from **2.114** following the sequence used with model substrate **2.104**, here leading to hydroxypyrone **2.116** as the substrate for (5+2) cycloaddition (*Scheme 109*).



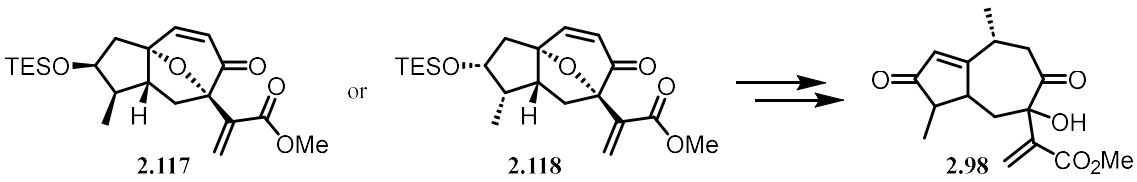
Scheme 109 Overall methyl acrylate addition into aldehyde **2.114** and oxidation into dihydropyran **2.116**. **Reagents and conditions: i)** DIBAL-H, methyl propiolate, HMPA, THF, 0 °C, 3 h then **2.114**, RT, 1 h; **ii)** MCPBA, DCM, 0 °C, 1.5 h.

As expected, the oxidopyrylium (5+2) cycloaddition of compound **2.116** proceeded differently to that of model substrate **2.106** (*Scheme 110*). The method used for the model system led to a complex crude product mixture but Suga's method,[49] using a combination of Boc anhydride and triethylamine, gave the cyclised product as a pair of diastereomers, identified by their different NOESY correlations (see *Appendix 15*).



Scheme 110 (5+2) Cycloaddition of **2.116** leading to 5,7-fused bicyclic systems **2.117** and **2.118**. **Reagents and conditions: i)** Boc_2O, DMAP, DCM, 0 °C, 1h then 3.75 eq. Et_3N, RT, 3h.

At this stage, from furan the 5,7-fused bicyclic intermediates **2.117** and **2.118** had been achieved in nine steps with very good stereoselectivity and satisfactory overall yield (9.2% for **2.117**, 2.3% for **2.118**). The next challenge was to modify the functional groups and open the oxa-bridge to obtain a suitable substrate for the IMDA reaction (*Scheme 111*).

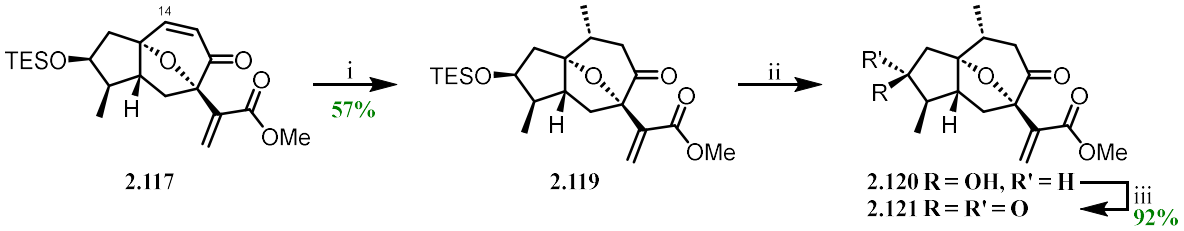


Scheme 111 Next key step for the total synthesis of daphnenoid A.

4.5 Synthesis of IMDA precursor

4.5.1 First generation with C14 methylation

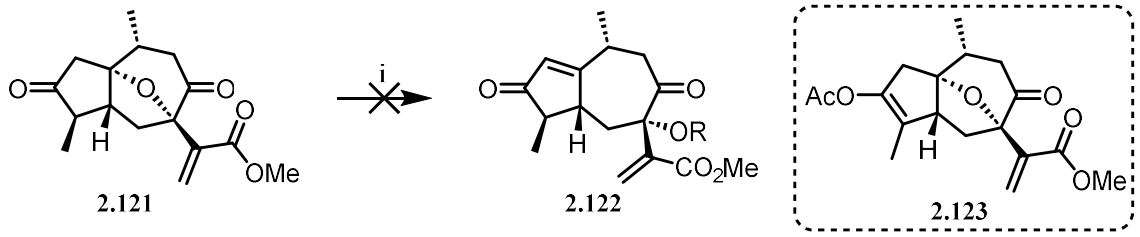
The major cycloaddition diastereomer **2.117** was used as the substrate for the next steps. Conjugate addition to the enone gave methylated product **2.119** in 57% yield as a single diastereomer (*Scheme 112*, *Appendix 15*). Deprotection of the TES group with TBAF, and Swern oxidation achieved the diketone **2.121** in nearly quantitative yield.



Scheme 112 Methyl addition to enone **2.117** and further conversion into diketone **2.121**. **Reagents and conditions: i)** MeLi, CuI, THF, 0 °C, 1.5 h; **ii)** TBAF, THF, 0 °C, 1 h; **iii)** oxalyl chloride, DMSO, Et_3N, DCM, –78 °C to RT, 2 h.

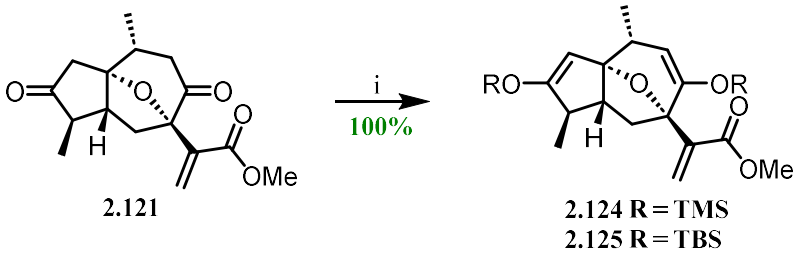
Cleavage of the oxa-bridge in diketone **2.121** proved to be a surprising bottleneck in progressing the synthesis. A variety of different bases and acids was tested but no reaction occurred (*Table 31, Entries 1,2; Appendix 16*), probably because the product of the reverse reaction, oxa-Michael addition, is more stable and any equilibrium lies wholly in favour of the starting material. With this in mind, it was suggested that the generated alcohol would need to be intercepted by a protecting group *in situ* to prevent equilibration. In the synthesis of mesembrine, Meyers' group used a combination of acetic anhydride/triethylamine as a solution to a related problem.[50] These conditions were tested on diketone **2.121** but again only the starting material was returned (*Entry 3*). The only conditions that led to a new product were $ZnCl_2$/acetic anhydride, intended to activate the oxa-bridge but giving instead enol acetate **2.123**.

Table 31 Attempted oxa-bridge cleavage of diketone **2.121** into enone **2.122**.



Entry	Reagents (eq.)	Solvent	temperature (°C)	Result
1	LHMDS (1)	THF	–78	n.r.
2	*p*-TsOH (1)	dioxane	60	n.r.
3	Et_3N (8) + Ac_2O (4)	THF	60	n.r.
4	$ZnCl_2$ (10)	Ac_2O	80	**2.123**, 57%

Work from the Mascareñas group suggested the possibility of a 'push and pull' process, activating the ketone by formation of the silyl enol ether (to 'push') and encouraging ring opening with a Lewis acid (to 'pull').[51] Accordingly, silyl enol ethers **2.124** and **2.125** were prepared from diketone **2.121** with excess base (*Scheme 113*).

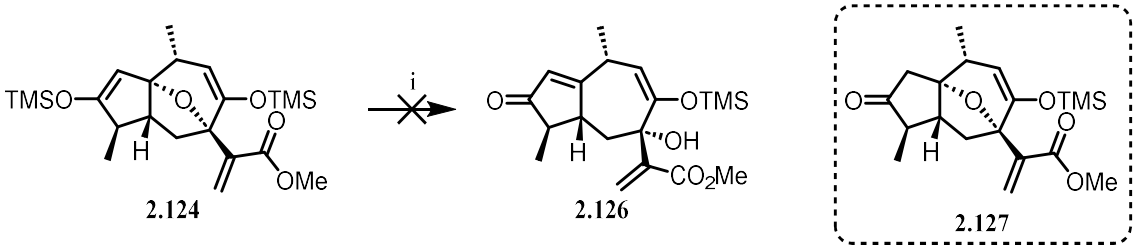


Scheme 113 Double protection of ketone **2.121** into dienol ether **2.124** and **2.125**. **Reagents and conditions: i)** TMSCl or TBSCl, LHMDS, THF, –78 °C, 1 h.

The push and pull strategy was tested on silyl enol ether **2.124** (*Table 32*). The use of BF_3 as Lewis acid gave mono-desilylated compound **2.127** which reverted to diketone **2.121** at higher temperature. (*Entries 1,2*) These results indicated that the push and pull process could be occurring but, as for the previous results in *Table 31* (*Appendix 16*), the generated hydroxy-enone (or *O*-silylenoxonium ion)

then immediately cyclised. The same reactivity was observed with the stronger Lewis acid $TiCl_4$ (*Entry 3*).

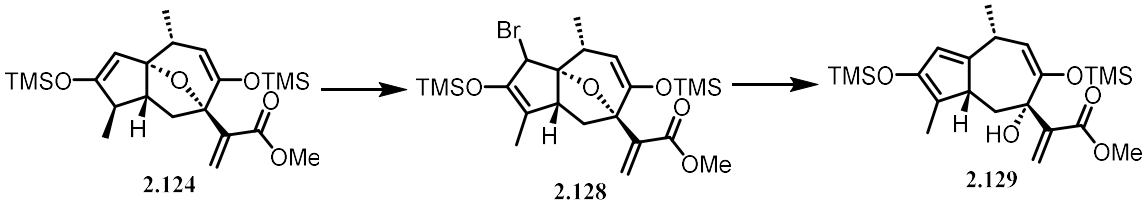
Table 32 Attempted push and pull oxa-bridge cleavage of dienol ether **2.124**.



2.124 **2.126** **2.127**

Entry	Conditions (i)	Result
1	2.4 eq. BF_3•OEt_2, THF, –78 °C	**2.127**
2	2.4 eq. BF_3•OEt_2, THF, –78 °C to 0 °C	**2.121**
3	2.7 eq. $TiCl_4$, 5.3 eq. TMSCl, THF, –78 °C	**2.127**

Another possibility considered was bromination then Boord-type elimination to form diene alcohol **2.129**, expected to be irreversible (*Scheme 114*).

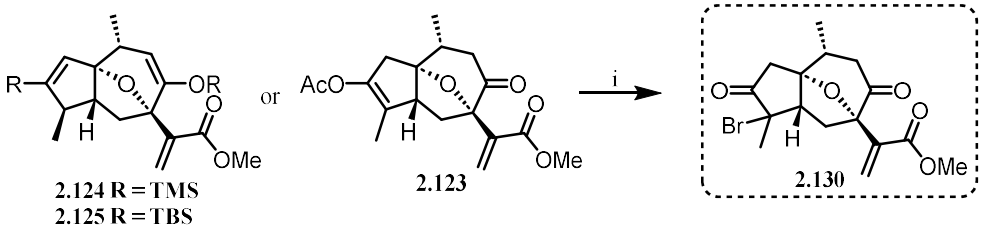


2.124 **2.128** **2.129**

Scheme 114 Proposed selective bromination of **2.124** and elimination into bromide into diene **4.33**.

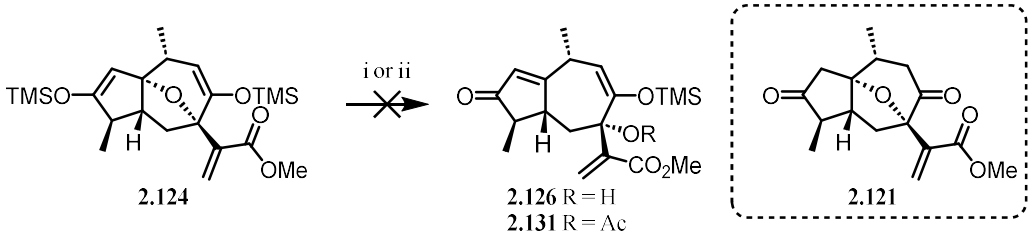
NBS bromination of either **2.124** or **2.125** led to decomposed mixtures (*Table 33, Entries 1,2*), as did milder chlorination (*Entry 3*). Enol acetate **2.123** gave bromination product **2.130**; however, without retention of the necessary enol ether structure, product **2.130** was deemed a dead end.

Table 33 Bromination or chlorination of different substrates.



Entry	substrate	reagent (eq.)	solvent	temperature (°C)	Result
1	**2.124**	NBS (1)	THF	–78	decomposed
2	**2.125**	NBS (1)	THF	–78	decomposed
3	**2.125**	NCS (1)	DCM	RT	decomposed
4	**2.123**	NBS (1.5)	THF	–78	**2.130**

Some other methods were also tested to install the enone (*Scheme 115*). Acetylation with excess acetic anhydride and DMAP led to no detectable reaction until the unstable silyl enol ether finally decomposed back into diketone **2.121**. A Saegusa–Ito oxidation with $Pd(OAc)_2$, based on the idea that an intermediate C-Pd σ-adduct might undergo *syn*-elimination of the oxa-bridge, led to a similarly unsuccessful result.

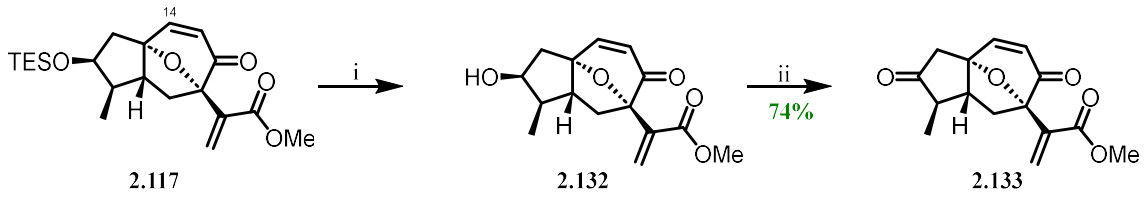


Scheme 115 Other methods attempted for enone generation from trimethylsilyl enol ether **2.124**. **Reagents and conditions: i)** Ac_2O, DMAP, THF, RT, 18 h; **ii)** $Pd(OAc)_2$, CH_3CN, 60 °C, 18 h

4.5.2 Second generation without C14 methylation

In a re-ordering of steps, an alternative substrate for oxa-bridge cleavage, diketone **2.133**, was then prepared without complication (*Scheme 116*). In contrast to the first substrate **2.121**, enone **2.133** was considered to be potentially more strained, the C-O bond to be cleaved would be weakened by virtue of

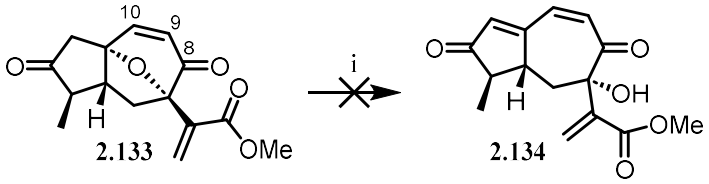
allylic activation, and the product of oxa-bridge cleavage would contain an extended conjugated system which, it was thought, would stabilise this ring-opened form.



2.117 2.132 2.133

Scheme 116 Deprotection and oxidation of **2.117** into ketone enone **2.133**. **Reagents and conditions: i)** TBAF, THF, 0 °C, 1 h; **ii)** oxalyl chloride, DMSO, Et_3N, DCM, –78 °C to RT, 2 h.

When diketone **2.133** was treated with LHMDS the starting material was fully recovered (*Scheme 117*).



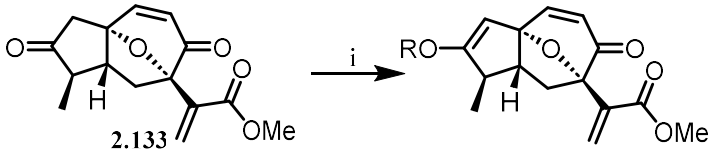
2.133 2.134

Scheme 117 Attempted oxa-bridge cleavage of **2.133** under basic conditions. **Reagents and conditions: i)** 1.2 eq. LHMDS, THF, –78 °C to 0 °C.

Thinking to apply the push and pull idea to this enone, the synthesis of various silyl enol ethers was attempted. In general, these attempts led to either complex mixtures or incomplete reactions (*Table 34*) but the triethylsilyl enol ether **2.136** could be formed cleanly (*Entry 6*).

With various silyl enol ethers in hand, efforts moved on to effecting the cleavage step. Exposure of trimethylsilyl enol ether **2.135** to BF_3 resulted in a new intermediate (TLC) but this intermediate did not survive the work-up and ketone substrate **2.133** was returned (*Table 35, Entry 1*). If this intermediate was, in fact, the target product **2.138** (or its silyl ether), the α-hydroxyketone might be stabilised by complexation with excess Lewis acid. Based on this, different additives were included, all unsuccessfully. Only acetic anhydride led to a new product, generating a mixture containing compound **2.139** (*Entry 2*). Other reagents only gave ketone **2.133** (*Entries 3,4*).

Table 34 Silylation of keto-enone **2.133**.

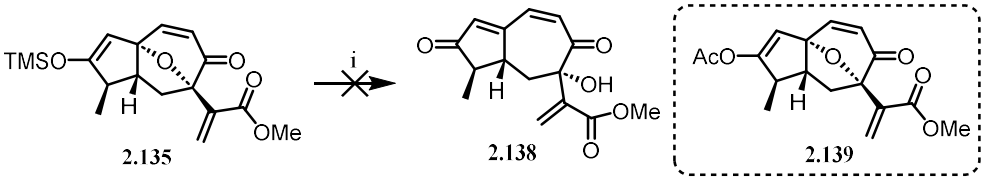


2.133

2.135 R = TMS
2.136 R = TES
2.137 R = TBS

Conditions (i) in THF, –78 °C to 0 °C, 2 h			
Entry	Reagent (eq.)	Base (eq.)	Result
1	TMSCl (4)	LHMDS (1.2)	**135**: **133** = 2:1
2	TMSCl (4)	LHMDS (2.8)	**135**: **133** = 1.3:1
3	TBSCl (3)	KHMDS (2.8)	decomposed
4	TIPSOTf (4)	KHMDS (2.8)	complex
5	TBSOTf (4.8)	KHMDS (1.4)	**137**: **133** = 1.2:1
6	TESCl (5)	KHMDS (1.4)	**136**

Table 35 Attempted oxa-bridge cleavage of TMS enol ether **2.135**.



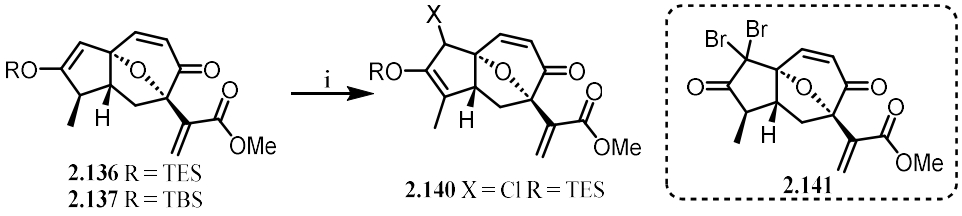
2.135 **2.138** **2.139**

Entry	Conditions (i)	Result
1	2.4 eq. BF_3•OEt_2, THF, –78 °C	**2.133**
2	2.4 eq. BF_3•OEt_2, 20 eq. Ac_2O, THF, –78 °C to RT	**2.139**/**2.133** = 2:1
3	22 eq. BF_3•OEt_2, 6 eq. TBSOTf, THF, –78 °C to RT	**2.133**
4	22 eq. BF_3•OEt_2, 20 eq. MeI, THF, –78 °C to RT	**2.133**

Halogenation, paralleling the reactions of **2.124** and **2.125** above, was also attempted (*Table 36*). Bromination with 1.5 eq. NBS led to *gem*-dibromide **2.141** (*Entry 1*); decreasing the loading of NBS failed to improve the reaction (*Entry 2*). Similar results were achieved with TBS enol ether **2.137** (*Entry*

3). Attempted chlorination of the TES enol ether led to a complex crude mixture but, in contrast to bromination, most of the crude consisted of isolable products, among which the desired allylic chloride **2.140** was identified and isolated (*Entry 4*).

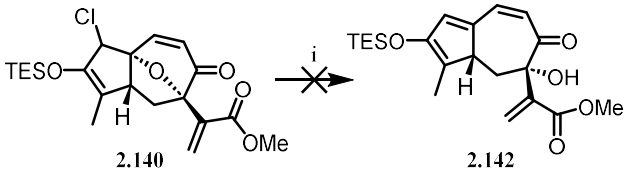
Table 36 Halogenation of silyl enol ethers.



Entry	Substrate	Reagent (eq.)	Solvent	Temperature (°C)	Result
1	**2.136**	NBS (1.5)	THF	0	**2.141**
2	**2.136**	NBS (1.2)	THF	0	complex
3	**2.137**	NBS (1.5)	THF	0	complex
4	**2.136**	NCS (1)	DCM	40	**16% 2.140**

Table 37 summarises the few attempts made to effect 1,2-elimination of the chloroether functionality in compound **2.140**. The widely used conditions with Zn[52] gave a complex crude mixture, possibly indicating over-reduction products (*Entries 1,2*). Use of *tert*-butyllithium led only to decomposed products (*Entry 3*).

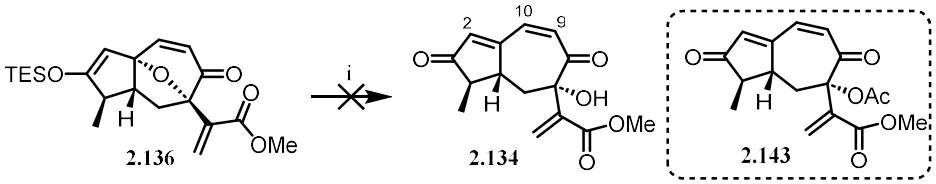
Table 37 Attempted elimination of chloroether **2.140** into diene **2.142.**



Entry	Conditions (i)	Result
1	Zn, MeOH, 70 °C	complex
2	Zn, MeOH, 100 °C	complex
3	*t*-BuLi, THF, –78 °C	complex

Reviewing these failed experiments, the conditions that led to the detection of non-isolable intermediate assigned as diene **2.134** came back into focus but this time using the more stable TES enol ether **2.136**. Here, more effort was put into capturing the proposed intermediate (*Table 38*). Lewis acid-mediated acetylation generated the intermediate (TLC) immediately but, after the work-up, only deprotected ketone **2.133** and enol acetate **2.139** were isolated (*Entry 1*). In deuterated solvent, monitored by NMR spectroscopy, the reaction generated a compound containing two enone groups (6.18 ppm dt for H10, 6.00 ppm d for H9 and 5.83 ppm d for H2), consistent with target product **2.134** (*Appendix 17*). Trying to capture the alcohol with a trimethylsilyl group failed (*Entry 3*), while heating the substrate with $ZnCl_2$ led to a complex mixture. Encouragingly, a combination of acetic anhydride/$ZnCl_2$/triethylamine gave the acetylated alcohol **2.143**, but in poor yield (*Entries 4,5*). Triethylamine was not necessary for the generation of product **2.143** but without the base an unknown side-product was generated, making purification more difficult (*Entry 6*). Finally, optimisation by controlling the reagent ratios and decreasing the reaction temperature led to a perfect yield for this step (*Entry 7*).

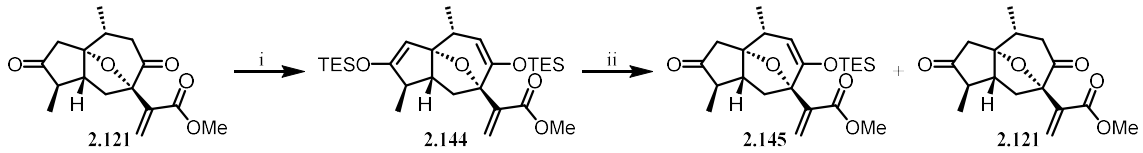
Table 38 Oxa-bridge cleavage of TES enol ether **2.136**.



Entry	Conditions (i)	Result
1	Ac_2O, $ZnCl_2$, toluene	**2.133** and **2.139**
2	Ac_2O, $ZnCl_2$, d_6-benzene	**2.133** and **2.139**
3	Ac_2O, $ZnCl_2$, d_6-benzene then TMSCl, Et_3N	**2.133**
4	$ZnCl_2$, d_6-benzene, 90 °C then Ac_2O, 90 °C	complex
5[a]	Ac_2O, Et_3N, then $ZnCl_2$, d_6-benzene, 90 °C	**2.143**
6[a]	Ac_2O, $ZnCl_2$, d_6-benzene, 90 °C	**2.143** and unknown product
7	48 eq. Ac_2O, 20 eq. $ZnCl_2$, d_6-benzene then 2 eq. Et_3N	94% **2.143**

[a] In a sealed tube.

This successful ring-opening method was also tested with substrate **2.144**, which was obtained by double TES protection of diketone **2.121** (*Scheme 118*), but this reaction led to TES deprotection, giving the mono TES-protected ketone **2.145** and regenerating diketone **2.121**.

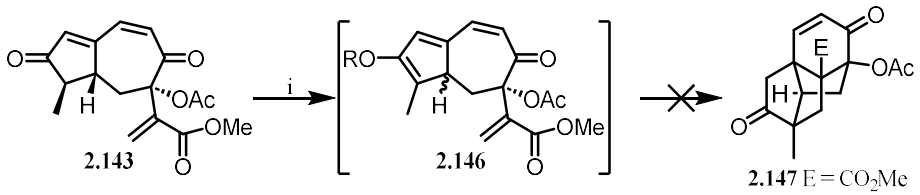


Scheme 118 Attempted ring cleavage of substrate **2.144**. **Reagents and conditions: i)** TESCl, KHMDS, THF, –78 °C, 0.5 h; **ii)** Ac_2O, $ZnCl_2$, Et_3N, benzene, 1 h.

The Ihara conditions used successfully in the model study were tested but with enone **2.143** these led to decomposition (*Table 39, Entry 1*). Considering that substrate **2.143** contains more functional groups than the model compound, milder conditions were explored aiming to avoid substrate decomposition. To this end, triethylsilyl chloride was substituted for trimethylsilyl chloride, and the reaction omitted $ZnCl_2$ and avoided high temperature, but these changes still did not lead to the desired cyclisation (*Entries 2–4*). Efforts then focused on generating the enol ether **2.146**. Various conditions were tested but none gave an isolable meaningful product (*Entries 4–7*). These decomposition results indicated there were other processes operating to destroy the substrate.

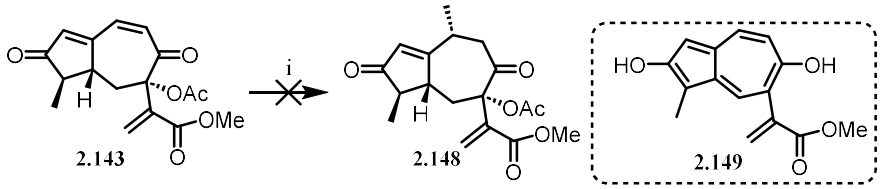
The conjugated dienone system that was crucial to the success of the oxa-bridge cleavage, by stabilising the generated enone, also confines the ring system to a plane, thus hindering access of the dienophile to the diene leading to failure of the IMDA reaction. To remove the need to distort the planar conjugated system in the IMDA reaction, several methods for conjugate methylation of dienone **2.143** were tested but most led to no reaction or to decomposition (*Appendix 18*). An exception among these was the reaction with lithium dimethylcuprate which led to a deep purple compound, assumed to be azulene derivative **2.149** or a related molecule (*Scheme 119*). The extended conjugation in **2.143** is apparently unreactive towards conjugate addition and so the cuprate reagent merely acted as a base to initiate elimination giving the aromatic product.

Table 39 Attempted IMDA reaction of substrate **2.143** into **2.147.**



Entry	Silylation reagent (eq.)	Base (eq.)	Solvent	Temperature	Result
1[a]	TMSCl (10) + $ZnCl_2$ (10)	Et_3N (10)	toluene	160	decomposed
2	TESCl (10) + $ZnCl_2$ (10)	Et_3N (10)	toluene	RT	n.r.
3[b]	TESCl (10)	Et_3N (10)	toluene	RT	decomposed
4	TESCl (1)	KHMDS (1)	THF	–78	part-decomposed
5	TESOTf (1)	Et_3N (1)	DCM	0 to RT	complex
6	TESCl (1)	imidazole (1)	DMF	0 to RT	n.r.
7	TESCl (1)	NaH (1)	DMF	0	decomposed

[a] In a sealed tube; [b] Then add $ZnCl_2$, 50 °C.

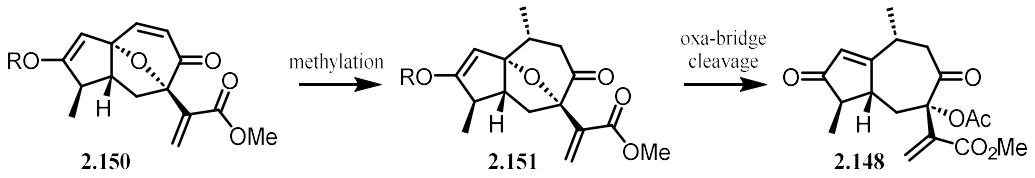


Scheme 119 Failed conjugate methylation of the dienone **2.143**. **Reagents and conditions: i)** MeLi, CuI, ether, 0 °C, 1 h

4.5.3 Third generation IMDA reaction substrate

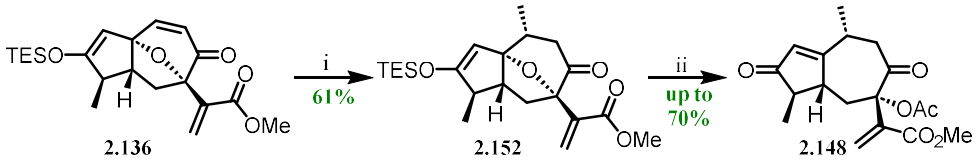
With the failure of both the IMDA reaction and 1,4-addition, dienone **2.143** was set aside in order to focus on other suitable substrates; however, it was still meaningful that a method for oxa-bridge cleavage had been discovered. This method was tested on various other substrates, including (5+2) cycloadduct **2.117** and dienol ether **2.124**, but both gave only desilylation. These results indicated that the enol in the five-membered ring plays a crucial role in activating the oxa-bridge and affording the stable enone structure, while the enone in the seven-membered ring could be safely removed. With these

considerations, the plan was revised to effect methyl addition to the silyl enol ether **2.150** then bridge cleavage (*Scheme 120*).



Scheme 120 The third plan of oxa-bridge cleavage.

Conjugate addition of methyl to TES enol ether **2.136** worked well to give the target product **2.152** (*Scheme 121*). The subsequent oxa-bridge cleavage step required some optimisation but, by adjusting the ratio of additives, the desired ring-opened product **2.148** could be achieved in 70% yield on a small scale (0.025 mmol). The reaction was found to be somewhat unreliable; when the reaction was scaled up, the yield suffered and sometimes only the diketone **2.121** was produced.

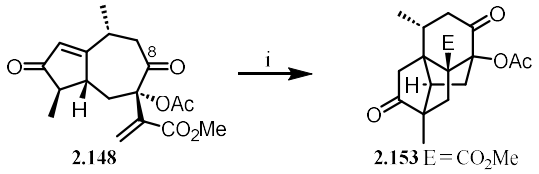


Scheme 121 Methyl addition to TES enol ether **2.136** and oxa-bridge cleavage into enone **2.148**. **Reagents and conditions: i)** MeLi, CuI, THF, 0 °C, 1 h; **ii)** 95 eq. $ZnCl_2$, 28 eq. Ac_2O, benzene, 1 h, then 18 eq. Et_3N, 1 h.

Enone **2.148** was considered a more promising substrate for the IMDA than dienone **2.143** because of its increased flexibility but there remained questions about the stability of this compound under the conditions needed for the IMDA reaction. Nevertheless, several conditions for the IMDA reaction were tested with enone **2.148** (*Table 40*). To preserve the many functional groups on substrate **2.148**, mild conditions reported by Kuwahara[53] were tested first, but no reaction occurred (*Entry 1*). Substituting bis(trimethylsilyl)amine for the stronger base triethylamine and increasing the reaction temperature introduced multiple side reactions (*Entry 2*). Application of the Ihara conditions used in the model system led to destruction of the starting material (*Entry 3*); the same result was obtained when the reaction temperature was decreased to 80 °C, and no reaction occurred when this method was conducted

at RT (*Entries 4,5*). Increasing the amount of trimethylsilyl chloride/triethylamine gave a complex mixture (*Entry 6*); by HRMS analysis, both the singly trimethylsilyl-protected and doubly trimethylsilyl-protected enol ether were detected, suggesting that in the initial enolisation step, both ketones react and it was supposed that the unwanted C8 trimethylsilyl enol ether might interfere with the dienophile's approach to the diene. Trimethylsilyl triflimide, previously shown to be an effective catalyst for Diels–Alder reactions and tolerating multiple functional groups,[26] led only to decomposition (*Entry 7*). No reaction occurred in an attempted base-catalysed double Michael addition (*Entry 10*), while increasing the loading of base led to decomposition (*Entry 11*). Attempts to protect the enolate intermediate in the base-mediated reaction also failed (*Entry 12*). Overall, the reaction requires deprotonation to generate the diene, however the seven-membered ring contains fragile functional groups which are readily destroyed by basic conditions.

Table 40 Attempted IMDA reaction of susbtrate **2.148** into **2.153.**

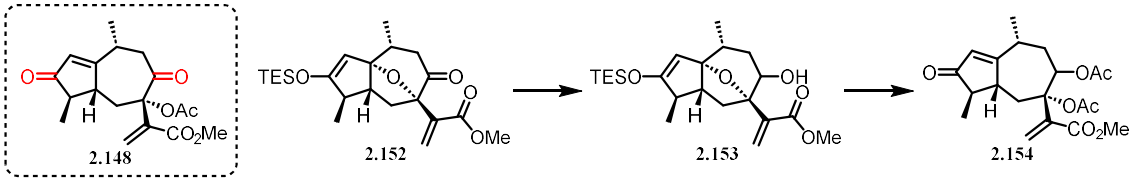


2.148 **2.153** E = CO_2Me

Entry	Conditions (i)	Result
1	5 eq. TMSOTf, 6 eq. HMDS, DCE, 0 °C	n.r.
2	10 eq. TMSOTf, 10 eq. Et_3N, benzene, 70 °C	complex
3	10 eq. TMSCl, 10 eq. Et_3N, 10 eq. $ZnCl_2$, toluene, 160 °C	decomposed
4	10 eq. TMSCl, 10 eq. Et_3N, 10 eq. $ZnCl_2$, toluene, 80 °C	decomposed
5	10 eq. TMSCl, 10 eq. Et_3N, 10 eq. $ZnCl_2$, toluene	n.r.
6	20 eq. TMSCl, 20 eq. Et_3N, 10 eq. $ZnCl_2$, benzene	complex
7	As *Entry 6* then 1 eq. $TMSNTf_2$	decomposed
8	1 eq. $TMSNTf_2$, benzene	complex
9	3 eq. $TMSNTf_2$, 2 eq. Et_3N, toluene	complex
10	0.3 eq. KO*t*-Bu, THF, 0 °C	n.r.
11	1 eq. KO*t*-Bu, THF, 0 °C	decomposed
12	2.5 eq. TESCl, 1 eq. KHMDS, THF, –78 °C	decomposed

4.5.4 Final version and IMDA reaction

From *Entry 6* in *Table* , it was worth noting that the cycloheptanone interfered with the initial enolisation step; therefore, it was suggested to remove this carbonyl group before the IMDA reaction. After the oxa-bridge cleavage, substrate **2.148** contains two ketone groups that would require selective reduction; therefore substrate **2.152**, with only one ketone group, was chosen for reduction (*Scheme 122*). It was expected that alcohol **2.153** would need to be protected during the ring-opening step to prevent its re-cyclisation as discussed earlier.



Scheme 122 Plan to remove the cycloheptanone carbonyl in substrate **2.148**.

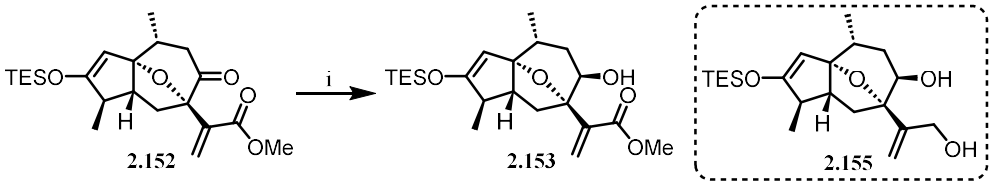
Various reduction methods were attempted with ketone **2.152** (*Table 41*). The commonly used $NaBH_4$/MeOH conditions afforded a complex mixture including desilylation (*Entry 1*). Milder conditions gave no reaction (*Entries 2–4*); however, DIBAL-H reactivity was improved in toluene and diol **2.155** was detected (*Entry 5*). With just 1 eq. DIBAL-H reduction of both the ester and ketone groups occurred unselectively (*Entry 6*). $LiBH_4$, as an analogue of $NaBH_4$ that can be used in aprotic solvents, was then considered. With excess $LiBH_4$ in ether at 0 °C, over-reduction occurred and the product was too unstable to be isolated (*Entry 7*). Decreasing the reaction temperature led to a new product which could be detected by TLC but this disappeared on reaching room temperature (*Entry 8*). Finally, maintaining the reaction temperature at –78 °C and quenching at this temperature resulted in the desired selective reduction product **2.153** (*Entry 9*) as a single diastereomer in which the configuration of the 2°-alcohol was assigned retrospectively, see below.

Oxa-bridge cleavage was then conducted with alcohol **2.153** and the target product **2.156** was achieved in satisfactory yield using the method developed previously (*Scheme 123*); however, similarly to its

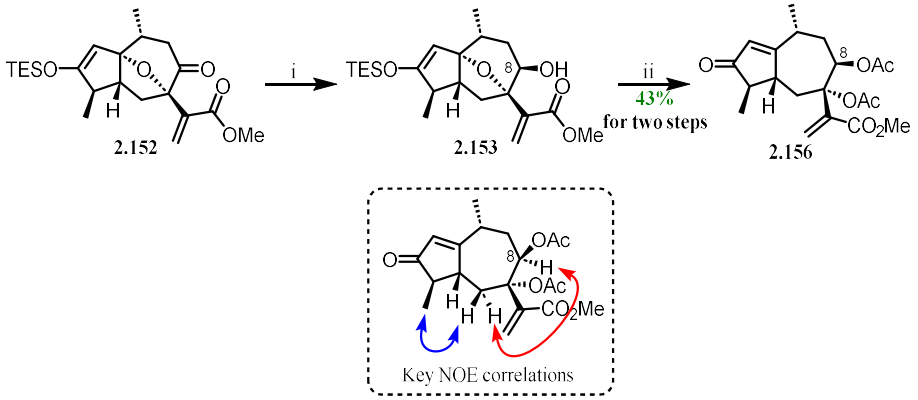
precursor **2.152**, the yield was only reproducible on a small scale (0.022 mmol). The C8 β-acetoxy configuration was confirmed by the long range n.O.e correlations shown (*Appendix 19*).

In an attempt to improve on the acetate protecting group, protection of the 1,2-diol using triphosgene was tested but the reaction gave a complicated mixture (*Scheme 124*).

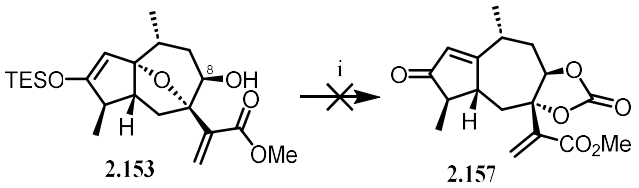
Table 41 Selective reduction of substrate **2.152** into **2.153.**



Entry	Reducing reagent (eq.)	Solvent	Temperature (°C)	Result
1	$NaBH_4$ (2)	MeOH	RT	complex
2	$NaBH_4$ (2)	MeOH/DCM (1:1)	–78	n.r.
3	DIBAL-H (1)	THF	–78	n.r.
4	DIBAL-H (3)	Et_2O	–78	n.r.
5	DIBAL-H (2)	toluene	–78	mixture containing **2.155**
6	DIBAL-H (1)	toluene	–78	unselective
7	$LiBH_4$ (3)	Et_2O	0	decomposed on work-up
8	$LiBH_4$ (6)	Et_2O	–78 to 0	decomposed on work-up
9	$LiBH_4$ (3)	Et_2O	–78	**2.153**



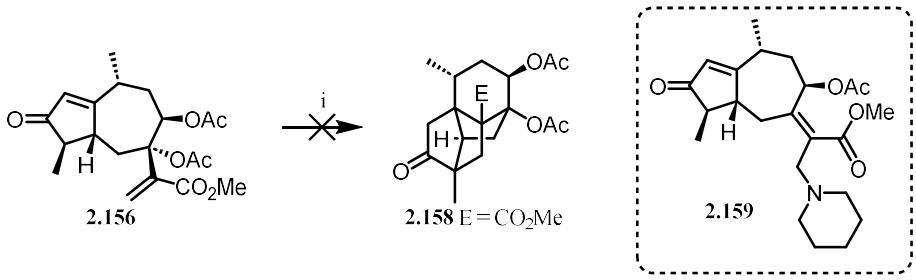
Scheme 123 Reduction of ketone **2.152** and further oxa-bridge cleavage into enone **2.156**. **Reagents and conditions: i)** $LiBH_4$, ether, –78 °C; **ii)** $ZnCl_2$, Et_3N, benzene, 1 h, then Et_3N, 1 h.



Scheme 124 Attempt to protect the forming 1,2-diol as its cyclic carbonate. **Reagents and conditions: i)** triphosgene, $ZnCl_2$, benzene, 1 h then Et_3N, 1 h.

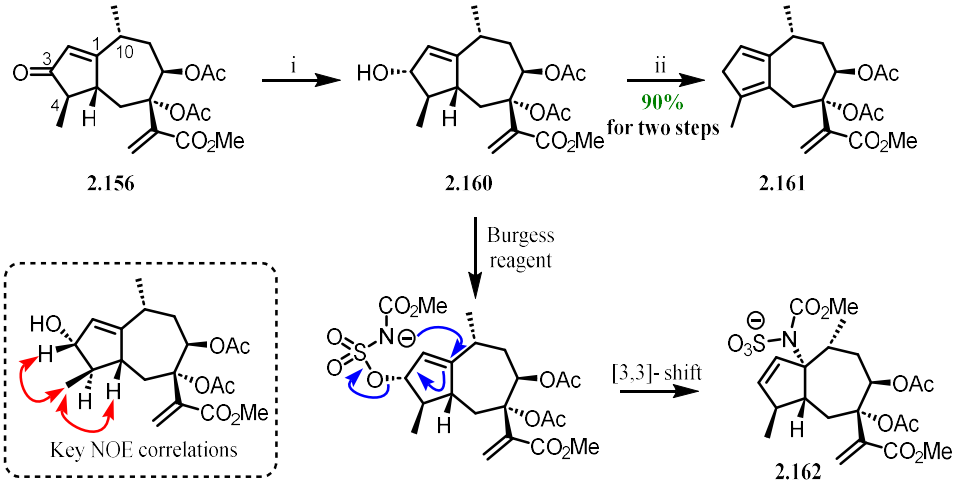
The IMDA reaction was then tested with substrate **2.156** (*Table 42*). The Lewis acid catalysed conditions still resulted in a complex mixture even though the C8 carbonyl was no longer present (*Entry 1*), and conditions for base-catalysed double Michael addition gave no reaction (*Entry 2*). The nucleophilic base piperidine was then tested, aiming to form an activated iminium intermediate but, from the crude product mixture, it was concluded that piperidine only attacked the unsaturated ester, removing the acetate group and giving the unstable product **2.159** (*Entry 3*). To check the possibility of forming an enolate from ketone **2.156**, the substrate was reacted with strong base then quenched with D_2O at –78 °C (*Entry 4*) but no deuterium incorporation could be detected, indicating that deprotonation failed. With more than 1 eq. of KHMDS the substrate decomposed (*Entry 5*).

Table 42 Attempted IMDA reactions of substrate **2.156** into **2.158.**



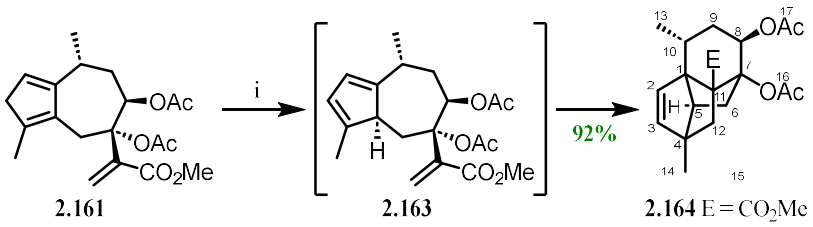
Entry	Conditions (i)	Result
1	5 eq. $TMSNTf_2$, 4.5 eq. Et_3N, toluene, RT to 50 °C	complex
2	0.76 eq. KO*t*-Bu, THF, 0 °C	n.r.
3	1 eq. piperidine, toluene	**2.159**
4	0.95 eq. KHMDS, THF, –78 °C then D_2O	n.r.
5	5 eq. KHMDS, THF, –78 °C	decomposed

Since enolisation of the cyclopentenone proved problematic, the strategy was revised in order to produce a cyclopentadiene unambiguously (*Scheme 125*). 1,2-Reduction of the ketone under Luche conditions led to allylic alcohol **2.160** with a *syn* relationship between C3-OH and C4-H (*Appendix 20*). The elimination step was expected to benefit from this relative configuration since a *syn* elimination could be set up with Burgess reagent, avoiding complications from a potential E1 mechanism. The potential side-reaction of [3,3]-sigmatropic rearrangement, leading to carbamate **2.162**, was inhibited by controlling the reaction temperature, and diene **2.161** was obtained as the major product, formed by sigmatropic [1,5]-H shift following the elimination.



Scheme 125 Conversion of enone **2.156** into diene **2.161**. **Reagents and conditions: i)** $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 1 h; **ii)** Burgess reagent, benzene, 32 °C.

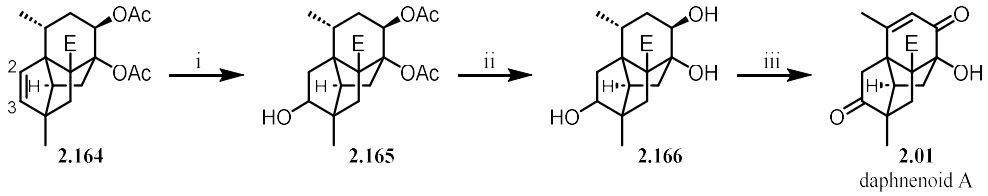
Substrate **2.161** contains a diene and dienophile suitable for IMDA reaction. Stirring this compound in toluene at 160 °C in a pressure tube finally gave the desired IMDA product **2.164**. In contrast to the model cyclised product **2.55**, compound **2.164** was found to be very stable and could be obtained pure in excellent yield following column chromatography (*Scheme 126*). The special ring system was confirmed by a series of characteristic features of the NMR spectroscopic data: (a) two mutually-coupling doublet alkene protons indicating H(2) and H(3); (b) H(12) is split into an AB-system; (c) HMBC showed correlations of C(12)-H(14), C(12)-H(5), C(3)-H(12) and C(1)-H(12). Under the high reaction temperature, the substrate diene undergoes a series of rapid sigmatropic [1,5]-H shifts such that the desired regioisomer with the α-C5-H is efficiently trapped as it forms.



Scheme 126 Successful IMDA reaction of **2.161** leading to tetracycle **2.164**. **Reagents and conditions: i)** toluene, 160 °C, pressure tube.

5. Progress towards daphnenoid A

This successful IMDA reaction is much more meaningful than the model product **2.55** as it contains the full carbon skeleton of the natural product and also contains sufficent functionality for conversion into daphnenoid A. It also contains a C2-C3 alkene that is a key structural feature of artatrovirenols A and B. The first proposed plan to complete the synthesis of daphnenoid A was as shown in *Scheme 127*. Here, the alkene would undergo hydroboration-oxidation to give alcohol **2.165**, predicted to show the desired regioselectivity based on an examination of molecular models, then double acetate hydrolysis would result in triol **2.166**, which would be oxidised fully to install both the ketone and the enone, delivering the natural product daphnenoid A in three steps.

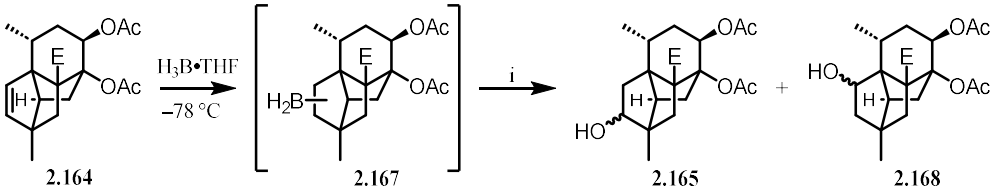


Scheme 127 Three-step plan to convert IMDA adduct **2.164** into daphnenoid A **2.01** [E = CO_2Me].

During the hydroboration step (*Table 43*), use of H_2O_2 oxidation in methanol destroyed the substrate, and no material was recovered upon work-up (*Entry 1*). Under basic conditions, it is likely that the acetate groups were cleaved and the resulting triol **2.166** remained in the aqueous phase during work-up. Milder conditions using $NaBO_3$ gave the hydroxylation successfully, but borane itself provided poor

regioselectivity and so the product was formed as a pair of regioisomers (**2.165** and **2.168** in nearly 1:1 ratio) (*Entry 2*).

Table 43 Hydroboration and oxidation of **2.164** into **2.165** [E = CO_2Me].

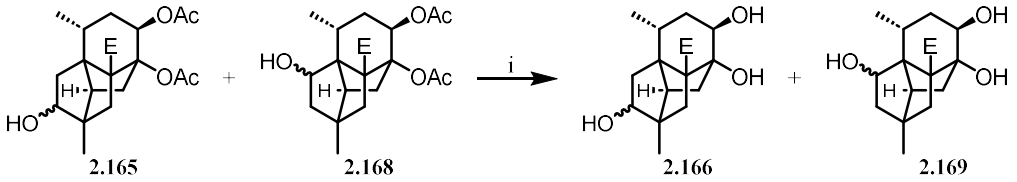


Entry	Oxidation conditions	Result
1	H_2O_2, K_2CO_3, MeOH	decomposed
2	$NaBO_3$•$4H_2O$, H_2O	**2.165** + **2.168**

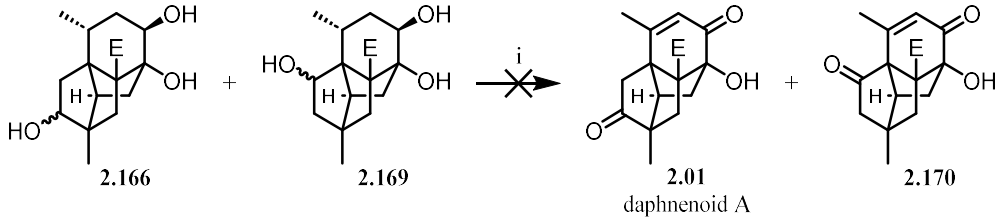
Deprotection of the acetates was tested with this alcohol mixture (*Table 44*). Lewis acid catalysed solvolysis using $ZrCl_4$, which has been reported as an effective method, failed for the **2.165**/**2.168** mixture, probably due to the sterically-hindered environment of the diol (*Entry 1*). A dilute acid-catalysed method gave no reaction (*Entry 2*). Base catalysis may have effected the reaction but the work-up removed any possible product into the aqueous phase (*Entries 3,4*). This problem was finally solved by using Amberlyst® 15 (hydrogen form) to neutralise the base, and the resulting mixture could be simply purified by filtration. After removal of the solvent, a complex without diacetate group peaks on NMR analysis was obtained which was assumed to be triols **2.166** and **2.169** (*Entry 5*).

The final step, oxidation of the two secondary alcohols into carbonyl groups, was tested with an IBX/DMSO system, but due to the very limited amount of substrate, nothing could be detected after reaction (*Scheme 128*), possibly because the product was dissolved by DMSO and hard to extract into the organic phase. Constraints on time in producing more substrate prevented further exploration on the synthesis of daphnenoid A.

Table 44 Solvolysis of diacetate **2.165/2.168** into triols **2.166/2.169** [E = CO_2Me].



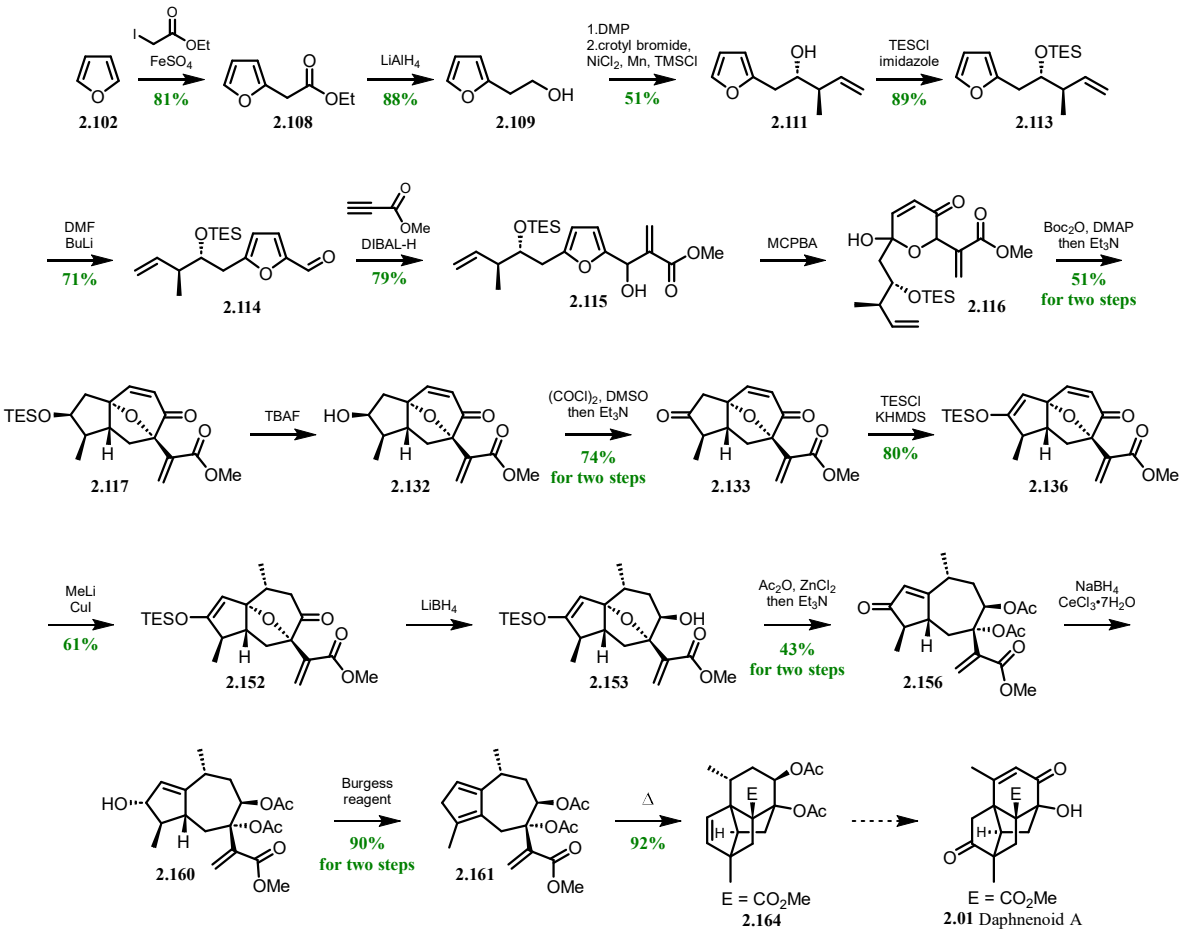
Entry	Conditions (i)	Result
1	$ZrCl_4$, MeOH	n.r.
2	1% HCl, MeOH	n.r.
3	K_2CO_3, MeOH	disappeared
4	1 eq. NaOMe, CD_3OD	n.r.
5	20 eq. NaOMe, MeOH, then quench with Amberlyst® 15	**2.166** and **2.169**



Scheme 128 Attempted oxidation of triol **2.166/2.169** into daphnenoid A **2.01** [E = CO_2Me]. **Reagents and conditions: i)** IBX, DMSO, RT, 1 h.

6. Conclusions and future work

This project aimed to complete the total synthesis of novel tetracyclic natural product daphnenoid A. A model study of the biomimetic IMDA reaction provided an efficient route towards the tetracyclic ring system. In the real synthesis (*Scheme 129*), oxidopyrylium (5+2) cycloaddition constructed the 5,7-fused bicyclic ring with multiple functional groups present and, after eventually finding a route to a successful IMDA substrate, the full carbon skeleton of daphnenoid A was achieved with high stereoselectivity and 1.1% overall yield in 17 steps. The final steps leading to daphnenoid A will continue within the group.



Scheme 129 Summary of the synthesis to an advanced intermediate towards daphnenoid A.

References

[1] P. Zhao, Z.-Y. Li, S.-Y. Qin, B.-S. Xin, Y.-Y. Liu, B. Lin, G.-D. Yao, X.-X. Huang and S.-J. Song, *J. Org. Chem.* **2021**, *86*, 15298–15306.

[2] a) U. R. Nayak and S. Dev, *Tetrahedron Lett.* **1963**, *4*, 243–246; b) A. Matsuo, H. Nozaki, M. Shigemori, M. Nakayama and S. Hayashi, *Experientia* **1977**, *33*, 991–992; c) M. Dong, B. Cong, S.-H. Yu, F. Sauriol, C.-H. Huo, Q.-W. Shi, Y.-C. Gu, L. O. Zamir and H. Kiyota, *Org. Lett.* **2008**, *10*, 701–704; d) F. Dos S. Junior, L. Velozo, E. De Carvalho, A. Marques, R. Borges, A. Trindade, M. Dos Santos, A. De Albuquerque, F. Costa, M. Kaplan and M. De Amorim, *Molecules* **2013**, *18*, 13520–13529.

[3] L.-H. Su, C.-A. Geng, T.-Z. Li, Y.-B. Ma, X.-Y. Huang, X.-M. Zhang and J.-J. Chen, *J. Org. Chem.* **2020**, *85*, 13466–13471.

[4] K.-I. Takao, R. Munakata and K.-I. Tadano, *Chem. Rev.* **2005**, *105*, 4779–4807.

[5] a) M. Juhl and D. Tanner, *Chem. Soc. Rev.* **2009**, *38*, 2983; b) M. M. Heravi and V. F. Vavsari, *RSC Advances* **2015**, *5*, 50890–50912.

[6] a) F. Bohlmann, C. Zdero, J. Jakupovic, H. Robinson and R. M. King, *Phytochemistry* **1981**, *20*, 2239–2244; b) S. Melching and W. A. König, *Phytochemistry* **1999**, *51*, 517–523; c) S. C. Pinto, G. G. Leitão, H. R. Bizzo, N. Martinez, E. Dellacassa, F. M. dos Santos, F. L. P. Costa, M. B. d. Amorim and S. G. Leitão, *Tetrahedron Lett.* **2009**, *50*, 4785–4787; d) P. Joseph-Nathan, S. G. Leitão, S. C. Pinto, G. G. Leitão, H. R. Bizzo, F. L. P. Costa, M. B. d. Amorim, N. Martinez, E. Dellacassa, A. Hernández-Barragán and N. Pérez-Hernández, *Tetrahedron Lett.* **2010**, *51*, 1963–1965.

[7] A. Y. Hong and B. M. Stoltz, *Angew. Chem. Int. Ed.* **2012**, *51*, 9674–9678.

[8] T. Magauer, J. Mulzer and K. Tiefenbacher, *Org. Lett.* **2009**, *11*, 5306–5309.

[9] K. C. Nicolaou, H. Ding, J.-A. Richard and D. Y. K. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 3815–3818.

[10] P. A. Peixoto, R. Severin, C.-C. Tseng and D. Y. K. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 3013–3016.

[11] M. Ihara and K. Fukumoto, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1010–1022.

[12] T. Kametani and T. Honda, *Heterocycles* **1981**, *16*, 1673–1676.

[13] M. Ihara, M. Toyota, K. Fukumoto and T. Kametani, *Tetrahedron Lett.* **1984**, *25*, 3235–3238.

[14] M. Ihara, Y. Takino, K. Fukumoto and T. Kametani, *Tetrahedron Lett.* **1988**, *29*, 4135–4138.

[15] M. Ihara, M. Suzuki, K. Fukumoto and C. Kabuto, *J. Am. Chem. Soc.* **1990**, *112*, 1164–1171.

[16] a) K. Takasu, S. Mizutani, M. Noguchi, K. Makita and M. Ihara, *J. Org. Chem.* **2000**, *65*, 4112–4119; b) M. Ihara, K. Makita and K. Takasu, *J. Org. Chem.* **1999**, *64*, 1259–1264; c) K. Takasu, S. Mizutani, M. Noguchi, K. Makita and M. Ihara, *Org. Lett.* **1999**, *1*, 391–394; d) K. Makita, K. Fukumoto and M. Ihara, *Tetrahedron Lett.* **1997**, *38*, 5197–5200; e) M. Ihara, K. Makita, Y. Fujiwara, Y. Tokunaga and K. Fukumoto, *J. Org. Chem.* **1996**, *61*, 6416–6421.

[17] A. S. Burns and S. D. Rychnovsky, *J. Am. Chem. Soc.* **2019**, *141*, 13295–13300.

[18] P. R. Carlson, A. S. Burns, E. A. Shimizu, S. Wang and S. D. Rychnovsky, *Org. Lett.* **2021**, *23*, 2183–2188.

[19] a) D. S. Pisoni, D. Gamba, C. V. Fonseca, J. S. D. Costa, C. L. Petzhold, E. R. D. Oliveira and M. A. Ceschi, *J. Braz. Chem. Soc.* **2006**, *17*; b) F. J. Moreno-Dorado, F. M. Guerra, F. L. Manzano, F. J. Aladro, Z. a. D. Jorge and G. M. Massanet, *Tetrahedron Lett.* **2003**, *44*, 6691–6693.

[20] M. Kourgiantaki, G. G. Bagkavou, C. I. Stathakis and A. L. Zografos, *Org. Chem. Front.* **2023**, *10*, 2095-2114.

[21] S. T. R. Müller, T. Hokamp, S. Ehrmann, P. Hellier and T. Wirth, *Chem. Eur. J.* **2016**, *22*, 11940–11942.

[22] M. Miyashita, D. Tanaka, T. Shiratani and H. Irie, *Chem. Pharm. Bull.* **1992**, *40*, 1614–1615.

[23] A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen, A. J. Lovey and W. P. Stephens, *J. Org. Chem.* **1978**, *43*, 138–147.

[24] M.-L. Leroux, T. Le Gall and C. Mioskowski, *Tetrahedron: Asymmetry* **2001**, *12*, 1817–1823.

[25] W. E. Noland, *Chem. Rev.* **1955**, *55*, 137–155.

[26] a) B. Mathieu and L. Ghosez, *Tetrahedron Lett.* **1997**, *38*, 5497–5500; b) B. Mathieu and L. Ghosez, *Tetrahedron* **2002**, *58*, 8219–8226.

[27] G. Blay, B. Garcia, E. Molina and J. R. Pedro, *Org. Lett.* **2005**, *7*, 3291–3294.

[28] M. E. Krafft and R. A. Holton, *J. Org. Chem.* **1984**, *49*, 3669–3670.

[29] C. Uyeda, A. R. Rötheli and E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2010**, *49*, 9753–9756.

[30] a) Z. Yin, Y. He and P. Chiu, *Chem. Soc. Rev.* **2018**, *47*, 8881–8924; b) K. E. O. Ylijoki and J. M. Stryker, *Chem. Rev.* **2013**, *113*, 2244–2266.

[31] a) J. B. Hendrickson and J. S. Farina, *J. Org. Chem.* **1980**, *45*, 3359–3361; b) J. B. Hendrickson and J. S. Farina, *J. Org. Chem.* **1980**, *45*, 3361–3363.

[32] H. Pellissier, *Adv. Synth. Catal.* **2018**, *360*, 1551–1583.

[33] a) P. A. Wender, K. D. Rice and M. E. Schnute, *J. Am. Chem. Soc.* **1997**, *119*, 7897–7898; b) P. A. Wender, H. Y. Lee, R. S. Wilhelm and P. D. Williams, *J. Am. Chem. Soc.* **1989**, *111*, 8954–8957; c) P. A. Wender, H. Kogen, H. Y. Lee, J. D. Munger, R. S. Wilhelm and P. D. Williams, *J. Am. Chem. Soc.* **1989**, *111*, 8957–8958; d) P. A. Wender and F. E. McDonald, *J. Am. Chem. Soc.* **1990**, *112*, 4956–4958.

[34] P. A. Roethle, P. T. Hernandez and D. Trauner, *Org. Lett.* **2006**, *8*, 5901–5904.

[35] Y. Li, C. C. Nawrat, G. Pattenden and J. M. Winne, *Org. Biomol. Chem.* **2009**, *7*, 639–640.

[36] G. Mei, X. Liu, C. Qiao, W. Chen and C.-C. Li, *Angew. Chem. Int. Ed.* **2015**, *54*, 1754–1758.

[37] X. Liu, J. Liu, J. Zhao, S. Li and C.-C. Li, *Org. Lett.* **2017**, *19*, 2742–2745.

[38] P. G. Sammes and L. J. Street, *J. Chem. Soc., Chem. Commun.* **1983**, 666–668.

[39] P. G. Sammes, L. J. Street, *J. Chem. Soc., Chem. Commun.* **1982**, 1056–1057

[40] P. Magnus and L. Shen, *Tetrahedron* **1999**, *55*, 3553–3560.

[41] P. Magnus, M. J. Waring, C. Ollivier and V. Lynch, *Tetrahedron Lett.* **2001**, *42*, 4947–4950.

[42] S. Celanire, F. Marlin, J. E. Baldwin and R. M. Adlington, *Tetrahedron* **2005**, *61*, 3025–3032.

[43] a) J. Son, *Bull. Korean Chem. Soc.* **2009**, *30*, 2517–2518; b) J.-H. Sohn, *Bull. Korean Chem. Soc.* **2010**, *31*, 1841–1842; c) J.-H. Sohn, *Bull. Korean Chem. Soc.* **2014**, *35*, 23–24.

[44] S. J. Hobson and R. Marquez, *Org. Biomol. Chem.* **2006**, *4*, 3808.

[45] A. Vilsmeier and A. Haack, *Berichte der Deutschen Chemischen Gesellschaft (A and B Series)* **1927**, *60*, 119–122.

[46] T. Tsuda, T. Yoshida and T. Saegusa, *J. Org. Chem.* **1988**, *53*, 1037–1040.

[47] E. Baciocchi, E. Muraglia and G. Sleiter, *J. Org. Chem.* **1992**, *57*, 6817–6820.

[48] A. Fürstner and N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357.

[49] Y. Toda, M. Shimizu, T. Iwai and H. Suga, *Adv. Synth. Catal.* **2018**, *360*, 2377–2381.

[50] A. I. Meyers, R. Hanreich and K. T. Wanner, *J. Am. Chem. Soc.* **1985**, *107*, 7776–7778.

[51] J. R. Rodríguez, L. Castedo and J. L. Mascareñas, *Synthesis* **2000**, *2000*, 980–984.

[52] T. Seiichi, S. Kiyohiro, S. Takumichi, S. Shigeki and O. Kunio, *Chem. Lett.* **1989**, *18*, 1777–1780.

[53] S. Kuwahara, S. Hamade, W. S. Leal, J. Ishikawa and O. Kodama, *Tetrahedron* **2000**, *56*, 8111–8117.

Experimental Details

General experimental

Unless specified otherwise, all reactions were carried out under nitrogen atmosphere in oven-dried glassware. Solvents were either used as commercially supplied or were purified by standard techniques. Tetrahydrofuran was freshly distilled over sodium and benzophenone prior to use. Toluene, DCM, DME, 1,4-dioxane and DMF were obtained from the communal solvent-drying apparatus of the Chemistry Research Laboratory, University of Oxford unless otherwise stated. All other reagents were used as obtained from the supplier.

Thin-layer chromatography (TLC) was performed on Merck DC-Alufolien 60 F254 0.2 mm pre-coated plates and visualised with ultraviolet light (λ_{max} = 254 nm), basic $KMnO_4$, vanillin stain, or phosphomolybdic acid (PMA) stain. Column chromatography was performed on Merck Geduran® 60 SiO_2 (40–60 μm) unless otherwise stated. Retention factors (R_f) of each product are quoted with the solvent system used for TLC.

^1H and ^{13}C NMR spectra were recorded using Bruker DPX-200, Bruker AVF-400, Bruker AVG-400, Bruker AVH-400, Bruker NEO-600 and Bruker AV-700 spectrometers using $CDCl_3$ (or other deuterated solvent as specified). Chemical shifts are quoted in ppm relative to tetramethylsilane (δ = 0) and referenced during processing in MestReNova to the solvent resonances. Coupling constants (J) are quoted in Hz, rounded to the nearest 0.5 Hz. The ^1H NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons assignment). All NMR assignments use arbitrary numbering independent from IUPAC naming due to the difficulty of assigning multiple ring systems in some molecules and were assisted using two-dimensional (COSY, HSQC, HMBC, NOESY) NMR spectroscopy. Where an assignment could not be made unambiguously, possible assignments are listed.

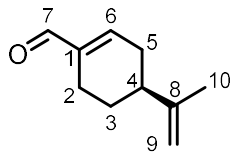
Low resolution mass spectrometry (LRMS) (EI) data were recorded on a Waters LCT Premier mass spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker μTOF mass spectrometer. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film on a diamond ATR module. Only selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

UV-vis spectra were acquired on a Varian CARY50 spectrometer at 30 °C using 1 cm pathlength quartz cuvettes. Specific rotations were determined using a Perkin-Elmer 241 polarimeter at a wavelength 589 nm and at 25 °C, and are quoted in units of 10^{-1} deg cm^2 g^{-1} ; concentrations (*c*) are expressed in g/100 mL. Melting points were recorded in degrees Celsius (°C), using a Griffin melting point apparatus. Boiling points for compounds purified by vacuum distillation were calculated using the Sigma Aldrich Pressure-Temperature Nomograph.

Compound names are as generated by CambridgeSoft ChemBioDraw Ultra 18.2 and procedures are organised in numerical order as they appear in each chapter.

Experimental procedures

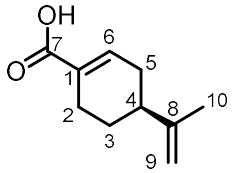
(*S*)-Perillyl aldehyde[1] (1.149)



To a solution of (*S*)-perillyl alcohol (**1.121**) (3.00 g, 19.7 mmol) in DCM (30 mL) in a 100 mL flask was added Dess–Martin periodinane (10.00 g, 23.58 mmol). The solution was stirred at RT for 2 h and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (pentane/EtOAc, 30:1) to afford product **1.149** as a colourless oil (2.37 g, 80%).

$\mathbf{R}_f$ 0.38 (pentane/EtOAc, 20:1); $\mathbf{[\alpha]_D^{25}}$ –137 (*c* 0.65, DCM) {lit., [1b] $\mathbf{[a]_D^{20}}$ -121° (*c* 0.27, EtOH)}; δ_H (400 MHz, $CDCl_3$) 9.37 (1H, s, H7), 6.79 – 6.72 (1H, m, H6), 4.73 – 4.65 (2H, m, H9), 2.46 – 2.33 (2H, m, H5 & H2), 2.24 – 1.99 (3H, m, H5′, H2′ & H4), 1.90 – 1.80 (1H, m, H3), 1.69 (3H, s, H10), 1.45 – 1.31 (1H, m, H3′); δ_C (101 MHz, $CDCl_3$) 193.9 (C7), 150.6 (C6), 148.4 (C8), 141.3 (C1), 109.5 (C9), 40.7 (C4), 31.7 (C5), 26.4 (C3), 21.6 (C2), 20.7 (C10).

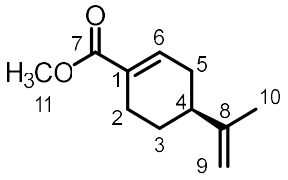
(*S*)-Perillyl acid[2] (1.150)



To a solution of $AgNO_3$ (5.10 g, 30.0 mmol) in water (15 mL) in a 100 mL flask was added a solution of NaOH (2.40 g, 60.0 mmol) in water (15 mL) and the resulting brown suspension was stirred at RT for 5 min. A solution of (*S*)-perillyl aldehyde (**1.149**) (2.16 g, 14.3 mmol) in ethanol (30 mL) was added and the resulting suspension was stirred for 3 h and then filtered. The filtrate was diluted with water (30 mL), washed with ether (50 mL), acidified with hydrochloric acid (4.0 M, 10 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to obtain product **1.150** as a white solid (2.10 g, 89%).

R_f 0.10 (pentane/EtOAc, 1:1); **M.p.** 127 °C; **$[\alpha]_D^{25}$** –72 (*c* 1.0, DCM) {lit.,[2b] **M.p.** 130–132 °C, **$[a]_D^{25}$** –97.7 (*c* 4.0, EtOH)}; **δ_H** (400 MHz, $CDCl_3$) 7.15 (1H, ddt, *J* = 5.5, 3.0, 1.5 Hz, H6), 4.81 – 4.70 (2H, m, H9), 2.53 – 2.42 (1H, m, H2), 2.41 – 2.32 (1H, m, H5), 2.29 – 2.20 (1H, m, H2′), 2.20 – 2.11 (2H, m, H4 & H5′), 1.97 – 1.85 (1H, m, H3), 1.75 (3H, s, H10), 1.55 – 1.39 (1H, m, H3′); **δ_C** (101 MHz, $CDCl_3$) 172.6 (C7), 148.7 (C8), 142.0 (C6), 129.4 (C1), 109.3 (C9), 40.0 (C4), 31.3 (C5), 27.0 (C3), 24.2 (C2), 20.7 (C10).

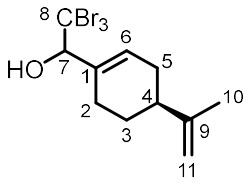
(*S*)-Methyl perillate[3] (1.151)



To a solution of (*S*)-perillic acid (**1.150**) (2.10 g, 12.7 mmol) in acetone (48 mL) in a 100 mL flask was added K_2CO_3 (2.60 g, 18.8 mmol) then iodomethane (1.58 mL, 25.4 mmol). The reaction mixture was stirred at 60 °C for 1.5 h then another aliquot of iodomethane (1.58 mL, 25.4 mmol) was added. The reaction mixture was stirred at 60 °C for 16 h then the solvent was removed under reduced pressure. Water (10 mL) and ether (40 mL) were added and the layers were separated. The aqueous layer was extracted with ether (2 × 30 mL); the combined organic layers were then dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (pentane/EtOAc, 30:1) to obtain ester **1.151** as a colourless oil (1.92 g, 84%).

$\mathbf{R}_f$ 0.67 (pentane/EtOAc, 30:1); $\mathbf{[\alpha]_D^{25}}$ –87 (*c* 0.87, DCM) {lit. $[\alpha]_D$ is not reported}; $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 7.02 – 6.91 (1H, m, H6), 4.74 (1H, m, H9), 4.70 (1H, dt, *J* = 2.0, 1.0 Hz, H9′), 3.71 (3H, s, H11), 2.51 – 2.40 (1H, m, H2), 2.36 – 2.27 (1H, m, H5), 2.27 – 2.19 (1H, m, H2′), 2.18 – 2.03 (2H, m, H4 & H5′), 1.91 – 1.83 (1H, m, H3), 1.73 (3H, s, H10), 1.51 – 1.39 (1H, m, H3′); $\mathbf{\delta_C}$ (101 MHz, $CDCl_3$) 167.8 (C7), 148.8 (C8), 139.2 (C6), 129.9 (C1), 109.2 (C8), 51.5 (C11), 40.1 (C4), 31.1 (C5), 27.1 (C3), 24.6 (C2), 20.7 (C10).

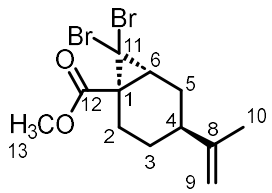
2,2,2-Tribromo-1-[(*S*)-4-(prop-1-en-2-yl)cyclohex-1-en-1-yl]ethan-1-ol (1.152)



To a solution of (*S*)-perillyl aldehyde (**1.149**) (75.0 mg, 0.50 mmol) and bromoform (65 μL, 0.75 mmol) in THF (5 mL) at –78 °C was added a solution of sodium bis(trimethylsilyl)amide in THF (1.0 M, 0.65 mL, 0.65 mmol) dropwise over 10 min. Upon completion of the addition, the reaction mixture was stirred for 4.5 h at –78 °C. The cold product mixture was diluted with water (10 mL), warmed to RT, transferred to a separatory funnel and extracted with ether (2 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue obtained was purified by flash column chromatography (pentane/EtOAc, 20:1) to afford product **1.152** as a pair of diasteromers (93.2 mg, 46%, dr = 2:1).

R_f 0.45 (pentane/EtOAc, 40:1); **IR** ν_{max}/cm^{-1}: 3556, 2937, 1643; **δ_H** (400 MHz, $CDCl_3$) 6.24 – 6.00 (1H, m, H6), 4.78 – 4.69 (2H, m, H11), 4.62 – 4.46 (1H, m, H7), 3.21 – 3.00 (1H, m, OH), 2.56 – 2.15 (4H, m, C2, C4 and C5), 2.13 – 1.96 (1H, m, C5′), 1.87 – 1.78 (1H, m, C3), 1.74 (3H, s, H10), 1.61 – 1.39 (1H, m, C3′); **δ_C** (101 MHz, $CDCl_3$) 149.3 (C9), 149.0 (C9), 133.8 (C1), 133.4 (C1), 132.3 (C6), 131.6 (C6), 109.1 (C11), 109.0 (C11), 88.5 (C7), 87.6 (C7), 53.6 (C8), 52.7 (C8), 40.9 (C4), 40.8 (C4), 40.3 (C4), 30.9 (C5), 30.7 (C5), 27.6 (C3), 27.3 (C3), 26.7 (C2), 26.0 (C2), 20.9 (C10), 20.7 (C10); **HRMS** (ESI+) *m/z* $[M+K]^+$ calcd. for $C_{11}H_{17}O^{79}Br_3K$ 440.8461, found, 440.8261.

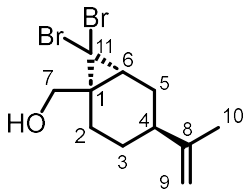
Methyl (1*S*,4*S*,6*R*)-7,7-dibromo-4-(prop-1-en-2-yl)bicyclo[4.1.0]heptane-1-carboxylate (1.153)



To a solution of (*S*)-methyl perillate (**1.151**) (1.07 g, 5.94 mmol) and bromoform (1.60 mL, 18.3 mmol) in THF (40 mL) was added a solution of sodium bis(trimethylsilyl)amide in THF (1.0 M, 9.0 mL, 9.0 mmol) dropwise over 30 min at –78 °C. Upon completion of the addition, the reaction mixture was stirred for 4.5 h at –78 °C. The cold product mixture was diluted with water (20 mL), and warmed to RT, transferred to a separatory funnel and extracted with EtOAc (2 × 50 mL). The organic layers were combined, washed with brine (70 mL), dried (Na_2SO_4) and concentrated. The residue obtained was purified by flash column chromatography (pentane/EtOAc, 30:1) to afford product **1.153** as a pale yellow oil (2.01 g, 97%).

R_f 0.67 (pentane/EtOAc, 30:1); **$[a]_D^{25}$** –71 (*c* 0.66 , DCM); **IR** ν_{max}/cm^{-1}: 2922, 1737, 1208; **δ_H** (400 MHz, $CDCl_3$) 4.71 (1H, m, H9), 4.67 (1H, dt, *J* = 2.0, 1.0 Hz, H9′), 3.77 (3H, s, H13), 2.60 (1H, dt, *J* = 15.5, 4.5 Hz, H2), 2.48 (1H, dd, *J* = 8.5, 1.5 Hz, H6), 2.13 (1H, tdd, *J* = 10.5, 6.0, 3.0 Hz, H4), 1.95 (1H, ddt, *J* = 15.5, 6.0, 1.0 Hz, H5), 1.88 – 1.71 (2H, m, H2′, H5′), 1.66 (3H, s, H10), 1.57 (1H, ddtd, *J* = 12.0, 4.5, 3.0, 1.5 Hz, H3), 1.15 (1H, dtd, *J* = 13.5, 12.0, 5.0 Hz, H3′); **δ_C** (101 MHz, $CDCl_3$) 170.0 (C12), 147.4 (C8), 108.8 (C9), 51.7 (C13), 38.4 (C11), 36.5 (C6), 35.1 (C1), 30.7 (C4), 24.7 (C3), 24.0 (C5), 23.9 (C2), 19.6 (C10); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{12}H_{17}O_2{}^{79}Br_2$ 350.9590, found, 350.9589.

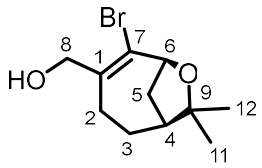
[(1*S*,4*S*,6*R*)-7,7-Dibromo-4-(prop-1-en-2-yl)bicyclo[4.1.0]heptan-1-yl]methanol (1.120)



To a solution of ester **1.153** (2.00 g, 5.72 mmol) in DCM (50 mL) in a 100 mL flask was added di*iso*butylaluminum hydride (1M solution in hexane, 12.0 mL, 12.0 mmol) at –78 °C. The mixture was stirred at -78 °C for 30 min, warmed to RT and stirred for an additional 2 h. The mixture was poured into ice water (50 mL) and acidified with 4M HCl (10 mL). The aqueous phase was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to yield product **1.120** as a white solid (1.76 g, 95%).

R_f 0.24 (pentane/EtOAc, 8:1); **M.p.** 72°C; **$[\alpha]_D^{25}$** –64 (*c* 3.6 , DCM); **IR** ν_{max}/cm^{-1}: 3240, 2923, 1642; **δ_H** (400 MHz, $CDCl_3$) 4.71 (1H, m, H9), 4.66 (1H, dt, *J* = 2.0, 1.0 Hz, H9′), 3.87 (1H, dd, *J* = 11.5, 7.5 Hz, H7), 3.68 (d, *J* = 11.5 Hz, 1H, H7′), 2.37 (1H, dt, *J* = 15.0, 4.5 Hz, H2), 2.12 (1H, dddd, *J* = 12.0, 10.0, 6.0, 3.0 Hz, H4), 1.99 – 1.85 (2H, m, H5 & OH), 1.75 – 1.64 (6H, m, H6 & H5′ & H2′ & H10), 1.63 – 1.52 (1H, m, H3), 1.15 (1H, tdd, *J* = 13.0, 12.0, 4.5 Hz, H3′); **δ_C** (101 MHz, $CDCl_3$) 149.2 (C8), 109.4 (C9), 71.3 (C7), 46.0 (C11), 38.2 (C4), 32.5 (C1), 31.5 (C6), 25.8 (C3), 25.4 (C5), 25.0 (C2), 20.6 (C10); **HRMS** (ESI+) *m/z* $[M+NH_4]^+$ calcd. for $C_{11}H_{20}NO^{79}Br_2$ 339.9906, found, 339.9895.

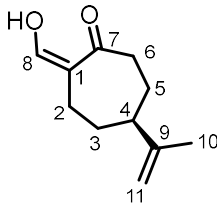
[(1*S*,6*S*)-5-Bromo-8,8-dimethyl-7-oxabicyclo[4.2.1]non-4-en-4-yl]methanol (1.158)



In a 25 ml pressure tube was dissolved alcohol **1.120** (64.8 mg, 0.201 mmol), silver perchlorate (62.2 mg, 0.300 mmol) in acetone (1.4 ml) and H_2O (0.6 ml). The mixture was stirred for 16 h at 100 °C. Upon completion of the reaction, the reaction mixture was cooled to RT and filtered. Water (5 mL) and ether (20 mL) were added and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were concentrated and purified by flash column chromatography (pentane/EtOAc, 3:1) to obtain product **1.158** as a colourless oil (16.8 mg, 32%).

R_f 0.15 (pentane/EtOAc, 5:1); **$[\alpha]_D^{25}$** +45 (*c* 3.7 , DCM); **IR** ν_{max}/cm^{-1}: 3448, 2970, 2927; **δ_H** (400 MHz, $CDCl_3$) 4.75 (1H, dd, *J* = 8.5, 1.0 Hz, H6), 4.27 (1H, d, *J* = 12.0 Hz, H8), 4.15 (1H, d, *J* = 12.0 Hz, H8′), 2.84 (1H, ddd, *J* = 16.0, 11.0, 4.5 Hz, H2), 2.57 – 2.41 (2H, m, H5 & H2′), 2.14 (1H, dt, *J* = 6.5, 4.0 Hz, H4), 2.01 (1H, ddtd, *J* = 15.5, 5.5, 4.0, 1.5 Hz, H3), 1.94 (1H, d, *J* = 12.5 Hz, H5′), 1.72 – 1.59 (2H, m, H3′ & OH), 1.41 (3H, s, H11), 1.20 (3H, s, H12); **δ_C** (101 MHz, $CDCl_3$) 138.7 (C7), 126.1 (C1), 84.4 (C6), 84.0 (C9), 68.8 (C8), 43.8 (C4), 37.9 (C6), 29.7 (C12), 28.6 (C2), 28.6 (C3), 22.7 (C11); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{11}H_{17}O_2{}^{79}Br$ 261.0485, found, 261.0486.

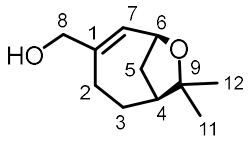
(*S*, *Z*)-2-(Hydroxymethylene)-5-(prop-1-en-2-yl)cycloheptan-1-one (1.159)



In a 25 ml pressure tube was dissolved alcohol **1.120** (64.8 mg, 0.201 mmol), silver tetrafluoroborate (58.0 mg, 0.298 mmol) in DMF (2 ml) and filled with argon. The mixture was stirred for 16 h at 100 °C. Upon completion of the reaction, the reaction mixture was cooled to RT and filtered. Water (10 mL) and ether (40 mL) were added. The organic layer was washed with water (2 ×10 mL), concentrated and purified by flash column chromatography (pentane/EtOAc, 20:1) to obtain product **1.159** as a colourless oil (7.0 mg, 19%).

R$_f$ 0.71 (pentane/EtOAc, 20:1); **[α]$_D^{25}$** +61 (*c* 0.41, DCM); **IR** ν_{max}/cm^{-1}: 2940, 1728, 1644; **δ_H** (400 MHz, $CDCl_3$) 14.63 (1H, d, *J* = 8.5 Hz, OH), 7.66 (1H, d, *J* = 8.5 Hz, H8), 4.72 – 4.67 (2H, m, H11), 2.64 (1H, ddd, *J* = 14.0, 12.0, 2.0 Hz, H6), 2.52 (1H, ddd, *J* = 14.0, 7.5, 1.5 Hz, H6′), 2.38 – 2.24 (2H, m, H2), 2.22 – 2.13 (1H, m, H4), 1.99 – 1.86 (2H, m, H5 & H3), 1.70 (3H, t, *J* = 1.1 Hz, H10), 1.53 – 1.44 (1H, m, H5′), 1.36 – 1.26 (1H, m, H3′); **δ_C** (101 MHz, $CDCl_3$) 203.6 (C8), 171.2 (C7), 150.2 (C9), 114.4 (C1), 109.4 (C11), 50.9 (C4), 40.8 (C6), 34.9 (C3), 29.4 (C5), 27.7 (C2), 20.6 (C10); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{11}H_{16}O_2$ 181.1223, found, 181.1224.

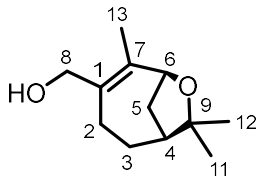
[(1*S*,6*S*)-8,8-Dimethyl-7-oxabicyclo[4.2.1]non-4-en-4-yl]methanol (1.161)



In a 25 mL pressure tube was added alcohol **1.158** (26.1 mg, 0.100 mmol), methylboronic acid (7.8 mg, 0.13 mmol), K_3PO_4 (63.7 mg, 0.300 mmol), $Pd(PPh_3)_4$ (5.8 mg, 0.0050 mmol), and THF (1 mL) and heated at 80 °C for 12 h. After completion, the reaction mixture was concentrated, and the crude product was purified by flash column chromatography (pentane/EtOAc, 3:1) to afford alcohol **1.161** as a colourless oil (trace).

R_f 0.18 (pentane/EtOAc, 3:1); **$[\alpha]_D^{25}$** +65º (*c* 0.080, DCM); **IR** ν_{max}/cm^{-1}: 3404, 2967, 2924; **δ_H** (400 MHz, $CDCl_3$) 5.86 (1H, dt, *J* = 6.0, 2.0 Hz, H7), 4.43 (1H, dd, *J* = 8.5, 6.0 Hz, H6), 3.89 (2H, t, *J* = 1.0 Hz, H8), 2.67 – 2.50 (1H, m, H2), 2.50 – 2.36 (1H, m, H5), 2.12 – 2.00 (2H, m, H4 & H2′), 1.97 – 1.87 (1H, m, H3), 1.75 (1H, d, *J* = 12.0 Hz, H5′), 1.66 – 1.54 (1H, m, H3′), 1.49 (1H, br, OH), 1.32 (3H, s, H11), 1.14 (3H, s, H12); **δ_C** (101 MHz, $CDCl_3$) 142.9 (C1), 128.8 (C7), 82.8 (C9), 74.2 (O6), 68.2 (C8), 44.9 (C4), 38.6 (C5), 30.2 (C12), 28.4 (C3), 27.1 (C2), 23.1 (C11); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{11}H_{18}O_2Na$ 205.1199, found, 205.1202.

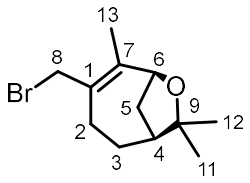
[(1*S*,6*S*)-5,8,8-Trimethyl-7-oxabicyclo[4.2.1]non-4-en-4-yl]methanol (1.160)



To a suspension of copper(I) iodide (7.6 mg, 0.040 mmol) in ether (2 mL) in a 25 ml flask was added methyllithium (1.6 M in ether, 0.125 mL, 0.200 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h then a solution of alcohol **1.158** (26.0 mg, 0.100 mmol) in ether (0.5 mL) was added into the solution dropwise. The resulting mixture was warmed to RT and stirred for 16 h. The reaction was quenched with satd aq NH_4Cl solution (5 mL). Ether (10 mL) was added and aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were concentrated and purified by flash column chromatography (pentane/EtOAc, 3:1) to obtain alcohol **1.160** as a colourless oil (10.0 mg, 51%).

R_f 0.18 (pentane/EtOAc, 3:1); **$[\alpha]_D^{25}$** +55 (*c* 0.39, DCM); **IR** ν_{max}/cm^{-1}: 3520, 2966, 2922; **δ_H** (400 MHz, $CDCl_3$) 4.28 (1H, dd, *J* = 9.0, 1.0 Hz, H6), 4.14 (1H, d, *J* = 11.5 Hz, H8), 3.96 (1H, d, *J* = 11.5 Hz, H8′), 2.91 (1H, dddq, *J* = 17.5, 12.0, 5.0, 2.5 Hz, H2), 2.52 (1H, dddd, *J* = 12.0, 9.0, 6.5, 2.0 Hz, H5), 2.19 (1H, dt, *J* = 17.5, 5.0 Hz, H2′), 2.07 (1H, dt, *J* = 6.0, 4.0 Hz, H4), 1.97 (1H, dqd, *J* = 15.0, 4.5, 2.0 Hz, H3), 1.76 (3H, d, *J* = 2.5 Hz, H13), 1.72 (1H, d, *J* = 12.0 Hz, H5′), 1.55 (1H, dddd, *J* = 14.5, 12.0, 5.0, 3.5 Hz, H3′), 1.45 (1H, br, OH), 1.41 (3H, s, H11), 1.19 (3H, s, H12); **δ_C** (101 MHz, $CDCl_3$) 139.0 (C1), 133.5 (C7), 83.2 (C9), 80.9 (C6), 65.1 (C8), 44.3 (C4), 38.7 (C5), 29.5 (C13), 29.4 (C3), 28.7 (C2), 22.3 (C11), 18.9 (C12); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{12}H_{20}O_2Na$ 219.1356, found, 219.1357.

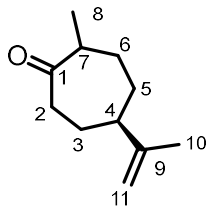
(1*S*,6*S*)-4-(Bromomethyl)-5,8,8-trimethyl-7-oxabicyclo[4.2.1]non-4-ene (1.162)



To a solution of carbon tetrabromide (79.6 mg, 0.240 mmol) and triphenylphosphine (47.2 mg, 0.180 mmol) in DCM (5 mL) in a 25 ml flask was added a solution of **1.160** (23.5 mg, 0.120 mmol) in DCM (5 mL). The solution was stirred for 20 min then diluted with satd aq $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography (pentane/EtOAc, 20:1) to obtain bromide **1.162** as a colourless oil (5.0 mg, 16%).

R_f 0.20 (pentane/EtOAc, 20:1); **$[\alpha]_D^{25}$** –0.4 (*c* 0.070, DCM); **IR** ν_{max}/cm^{-1}: 2958, 2913, 1710; **δ_H** (400 MHz, $CDCl_3$) 4.29 (1H, dd, *J* = 9.0, 1.0 Hz, H6), 4.12 (1H, d, *J* = 9.5 Hz, H8), 3.82 (1H, d, *J* = 9.5 Hz, H8′), 2.95 (1H, dddq, *J* = 16.5, 11.5, 4.5, 2.5 Hz, H2), 2.55 – 2.43 (1H, m, H5), 2.16 (1H, dt, *J* = 16.0, 4.5 Hz, H2′), 2.09 (1H, dt, *J* = 6.5, 4.0 Hz, H4), 1.98 (1H, dqd, *J* = 15.0, 4.5, 2.0 Hz, H3), 1.77 (3H, d, *J* = 2.5 Hz, H13), 1.72 (1H, d, *J* = 12.0 Hz, H5′), 1.60 (1H, dddd, *J* = 14.5, 12.0, 5.0, 3.5 Hz, H3′), 1.41 (3H, s, H11), 1.19 (3H, s, H12); **δ_C** (101 MHz, $CDCl_3$) 141.6 (C1), 130.6 (C7), 83.3 (C9), 80.8 (C6), 44.2 (C4), 38.6 (C8), 38.2 (C5), 30.1 (C2), 29.5 (C13), 29.4 (C3), 22.4 (C11), 19.1 (C12); **HRMS** (ESI+) *m/z* $[M+NH_4]^+$ calcd. for $C_{12}H_{23}N^{79}Br$ 260.1008, found, 260.1032.

(5R)-2-Methyl-5-(prop-1-en-2-yl)cycloheptan-1-one (1.164)

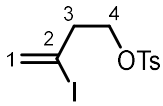


To a solution of dihydrocarvone **1.82** (3.04g, 20.0 mmol) in dry ether (80 mL) in a 250 mL flask was added boron trifluoride etherate (3.76 mL, 30.0 mmol) at 0 °C. A solution of ethyl diazoacetate (3.16 mL, 30 mmol) in dry ether (10 mL) was then added over a period of 15 min and the resulting solution was stirred at RT for 3 h. The mixture was cooled to 0 °C and neutralised with satd aq $NaHCO_3$ solution (40 mL). The resulting mixture was extracted with chloroform (3 × 30 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The crude material was purified by flash column chromatography (pentane/EtOAc, 25:1) to obtain inseparable keto esters (**1.167**) as a mixture (4.52 g).

This ketone ester was dissolved in methanol (35 mL) in a 250 mL flask. A solution of NaOH (1.90 g, 47.4 mmol) in water (40 mL) was added into the flask at RT. After heating to reflux for 3 h, the reaction mixture was cooled to RT, diluted with 1 M HCl (30 mL), and extracted with ether (3 × 20 mL). The extract was successively washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (pentane/EtOAc, 20:1) to give ketone **1.164** as a colourless oil and as a pair of diastereomers (2.46 g, 74%, dr = 3:1).

R_f 0.40 (pentane/EtOAc, 20:1); **IR** ν_{max}/cm^{-1}: 2926, 2855, 1702; **δ_H** (400 MHz, $CDCl_3$) δ 4.69 – 4.56 (2H, m, H11), 2.65 – 2.21 (3H, m, H2 & H7), 2.01 – 1.88 (1H, m, H4), 1.88 – 1.71 (3H, m, H3, H5, H6), 1.68 – 1.55 (4H, m, H5′ & H10), 1.43 – 1.31 (2H, m, H3′, H6′), 1.09 (0.75H, d, *J* = 7.0 Hz, H8), 1.05 (2.25H, d, *J* = 7.0 Hz, H8); **δ_C** (101 MHz, $CDCl_3$) 216.4/215.9 (C1), 150.6/149.7 (C9), 108.9/109.4 (C11), 49.2/48.4 (C4), 46.8/45.7 (C7), 41.5/41.1 (C2), 34.9/30.2 (C3), 33.1/30.1 (C6), 29.7/29.7 (C5), 20.5/20.8 (C10), 17.8/16.0 (C8); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd for $C_{11}H_{19}O$, 167.1430, found, 167.1432.

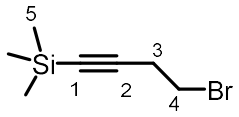
3-Iodobut-3-en-1-yl 4-methylbenzenesulfonate[4] (1.171)



To a solution of NaI (6.00 g, 40.0 mmol) in acetonitrile (30 mL) was added TMSCl (5.08 mL, 40.0 mmol) and water (0.360 mL, 20.0 mmol) and stirred for 10 min. A solution of 3-butyn-1-ol (1.40 g, 20.0 mmol) in acetonitrile (5 mL) was added then the resulting mixture was stirred for 1 h at RT. The reaction was quenched with water (60 mL) and extracted with ether (3 × 30 mL), dried over $MgSO_4$ and concentrated to give crude iodo alcohol (3.80 g) as a reddish brown oil. This crude iodo alcohol was dissolved in DCM (25 mL), and cooled to 0 °C. To the stirred solution was added 4-toluenesulfonyl chloride (5.72g, 35.0 mmol), triethylamine (5.58 mL, 30.0 mmol), and trimethylamine hydrochloride (0.19 g, 2.0 mmol) and stirred at 0 °C for 1 h. The reaction was quenched with water (50 mL) and extracted with ether (3 × 60 mL). The combined extracts were washed with 1M aq $KHSO_4$ solution (50 mL), satd aq $Na_2S_2O_3$ solution (30 mL), water (40 mL), and brine (50 mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (pentane/ether, 5:1) to obtain tosylate **1.171** as a pale brown oil (2.22 g, 33%).

R_f 0.20 (pentane/Et_2O, 5:1); **IR** ν_{max}/cm^{-1}: 2955, 1358, 1174; **δ_H** (400 MHz, $CDCl_3$) 7.80 – 7.68 (2H, m, Ar), 7.35 – 7.24 (2H, m, Ar), 6.04 (1H, q, J = 1.5 Hz, H1), 5.76 – 5.69 (1H, m, H1′), 4.06 (2H, t, J = 6.0 Hz, H4), 2.67 – 2.62 (2H, m, H3), 2.38 (3H, s, CH_3); **δ_C** (101 MHz, $CDCl_3$) 144.9 (Ar), 132.9 (Ar), 129.9 (Ar-H), 129.2 (C1), 128.0 (Ar-H), 103.6 (C2), 68.11 (C4), 44.41 (C3), 21.67 (CH_3).

(4-Bromobut-1-yn-1-yl)trimethylsilane[5] (1.176)

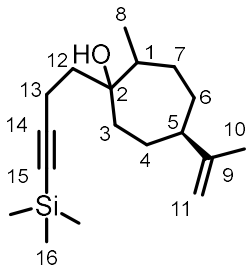


To a solution of 3-butyl-1-ol (1.52 mL, 20.0 mmol) in THF (80 mL) at –78 °C was added BuLi (1.6 M in hexane, 27.5 mL, 44.0 mmol). The cloudy solution was stirred for 1 hour at –78 °C follow by the addition of chlorotrimethylsilane (7.48 mL, 30.0 mmol). The solution was warmed to RT and stirred for 2 h. The reaction was quenched with 2M HCl (20 mL) and extracted with ether (3 × 20 mL). The combined organic layer was washed with satd aq $NaHCO_3$ solution (30 mL), brine (20 mL), dried over $MgSO_4$ and concentrated to obtain 4-trimethylsilyl-3-butyn-1-ol without purification.

The crude 4-trimethylsilyl-3-butyn-1-ol (20.0 mmol) was dissolved in DCM (45 mL) and CBr_4 (7.96 g, 24.0 mmol) added at –30 °C in one portion. The mixture was stirred vigorously for 10 min and a solution of PPh_3 (5.24g, 20.0 mmol) in DCM (15 mL) added. The solution was stirred for 2 h, warmed to 0 °C, and then stirred another 1.5 h. The crude reaction mixture was filtered through a thin layer of silica gel, concentrated and purified by column chromatography (pentane) to obtain bromide **1.176** as a colourless oil (3.34 g, 81%).

$\mathbf{R}_f$ 0.50 (pentane); δ_H (400 MHz, $CDCl_3$) 3.43 (2H, t, J = 7.5 Hz, H4), 2.77 (2H, t, J = 7.5 Hz, H3), 0.16 (9H, s, H5); δ_C (101 MHz, $CDCl_3$) 103.24 (C1), 87.08 (C2), 29.22 (C4), 24.35(C3), 0.00 (C5).

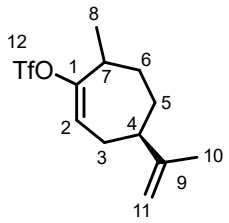
(5*R*)-2-Methyl-5-(prop-1-en-2-yl)-1-[4-(trimethylsilyl)but-3-yn-1-yl]cycloheptan-1-ol (1.177)



A dry and argon-flushed flask was charged with dry LiCl (94.0 mg, 2.22 mmol) and magnesium turnings (0.30 g, 12 mmol) in THF (3 mL). Bromide **1.176** (0.41 g, 2.0 mmol) in THF (2 mL) was added slowly at 0 °C. The reaction mixture was stirred at RT for 2 h to form the turbo Grignard reagent as a black solution.[6] A 25 mL round-bottom flask charged with ketone **1.164** (40.0 mg, 0.241 mmol) was evacuated and backfilled with argon. $LaCl_3$•2LiCl (0.6 M in THF, 1.00 mL, 0.600 mmol) was added, and the resulting mixture was stirred at RT for 1 h. To another flame-dried 25 mL flask charged with the freshly prepared solution of turbo Grignard (2.5 equiv) at 0 °C, was added the freshly prepared metal complexes of ketone **1.164** in dropwise manner via a syringe pump over a period of 10 min, and the mixture was stirred for additional 15 min at 0 °C. Upon completion (detected by TLC), the reaction was quenched with satd aq NH_4Cl (10 mL) at 0 °C. The aqueous layer was extracted with ether (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (pentane/EtOAc, 20:1) to give alcohol **1.177** as a colourless oil and as a pair of diastereomers (256.3 mg, 88%, dr = 3:1).

R_f 0.18 (pentane/EtOAc, 20:1); **IR** (film) ν_{max}/cm^{-1}: 3550, 2920, 841; **δ_H** (400 MHz, $CDCl_3$) δ 4.67 – 4.61 (2H, m, H11), 2.40 – 2.22 (2H, m, H13), 2.21 – 2.15 (1H, m, H5), 1.84 – 1.64 (6H, m, H12, H3, H4, H6, H7), 1.69 (3H, s, H10), 1.65 – 1.55 (2H, m, H1 & H6′), 1.58 – 1.47 (2H, m, H3′ & H7′), 1.38 – 1.30 (1H, m, H4′), 0.96 (2.25H, d, *J* = 7.0 Hz, H8), 0.91 (0.75H, d, *J* = 7.0 Hz, H8), 0.14 (9H, s, H16); **δ_C** (101 MHz, $CDCl_3$) 152.2/151.2 (C9), 108.5/108.2 (C11), 107.9/107.9 (C15), 85.1/85.1 (C14), 75.2/75.2 (C2), 48.9/41.8 (C1), 44.1/40.6 (C12), 45.9/39.0 (C5), 45.3/36.5 (C3), 34.6/29.9 (C6), 31.5/29.2 (C4), 26.2/25.5 (C7), 20.8/20.4 (C10), 25.0/16.7 (C8), 14.9/14.8 (C13) , 0.2/0.2 (C16); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{18}H_{33}OSi$ 293.2295, found, 293.2298.

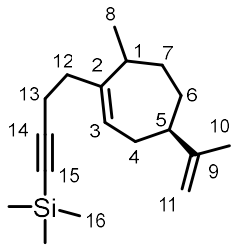
(4*R*)-7-Methyl-4-(prop-1-en-2-yl)cyclohept-1-en-1-yl trifluoromethanesulfonate (1.182)



To a 25 mL round bottom flask was added ketone **1.164** (0.33 g, 2.0 mmol) in dry THF (10 mL) and the mixture cooled to –78 ºC. LHMDS (1M in THF, 2.40 mL, 2.40 mmol) was added dropwise to this solution. The solution was stirred at –78 ºC for 1h, then warmed to RT and stirred for another 2 h. A solution of 2-[*N*,*N*-bis(tri-fluoromethylsulfonyl)amino]-5-chloropyridine (Comins′ reagent) (1.10 g, 2.80 mmol) in THF (5 mL) was added and the mixture was stirred at RT for 18 h. The mixture was diluted with ether and washed with satd aq NH_4Cl solution (10 mL) and then brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (pentane/EtOAc, 100:1) to give triflate **1.182** as a colourless oil and as a pair of diastereomers (0.48 g, 81%, dr = 3:1).

R_f 0.28 (pentane); **IR** ν_{max}/cm^{-1}: 2941, 1413, 1141; **δ_H** (400 MHz, $CDCl_3$) δ 5.75 (1H, td, *J* = 6.8, 0.7 Hz, H2), 4.65 – 4.61 (2H, m, H11), 2.70 – 2.55 (1H, m, H7), 2.34 – 2.24 (1H, m, H4), 2.21 – 2.14 (2H, m, H3), 1.91 – 1.82 (2H, m, H5, H6), 1.68 – 1.64 (3H, m, H10), 1.56 – 1.44 (2H, m, H5', H6′), 1.22 (0.75H, d, *J* = 7.0 Hz, H8), 1.14 (2.25H, d, *J* = 7.0 Hz, H8); **δ_C** (101 MHz, $CDCl_3$) 156.4/155.7 (C1), 150.3/149.7 (C9), 120.5/120.4 (C2), 118.6 (q, *J* = 319.5 Hz, C12), 109.7/109.4 (C11), 45.5/45.0 (C4), 38.1/37.8 (C7), 31.3/30.8 (C5), 30.5/30.1 (C6), 29.1/28.0 (C3), 20.6/20.4 (C10), 17.5/17.1 (C8); **HRMS** (APCI–) *m/z* $[M–H^+]^-$ calcd. for $C_{12}H_{16}O_3F_3S$ 297.0778, found, 297.0765.

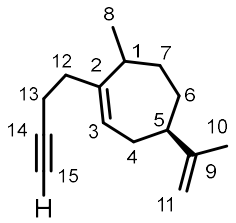
Trimethyl[4-[(4*R*)-7-methyl-4-(prop-1-en-2-yl)cyclohept-1-en-1-yl]but-1-yn-1-yl]silane (1.179)



A solution of turbo Grignard of bromide **1.176** (65.6 mg, 0.320 mmol) in THF (5 mL) was rapidly added to a solution of enol triflate **1.182** (63.0 mg, 0.210 mmol) and $Fe(acac)_3$ (7.5 mg, 0.021 mmol) in THF (5 mL) and NMP (0.25 mL) at –30 °C under argon, causing an immediate color change from orange to black. The mixture was stirred for 15 min at that temperature before it was quenched with satd aq NH_4Cl solution (5 mL). The aqueous phase was extracted with ether (3 × 20 mL), the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (pentane/EtOAc, 100:1) to obtain compound **1.179** as a colourless oil (43.7 mg, 76%).

R_f 0.29 (pentane); **IR** ν_{max}/cm^{-1}: 2962, 2916, 839; **δ_H** (400 MHz, $CDCl_3$) 5.52 – 5.45 (1H, m, H3), 4.74 – 4.58 (2H, m, H11), 2.49 – 2.41 (1H, m, H1), 2.30 (2H, dd, *J* = 7.6, 6.5 Hz, H13), 2.26 – 2.08 (5H, m, H4, H5, H12), 1.93 – 1.84 (1H, m, H6), 1.78 – 1.71 (1H, m, H7), 1.71 – 1.66 (3H, m, H10), 1.65 – 1.56 (1H, m, H6′), 1.46 – 1.37 (1H, m, H7′), 1.09 (3H, d, *J* = 7.5 Hz, H8), 0.15 (9H, s, H16); **δ_C** (101 MHz, $CDCl_3$) 151.1 (C9), 145.0 (C2), 124.3 (C3), 108.2 (C11), 107.3 (C15), 84.5 (C14), 44.9 (C5), 36.2 (C1), 34.7 (C12), 32.5 (C6), 32.3 (C7), 31.2 (C4), 20.4 (C10), 20.0 (C13), 18.6 (C8), 0.0 (C16); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{18}H_{31}Si$ 275.2190, found, 275.2189.

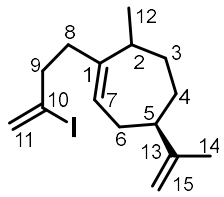
(4*R*)-1-(But-3-yn-1-yl)-7-methyl-4-(prop-1-en-2-yl)cyclohept-1-ene (1.183)



To a 25 mL round bottom flask was added enyne **1.179 (**0.33 g, 1.2 mmol) in dry THF (5 mL). TBAF (1.0 M in THF, 2.4 mL, 2.4 mmol) was added into this solution. The mixture was stirred for 2 h at RT. The mixture was quenched with satd aq NH_4Cl solution (10 mL) and aqueous layer was extracted with ether (3 × 10 mL). The organic layers were collected and dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (pentane/EtOAc, 1000:1) to obtain product **1.183** as a colourless oil and as a pair of diastereomers (0.13 g, 53%, dr = 5:1).

R_f 0.31 (pentane); **IR** ν_{max}/cm^{-1}: 3216; **δ_H** (400 MHz, $CDCl_3$) 5.54 – 5.45 (0.83H, m, H3), 5.30 (0.16H, m, H3), 4.68 – 4.59 (2H, m, H11), 2.48 – 2.38 (1H, m, H1), 2.33 – 2.07 (7H, m, H4, H5,H12, H13), 1.98 – 1.93 (1H, m, H15), 1.92 – 1.85 (1H, m, H6), 1.81 – 1.71 (1H, m, H7), 1.72 – 1.67 (3H, m, H10), 1.64 – 1.54 (1H, m, H6′), 1.46 – 1.36 (1H, m, H7′), 1.09 (2.50H, d, *J* = 7.0 Hz, H8), 1.03 (0.50H, d, *J* = 7.0 Hz, H8); **δ_C** (101 MHz, $CDCl_3$) 152.4/151.3 (C9), 145.1/139.7 (C2), 135.1/124.5 (C3), 108.6/108.2 (C11), 84.7/84.5 (C14), 68.6/68.5 (C15), 45.2/44.8 (C5), 39.1/34.9 (C12), 38.4/31.5 (C4), , 36.5/33.8 (C1), 38.0/32.7 (C6), 36.1/32.6 (C7), 23.7/18.9 (C8), 20.7/20.5 (C10), 18.6/17.8 (C13); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{23}$ 203.1794, found, 203.1798.

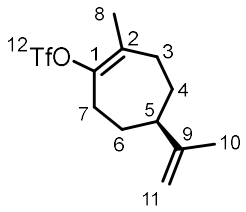
(4*R*)-1-(3-Iodobut-3-en-1-yl)-7-methyl-4-(prop-1-en-2-yl)cyclohept-1-ene (1.184)



To a flame-dried N_2-filled flask was added compound **1.183** (20.2 mg, 0.100 mmol) in dry DCM (1 mL). The solution was cooled to 0 ºC and a solution of B-I-9-BBN (1.0 M in hexanes, 0.10 ml, 0.10 mmol) was added and the reaction flask covered with foil and stirred for 1 h. A solution of glacial acetic acid (5.7 μL, 0.10 mmol) in dry DCM (1 mL) was added and the reaction mixture stirred for 1 h, after which time it was poured into satd aq $NaBO_3$ solution (5 mL). After 30 min the reaction mixture was extracted with DCM (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (pentane/EtOAc, 100:1) to obtain compound **1.184** as a colourless oil and as a pair of diastereomers (7.3 mg, 22%, dr = 5:1).

R_f 0.5 (pentane); **IR** ν_{max}/cm^{-1} 2930s, 1644w, 1617w, 892s, 643s; **δ_H** (400 MHz, $CDCl_3$) 6.02 – 5.97 (1H, m, H11), 5.71 – 5.65 (1H, m, H11′), 5.52 – 5.40 (1H, m, H7), 4.70 – 4.59 (2H, m, H15), 2.51 – 2.45 (2H, m, H9), 2.44 – 2.36 (1H, m, H2), 2.24 – 2.09 (5H, m, H5, H6, H8), 1.95 – 1.84 (1H, m, H4), 1.79 – 1.71 (1H, m, H3), 1.71 – 1.67 (3H, m, H14), 1.65 – 1.56 (1H, m, H4′), 1.46 – 1.35 (1H, m, H3′), 1.11 (2.50H, d, *J* = 7.0 Hz, H12), 1.08 (0.50H, d, *J* = 7.0 Hz, H12); **δ_C** (101 MHz, $CDCl_3$) 151.3/150.2 (C13), 146.5 (C10), 144.9 (C1), 125.5/124.3 (C11), 124.6 (C7), 108.6/108.7 (C15), 45.4 (C9), 45.2/45.2 (C5), 36.7/36.6 (C2), 35.9/35.7 (C8), 32.6/32.6 (C4), 32.5/32.5 (C3), 31.5 (C6), 20.7/20.8 (C14), 18.9/18.8 (C12); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{24}I$ 331.0917, found, 331.0917.

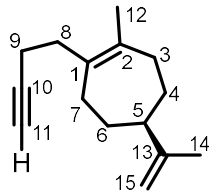
(5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohept-1-en-1-yl trifluoromethanesulfonate (1.181)



To a suspension of $FeCl_3$ (1.20 g, 7.46 mmol) in ether (40 mL) in a 100 mL flask under argon at 0 °C was added methylmagnesium bromide (3.0 M in ether, 7.50 mL, 22.5 mmol) dropwise and the mixture stirred at RT for 1 h. A solution of ketone **1.164** (0.83 g, 5.0 mmol) in ether (5 mL) was transferred into the flask, the resulting suspension was stirred for 30 min and then trimethylsilyl chloride (1.90 mL, 15.0 mmol), triethylamine (2.10 mL, 15.0 mmol), and HMPA (0.87 mL, 5.0 mmol) added sequentially. The mixture was stirred for 14 h at RT then diluted with ether (40 mL), washed with cold satd aq $NaHCO_3$ solution (2 × 10 mL), dried over $MgSO_4$, and concentrated. The crude silyl enol ether was dissolved in THF (40 mL) in a dried (heatgun) 100 mL flask under argon and cooled to 0 °C. Methyllithium (1.6 M in ether, 4.4 mL, 7.0 mmol) was added dropwise then the mixture was allowed to warm to RT and stirred for 30 min. The solution was re-cooled to –78 °C, a solution of Comins′ reagent (3.10 g, 7.89 mmol) in THF (10 mL) was added dropwise, and then the mixture reaction was allowed to warm slowly to RT and stirred for a further 2 h. The solvent was removed under vacuum and the residue was purified by chromatography (pentane) to give enol triflate **1.181** as a yellow oil (721 mg, 48%).

R_f 0.38 (pentane); **$[\alpha]_D^{25}$** +3.8 (*c* 0.62, $CHCl_3$); **IR** ν_{max}/cm^{-1} 2937m, 1413m, 1245m, 1207s,1143s; **δ_H** (400 MHz, $CDCl_3$) 4.72 – 4.69 (1H, m, H11), 4.69 – 4.67 (1H, m, H11′), 2.62 – 2.54 (1H, m, H7), 2.45 (1H, ddd, *J* = 16.5, 7.0, 2.0 Hz, H7′), 2.26 – 2.15 (2H, m, H3), 2.11 (1H, tt, *J* = 10.5, 4.0 Hz, H5), 1.86 – 1.75 (2H, m, H4, H6) overlaying 1.81 (3H, d, *J* = 2.0 Hz, H8), 1.71 (3H, t, *J* = 1.0 Hz, H10), 1.60 – 1.49 (1H, m, H6′), 1.48 – 1.37 (1H, m, H4′); **δ_C** (151 MHz, $CDCl_3$) 150.1 (C9), 146.1 (C1), 131.4 (C2), 118.4 (q, *J* = 319.5 Hz, C12), 109.2 (C11), 49.1 (C5), 31.8 (C3), 31.4 (C7), 30.0 (C4), 29.6 (C6), 21.0 (C10), 19.4 (C8); **HRMS** (APCI–) *m/z* $[M–H^+]^-$ calcd. for $C_{12}H_{16}O_3F_3S$ 297.0778, found, 297.0765.

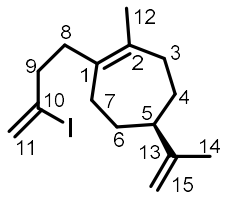
(5*R*)-1-(But-3-yn-1-yl)-2-methyl-5-(prop-1-en-2-yl)cyclohept-1-ene (1.172)



A solution of [4-(trimethylsilyl)but-3-yn-1-yl]magnesium bromide in THF was prepared by adding (4-bromobut-1-yn-1-yl)trimethylsilane (0.16 g, 0.76 mmol) into a suspension of Mg (0.19 g, 7.6 mmol) in THF (10 mL). After formation of the grey Grignard solution was complete, it was added into a solution of enol triflate **1.181** (0.11 mg, 0.38 mmol), $Fe(acac)_3$ (7.0 mg, 0.020 mmol), and NMP (0.30 mL, 3.1 mmol) in THF (10 mL) at –30 °C under argon, leading to an immediate colour change from orange to black. The mixture was stirred for 1 h at –30 °C and was then quenched with satd aq NH_4Cl solution (10 mL). The aqueous phase was extracted with ether (3 × 10 mL) then the combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue (**1.172-**$SiMe_3$) was dissolved in dry THF (5 mL) in a 50 mL flask under N_2 then TBAF (1.0 M in THF, 0.19 mL, 0.19 mmol) was added and the mixture stirred for 1 h at RT. Satd aq NH_4Cl solution (10 mL) was added and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (pentane) to give compound **1.172** as a colourless oil (18.6 mg, 24% – loss due to volatilty). This compound is volatile and was used directly in the next step.

$\mathbf{R}_f$ 0.42 (pentane); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 4.64 – 4.62 (2H, m, H15), 2.37 – 2.16 (6H, m, H3, H7, H8, H9), 2.11 (1H, tt, J = 11.5, 3.5 Hz, H5), 2.08 – 1.94 (2H, m, H3′, H7′), 1.92 (1H, t, J = 2.5 Hz, H11), 1.75 – 1.65 (2H, m, H4, H6) overlaying 1.70 (3H, d, J = 1.5 Hz, H12) and 1.68 (3H, t, J = 1.0 Hz, H14), 1.25 – 1.19 (2H, m, H4′, H6′); $\boldsymbol{\delta}_\mathbf{C}$ (101 MHz, $CDCl_3$) 151.9 (C13), 134.4 (C1), 134.0 (C2), 108.4 (C15), 84.8 (C10), 68.2 (C11), 51.7 (C5), 34.9 (C8), 34.4 (C7), 32.8 (C3), 32.0 (C6), 31.2 (C4), 21.1 (C12), 20.9 (C14), 17.7 (C9).

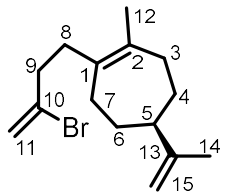
(5*R*)-1-(3-Iodobut-3-en-1-yl)-2-methyl-5-(prop-1-en-2-yl)cyclohept-1-ene (1.166)



To a solution of Ni(dppp)Cl_2 (47.0 mg, 0.0870 mmol) in dry THF (10 mL) in a dried (heatgun) flask under argon was added DIBAL-H (1.2 M in toluene, 0.72 mL, 0.86 mmol) dropwise. The mixture was cooled to 0 °C and alkyne **1.172** (87.8 mg, 0.434 mmol) was added via syringe into the black solution, the mixture was warmed to RT and stirred for 1 h then cooled to 0 °C. A solution of *N*-iodosuccinimide (0.29 g, 1.3 mmol) in dry THF (2 mL) was added dropwise, the solution was then warmed to RT and stirring continued for a further 1 h. The solution was quenched with satd aq Rochelle salt solution (10 mL), the aqueous phase was extracted with ether (3 × 20 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (pentane/Et_3N, 100:1) to give vinyl iodide **1.166** as a colourless oil (86.4 mg, 60%).

R_f 0.25 (pentane); **$[\alpha]_D^{25}$** +8.3 (*c* 0.29, $CHCl_3$); **IR** ν_{max}/cm^{-1} 2981s, 1382m, 1252m, 1151m, 955m; **δ_H** (400 MHz, $CDCl_3$) 6.00 (1H, q, *J* = 1.5 Hz, H11), 5.68 (1H, d, *J* = 1.5 Hz, H11′), 4.65 – 4.62 (2H, m, H15), 2.50 – 2.40 (2H, m, H9), 2.33 – 2.20 (4H, m, H8, H3, H7), 2.15 – 2.08 (1H, m, H5), 2.08 – 1.95 (2H, m, H3′, H7′), 1.75 – 1.65 (2H, m, H4, H6) overlaying 1.72 (3H, d, *J* = 1.5 Hz, H14) and 1.68 (3H, t, *J* = 1.0 Hz, H12), 1.24 – 1.08 (2H, m, H4′, H6′); **δ_C** (101 MHz, $CDCl_3$) 151.8 (C13), 134.0 (C2), 133.8 (C1), 125.3 (C11), 112.3 (C10), 108.4 (C15), 51.7 (C5), 44.5 (C9), 35.5 (C8), 34.9 (C3), 33.1 (C7), 32.1 (C6), 31.3 (C4), 21.2 (C12), 21.0 (C14); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{24}I$ 331.0917, found, 331.0916.

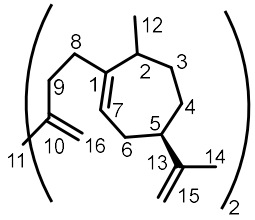
(*R*)-1-(3-Bromobut-3-en-1-yl)-2-methyl-5-(prop-1-en-2-yl)cyclohept-1-ene (1.118)



To a solution of Ni(dppp)Cl_2 (10.0 mg, 0.0184 mmol) in dry THF (4 mL) in a dried (heatgun) flask under argon was added DIBAL-H (1.2 M in toluene, 0.15 mL, 0.18 mmol) dropwise. The mixture was cooled to 0 °C and alkyne **1.172** (18.6 mg, 0.0919 mmol) was added via syringe into the black solution, the mixture was warmed to RT and stirred for 1 h then cooled to 0 °C. A solution of *N*-bromosuccinimide (62.0 g, 0.276 mmol) in dry THF (2 mL) was added dropwise, the solution was then warmed to RT and stirring continued for a further 1 h. The solution was quenched with satd aq Rochelle salt solution (10 mL), the aqueous phase was extracted with ether (3 × 20 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (pentane/Et_3N, 100:1) to give an inseparable mixture as a colourless oil (17.2 mg) from which the target vinyl bromide **1.118** could be characterised by NMR analysis.

$\mathbf{R_f}$ 0.30 (pentane); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.55 (1H, q, J = 1.5 Hz, H11), 5.38 (1H, d, J = 1.5 Hz, H11′), 4.64 (2H, d, J = 1.5 Hz, H15), 2.52 – 2.39 (2H, m, H9), 2.31 – 2.18 (3H, m, H7, H8), 2.16 – 1.90 (4H, m, H3, H5, H7′), 1.74 – 1.64 (2H, m, H4, H6) overlaying 1.72 (3H, m, H14) and 1.68 (3H, m, H12), 1.24 – 1.09 (2H, m, H4′, H6′); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 151.8 (C15), 134.0 (C2), 133.9 (C1), 116.4 (C11), 108.4 (C15), 104.3 (C10), 51.7 (C5), 40.5 (C9), 34.9 (C8), 34.4 (C3), 33.0 (C7), 32.1 (C6), 31.3 (C4), 21.1 (C12), 20.9 (C14); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{24}{}^{79}Br$ 283.1056, found, 283.1064.

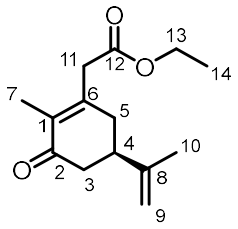
(5*R*,5'*R*)-2,2'-(3,5-dimethyleneheptane-1,7-diyl)bis[1-methyl-5-(prop-1-en-2-yl)cyclohept-1-ene] (1.189)



To a solution of vinyl iodide **1.184** (10.0 mg, 0.0303 mmol) in DMF (2 mL) in a 25 mL flask was added $Pd(OAc)_2$ (1.4 mg, 0.0062 mmol), PPh_3 (6.2 mg, 0.024 mmol) and K_2CO_3 (33.2 mg, 0.240 mmol) and the mixture stirred at 80 °C for 18 h. The reaction was cooled to RT and quenched with water (5 mL). The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (pentane) to obtain dimer **1.189** as a colourless oil (2.1 mg, 17%).

R_f 0.40 (pentane); **IR** ν_{max}/cm^{-1} 2950s, 1644w, 1611w, 897s; **δ_H** (400 MHz, $CDCl_3$) 5.51 – 5.41 (1H, m, H7), 5.10 – 5.03 (1H, m, H16), 4.96 – 4.90 (1H, m, H16′), 4.68 – 4.57 (2H, m, H15), 2.45 (1H, qt, *J* = 7.5, 4.0 Hz, H2), 2.37 – 2.25 (2H, m, H9), 2.24 – 2.15 (2H, m, H5, H6), 2.11 (3H, m, H6′, H8), 1.95 – 1.85 (1H, m, H4), 1.76 (1H, m, H3), 1.71 – 1.68 (3H, m, H14), 1.60 (1H, tdd, *J* = 13.5, 8.0, 4.0 Hz, H4′), 1.48 – 1.39 (1H, m, H3′), 1.10 (3H, d, *J* = 7.5 Hz, H12); **δ_C** (101 MHz, $CDCl_3$) 151.5 (C13), 147.9 (C10), 147.0 (C1), 123.4 (C7), 111.7 (C16), 108.5 (C15), 45.3 (C5), 36.7 (C2), 35.5 (C8), 34.4 (C9), 32.7 (C4), 32.6 (C3), 31.6 (C6), 20.7 (C14), 18.9 (C12); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{30}H_{47}$ 407.3672, found, 407.3672.

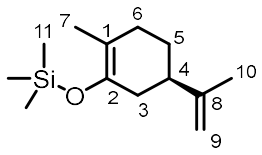
Ethyl (*R*)-2-(2-methyl-3-oxo-5-(prop-1-en-2-yl)cyclohex-1-en-1-yl)acetate (1.197)



To a solution of (*R*)-carvone (31 μL, 0.20 mmol) in DCM (3 mL) in a 25 mL flask was added $SbCl_5$ (1.0 M in DCM, 0.10 mL, 0.10 mmol) at –78 °C and the mixture stirred for 0.5 h. A solution of ethyl diazoacetate (44 μL, 0.42 mmol) in DCM (2 mL) was added and the mixture was stirred at –78 °C for 2 h. The reaction was quenched with satd aq $NaHCO_3$ solution (10 mL) at 0 °C and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (pentane/EtOAc, 10:1) to give ester **1.197** as a pale yellow oil (24.6 mg, 52%).

R_f 0.15 (pentane/EtOAc, 10:1); **$[\alpha]_D^{25}$** –44 (*c* 0.05, DCM); **IR** ν_{max}/cm^{-1} 2982w, 2918w, 1736s, 1672s, 1189m; **δ_H** (400 MHz, $CDCl_3$) 4.82 – 4.74 (2H, m, H9), 4.17 (2H, q, *J* = 7.0 Hz, H13), 3.35 – 3.25 (2H, m, H11), 2.67 (1H, ddd, *J* = 14.0, 10.0, 5.0 Hz, H4), 2.59 (1H, ddd, *J* = 16.0, 4.0, 1.5 Hz, H3), 2.52 – 2.41 (2H, m, H5), 2.33 (2H, dd, *J* = 16.0, 13.0 Hz, H3′), 1.82 – 1.79 (3H, m, H7), 1.75 (3H, t, *J* = 1.0 Hz, H10), 1.27 – 1.24 (3H, m, H14); **δ_C** (101 MHz, $CDCl_3$) 199.2 (C2), 169.8 (C12), 149.0 (C8), 146.6 (C6), 133.5 (C1), 110.7 (C9), 61.3 (C13), 42.6 (C3), 41.4 (C4), 40.8 (C11), 36.7 (C5), 20.6 (C10), 14.3 (C14), 11.1 (C7); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{14}H_{21}O_3$ 237.1485, found, 237.1534.

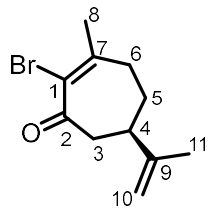
(*R*)-Trimethyl[(2-methyl-5-(prop-1-en-2-yl)cyclohex-1-en-1-yl)oxy)silane[7] (1.198)



To a solution of dihydrocarvone **1.82** (1.8 mL, 11 mmol) in acetonitrile (50 mL) in a 150 mL flask was added triethylamine (2.8 mL, 20 mmol), trimethylchlorosilane (2.5 mL, 20 mmol) and sodium iodide (3.00 g, 20.0 mmol) and stirred at 80 °C for 18 h. The mixture was cooled to RT and extracted with pentane (3 × 50 mL) and the combined organic extracts were concentrated. The residue was purified by column chromatography (pentane) to give enol ether **1.198** as a colourless oil (1.54 g, 62%).

δ_H (400 MHz, $CDCl_3$) 4.72 (2H, ddq, *J* = 5.0, 2.0, 1.0 Hz, H9), 2.29 – 2.17 (1H, m, H4), 2.12 – 1.89 (4H, m, H3, H6), 1.78 – 1.67 (4H, m, H5, H10), 1.56 (3H, dquin, *J* = 2.0, 1.0 Hz, H7), 1.46 – 1.31 (1H, m, H5′), 0.17 (9H, s, H11); **δ_C** (101 MHz, $CDCl_3$) 149.6 (C8), 142.4 (C2), 111.5 (C1), 108.8 (C9), 42.6 (C4), 35.7 (C6), 30.3 (C3), 28.1 (C5), 20.9 (C10), 16.3 (C7), 0.9 (C11).

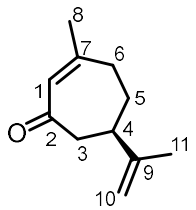
(*R*)-2-Bromo-3-methyl-6-(prop-1-en-2-yl)cyclohept-2-en-1-one[7] (1.199)



To a solution of trimethylsilyl enol ether **1.198** (0.50 g, 2.2 mmol) and potassium *tert*-butoxide (1.50 g, 13.4 mmol) in hexane (18 mL) was dropwise a solution of bromoform (0.97 mL, 11 mmol) in hexane (2 mL) at –30 °C. The mixture was warmed to RT and stirred vigorously for 18 h. The mixture was diluted with hexane (20 mL), quenched by pouring into ice water (20 mL) and extracted with pentane (3 × 40 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (pentane/EtOAc, 20:1) to give ketone **1.199** as a pale yellow oil (75.9 mg, 14%).

δ_H (400 MHz, $CDCl_3$) 4.78 (1H, m, H10), 4.76 (1H, m, H10′), 2.80 – 2.75 (2H, m, H2), 2.66 (1H, ddd, *J* = 17.0, 10.5, 3.0 Hz, H6), 2.61 – 2.53 (1H, m, H4), 2.49 (1H, ddd, *J* = 17.0, 6.5, 3.0 Hz, H6′), 2.22 (3H, s, H8), 1.97 – 1.86 (1H, m, H5), 1.80 – 1.71 (4H, m, H5′, H11); **δ_C** (101 MHz, $CDCl_3$) 196.4 (C2), 156.2 (C7), 147.2 (C9), 124.0 (C1), 110.6 (C9), 45.6 (C3), 40.1 (C4), 34.2 (C6), 30.0 (C5), 28.7 (C8), 21.1 (C11).

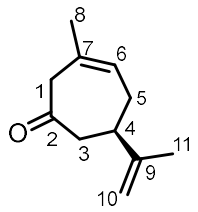
(*R*)-3-Methyl-6-(prop-1-en-2-yl)cyclohept-2-en-1-one[7] (1.194)



To a solution of ketone **1.199** (0.24 g, 0.99 mmol) in glacial acetic acid (1.5 mL) in a 25 mL flask was added zinc powder (0.23 g, 3.5 mmol) and the mixture stirred at 90 °C for 1.5 h. The mixture was then cooled to RT and neutralised with satd aq $NaHCO_3$ (10 mL) and extracted with ether (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (pentane/EtOAc, 20:1) to give ketone **1.194** as a pale yellow oil (15.6 mg, 37%).

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.92 (1H, s, H1), 4.73 (2H, m, H10), 2.73 – 2.60 (2H, m, H3), 2.51 (2H, m, H4, H6), 2.33 (1H, ddd, *J* = 17.5, 8.0, 3.5 Hz, H6′), 1.97 – 1.87 (4H, m, H5, H8), 1.83 – 1.75 (1H, m, H5′), 1.72 (3H, t, *J* = 1.0 Hz, H11); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 202.5 (C2), 158.8 (C7), 148.4 (C9), 129.9 (C1), 110.1 (C10), 47.8 (C3), 40.7 (C4), 33.8 (C6), 31.2 (C5), 27.6 (C8), 20.7 (C11)

(*R*)-3-Methyl-6-(prop-1-en-2-yl)cyclohept-3-en-1-one[8] (1.205)



BuLi (1.6 M in hexane, 26.0 mL, 41.6 mmol) was added dropwise into DMSO (12.5 mL) in a 100 mL flask at RT and the resulting mixture was stirred for 1 h. This dimsyl-Li solution in DMSO was added dropwise to a solution of trimethylsulfonium iodide (8.16 g, 40.0 mmol) in THF/DMSO (48 mL/13 mL) at –10 °C and the mixture was stirred at the same temperature for 30 min. A solution of (*R*)-carvone (3.00 g, 20.0 mmol) in THF (5 mL) was added and the mixture was stirred for 3 h at –10 °C. The reaction was quenched with cold water (30 mL) and extracted with pentane (5 × 30 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated. The crude epoxide **1.202** (3.85 g) was used directly in the next step without purification.

To a solution of epoxide **1.202** (3.85 g) in DMF (45 mL) in a 250 flask was added phthalimide (2.50 g, 17.1 mmol) and potassium phthalimide (0.55 g, 3.1 mmol) and the mixture heated at 160 °C for 3 h. The mixture was cooled to RT then diluted with ether (100 mL), water (50 mL) and brine (50 mL). The aqueous layer was extracted with ether (3 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL) and concentrated to give crude product **1.203** as a brown oil (5.46 g) that was used in next step without purification.

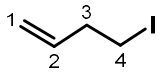
To a suspension of crude product **1.203** (5.46 g) in ethanol (50 mL) in a 150 mL flask was added hydrazine monohydrate (1.45 mL, 24.2 mmol) and stirred at 80 °C for 3 h. The mixture was cooled to RT and filtered. The filtrate was concentrated to give the crude amine alcohol product **1.204** (3.47 g) which was used directly in next step without purification.

To a solution of the crude amino alcohol product **1.204** (3.47 g) in 10% (v/v) aq AcOH (40 mL) in a 250 mL flask was added aq $NaNO_2$ (1.25 M, 28 mL, 35 mmol) at 0 °C and stirred for 3 h. The aqueous phase was extracted with ether (5 × 30 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (30 mL), water (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, concentrated. The residue

was purified by column chromatography (pentane/EtOAc, 20:1) to give ketone **1.205** as a pale yellow oil (1.31 g, 40% over four steps).

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.57 (1H, ddt, *J* = 7.0, 5.0, 1.5 Hz, H6), 4.80 – 4.70 (2H, m, H10), 3.31 (1H, d, *J* = 15.0 Hz, H1), 3.00 (1H, d, *J* = 15.0 Hz, H1′), 2.83 – 2.69 (1H, m, H4), 2.60 (2H, m, H3), 2.35 – 2.16 (2H, m, H5), 1.79 (3H, quin, *J* = 1.5 Hz, H8), 1.73 (3H, s, H11); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 208.1 (C2), 148.3 (C9), 130.4 (C7), 124.6 (C6), 110.2 (C10), 49.0 (C3), 48.3 (C1), 43.3 (C4), 33.1 (C5), 26.2 (C8), 20.5 (C11)

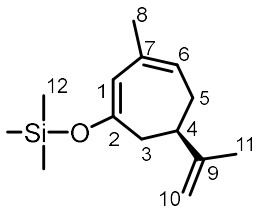
4-Iodobut-1-ene[9] (1.207)



To a solution of 4-bromo-1-butene **1.206** (1.52 mL, 15.0 mmol) in acetone (50 mL) in a 150 mL flask was added a solution of sodium iodide (4.50 g, 30.0 mmol) in acetone (25 mL). The solution was stirred at 60 °C for 1 h. The mixture was cooled to RT, concentrated and filtered through a plug of silica gel (wash with pentane). The filtrate was concentrated to give iodide **1.207** as a yellow oil (2.18 g, 80%).

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.82 – 5.69 (1H, m, H2), 5.16 – 5.05 (2H, m, H1), 3.19 (2H, t, *J* = 7.0 Hz, H4), 2.62 (2H, qt, *J* = 7.0, 1.5 Hz, H3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 137.0 (C2), 117.2 (C1), 37.8 (C3), 4.8 (C4).

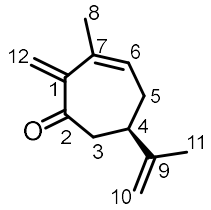
(*R*)-Trimethyl[[3-methyl-6-(prop-1-en-2-yl)cyclohepta-1,3-dien-1-yl]oxy]silane (1.209)



To a solution of ketone **1.194** (20.0 mg, 0.122 mmol) in DMF (3 mL) in a 25 mL flask was added KHMDS (1.0 M in THF, 0.20 mL, 0.20 mmol) and the mixture stirred at RT for 1 h. Trimethylchlorosilane (50 μL, 0.40 mmol) was added and the resulting mixture was stirred at RT for 2 h. The reaction was quenched with satd aq $NaHCO_3$ solution (10 mL) and extracted with pentane (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated to give pure enol ether **1.209** as a colourless oil (28.0 mg, 97%).

R_f 0.4 (pentane); **$[a]_D^{25}$** +68 (*c* 0.80, DCM); **IR** ν_{max}/cm^{-1} 2966m, 1645w, 1625s, 890s, 848s; **δ_H** (400 MHz, $CDCl_3$) 5.47 (1H, ddt, *J* = 6.5, 5.0, 1.5 Hz, H6), 5.09 (1H, s, H1), 4.71 – 4.66 (2H, m, H10), 2.63 – 2.53 (1H, m, H4), 2.48 – 2.35 (1H, m, H3), 2.32 – 2.24 (1H, m, H3′), 2.22 – 2.09 (2H, m, H5), 1.76 – 1.68 (6H, m, H8, H11), 0.22 (9H, s, H12); **δ_C** (101 MHz, $CDCl_3$) 155.7 (C2), 150.0 (C9), 131.4 (C7), 122.8 (C6), 110.4 (C1), 109.0 (C10), 46.0 (C4), 41.5 (C3), 34.2 (C5), 25.6 (C11), 20.6 (C8), 0.5 (C12); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{14}H_{25}OSi$ 237.1669, found, 237.1669.

(*R*)-3-Methyl-2-methylene-6-(prop-1-en-2-yl)cyclohept-3-en-1-one (1.210)

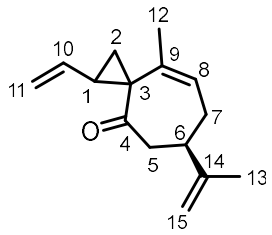


To a solution of enol ether **1.209** (63.6 mg, 0.244 mmol) in DCM (3 mL) in a 25 mL flask was added Eschenmoser's salt (74.7 mg, 0.404 mmol) and the mixture stirred at RT for 1 h. The mixture was diluted with DCM (5 mL) and 1M HCl (10 mL) and extracted with 1M HCl (3 × 5 mL). The combined aqueous extracts were basified with 3M aq NaOH solution (40 mL) until pH = 14 and extracted with DCM (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to give crude amine **1.211** as a colourless oil (54.0 mg) without purification.

To a solution of amine **1.211** (54.0 mg) in DCM (5 mL) in a 25 mL flask was added MCPBA (75% w/w, 84.2 mg, 0.366 mmol) and stirred at RT for 15 min. The mixture was concentrated and the residue was purified by column chromatography (pentane/EtOAc, 10:1) to give ketone **1.210** as a colourless oil (3.6 mg, 8.4% over two steps).

R_f 0.21 (pentane/EtOAc, 10:1); **[a]$_D^{25}$** +24 (*c* 0.20, DCM); **IR** ν_{max}/cm^{-1} 2930m, 1660s, 1592w, 1442m, 894m; **δ_H** (400 MHz, $CDCl_3$) 5.97 (1H, d, *J* = 2.0 Hz, H6), 5.34 (1H, d, *J* = 1.0 Hz, H12), 5.27 (1H, q, *J* = 1.0 Hz, H12′), 4.77 (2H, m, H10), 2.71 – 2.55 (4H, m, H3, H4, H5), 2.47 – 2.38 (1H, m, H5′), 2.09 (3H, d, *J* = 1.0 Hz, H8), 1.82 – 1.69 (3H, m, H11); **δ_C** (101 MHz, $CDCl_3$) 202.1 (C2), 153.9 (C7), 147.6 (C9), 146.4 (C1), 130.3 (C6), 119.0 (C12), 110.6 (C10), 47.3 (C3), 42.3 (C5), 41.4 (C4), 24.6 (C8), 20.9 (C11); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{12}H_{16}ONa$ 199.1093, found, 199.1088.

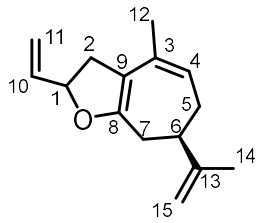
(6*R*)-9-Methyl-6-(prop-1-en-2-yl)-1-vinylspiro[2.6]non-8-en-4-one (1.214)



To a suspension of NaH (60% in mineral oil, 267 mg, 6.68 mmol) in dry toluene (80 mL) in a dried (heatgun) 100 mL flask under Ar was added KO*t*-Bu (1.0 M in THF, 4.0 mL, 4.0 mmol) dropwise and the mixture stirred for 1 h. A solution of ketone **1.205** (550 mg, 3.35 mmol) in dry toluene (10 mL) was added via syringe, stirring continued for 1 h then the enolate solution was cooled to –78 °C and a solution of (*E*)-1,4-dibromo-2-butene (2.86 g, 13.4 mmol) in dry toluene (20 mL) was added dropwise over 10 min. The mixture was warmed slowly to RT and stirred for 2 h then quenched with satd aq NH_4Cl solution (20 mL), extracted with ether (3 × 20 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$, and concentrated to give a residue that was purified by chromatography (pentane/EtOAc, 20:1), affording product **1.214** as a yellow oil and as a pair of diastereomers (527 mg, 73%, dr = 1:1).

R_f 0.54 (pentane/EtOAc, 20:1); **IR** ν_{max}/cm^{-1} 2966m, 2917m, 1686s, 1645m, 1439m; **δ_H** (600 MHz, $CDCl_3$) 5.87 – 5.73 (2H, m, H10, H8), 5.26 – 5.16 (1H, m, H11), 5.07 – 5.00 (1H, m, H11′), 4.75 – 4.73 (1H, m, H15), 4.73 – 4.70 (1H, m, H15′), 2.85 – 2.76 (1H, m, H6), 2.76 – 2.67 (0.5H, m, H5), 2.66 – 2.62 (1H, m, H5′), 2.51 – 2.43 (1H, m, 0.5 H5, 0.5 H7), 2.30 – 2.24 (1H, m, H7′), 2.21 – 2.11 (1H, m, 0.5 H1, 0.5 H7), 1.98 (0.5H, td, *J* = 9.0, 7.5 Hz, H1), 1.90 (0.5H, dd, *J* = 7.5, 4.5 Hz, H2), 1.76 (0.5H, dd, *J* = 7.5, 4.5 Hz, H2), 1.73 – 1.65 (6H, m, H12, H13), 1.44 (0.5H, dd, *J* = 8.5, 5.0 Hz, H2′), 1.31 (0.5H, dd, *J* = 8.5, 4.5 Hz, H2′); **δ_C** (151 MHz, $CDCl_3$) 209.3/208.7 (C4), 148.4/148.2 (C14), 137.5/136.0 (C9), 135.8/135.4 (C10), 126.4/125.9 (C8), 116.5/116.5 (C11), 110.2/109.9 (C15), 46.5/45.9 (C5), 46.2/42.7 (C6), 42.9/42.2 (C3), 36.8/36.0 (C1), 31.2/29.4 (C7), 21.9/21.1 (C12), 21.2/21.0 (C2), 20.7/20.7 (C13); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{21}O$ 217.1587, found, 217.1586.

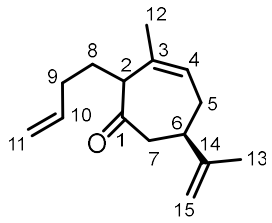
(2*R*/*S*,7*R*)-4-methyl-7-(prop-1-en-2-yl)-2-vinyl-3,6,7,8-tetrahydro-2*H*-cyclohepta[b]furan (1.215)



To a RT solution of $Pd_2(dba)_3$ (1.8 mg, 0.002 mmol) and tributylphosphine (4.0 μL, 0.016 mmol) in dry toluene (2.5 mL) in a 10 mL flask under Ar was added diethylzinc (1.0 M in hexane, 0.3 mL, 0.3 mmol) dropwise. The resulting solution was stirred for 5 min then a solution of ketone **1.214** (21.6 mg, 0.100 mmol) in dry toluene (0.5 mL) was added. The mixture was stirred for 10 min, then heated at 75 °C for 1 h, and cooled to RT. Cold water (10 mL) was added and the product extracted into ether (3 × 10 mL); the combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated to give crude product **1.215** as a yellow oil and as a pair of diastereomers (26.8 mg, contains solvent, dr = 1:1). This compound was unstable upon chromatography and was therefore characterised in crude form.

R_f 0.32 (pentane/EtOAc, 30:1); **IR** ν_{max}/cm^{-1} 2918m, 1646m, 1624m, 1437m, 1156s; **δ_H** (400 MHz, $CDCl_3$) 6.01 – 5.91 (1H, m, H10), 5.44 – 5.38 (1H, m, H4), 5.31 – 5.24 (1H, m, H11), 5.18 – 5.12 (1H, m, H11′), 4.93 – 4.85 (1H, m, H1), 4.70 – 4.66 (2H, m, H15), 3.09 – 3.00 (0.5H, m, H2), 2.96 – 2.88 (0.5H, m, H2), 2.70 – 2.62 (0.5H, m, H2′), 2.60 – 2.53 (0.5H, m, H2′), 2.52 – 2.40 (~2H, m, H7, H6), 2.41 – 2.32 (~1H, m, H7, H6), 2.24 – 2.16 (~2H, m, H5), 1.75 (3H, br s, H12), 1.72 (3H, br s, H14); **δ_C** (101 MHz, $CDCl_3$) 154.0/153.9 (C8), 149.7/149.6 (C13), 138.4/138.3 (C10), 129.7/129.6 (C3), 122.1/122.1 (C4), 116.1/115.7 (C11), 109.1/109.1 (C15), 108.9/108.4 (C9), 80.7/80.4 (C1), 41.6/41.4 (C6), 39.7/39.5 (C2), 35.0/35.0 (C7), 34.2/34.2 (C5), 23.2/23.1 (C12), 20.5/20.4 (C14); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{21}O$ 217.1587, found, 217.1588.

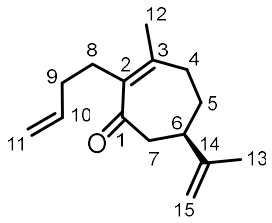
(2*R*/*S*,6*R*)-2-(But-3-en-1-yl)-3-methyl-6-(prop-1-en-2-yl)cyclohept-3-en-1-one (1.208)



To a RT solution of $Pd_2(dba)_3$ (44.7 mg, 0.049 mmol) and tributylphosphine (98 μl, 0.39 mmol) in dry toluene (35 mL) in a 50 mL flask under Ar was added triethylamine (1.4 mL, 10 mmol) then formic acid (1.3 mL, 34 mmol); the resulting suspension was stirred for 5 min heated to 105 °C. A solution of ketone **1.214** (0.53 mg, 2.4 mmol) in dry toluene (5 mL) was added dropwise into the heated mixture over 5 min and stirring continued at 105 °C for 2 h. The mixture was cooled to RT and water (20 mL) was added. The resulting mixture was extracted with ether (3 × 20 mL), and the combined extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (pentane/EtOAc, 30:1) to give compound **1.208** as a yellow oil and as a pair of diastereomers (0.47 g, 88%, dr = 2:1).

R_f 0.31 (pentane/EtOAc, 30:1); **IR** ν_{max}/cm^{-1} 2935m, 2857m, 1707s, 1643m, 1447m; **δ_H** (400 MHz, $CDCl_3$) (for major diastereomer) 5.85 – 5.74 (1H, m, H10), 5.68 – 5.57 (1H, m, H4), 5.06 – 4.93 (2H, m, H11), 4.80 – 4.67 (2H, m, H15), 3.26 (0.67H, dd, *J* = 8.5, 5.0 Hz, H2), 3.11 (0.33H, dd, *J* = 8.5, 5.0 Hz, H2), 2.72 – 2.62 (2.33H, m, H7, H6), 2.55 – 2.48 (0.67H, m, H7′), 2.37 – 2.25 (1H, m, H5), 2.26 – 2.13 (1H, m, H5′), 2.09 – 2.00 (2H, m, H9), 2.00 – 1.92 (2H, m, H8), 1.77 (1H, br s, H8′), 1.75 (3H, br s, H12), 1.73 – 1.72 (3H, m, H13); **δ_C** (101 MHz, $CDCl_3$) 209.5/210.1 (C1), 148.2/148.4 (C14), 138.4/138.2 (C10), 135.9/135.5 (C3), 125.3/124.9 (C4), 115.2/115.3 (C11), 110.0/110.2 (C15), 56.0/57.0 (C2), 48.9/46.9 (C7), 47.4/45.2 (C6), 31.9/31.8 (C9), 30.5/31.7 (C5), 26.9/27.7 (C8), 22.2/24.2 (C12), 20.6/20.8 (C13); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{23}O$ 219.1743, found, 219.1745.

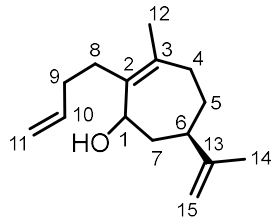
(2*R*/*S*,6*R*)-2-(But-3-en-1-yl)-3-methyl-6-(prop-1-en-2-yl)cyclohept-2-en-1-one (1.193)



A solution of potassium *tert*-butoxide (0.030 mL, 1.0 M in THF, 0.030 mmol) was added to an RT solution of ketone **18** (22 mg, 0.10 mmol) in dry toluene (2 mL) under N_2. The mixture was heated to 90 °C and stirred for 4 h. The resulting orange solution was cooled to RT and quenched with satd aq NH_4Cl solution (5 mL) then extracted with ether (3 × 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 30:1) to give ketone **1.193** as a colourless oil (7.0 mg, 32%) and recovered ketone **1.208** (6.0 mg, 27%).

R_f 0.22 (pentane/EtOAc, 10:1); **$[\alpha]_D^{25}$** +59.8 (*c* 0.22, $CHCl_3$); **IR** ν_{max}/cm^{-1} 2980s, 1660s, 1447m, 1376m, 908s; **δ_H** (400 MHz, $CDCl_3$) 5.76 (1H, ddt, *J* = 17.0, 10.0, 7.0 Hz, H10), 5.00 – 4.94 (1H, m, H11), 4.93 – 4.89 (1H, m, H11′), 4.74 – 4.72 (2H, m, H15), 2.61 – 2.56 (2H, m, H7), 2.54 – 2.45 (2H, m, H6, H4), 2.44 – 2.31 (2H, m. H8), 2.23 (1H, ddd, *J* = 16.5, 6.0, 3.0 Hz, H4′), 2.10 – 2.02 (2H, m, H9), 1.92 (3H, s, H12), 1.88 – 1.74 (1H, m, H5), 1.72 (3H, br s, H13), 1.66 (1H, dddd, *J* = 14.0, 7.5, 6.0, 4.0 Hz, H5′); **δ_C** (101 MHz, $CDCl_3$) 205.4 (C1), 150.0 (C3), 148.0 (C14), 138.5 (C10), 137.9 (C2), 114.9 (C11), 109.9 (C15), 46.8 (C7), 40.2 (C6), 33.7 (C4), 33.5 (C9), 29.8 (C5), 28.4 (C8), 23.0 (C12), 21.1 (C13); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{23}O$ 219.1743, found, 219.1743.

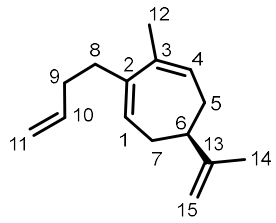
(1*R*/*S*,6*R*)-2-(But-3-en-1-yl)-3-methyl-6-(prop-1-en-2-yl)cyclohept-2-en-1-ol (1.216)



$CeCl_3$•$7H_2O$ (109 mg, 0.292 mmol) was dissolved in a stirred solution of ketone **1.193** (58.0 mg, 0.266 mmol) in methanol (25 mL), in a 25 mL flask under N_2. The mixture was cooled to 0 °C, $NaBH_4$ (11.1 mg, 0.292 mmol) added, and stirring continued at 0 °C for 1 h by which time the reaction was complete (TLC). Water (10 mL) was added and the mixture was extracted with ether (4 × 20 mL); the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give alcohol **1.216** as a colourless solid and as a pair of diastereomers (32.5 mg, 55%, dr ~ 6:1).

R_f 0.35 (pentane/EtOAc, 10:1); **m.p.** 41ºC; **IR** ν_{max}/cm^{-1} 3661w, 2981s, 2890m, 1461m, 1153m; **δ_H** (600 MHz, C_6D_6) (major diastereomer) 5.94 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, H10), 5.14 – 5.09 (1H, m, H11), 5.03 – 4.99 (1H, m, H11′), 4.75 – 4.73 (2H, m, H15), 4.28 (1H, d, *J* = 10.0 Hz, H1), 2.45 – 2.35 (2H, m, H8), 2.34 – 2.23 (2H, m, H9), 2.11 (1H, tt, *J* = 12.0, 4.0 Hz, H6), 2.07 – 2.01 (1H, m, H5), 1.82 (1H, ddd, *J* = 14.5, 7.0, 1.5 Hz, H5′), 1.64 (3H, d, *J* = 1.5 Hz, H12), 1.60 (3H, t, *J* = 1.0 Hz, H14), 1.58 – 1.47 (3H, m, H4, H7), 1.04 (1H, dtd, *J* = 13.5, 12.0, 1.5 Hz, H7′); **δ_C** (151 MHz, C_6D_6) (major diastereomer) 150.7 (C13), 139.6 (C10), 138.8 (C2), 130.5 (C3), 114.5 (C11), 109.3 (C15), 72.0 (C1), 49.0 (C6), 43.1 (C4), 34.7 (C9), 33.9 (C5), 30.5 (C7), 28.0 (C8), 21.3 (C12), 20.6 (C14); **HRMS** (ESI+) *m/z* $[M+H–H_2O]^+$ calcd. for $C_{15}H_{23}$ 203.1794, found, 203.1794.

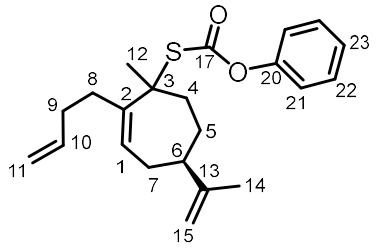
(6*R*)-2-(But-3-en-1-yl)-3-methyl-6-(prop-1-en-2-yl)cyclohepta-1,3-diene (1.220)



A solution of alcohol **1.216** (10 mg, 0.045 mmol) in dry dichloromethane (5 mL) in a 25 mL oven-dried flask under N_2 was cooled to –46 °C and tetrabromomethane (17 mg, 0.05 mmol) was added. A solution of triphenylphosphine (13 mg, 0.05 mmol) in dry dichloromethane (0.5 mL) was added then the mixture was allowed to warm slowly to RT and stirred for a further 30 min. The solvent was evaporated carefully (the product is very volatile) pentane (20 mL) added to give a suspension; this mixture was filtered and the filtrate concentrated carefully under vacuum. The residue was purified by chromatography (pentane) to give the eliminated product **1.220** as a colourless oil (3.3 mg, 36%).

R_f 0.25 (pentane); **$[\alpha]_D^{25}$** +62 (*c* 0.09, $CHCl_3$); **IR** ν_{max}/cm^{-1} 2981s, 2889m, 1382m, 1152m, 772m; **δ_H** (400 MHz, $CDCl_3$) 5.90 (1H, tq, *J* = 7.0, 1.5 Hz, H4), 5.85 (1H, br t, *J* = 7.0 Hz, H1), 5.81 (1H, ddt, *J* = 17.0, 10.5, 6.5 Hz, H10), 5.00 (1H, dq, *J* = 17.0, 1.5 Hz, H11), 4.94 (1H, ddt, *J* = 10.5, 2.0, 1.0 Hz, H11′), 4.72 – 4.70 (1H, m, H15), 4.62 – 4.60 (1H, m, H15′), 2.92 (1H, quin, *J* = 7.0 Hz, H6), 2.22 (2H, dd, *J* = 9.0, 6.5 Hz, H8), 2.10 (2H, dtd, *J* = 7.5, 6.0, 3.0 Hz, H9), 2.05 – 1.94 (2H, m, H5, H7), 1.93 – 1.84 (2H, m, H5′, H7′), 1.79 – 1.77 (3H, m, H12), 1.71 (3H, dd, *J* = 1.5, 1.0 Hz, H14); **δ_C** (101 MHz, $CDCl_3$) 150.2 (C13), 143.2 (C3), 138.9 (C10), 138.0 (C2), 128.5 (C4), 126.9 (C1), 114.6 (C11), 108.7 (C15), 58.3 (C6), 34.2 (C8), 33.2 (C9), 31.2 (two peaks, C5, C7), 21.6 (C14), 20.6 (C12); **HRMS** (ESI+) *m/z* $[M+H]^+$calcd. for $C_{15}H_{23}$ 203.1794, found, 203.1795.

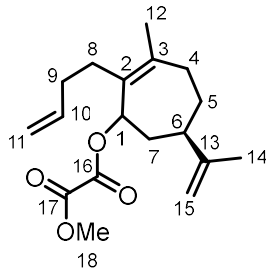
***S*-[(1*R*/*S*,5*R*)-2-(But-3-en-1-yl)-1-methyl-5-(prop-1-en-2-yl)cyclohept-2-en-1-yl] *O*-phenyl carbonothioate (1.218)**



A solution of alcohol **1.216** (30.0 mg, 0.135 mmol) and dry pyridine (0.044 mL, 0.54 mmol) in dry dichloromethane (10 mL) in a 25 mL oven-dried flask under N_2 was cooled to 0 °C and *O*-phenyl chlorothionoformate (0.0285 mL, 0.206 mmol) added. The reaction mixture was warmed slowly to RT, stirred for 2 h, then quenched with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by chromatography (pentane/EtOAc, 30:1) to give the title compound **1.218** as a colourless oil and, apparently, as a single diastereomer (15 mg, 31%, unassigned).

R_f 0.45 (pentane/EtOAc, 30:1); **$[\alpha]_D^{25}$** –107 (*c* 0.27, $CHCl_3$); **IR** ν_{max}/cm^{-1} 2926m, 1723s, 1189m, 1161m ,1074s; **δ_H** (400 MHz, $CDCl_3$) 7.41 – 7.34 (2H, m, H22), 7.22 (1H, tt, *J* = 7.5, 1.0 Hz, H23), 7.18 – 7.12 (2H, m, H21), 5.89 – 5.78 (1H, m, H10), 5.77 (1H, dd, *J* = 9.5, 4.0 Hz, H1), 5.05 (1H, ddq, *J* = 17.0, 7.0, 1.5 Hz, H11), 4.98 (1H, ddt, *J* = 10.0, 2.0, 1.0 Hz, H11′), 4.73 – 4.70 (1H, m, H15), 4.68 – 4.66 (1H, m, H15′), 2.70 – 2.61 (2H, m, H4, H7), 2.35 – 2.13 (4H, m, H8, H9), 2.12 – 2.04 (2H, m, H6, H7′), 1.97 – 1.87 (2H, m, H5), 1.82 – 1.76 (1H, m, H4′), 1.74 (3H, s, H12), 1.73 (3H, dd, *J* = 1.5, 1.0 Hz, H14); **δ_C** (101 MHz, $CDCl_3$) 169.3 (C17), 151.1 (two peaks, C13, C20), 142.5 (C2), 138.4 (C10), 130.8 (C1), 129.6 (C22), 126.1 (C23), 121.7 (C21), 114.9 (C11), 108.7 (C15), 59.1 (C3), 45.2 (C6), 38.5 (C4), 34.8 (C8), 34.7 (C9), 32.5 (C7), 32.0 (C5), 27.0 (C12), 20.5 (C14); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{29}O_2S$ 357.1883, found, 357.1884.

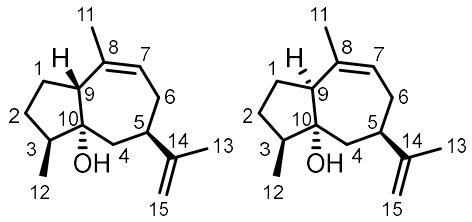
(1*R*/*S*,6*R*)-2-(But-3-en-1-yl)-3-methyl-6-(prop-1-en-2-yl)cyclohept-2-en-1-yl methyl oxalate (1.219)



To a solution of alcohol **1.216** (18.0 mg, 0.0817 mmol) in DCM (7 mL) in a 25 mL flask was added pyridine (26 μL, 0.33 mmol) and methyl chlorooxoacetate (11 μL, 0.12 mmol) and the mixture stirred at RT for 30 min. The reaction was quenched with water (10 m) and the mixture was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to give an unstable crude mixture (27.1 mg) from which the major component could be characterised by NMR analysis as the oxalyl ester **1.219** as a single diastereomer (unassigned).

δ_H (400 MHz, C_6D_6) 5.93 – 5.83 (1H, m, H10), 5.81 (1H, dt, *J* = 10.5, 1.5 Hz, H1), 5.13 – 5.06 (1H, m, H11), 5.00 (1H, ddt, *J* = 10.0, 2.0, 1.0 Hz, H11′), 4.71 – 4.63 (2H, m, H15), 3.22 (3H, s, H18), 2.38 – 2.30 (1H, m, H8), 2.29 – 2.13 (4H, m, H6, H8′, H9), 2.00 (1H, ddd, *J* = 15.0, 11.5, 1.5 Hz, H4), 1.91 (1H, ddt, *J* = 12.5, 3.5, 1.5 Hz, H7), 1.78 (1H, ddd, *J* = 15.0, 7.5, 2.0 Hz, H4′), 1.68 – 1.61 (1H, m, H7), 1.56 – 1.44 (7H, m, H5, H12, H14), 1.00 (1H, dtd, *J* = 13.5, 11.5, 2.0 Hz, H5′); **δ_C** (101 MHz, C_6D_6) 159.0 (C16), 157.6 (C17), 149.7 (C13), 138.8 (C10), 133.8 (C2), 133.5 (C3), 114.9 (C11), 109.8 (C15), 77.4 (C1), 52.5 (C18), 47.6 (C6), 38.6 (C7), 34.0 (C9), 33.7 (C4), 30.1 (C5), 29.0 (C8), 21.1 (C12), 20.7 (C14).

(3*S*,3a*R*,5*R*,8a*R*)-3,8-Dimethyl-5-(prop-1-en-2-yl)-2,3,4,5,6,8a-hexahydroazulen-3a(1*H*)-ol (1.259) and (3*S*,3a*R*,5*R*,8a*S*)-3,8-dimethyl-5-(prop-1-en-2-yl)-2,3,4,5,6,8a-hexahydroazulen-3a(1*H*)-ol (1.260)



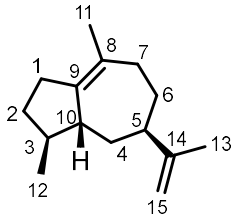
To a suspension of Sm powder (0.36 g, 2.4 mmol) in dry THF (14 mL) in a dried (heatgun) 50 mL flask under Ar was added 1,2-diiodoethane (0.39 g, 1.4 mmol). The resulting solution was stirred for 2 h to yield a deep blue SmI_2 solution. Dry HMPA (1.0 mL, 5.7 mmol) was then added to generate a deep purple solution. A solution of ketone **1.208** (0.12 g, 0.55 mmol) and dry *tert*-butanol (1.0 ml, 1.1 mmol) in THF (3 mL) was transferred into the HMPA/SmI_2 solution dropwise by syringe over 5 min and the mixture was stirred for 30 min. Satd aq $NaHCO_3$ solution (10 mL) was added, the mixture was extracted with ether (3 × 10 mL), and the combined extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on basic alumina (pentane/EtOAc , 30:1) to give the *trans*-fused bicyclic alcohol **1.259** as a yellow oil (43.0 mg, 35%).

R_f 0.56 (pentane/EtOAc, 10:1); **$[\alpha]_D^{25}$** +31 (*c* 0.25, CH_2Cl_2); **IR** ν_{max}/cm^{-1} 3567w, 2934s, 2854m, 1644m, 1446s; **δ_H** (600 MHz, acetone-d_6) 5.74 – 5.70 (1H, m, H7), 4.68 – 4.67 (1H, m, H15), 4.64 – 4.62 (1H, m, H15′), 2.77 (1H, br t, *J* = 9.5 Hz, H9), 2.60 (1H, s, OH), 2.27 (1H, tdd, *J* = 11.0, 3.0, 1.5 Hz, H5), 2.21 – 2.12 (1H, m, H6), 2.09 – 1.95 (3H, m, H2, H3, H6′), 1.92 – 1.84 (2H, m, H1, H4), 1.78 – 1.72 (1H, m, H1′), 1.71 – 1.70 (6H, m, H11, H13), 1.64 (1H, dd, *J* = 13.5, 12.0 Hz, H4′), 1.12 (1H, ddt, *J* = 12.0, 9.5, 7.0 Hz, H2′), 0.93 (3H, d, *J* = 7.0 Hz, H12); **δ_C** (151 MHz, acetone-d_6) 153.0 (C14), 139.3 (C8), 126.3 (C7), 108.9 (C15), 79.3 (C10), 51.0 (C9), 47.6 (C3), 46.6 (C4), 39.8 (C5), 34.2 (C6), 33.8 (C2), 27.2 (C1), 23.7 (C11), 20.8 (C13), 17.6 (C12); **HRMS** (ESI+) *m/z* $[M+H–H_2O]^+$ calcd. for $C_{15}H_{23}$ 203.1794, found, 203.1796.

The *cis*-fused bicyclic alcohol **1.260** was also obtained as a yellow oil (33.0 mg, 27%). **R_f** 0.30 (pentane/EtOAc, 10:1); **$[\alpha]_D^{25}$** +47 (*c* 0.11, CH_2Cl_2); **IR** ν_{max}/cm^{-1} 3447w, 2923s, 1457m; **δ_H** (600 MHz,

acetone-d_6) 5.54 (1H, tq, J = 6.0, 1.5 Hz, H7), 4.70 – 4.69 (1H, m, H15), 4.64 – 4.63 (1H, m, H15′), 3.30 (1H, d, J = 1.0 Hz, OH), 2.57 – 2.52 (1H, m, H5), 2.48 – 2.44 (1H, m, H9), 2.11 – 2.06 (2H, m, H6), 2.01 – 1.88 (3H, m, H1, H2, H3), 1.76 – 1.70 (7H, m, H11, H13, H4), 1.66 – 1.60 (1H, m, H4′), 1.59 – 1.53 (1H, m, H1′), 1.31 – 1.25 (1H, m, H2′), 0.89 (3H, d, J = 6.5 Hz, H12); δ_C (151 MHz, acetone-d_6) δ_C 153.5 (C14), 138.6 (C8), 123.8 (C7), 108.6 (C15), 78.8 (C10), 57.6 (C9), 47.4 (C3), 39.6 (C5), 38.8 (C4), 35.1 (C6), 29.0 (C2), 28.1 (C11), 26.6 (C1), 21.0 (C13), 14.1 (C12); **HRMS** (ESI+) *m/z* $[M+H–H_2O]^+$ calcd. for $C_{15}H_{23}$ 203.1794, found, 203.1795.

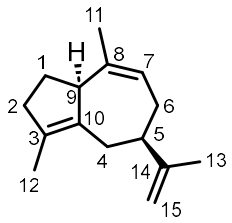
(3*S*,3a*R*,5*R*)-3,8-Dimethyl-5-(prop-1-en-2-yl)-1,2,3,3a,4,5,6,7-octahydroazulene [5-*epi*-bulnesene] (1.264)



A solution of alcohol **1.259** (39.0 mg, 0.175 mmol) and triethylsilane (168 μL, 1.05 mmol) in DCM (2 mL) in a 25 ml flask under N_2 was was cooled to –78 °C and a solution of BF_3•OEt_2 (15 μL, 0.12 mmol) in DCM (1.5 mL) was added dropwise over 5 min. The resulting mixture was allowed to warm slowly to 0 °C and was then stirred for 1 h. Satd aq $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated carefully under vacuum. The residue was purified with chromatography (pentane) to give the bulnesene epimer **1.264** as a volatile, colourless oil (19.4 mg, 55%).

R_f 0.63 (pentane); **$[\alpha]_D^{25}$** +41 (*c* 0.95, DCM); **IR** ν_{max}/cm^{-1} 2923s, 2866s, 1643m,1456m,1375m; **δ_H** (600 MHz, $CDCl_3$) 4.73 – 4.72 (1H, m, H15), 4.71 – 4.69 (1H, m, H15′), 2.35 – 2.30 (1H, m, H5), 2.28 – 2.22 (1H, m, H1), 2.21 – 2.10 (3H, m, H1′, H7), 2.05 (1H, tq, *J* = 10.0, 2.5 Hz, H10), 1.89 – 1.82 (1H, m, H6), 1.82 – 1.77 (2H, m, H2, H4), 1.77 – 1.74 (3H, m, H13), 1.72 – 1.65 (1H, m, H4′), 1.65 – 1.59 (1H, m, H6′), 1.59 – 1.56 (3H, m, H11), 1.36 (1H, ddt, *J* = 12.0, 10.5, 6.0 Hz, H3), 1.13 (1H, qd, *J* = 11.5, 8.5 Hz, H2′), 0.99 (3H, d, *J* = 6.5 Hz, H12); **δ_C** (151 MHz, $CDCl_3$) 150.8 (C14), 140.8 (C9), 126.6 (C8), 108.5 (C15), 46.1 (C10), 43.5 (C5), 42.5 (C3), 34.7 (C4), 34.1 (C7), 33.8 (C2), 31.0 (C1), 29.6 (C6), 22.1 (C13), 21.6 (C11), 18.3 (C12); **HRMS** (EI) *m/z* $[M]^{\bullet+}$ calcd. for $C_{15}H_{24}$ 204.1873, found, 204.1878.

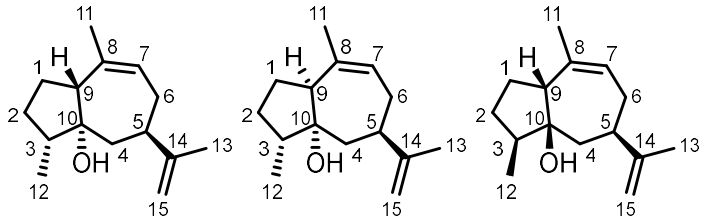
(5*R*,8a*S*)-3,8-Dimethyl-5-(prop-1-en-2-yl)-1,2,4,5,6,8a-hexahydroazulene (1.265)



To a solution of alcohol **1.260** (22.0 mg, 0.100 mmol) in THF (2 mL) in a 25 mL flask was added Burgess reagent (47.7 mg, 0.200 mmol) at 0 °C. The mixture was stirred at RT for 1 h and water (10 mL) was added. The mixture was extracted with ether (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated carefully under vacuum. The residue was purified with chromatography (pentane) to give compound **1.265** as a colourless oil (10.8 mg, 53%).

R_f 0.71 (pentane); **$[\alpha]_D^{25}$** +18 (*c* 0.05, DCM); **IR** ν_{max}/cm^{-1} 2981m, 2930m, 1376m, 912m, 738s; **δ_H** (400 MHz, $CDCl_3$) 5.36 (1H, ddq, *J* = 9.0, 4.0, 1.5 Hz, H7), 4.68 – 4.57 (2H, m, H15), 3.11 (1H, s, H9), 2.56 – 2.47 (1H, m, H5), 2.43 (1H, dd, *J* = 14.0, 5.5 Hz, H4), 2.37 – 2.23 (3H, m, H2, H4′, H6), 2.22 – 2.08 (2H, m, H1, H2′), 1.76 – 1.70 (4H, m, H6′, H13), 1.69 (3H, *J* = 2.0 Hz, H11), 1.62 (4H, m, H1′, H12); **δ_C** (101 MHz, $CDCl_3$) 151.2 (C14), 140.5 (C3), 135.2 (C8), 133.2 (C10), 122.4 (C7), 108.4 (C15), 55.1 (C9), 44.2 (C5), 36.6 (C2), 31.1 (C4), 29.9 (C6), 29.8 (C1), 24.1 (C11), 21.0 (C13), 14.7 (C12); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{23}$ 203.1794, found, 203.1790.

(3*R*,3a*R*,5*R*,8a*R*)-3,8-Dimethyl-5-(prop-1-en-2-yl)-2,3,4,5,6,8a-hexahydroazulen-3a(1*H*)-ol (1.267); and (3*R*,3a*R*,5*R*,8a*S*)-3,8-dimethyl-5-(prop-1-en-2-yl)-2,3,4,5,6,8a-hexahydroazulen-3a(1*H*)-ol (1.268); and (3*S*,3a*S*,5*R*,8a*R*)-3,8-dimethyl-5-(prop-1-en-2-yl)-2,3,4,5,6,8a-hexahydroazulen-3a(1*H*)-ol (1.269)



A suspension of $HgCl_2$ (15.0 mg, 0.0552 mmol) and Mg (50.0 mg, 2.06 mmol) in THF (2 mL) in a dried (heatgun) 50 ml flask under Ar was sonicated (ultrasonic cleaning bath) for 20 min. The resulting grey suspension was diluted with THF (15 mL) and cooled to 0 °C then $TiCl_4$ (113 μL, 1.03 mmol) was added over 3 min and the mixture was stirred for a further 30 min to generate a green suspension. Ketone **9** (0.15 g, 0.69 mmol) was then added and the mixture stirred at 0 °C for 2 h. Satd aq K_2CO_3 solution (10 mL) and 10 mL water were added and the mixture was extracted with ether (3 × 20 mL); the combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (pentane/EtOAc, 20:1) to give the first diastereomer **1.267** of the bicyclic alcohol as a colourless oil (7.9 mg, 5.2%).

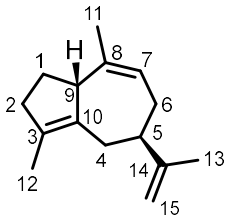
R_f 0.40 (pentane/EtOAc, 10:1); **$[\alpha]_D^{25}$** +44 (*c* 0.06, $CHCl_3$); **IR** ν_{max}/cm^{-1} 3649w, 2980m, 1376m, 772s; **δ_H** (600 MHz, acetone-*d*) 5.75 – 5.71 (1H, m, H7), 4.67 – 4.65 (1H, m, H15), 4.63 – 4.61 (1H, m, H15′), 2.90 (1H, br t, *J* = 9.5 Hz, H9), 2.44 (1H, s, OH), 2.27 – 2.14 (2H, m, H5, H6), 2.08 – 2.05 (1H, m, H4), 2.03 – 1.94 (2H, m, H2, H6′), 1.80 – 1.72 (3H, m, H1, H2′, H3), 1.70 (3H, d, *J* = 1.5 Hz, H11), 1.70 – 1.69 (3H, m, H13), 1.46 (1H, dd, *J* = 13.5, 12.0 Hz, H4′), 1.45 – 1.41 (1H, m, H1′), 0.92 (3 H, d, *J* = 6.5 Hz, H12); **δ_C** (151 MHz, acetone-d_6) 152.8 (C14), 139.2 (C8), 126.8 (C7), 108.8 (C15), 78.7 (C10), 51.5 (C9), 48.2 (C4), 46.4 (C3), 40.1 (C5), 34.5 (C6), 31.4 (C1), 25.7 (C2), 24.3 (C11), 20.7 (C13), 13.6 (C12); **HRMS** (ESI+) *m/z* $[M+H–H_2O]^+$ calcd. for $C_{15}H_{23}$ 203.1794, found, 203.1795.

Further elution (pentane/EtOAc, 5:1) gave diasteromer **1.268** as a colourless oil (12.7 mg, 8.3%). **R_f** 0.20 (pentane/EtOAc, 10:1); **$[\alpha]_D^{25}$** –35 (*c* 0.22, $CHCl_3$); **IR** ν_{max}/cm^{-1} 3484w, 2935s, 2871m, 1456m,

886m; δ_H (600 MHz, acetone-d_6) 5.49 (1H, tquin, J = 7.0, 1.5 Hz, H7), 4.66 – 4.65 (1H, m, H15), 4.61 – 4.60 (1H, m, H15′), 3.04 (1H, s, OH), 2.73 (1H, t, J = 9.0 Hz, H9), 2.58 – 2.51 (1H, m, H5), 2.49 – 2.43 (1H, m, H6), 2.00 – 1.94 (1H, m, H6′), 1.91 – 1.85 (1H, m, H1), 1.75 (1H, ddd, J = 7.5, 5.0, 2.5 Hz, H2), 1.72 – 1.71 (3H, m, H11), 1.69 (3H, dd, J = 1.5, 1.0 Hz, H13), 1.67 – 1.62 (2H, m, H1′, H4), 1.48 (1H, dd, J = 13.5, 11.5 Hz, H4′), 1.45 – 1.37 (2H, m, H2′, H3), 0.93 (3H, d, J = 6.5 Hz, H12); δ_C (151 MHz, acetone-d_6) 152.5 (C14), 139.2 (C8), 123.0 (C7), 108.9 (C15), 80.3 (C10), 54.0 (C9), 46.3 (C3), 41.3 (C4), 38.8 (C5), 31.8 (C2), 31.7 (C6), 26.8 (C1), 24.2 (C11), 21.3 (C13), 14.4 (C12); **HRMS** (ESI+) *m/z* $[M+H–H_2O]^+$ calcd. for $C_{15}H_{23}$ 203.1794, found, 203.1795.

Finally, diastereomer **1.269** was obtained also as a colourless oil (3.3 mg, 2.2%). R_f 0.17 (pentane/EtOAc, 10:1); $[\alpha]_D^{25}$ –22 (*c* 0.04, $CHCl_3$); **IR** ν_{max}/cm^{-1} 3735w, 2919m, 1541m, 772s; δ_H (600 MHz, acetone-d_6) 5.37 – 5.33 (1H, m, H7), 4.72 – 4.71 (1H, m, H15), 4.63 – 4.62 (1H, m, H15′), 2.93 (1H, s, OH), 2.45 (1H, dd, J = 11.0, 8.5 Hz, H9), 2.32 (1H, ddd, J = 10.5, 6.5, 4.0 Hz, H5), 2.28 – 2.20 (1H, m, H6), 2.04 – 1.92 (3H, m, H1, H3, H6′), 1.76 – 1.67 (9H, m, H2, H4, H11, H13), 1.40 – 1.33 (2H, m, H1′, H2′), 0.96 (3H, d, J = 7.0 Hz, H12); δ_C (151 MHz, acetone-d_6) 151.8 (C14), 139.5 (C8), 120.8 (C7), 109.2 (C15), 81.2 (C10), 59.5 (C9), 42.2 (C3), 41.4 (C4), 41.1 (C5), 32.8 (C2), 32.5 (C1), 32.1 (C6), 27.8 (C11), 21.0 (C13), 13.4 (C12); **HRMS** (ESI+) *m/z* $[M+H–H_2O]^+$ calcd. for $C_{15}H_{23}$ 203.1794, found, 203.1796.

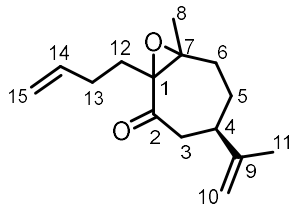
(5R,8aR)-3,8-dimethyl-5-(prop-1-en-2-yl)-1,2,4,5,6,8a-hexahydroazulene (1.272)



To a solution of alcohol **1.259** (10.0 mg, 0.0454 mmol) in THF (2 mL) in a 25 mL flask was added Burgess reagent (23.8 mg, 0.100 mmol) at 0 °C. The mixture was stirred at RT for 1 h and water (10 mL) was added. The mixture was extracted with ether (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated carefully under vacuum. The residue was purified with chromatography (pentane) to give compound **1.272** as a colourless oil (8.0 mg, 87%).

R_f 0.70 (pentane); **$[\alpha]_D^{25}$** –42 (*c* 0.095, DCM); **IR** ν_{max}/cm^{-1} 2926s, 2855m, 1645w, 1450m, 888m; **δ_H** (400 MHz, $CDCl_3$) 5.34 (1H, dddd, *J* = 9.0, 6.5, 3.0, 1.5 Hz, H7), 4.76 – 4.64 (2H, m, H15), 3.09 (1H, d, *J* = 8.5 Hz, H9), 2.64 – 2.55 (1H, m, H4), 2.41 (1H, dddt, *J* = 14.5, 6.5, 5.5, 1.0 Hz, H6), 2.32 – 2.18 (3H, m, H2, H5), 2.16 – 2.08 (1H, m, H1), 1.99 – 1.92 (1H, m, H4′), 1.91 – 1.85 (1H, m, H6′), 1.77 – 1.72 (3H, m, H13), 1.70 (3H, dq, *J* = 1.5, 0.5 Hz, H11), 1.65 (3H, tt, *J* = 2.0, 1.5 Hz, H12), 1.63 – 1.59 (1H, m, H1′); **δ_C** (101 MHz, $CDCl_3$) 151.0 (C14), 140.6 (C3), 136.3 (C8), 130.9 (C10), 120.9 (C7), 108.7 (C15), 55.1 (C9), 45.6 (C5), 36.9 (C2), 31.3 (C4), 29.9 (C6), 29.9 (C1), 24.3 (C11), 21.2 (C13), 14.0 (C12); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{23}$ 203.1794, found, 203.1790.

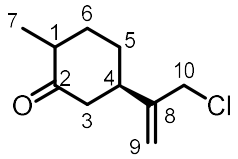
(4R)-1-(but-3-en-1-yl)-7-methyl-4-(prop-1-en-2-yl)-8-oxabicyclo[5.1.0]octan-2-one (1.276)



To a solution of ketone **1.193** (33.6 mg, 0.154 mmol) in methanol (2 mL) in a 25 mL flask was added hydrogen peroxide solution (30% w/w, 0.24 mL, 2.3 mmol) and 6M NaOH (0.20 mL, 1.2 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 18 h and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give epoxide **1.276** as a colourless oil and as a pair of diastereomers (22.7 mg, 63%, dr = 2:1).

R_f 0.50 (pentane/EtOAc, 8:1); **IR** ν_{max}/cm^{-1} 2926s, 2855m, 1703m, 1446m, 912s; **δ_H** (400 MHz, $CDCl_3$) 5.85 – 5.70 (1H, m, H14), 5.08 – 4.92 (2H, m, H15), 4.79 – 4.64 (2H, m, H10), 2.97 – 2.86 (1H, m, H3), 2.53 – 2.40 (1H, m, H12), 2.30 – 2.18 (1H, m, H13), 2.14 – 2.01 (3H, m, H3′, H6, H13′), 1.90 – 1.76 (3H, m, H4, H5, H6′), 1.71 – 1.67 (3H, m, H11), 1.64 – 1.42 (2H, m, H5′, H12′), 1.40 – 1.35 (3H, m, H8); **δ_C** (101 MHz, $CDCl_3$) 213.5/210.1 (C2), 149.0/147.7 (C9), 137.9/137.6 (C14), 115.7/115.5 (C15), 110.0/110.9 (C10), 71.4/71.5 (C1), 64.2/63.5 (C7), 45.6/45.8 (C4), 45.3/45.3 (C3), 33.8/34.8 (C6), 29.7/29.4 (C13), 29.1/28.3 (C5), 28.9/28.2 (C12), 21.9/21.0 (C8), 20.4/19.7 (C11); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{15}H_{22}O_2Na$ 257.1512, found, 257.1523.

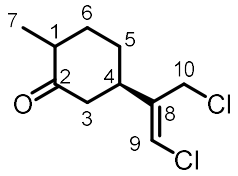
(5*R*)-5-(3-Chloroprop-1-en-2-yl)-2-methylcyclohexan-1-one[10] (2.43)



To a solution of dihydrocarvone (0.15 g, 1.0 mmol) in DCM/water (6 mL/4 mL) was added $NaHCO_3$ (0.34 g, 4.0 mmol) and trimethylchlorosilane (0.19 mL, 1.5 mmol) at RT. Oxone® (0.92 g, 1.5 mmol) was added portionwise, accompanied by the addition of dry ice. Upon the completion (2 h, monitored by TLC), the mixture was diluted with water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 20:1) to give ketone **2.43** as a pale yellow oil and as a pair of diastereomers (0.16 g, 86%, dr = 5:1).

δ_H (400 MHz, $CDCl_3$) 5.28 – 5.20 (1H, m, H9), 5.08 – 4.96 (1H, m, H9′), 4.14 – 3.99 (2H, m, H10), 2.63 – 2.46 (2H, m, H3, H4), 2.43 – 2.33 (1H, m, H1), 2.43 – 2.33 (1H, m, H3′), 2.19 – 2.08 (1H, m, H6), 2.07 – 2.00 (1H, m, H5), 1.73 – 1.60 (1H, m, H5′), 1.46 – 1.33 (1H, m, H6′), 1.07 (0.5H, d, J = 6.5, H7), 1.04 (2.5H, d, J = 6.5, H1); **δ_C** (101 MHz, $CDCl_3$) 211.8/213.3 (C2), 147.8/146.6 (C8), 114.5/116.6 (C9), 47.2/47.5 (C3), 47.1/44.8 (C10), 44.9/44.2 (C1), 42.5/39.5 (C4), 34.8/30.8 (C6), 31.3/26.6 (C5), 14.4/15.5 (C7).

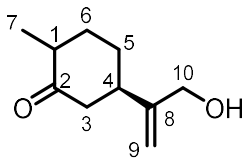
(5*R*)-5-[(*Z*)-1,3-Dichloroprop-1-en-2-yl]-2-methylcyclohexan-1-one (2.44)



To a solution of dihydrocarvone (1.52 g, 10.0 mmol) in DCM/water (60 mL/40 mL) was added $NaHCO_3$ (3.36 g, 40.0 mmol) and trimethylchlorosilane (3.80 mL, 30.0 mmol) at RT. Oxone® (18.4 g, 15.0 mmol) was added portionwise, accompanied by the addition of dry ice. Upon the completion (monitored by TLC), the mixture was diluted with water (50 mL) and extracted with DCM (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give a red oil (1.74 g) from which major component could be characterised as ketone **2.44** by NMR analysis.

$\boldsymbol{\delta_H}$ (700 MHz, $CDCl_3$) 6.12 (1H, d, J = 1.0 Hz, H9), 4.27 – 4.21 (2H, m, H10), 2.71 – 2.64 (1H, m, H4), 2.55 – 2.48 (1H, m, H3), 2.41 – 2.31 (2H, m, H1, H3′), 2.16 (1H, m, H6), 2.04 – 2.00 (1H, m, H5), 1.78 – 1.71 (1H, m, H5′), 1.44 – 1.36 (1H, m, H6′), 1.04 (3H, d, J = 6.5 Hz, H7); $\boldsymbol{\delta_C}$ (176 MHz, $CDCl_3$) 210.8 (C2), 140.7 (C8), 119.6 (C9), 46.7 (C3), 44.9 (C1), 43.7 (C4), 39.7 (C10), 34.5 (C6), 30.9 (C5), 14.4 (C7).

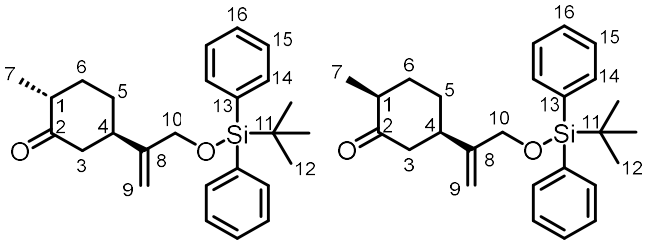
(5*R*)-5-(3-Hydroxyprop-1-en-2-yl)-2-methylcyclohexan-1-one (2.42)



To a solution of ketone **2.43** (0.11 g, 0.59 mmol) in dioxane/water (2.5 mL/7.5 mL) in a 50 mL flask was added $NaHCO_3$ (0.13 g, 1.5 mmol). The mixture was stirred at 100°C for 12 h, cooled to RT and quenched with satd aq NH_4Cl solution (20 mL). The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 2:1) to give alcohol **2.42** as a colourless oil and as a pair of diastereomers (61.5 mg, 62%, dr = 3.5:1).

R_f 0.15 (pentane/EtOAc, 5:1); **IR** ν_{max}/cm^{-1} 3439br, 2933m, 1710s, 1651w, 907m; **δ_H** (400 MHz, $CDCl_3$) 5.19 – 5.07 (1H, m, H9), 4.97 – 4.84 (1H, m, H9′), 4.15 – 4.02 (2H, m, H10), 2.50 – 2.25 (4H, m, H1, H3, H4), 2.16 – 2.07 (1H, m, H6), 2.01 – 1.95 (1H, m, H5), 1.71 – 1.59 (1H, m, H5′), 1.43 – 1.30 (1H, m, H6′), 1.07 (0.66H, d, J = 6.5 Hz, H7), 1.02 (2.26H, d, J = 6.5 Hz, H7); **δ_C** (101 MHz, $CDCl_3$) (for major isomer) 212.5 (C2), 151.4 (C8), 109.6 (C9), 65.0 (C10), 47.3 (C3), 44.9 (C1), 42.8 (C4), 35.1 (C6), 31.4 (C5), 14.5 (C7); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{10}H_{16}O_2Na$ 191.1043, found, 191.1051.

(2*R*,5*R*)-5-[3-[(*tert*-Butyldiphenylsilyl)oxy]prop-1-en-2-yl]-2-methylcyclohexan-1-one (2.45) and (2*S*,5*R*)-5-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-en-2-yl]-2-methylcyclohexan-1-one (2.46)



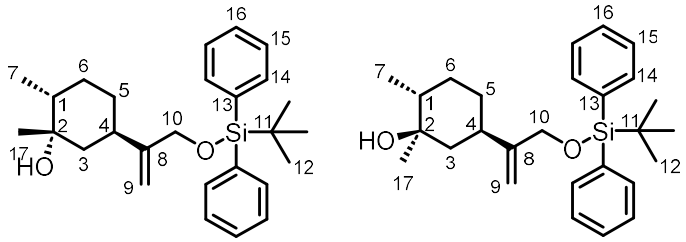
To a solution of alcohol **2.42** (1.92 g, 11.4 mmol) in DMF (100 mL) in a 25 mL flask was added *tert*-butyl(chloro)diphenylsilane (3.8 mL, 15 mmol), 4-(dimethylamino)pyridine (0.28 g, 2.3 mmol) and imidazole (2.02 g, 29.6 mmol). The mixture was stirred at RT for 3 h and diluted with brine (20 mL). 1M HCl (20 mL) was added and the aqueous layer was extracted with ether (3 × 60 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 20:1) to give protected alcohol **2.45** as a colourless oil (2.83 g, 61%).

R$_f$ 0.45 (pentane/EtOAc, 15:1); **[α]$_D^{25}$** +5 (*c* 0.20, DCM); **IR** ν_{max}/cm^{-1} 2961m, 2933m, 1715s, 1113m, 706s; **δ$_H$** (400 MHz, $CDCl_3$) 7.69 – 7.63 (4H, m, H15), 7.45 – 7.35 (6H, m, H14, H16), 5.23 (1H, q, *J* = 1.5 Hz, H9), 4.93 (1H, q, *J* = 1.5 Hz, H9′), 4.14 (2H, t, *J* = 1.5 Hz, H10), 2.42 (1H, dt, *J* = 11.0, 2.5 Hz, H3), 2.38 – 2.27 (3H, m, H1, H3′, H4), 2.12 – 2.04 (1H, m, H6), 1.94 – 1.86 (1H, m, H5), 1.62 (1H, tdd, *J* = 13.5, 11.5, 3.5 Hz, H5′), 1.31 (1H, qd, *J* = 13.0, 3.5 Hz, H6′), 1.06 (9H, s, H12), 1.02 (3H, d, *J* = 6.5 Hz, H7); **δ$_C$** (101 MHz, $CDCl_3$) 212.5 (C2), 150.7 (C8), 135.7 (C15), 133.6 (C13), 129.9 (C16), 127.9 (C14), 108.7 (C9), 65.6 (C10), 47.3 (C3), 44.9 (C1), 42.7 (C4), 35.2 (C6), 31.5 (C5), 27.0 (C12), 19.4(C11), 14.5 (C7); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{26}H_{34}O_2SiNa$ 429.2220, found, 429.2223.

Further elution (pentane/EtOAc, 15:1) gave diasteromer **2.46** as a colourless oil (1.24 g, 26%). **R**$_f$ 0.43 (pentane/EtOAc, 15:1); **[α]$_D^{25}$** +4 (*c* 0.29, DCM); **IR** ν_{max}/cm^{-1} 2959m, 2933m, 1712m, 1114s, 705s; **δ$_H$** (400 MHz, $CDCl_3$) 7.67 (4H, m, H15), 7.45 – 7.33 (6H, m, H14, H16), 5.27 – 5.24 (1H, m, H9), 4.89 – 4.83 (1H, m, H9′), 4.14 – 4.09 (2H, m, H10), 2.69 (1H, q, *J* = 5.5 Hz, H4), 2.55 (1H, ddd, *J* = 14.5, 6.5, 1.0 Hz, H3), 2.43 – 2.31 (2H, m, H1, H3′), 1.86 – 1.69 (3H, m, H5, H6), 1.58 – 1.50 (1H, m, H6′), 1.07 (12H, m, H7, H12); **δ$_C$** (101 MHz, $CDCl_3$) 214.0 (C2), 149.7 (C8), 135.7 (C15), 133.6 (C13), 129.9

(C16), 127.9 (C14), 110.7 (C9), 65.9 (C10), 44.8 (C1), 44.3 (C3), 39.7 (C4), 30.8 (C6), 26.9 (C12), 26.9 (C5), 19.4 (C11), 15.7 (C7); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{26}H_{34}O_2SiNa$ 429.2220, found, 429.2228.

(1*S*,2*R*,5*R*)-5-[3-[(*tert*-Butyldiphenylsilyl)oxy]prop-1-en-2-yl]-1,2-dimethylcyclohexan-1-ol (2.48-1) and (1*R*,2*R*,5*R*)-5-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-en-2-yl]-1,2-dimethylcyclohexan-1-ol (2.48-2)



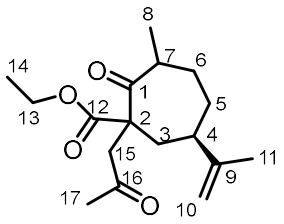
To a solution of protected alcohol **2.45** (81.2 mg, 0.200 mol) in toluene (3 mL) in a 25 mL flask was added trimethylaluminum (2.0 M in hexane, 40 μL, 0.080 mmol) and the mixture cooled to –78 °C. A solution of ethyl diazoacetate (23 μL, 0.22 mmol) in toluene (0.5 mL) was added and the mixture was stirred at –78 °C for 2 h. The reaction was quenched with 1M HCl (10 mL) and the mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 15:1) to give alcohol **2.48-1** as a colourless oil (25.1 mg, 30%).

R_f 0.40 (pentane/EtOAc, 15:1); **$[\alpha]_D^{25}$** +6 (*c* 0.26, DCM); **IR** ν_{max}/cm^{-1} 2931m, 2857m, 1429w, 1114s, 705s; **δ_H** (400 MHz, $CDCl_3$) 7.72 – 7.66 (4H, m, H15), 7.44 – 7.36 (6H, m, H14, H16), 5.24 (1H, q, *J* = 1.5 Hz, H9), 4.89 (1H, q, *J* = 1.5 Hz, H9′), 4.16 (2H, m, H10), 2.19 (1H, tt, *J* = 12.5, 3.5 Hz, H4), 1.75 – 1.62 (2H, m, H3, H5), 1.50 – 1.42 (1H, m, H6), 1.35 – 1.24 (3H, m, H1, H5′, H6′), 1.16 (4H, m, H3′, H17), 1.07 (9H, s, H12), 0.90 (3H, d, *J* = 6.0 Hz, H7); **δ_C** (101 MHz, $CDCl_3$) 152.8 (C8), 135.7 (C15), 133.8 (C13), 129.8 (C16), 127.8 (C14), 107.1 (C9), 71.5 (C2), 65.8 (C10), 46.0 (C3), 40.1 (C1), 36.2 (C4), 32.2 (C5), 30.9 (C6), 29.0 (C17), 27.0 (C12), 19.4 (C11), 15.1 (C7); **HRMS** (ESI+) *m/z* $[M+NH_4]^+$ calcd. for $C_{27}H_{42}NO_2Si$ 440.2979, found, 440.2991.

Further elution (pentane/EtOAc, 15:1) gave another diasteromer **2.48-2** (1.2 mg, 1.5%) as a colourless oil. **R_f** 0.21 (pentane/EtOAc, 15:1); **$[\alpha]_D^{25}$** +5 (*c* 0.12, DCM); **IR** ν_{max}/cm^{-1} 2932m, 2858m, 1461m, 1114s, 705s; **δ_H** (400 MHz, $CDCl_3$) 7.73 – 7.64 (4H, m, H15), 7.50 – 7.33 (6H, m, H14, H16), 5.16 (1H, q, *J* = 1.5 Hz, H9), 4.88 (1H, q, *J* = 1.5 Hz, H9′), 4.15 (2H, d, *J* = 1.5 Hz, H10), 2.03 (1H, t, *J* = 12.5

Hz, H4), 1.81 – 1.71 (1H, m, H3), 1.71 – 1.60 (2H, m, H5, H6), 1.43 (1H, dtd, *J* = 13.5, 6.5, 4.0 Hz, H1), 1.33 (1H, t, *J* = 12.5 Hz, H3′), 1.18 – 1.08 (2H, m, H5′, H6′), 1.08 – 1.03 (12H, m, H12, H17), 0.91 (3H, d, *J* = 6.5 Hz, H7); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 152.2 (C8), 135.7 (C15), 133.8 (C13), 129.8 (C16), 127.8 (C14), 107.6 (C9), 73.5 (C2), 65.9 (C10), 47.8 (C3), 42.6 (C1), 38.6 (C4), 32.4 (C5), 32.3 (C6), 26.9 (C12), 20.3 (C17), 19.4 (C11), 15.1 (C7); **HRMS** (ESI+) *m/z* $[M+K]^+$ calcd. for $C_{27}H_{38}O_2SiK$ 461.2273, found, 461.2247.

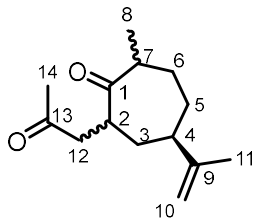
Ethyl (6*R*)-3-methyl-2-oxo-1-(2-oxopropyl)-6-(prop-1-en-2-yl)cycloheptane-1-carboxylate (2.53)



To a solution of keto ester **1.167** (0.14 g, 0.59 mmol) in DMF (6 mL) in a 25 mL flask was added NaI (0.11 g, 0.73 mmol), Cs_2CO_3 (0.34 g, 1.0 mmol) and chloroacetone (60 μL, 0.75 mmol). The mixture was stirred at RT for 18 h then water (10 mL) was added. The mixture was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 5:1) to give diketone **2.53** as a pale yellow oil and as a single diastereomer (93.3 mg, 55%, not assigned).

R_f 0.15 (pentane/EtOAc, 5:1); **$[\alpha]_D^{25}$** –56 (*c* 0.57, DCM); **IR** ν_{max}/cm^{-1} 2979m, 2933m, 1734s, 1706s, 1208m; **δ_H** (700 MHz, $CDCl_3$) 4.68 – 4.64 (2H, m, H10), 4.24 – 4.15 (2H, m, H13), 3.14 (1H, d, *J* = 17.5 Hz, H15), 2.99 (1H, d, *J* = 17.5 Hz, H15′), 2.92 (1H, dtd, *J* = 11.0, 6.5, 2.0 Hz, H7), 2.17 – 2.09 (5H, m, H3, H4, H17), 1.97 (1H, dd, *J* = 14.5, 10.5 Hz, H3′), 1.89 – 1.82 (1H, m, H5), 1.73 – 1.66 (4H, m, H6, H11), 1.64 – 1.57 (1H, m, H6′), 1.53 (1H, tdd, *J* = 13.0, 11.5, 3.5 Hz, H5′), 1.27 (3H, t, *J* = 7.0 Hz, H14), 1.13 (3H, d, *J* = 6.5 Hz, H8); **δ_C** (176 MHz, $CDCl_3$) 211.7 (C1), 205.3 (C16), 172.6 (C12), 150.8 (C9), 109.0 (C10), 61.5 (C13), 61.3 (C2), 51.9 (C15), 45.9 (C1), 44.6 (C4), 39.0 (C3), 36.2 (C5), 33.4 (C6), 30.4 (C17), 20.7 (C11), 18.0 (C8), 14.3 (C14); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{26}O_4Na$ 317.1723, found, 317.1727.

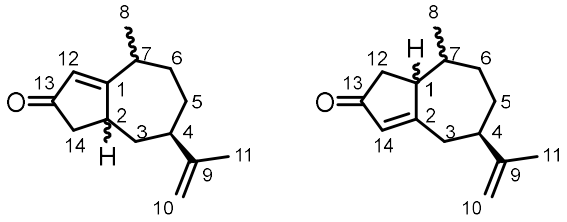
(4*R*)-7-Methyl-2-(2-oxopropyl)-4-(prop-1-en-2-yl)cycloheptan-1-one (2.51)



To a solution of diketone ester **2.53** (0.14 g, 0.47 mmol) in methanol (10 mL) in a 50 mL flask was added a solution of NaOH (45.2 mg, 1.13 mmol) in water (2.5 mL). The mixture was stirred at 80°C for 3 h and cooled to RT. The solution was diluted with 1M HCl (10 mL) and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over Na_2SO_4 and concentrated to give a complex of diastereomers (77.3 mg, 74%) which was used directly for next step without purification.

R_f 0.31 (pentane/EtOAc, 4:1); **IR** ν_{max}/cm^{-1} 2929m, 1706s, 1645w, 1465m, 891m; **δ_H** (400 MHz, $CDCl_3$) selected peaks are reported here 4.70 – 4.61 (2H, m, H10), 2.18 – 2.09 (3H, m, H14), 1.68 – 1.63 (3H, m, H11), 1.18 – 1.01 (3H, m, H8); **HRMS** (ESI+) *m/z* $[M+K]^+$ calcd. for $C_{14}H_{22}O_2K$ 261.1251, found, 261.1261.

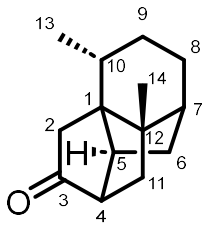
(7*R*)-4-Methyl-7-(prop-1-en-2-yl)-4,5,6,7,8,8a-hexahydroazulen-2(1*H*)-one and (5*R*)-8-methyl-5-prop-1-en-2-yl)-4,5,6,7,8,8a-hexahydroazulen-2(1*H*)-one (2.50)



To a solution of diketone **2.51** (22.2 mg, 0.100 mmol) in ethanol (5 mL) in a 25 mL flask was added KOH (5.6 mg, 0.10 mmol) and the suspension was stirred at 90 °C for 18 h. The reaction was cooled to RT and quenched with satd aq NH_4Cl solution (10 mL). The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to give a complex of isomers **2.50** (including diastereomers and regioisomers) (36.7 mg, 53%) which was used directly for next step without purification.

R_f 0.20 (pentane/EtOAc, 4:1); **IR** ν_{max}/cm^{-1} 2971m, 1701s, 1645w, 1604m, 890m; **δ_H** (400 MHz, $CDCl_3$) selected peaks are reported here 6.01 – 5.87 (1H, m, =CH), 4.76 – 4.56 (2H, m, H10), 1.75 – 1.65 (3H, m, H11), 1.24 – 0.95 (3H, m, H8); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{14}H_{20}ONa$ 227.1406, found, 227.1416.

(4*R*,8a*S*,9*S*)-4,9-Dimethylhexahydro-1*H*-3a,7,1-(epiethane[1,1,2]triyl)azulen-2(3H)-one (2.55)

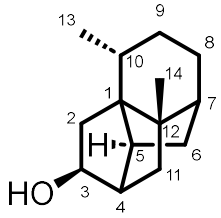


A suspension of enone mixture **2.50** (0.20 g, 0.98 mmol), $ZnCl_2$ (1.36 g, 10.0 mmol), triethylamine (1.4 mL, 10 mmol) and trimethylchlorosilane (1.3 mL, 10 mmol) in toluene (10 mL) in a pressure tube was heated to 160 °C for 24 h. The suspension was cooled to RT and washed with 10% HCl (20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and concentrated to give IMDA product **2.55** as an orange oil (0.17 g, 85%) that was unsuitable for chromatographic purification.

$[\alpha]_D^{25}$ +37 (*c* 0.13, DCM); **IR** ν_{max}/cm^{-1} 2932m, 2874m, 1749s, 1464w, 652w; **δ_H** (600 MHz, $CDCl_3$) 2.28 (1H, d, *J* = 5.5 Hz, H5), 2.24 (1H, d, *J* = 6.5 Hz, H4), 2.14 (1H, dd, *J* = 19.0, 1.5 Hz, H2), 1.90 (1H, dd, *J* = 19.0, 1.5 Hz, H2′), 1.80 – 1.69 (3H, m, H7, H8, H10), 1.64 – 1.57 (1H, m, H11), 1.57 – 1.43 (3H, m, H6, H9), 1.34 – 1.24 (2H, m, H8′, H9′), 1.12 (1H, dt, *J* = 13.0, 1.0 Hz, H11′), 0.99 (3H, s, H14), 0.87 (3H, d, *J* = 6.5 Hz, H13); **δ_C** (151 MHz, $CDCl_3$) 217.0 (C3), 55.4 (C4), 54.9 (C1), 45.7 (C7), 45.1 (C12), 44.7 (C5), 38.1 (C2), 37.2 (C11), 28.7 (C10), 27.9 (C9), 26.9 (C6), 26.2 (C8), 19.0 (C13), 13.9 (C14); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{14}H_{20}ONa$ 227.1406, found, 227.1409.

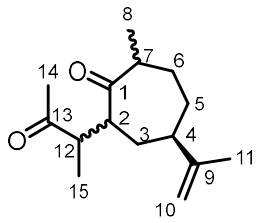
(2*R*,4*R*,8a*S*,9*S*)-4,9-Dimethyloctahydro-1*H*-3a,7,1-(epiethane[1,1,2]triyl)azulen-2-ol (2.56)

(*Appendix 21*)



To a solution of IMDA product **2.55** (0.17 g, 0.83 mmol) in methanol (10 mL) in a 25 mL flask was added $NaBH_4$ (47.6 mg, 1.26 mmol) at 0 °C. The suspension was stirred at 0 °C for 2.5 h and quenched with satd aq NH_4Cl solution (10 mL). The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 6:1) to give alcohol **2.56** as a white solid (55.8 mg, 33%). **R_f** 0.24 (pentane/EtOAc, 6:1); **M.p.** 95 °C; **$[\alpha]_D^{25}$** +94 (*c* 0.070, DCM); **IR** ν_{max}/cm^{-1} 3344br, 2937s, 1468m, 1204m, 738m; **δ_H** (600 MHz, $CDCl_3$) 4.20 – 4.15 (1H, m, H3), 2.00 – 1.94 (2H, m, H2, H5), 1.81 (1H, dt, *J* = 6.0, 2.5 Hz, H4), 1.71 – 1.67 (1H, m, H8), 1.60 – 1.56 (2H, m, H7, H10), 1.49 – 1.36 (4H, m, H6, H9, H11), 1.23 – 1.15 (2H, m, H8′, H9′), 1.06 (1H, ddd, *J* = 12.5, 5.5, 1.5 Hz, H11′), 0.96 (3H, s, H14), 0.92 – 0.88 (1H, m, H2′), 0.84 (3H, d, *J* = 6.5 Hz, H13); **δ_C** (151 MHz, $CDCl_3$) 73.8 (C3), 56.8 (C1), 48.4 (C4), 46.8 (C12), 44.9 (C7), 44.6 (C5), 33.1 (C11), 32.8 (C2), 28.6 (C10), 28.4 (C9), 27.4 (C6), 26.4 (C8), 19.3 (C13), 13.0 (C14); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{14}H_{23}O$ 207.1743, found, 207.1767.

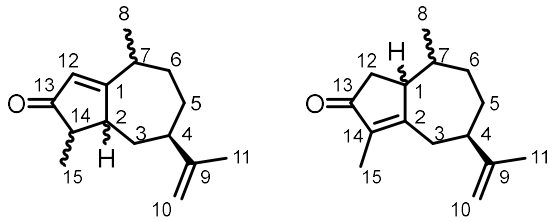
(4*R*)-7-Methyl-2-(3-oxobutan-2-yl)-4-(prop-1-en-2-yl)cycloheptan-1-one (2.61)



To a solution of ketone **1.164** (0.12 g, 0.75 mmol) in THF (10 mL) in a 25 mL flask was added LHMDS (1.0 M in THF, 0.90 mL, 0.90 mmol) at –78 °C. The mixture was stirred at –78 °C for 1 h then 2-nitro-2-butene **2.59** (0.11 g, 1.1 mmol) was added and the reaction continued at –78 °C for 1 h. The mixture was warmed to 0 °C and 3M HCl (20 mL) was added. The mixture was stirred at RT for 2 h then extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (pentane/EtOAc, 20:1) giving diketone **2.61** as a colourless oil (66.1 mg, 37%) and as a mixture of diastereomers. (*Appendix 13*)

R_f 0.35 (pentane/EtOAc, 5:1); **IR** ν_{max}/cm^{-1} 2930m, 1703s, 1645w, 1458m, 891m; **δ_H** (400 MHz, $CDCl_3$) selected peaks are reported here 4.76 – 4.60 (2H, m, H10), 2.22 – 2.15 (3H, m, H14), 1.72 – 1.62 (3H, m, H11), 1.15 – 0.98 (6H, m, H8, H15); **HRMS** (ESI+) *m/z* $[M+K]^+$ calcd. for $C_{15}H_{24}O_2K$ 275.1408, found, 275.1412.

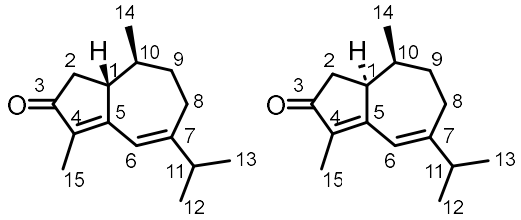
(7*R*)-1,4-Dimethyl-7-(prop-1-en-2-yl)-4,5,6,7,8,8a-hexahydroazulen-2(1H)-one (2.57) and (5*R*)-3,8-dimethyl-5-(prop-1-en-2-yl)-4,5,6,7,8,8a-hexahydroazulen-2(1H)-one (2.62)



To a solution of diketone **2.61** (0.12 g, 0.51 mmol) in benzene (5 mL) in a 25 mL flask was added NaH (60% in mineral oil, 23.0 mg, 0.575 mmol) and *tert*-butyl alcohol (15 μL, 0.16 mmol) and the suspension was stirred at 90 °C for 15 min. The reaction was cooled to RT and quenched with cold water (10 mL). The mixture was extracted with ether (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to give a crude mixture of isomers **2.57** and **2.63** (including diastereomers and regioisomers) (92.4 mg, 83%) which was used directly for next step without purification. (*Appendix 13*)

R_f 0.33 (pentane/EtOAc, 5:1); **IR** ν_{max}/cm^{-1} 2923m, 1703s, 1645m, 1604m, 1456m; **δ_H** (400 MHz, $CDCl_3$) selected peaks are reported here 5.97 – 5.80 (~1H, m, H12 in **2.57**), 4.80 – 4.59 (2H, m, H10), 1.75 – 1.65 (~3H, m, H11), 1.26 – 1.01 (~6H, m, H8, H15); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{15}H_{22}ONa$ 241.1563, found, 241.1558.

(8*S*,8a*R*)-5-Isopropyl-3,8-dimethyl-6,7,8,8a-tetrahydroazulen-2(1H)-one[11] (2.63) and (8*S*,8a*S*)-5-Isopropyl-3,8-dimethyl-6,7,8,8a-tetrahydroazulen-2(1H)-one[11] (2.64)

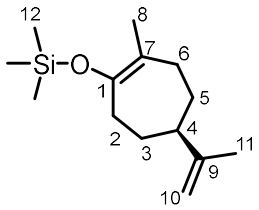


To a solution of enone mixture **2.57** and **2.62** (12.1 mg, 0.0554 mmol) in toluene (2 mL) in a 25 mL flask was added *N*-(trimethylsilyl)bis(trifluoromethanesulfonyl)imide (75 μL, 0.29 mmol) and the mixture stirred at RT for 15 min. Triethylamine (35 μL, 0.25 mmol) was added and the reaction was heated to 110 °C for 30 min. The mixture was cooled to RT and diluted with water (10 mL). The aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 6:1) to give regioisomer **2.63** as a colourless oil (2.5 mg, 21%).

δ_H (600 MHz, $CDCl_3$) 6.30 (1H, dd, *J* = 2.0, 1.0 Hz, H6), 2.65 – 2.61 (1H, m, H1), 2.61 – 2.54 (1H, m, H2), 2.49 – 2.40 (2H, m, H8, H11), 2.15 – 2.10 (2H, m, H2′, H8′), 1.83 – 1.77 (1H, m, H9), 1.74 (3H, d, *J* = 1.5 Hz, H15), 1.62 – 1.54 (2H, m, H9′, H10), 1.09 (6H, m, H12, H13), 1.06 (3H, d, *J* = 6.5 Hz, H14); **δ_C** (151 MHz, $CDCl_3$) 209.0 (C3), 169.0 (C5), 162.8 (C7), 135.0 (C4), 119.1 (C6), 46.7 (C1), 42.3 (C2), 38.9 (C10), 38.8 (C11), 35.4 (C9), 27.0 (C8), 22.1 (C14), 21.4 (C12), 21.1 (C13), 8.3 (C15).

Further elution (pentane/EtOAc, 6:1) gave diasteromer **2.64** as a colourless oil (1.4 mg, 11%). **δ_H** (600 MHz, $CDCl_3$) 6.33 (1H, s, H6), 3.27 (1H, m, H1), 2.54 – 2.41 (3H, m, H2, H8, H11), 2.27 – 2.18 (3H, m, H2′, H8′, H10), 2.07 (1H, ddd, *J* = 14.0, 6.0, 3.0 Hz, H9), 1.75 (3H, d, *J* = 2.0 Hz, H15), 1.56 – 1.49 (1H, m, H9′), 1.09 (6H, ddd, *J* = 7.0, 2.5, 1.0 Hz, H12, H13), 0.71 (3H, dd, *J* = 7.0, 1.0 Hz, H14); **δ_C** (151 MHz, $CDCl_3$) 209.3 (C3), 167.8 (C7), 161.7 (C5), 136.0 (C4), 119.3 (C6), 44.3 (C1), 39.8 (C2), 39.3 (C11), 34.9 (C9), 33.0 (C10), 28.1 (C8), 21.4 (C12), 21.3 (C13), 14.1 (C14), 8.2 (C15).

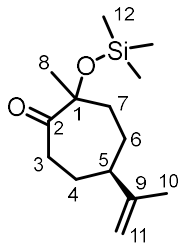
(*R*)-Trimethyl[[2-methyl-5-(prop-1-en-2-yl)cyclohept-1-en-1-yl]oxy]silane[12] (1.186)



To a solution of $FeCl_3$ (89.2 mg, 0.550 mmol) in ether (8 mL) in a 25 mL flask was added methylmagnesium bromide (3.0 M in ether, 0.55 mL, 1.7 mmol) at 0 °C and the mixture was stirred at RT for 1 h. A solution of ketone **1.164** (83.0 mg, 0.500 mmol) in ether (2 mL) was added and the mixture was stirred at RT for 30 min. Trimethylchlorosilane (0.21 mL, 1.7 mmol), triethylamine (0.24 mL, 1.7 mmol) and hexamethylphosphoramide (96 μL, 0.55 mmol) were added and the reaction was continued at RT for 10 h. The mixture was diluted with pentane (30 mL), washed with cold satd aq $NaHCO_3$ solution (3 × 10 mL), dried over Na_2SO_4 and concentrated to give enol ether **1.186** as a pale yellow oil (107.2 mg, 90%) which was used directly in next step without purification.

δ_H (400 MHz, $CDCl_3$) 4.69 – 4.59 (2H, m, H10), 2.44 – 2.33 (1H, m, H6), 2.17 – 2.08 (2H, m, H2, H6′), 2.05 (1H, dt, *J* = 11.0, 3.5 Hz, H4), 1.97 (1H, ddd, *J* = 15.0, 7.5, 1.5 Hz, H2′), 1.76 – 1.66 (5H, m, H3, H5, H11), 1.61 (3H, d, *J* = 1.5 Hz, H8), 1.46 – 1.35 (1H, m, H5′), 1.35 – 1.26 (1H, m, H3′), 0.17 (9H, s, H12); δ_C (101 MHz, $CDCl_3$) 151.6 (C1), 147.7 (C9), 116.7 (C7), 108.5 (C10), 50.6 (C4), 34.1 (C6), 31.9 (C2), 31.6 (C3), 30.6 (C5), 21.0 (C11), 18.7 (C8), 0.7 (C12).

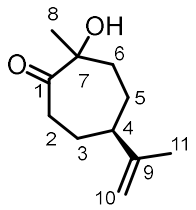
(5*R*)-2-Methyl-5-(prop-1-en-2-yl)-2-[(trimethylsilyl)oxy]cycloheptan-1-one (2.66)



A solution of trimethylsilyl enol ether **1.186** (0.21 g, 0.88 mmol) in dry DCM (10 mL) in a 25 mL flask was cooled to 0 °C, and MCPBA (75% w/w, 0.24 g, 1.1 mmol) was added. The mixture was stirred at 0 °C for 1 h. Satd aq Na_2SO_3 solution (10 mL) was added and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with water (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give protected alcohol **2.66** as a colourless oil and as a single diastereomer (92.4 mg, 41%, not assigned).

R_f 0.62 (pentane/EtOAc, 10:1); **$[\alpha]_D^{25}$** –18 (*c* 0.25, DCM); **IR** ν_{max}/cm^{-1} 2944w, 2865w, 1719m, 1252m, 842s; **δ_H** (400 MHz, $CDCl_3$) 4.71 – 4.64 (2H, m, H11), 2.91 (1H, td, *J* = 12.0, 3.5 Hz, H3), 2.36 (1H, ddd, *J* = 11.5, 7.0, 3.0 Hz, H3′), 2.17 (1H, tt, *J* = 11.0, 3.5 Hz, H5), 1.99 (1H, ddd, *J* = 14.5, 9.0, 1.5 Hz, H7), 1.94 – 1.85 (1H, m, H4), 1.85 – 1.70 (2H, m, H6, H7′), 1.67 (3H, dd, *J* = 1.5, 1.0 Hz, H10), 1.61 – 1.48 (1H, m, H4′), 1.32 (3H, d, *J* = 0.5 Hz, H8), 1.16 (1H, dtd, *J* = 15.0, 10.5, 1.5 Hz, H6′), 0.11 (9H, s, H12); **δ_C** (101 MHz, $CDCl_3$) 212.5 (C2), 149.7 (C9), 109.6 (C11), 80.5 (C1), 48.5 (C5), 40.0 (C7), 37.5 (C3), 31.8 (C4), 29.0 (C6), 24.3 (C8), 20.8 (C10), 2.3 (C12); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{14}H_{26}O_2SiNa$ 277.1594, found, 277.1588.

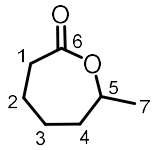
(5*R*)-2-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cycloheptan-1-one (2.67)



To a solution of protected alcohol **2.66** (25.4 mg, 0.100 mmol) in DMF (5 mL) in a 25 mL flask was added KHMDS (1.0 M in THF, 0.11 mL, 0.11 mmol) at –78 °C and the mixture was stirred at –78 °C for 10 min. A solution of 3-chloro-2-butanone (12 μL, 0.12 mmol) and NaI (18.0 mg, 0.120 mmol) in DMF (1 mL) was added and the reaction was stirred at –78 °C for 10 min then warmed to RT for 3 h. Satd aq NH_4Cl solution (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 5:1) to give ketone alcohol **2.67** as a colourless oil and as a single diastereomer (1.8 mg, 10%, not assigned).

R_f 0.15 (pentane/EtOAc, 5:1); **$[\alpha]_D^{25}$** +16 (*c* 0.12, DCM); **IR** ν_{max}/cm^{-1} 3496br, 2940m, 1711s, 1455m, 1376m; **δ_H** (400 MHz, $CDCl_3$) 4.80 (1H, dd, *J* = 2.0, 1.5 Hz, H10), 4.73 (1H, tt, *J* = 1.5, 1.0 Hz, H10′), 3.90 (1H, d, *J* = 1.0 Hz, OH), 2.86 (1H, ddd, *J* = 14.5, 8.0, 4.0 Hz, H2), 2.52 (1H, ddd, *J* = 14.5, 9.5, 4.5 Hz, H2′), 2.12 (1H, td, *J* = 8.0, 4.0 Hz, H4), 2.02 – 1.94 (1H, m, H3), 1.93 – 1.84 (1H, m, H6), 1.81 – 1.74 (1H, m, H3′), 1.72 (3H, m, H11), 1.71 – 1.63 (3H, m, H5, H6′), 1.37 (3H, s, H8); **δ_C** (101 MHz, $CDCl_3$) 215.7 (C1), 148.7 (C9), 110.1 (C10), 78.8 (C7), 45.0 (C4), 37.2 (C2), 35.9 (C6), 29.0 (C3), 28.5 (C5), 25.3 (C8), 21.4 (C11); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{11}H_{18}O_2Na$ 205.1199, found, 205.1198.

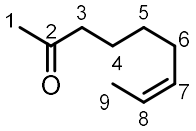
7-Methyloxepan-2-one[13] (2.70)



A solution of 2-methylcyclohexanone **2.69** (2.04 g, 18.1 mmol) in DCM (85 mL) in a 150 mL flask was cooled to 0 °C and MCPBA (75% w/w, 10.00 g, 43.46 mmol) was added. The reaction was stirred vigorously at 0 °C for 18 h. Satd aq $Na_2S_2O_3$ solution (100 mL) was added and the mixture was extracted with DCM (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 7:1) to give lactone **2.70** as a colourless oil (2.15 g, 93%).

R_f 0.11 (pentane/EtOAc, 7:1); **IR** ν_{max}/cm^{-1} 2938w, 1731s, 1180s, 1017m; **δ_H** (400 MHz, $CDCl_3$) 4.44 (1H, dq, *J* = 8.5, 6.5 Hz, H5), 2.72 – 2.53 (2H, m, H1), 2.02 – 1.81 (3H, m, H2, H3, H4), 1.74 – 1.50 (3H, m, H2′, H3′, H4′), 1.35 (3H, d, *J* = 6.5 Hz, H7); **δ_C** (101 MHz, $CDCl_3$) 175.7 (C6), 77.0 (C5), 36.4 (C4), 35.2 (C1), 28.5 (C3), 23.1 (C2), 22.8 (C7); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_7H_{12}O_2Na$ 151.0730, found, 151.0726.

(*Z*)-Non-7-en-2-one[14] (2.73)



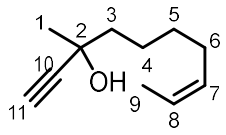
To a solution of lactone **2.70** (2.15 g, 16.8 mmol) in THF (70 mL) in a 250 mL flask was added DIBAL-H (1.2 M in toluene, 14.7 mL, 17.6 mmol) at –78 °C. The mixture was stirred for 0.5 h and warmed up to 0 °C. Water (70 mL) was added and the organic phase was extracted with ether (3× 30 mL). The combined organic extracts were filtered through a layer of Al_2O_3 and dried over Na_2SO_4 and concentrated to give crude hemiacetal **2.71** which was used directly in the next step without purification.

To a suspension of ethyltriphenylphosphonium bromide (2.45 g, 6.60 mmol) in dry THF (40 mL) in a 250 mL flask was added BuLi (1.6 M in hexane, 4.1 mL, 6.6 mmol) at –78 °C. The solution was warmed to RT, stirred for 1 h and then cooled to –78 °C. A solution of hemiacetal **2.71** in THF (10 mL) was added into the mixture. The mixture was warmed to RT and stirred for 18 h. The mixture was diluted with ether (50 mL) and quenched with water (2 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was diluted with methyl *tert*-butyl ether (50 mL) and filtered through a layer of Al_2O_3 and concentrated to get crude alcohol **2.72**.

To a suspension of PCC (1.94 g, 9.00 mmol) in DCM (40 mL) in a 150 mL flask was added a solution of alcohol **2.72** in DCM (10 mL) at RT. The mixture was stirred for 2 h and diluted with ether (50 mL). The suspension was filered through a layer of Al_2O_3 and dried over Na_2SO_4 and concentrated to get crude ketone **2.73** (0.89 g) having NMR data matching with reported data. It was used directly for next step without purification.

$\mathbf{R}_f$ 0.62 (pentane/EtOAc, 2:1); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 5.51 – 5.32 (2H, m, H7, H8), 2.43 (2H, t, J = 7.5 Hz, H3), 2.13 (3H, s, H1), 2.05 (2H, m, two protons from H4, H5, H6), 1.67 – 1.54 (5H, m, H9 and two protons from H4, H5, H6), 1.35 (2H, m, two protons from H4, H5, H6).

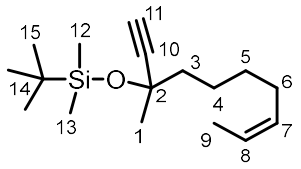
(*Z*)-3-Methyldec-8-en-1-yn-3-ol (2.74)



To a solution of crude ketone **2.73** (0.84 g, 6.0 mmol) in dry THF (30 mL) was added ethynylmagnesium bromide (0.5 M in THF, 18.0 mL, 9.00 mmol) at –78 °C. The solution was warmed to RT and stirred for 1 h and was then quenched with satd aq NH_4Cl solution (20 mL). The aqueous phase was extracted with ether (3 × 20 mL) then the combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 5:1) to give alcohol **2.74** as an orange oil (0.45 g, 46%).

R_f 0.20 (pentane/EtOAc, 10:1); **IR** ν_{max}/cm^{-1} 3308w, 2940m, 1121w, 912m, 736s; **δ_H** (400 MHz, $CDCl_3$) 5.52 – 5.32 (2H, m, H7, H8), 2.43 (1H, s, H11), 2.13 – 2.02 (2H, m, H6), 1.93 (1H, d, *J* = 1.5 Hz, OH), 1.71 – 1.64 (2H, m, H3), 1.61 – 1.58 (3H, m, H9), 1.56 – 1.48 (5H, m, H1, H4), 1.45 – 1.34 (2H, m, H5); **δ_C** (101 MHz, $CDCl_3$) 130.6 (C7), 124.1 (C8), 87.9 (C10), 71.4 (C11), 68.2 (C2), 43.5 (C3), 29.9 (C1), 29.7 (C5), 26.9 (C6), 24.4 (C4), 12.9 (C9); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{11}H_{19}O$ 167.1430, found, 167.1426.

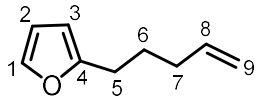
(*Z*)-*tert*-Butyldimethyl[(3-methyldec-8-en-1-yn-3-yl)oxy]silane (2.75)



To a solution of alcohol **2.74** (0.454 g, 2.74 mmol) in DCM (20 mL) in a 100 mL flask was added triethylamine (1.15 mL, 8.22 mmol). The solution was cooled to 0 °C and added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.944 mL, 4.11 mmol). The mixture was warmed to RT and stirred for 2 h. Satd aq $NaHCO_3$ solution (20 mL) was added and the organic phase was extracted with DCM (3 × 20 mL); the combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane, 100%) to give product **2.75** as a colourless oil (0.737 g, 96%).

R_f 0.70 (pentane, 100%); **IR** ν_{max}/cm^{-1} 2933w, 1254m, 1052m, 838s, 777s; **δ_H** (400 MHz, $CDCl_3$) 5.51 – 5.33 (2H, m, H7, H8), 2.39 (1H, s, H11), 2.12 – 1.98 (2H, m, H6), 1.67 – 1.57 (5H, m, H3, H9), 1.53 – 1.45 (2H, m, H4), 1.43 (3H, s, H1), 1.41 – 1.31 (2H, m, H5), 0.86 (9H, s, H15), 0.20 – 0.12 (6H, m, H12, H13); **δ_C** (101 MHz, $CDCl_3$) 130.8 (C7), 123.9 (C8), 88.6 (C10), 71.8 (C11), 69.2 (C2), 45.2 (C3), 31.1 (C1), 29.8 (C5), 27.0 (C6), 25.9 (C15), 24.3 (C4), 18.2 (C14), 12.9 (C9), -3.0 (C12, C13); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{17}H_{33}OSi$ 281.2295, found, 281.2293.

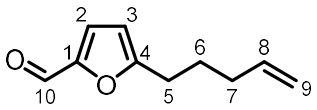
2-(Pent-4-en-1-yl)furan[15] (2.103)



To a solution of furan **2.102** (2.9 mL, 40 mmol) in dry THF (21 mL) in a 100 mL flask was cooled to 0 °C and BuLi (1.6 M in hexane, 18.8 mL, 30.1 mmol) added. The mixture was stirred at 0 °C for 1 h then a solution of 5-bromo-1-pentene (1.2 mL, 10 mmol) in dry THF (5 mL) added. The solution was then warmed to RT and stirred for 18 h. The reaction was quenched with satd aq NH_4Cl solution (20 mL). The aqueous phase was extracted with ether (3 × 20 mL) then the combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue crude product **2.103** (1.18 g, 86%) was used directly in the next step without further purification.

$\mathbf{R}_f$ 0.72 (pentane/EtOAc, 20:1); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.30 (1H, dd, *J* = 2.0, 1.0 Hz, H1), 6.28 (1H, dd, *J* = 3.0, 2.0 Hz, H2), 5.98 (1H, dt, *J* = 3.0, 1.0 Hz, H3), 5.82 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, H8), 5.07 – 4.95 (2H, m, H9), 2.67 – 2.59 (2H, m, H5), 2.14 – 2.05 (2H, m, H7), 1.80 – 1.68 (2H, m, H6); $\boldsymbol{\delta}_\mathbf{C}$ (101 MHz, $CDCl_3$) 156.3 (C4), 140.9 (C1), 138.4 (C8), 115.1 (C9), 110.2 (C2), 104.9 (C3), 33.3 (C7), 27.5 (C6), 27.4 (C5).

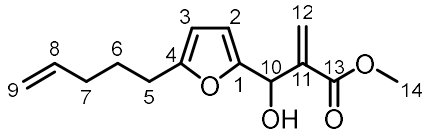
5-(Pent-4-en-1-yl)furan-2-carbaldehyde (2.104)



To a solution of dimethylformamide (0.93 mL, 12 mmol) in dry DCM (10 mL) in a 50 mL flask was cooled to 0 °C and $POCl_3$ (1.12 mL, 12.0 mmol) added. The mixture was stirred at 0 °C for 30 min and the crude substrate **2.103** (1.17 g, 8.60 mmol) added. The mixture was stirred at 0 °C for 30 min and quenched with satd aq Na_2CO_3 solution (20 mL). The mixture was extracted with DCM (3 × 20 mL) then the combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by chromatography (pentane/EtOAc, 20:1) to give aldehyde **2.104** as a colourless oil (1.20 g, 73%).

R_f 0.21 (pentane/EtOAc, 20:1); **IR** ν_{max}/cm^{-1} 2936w, 1677s, 1519s, 1023m, 766m; **δ_H** (400 MHz, $CDCl_3$) 9.52 (1H, s, H10), 7.17 (1H, d, *J* = 3.5 Hz, H2), 6.24 (1H, dt, *J* = 3.5, 1.0 Hz, H3), 5.79 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, H8), 5.07 – 4.96 (2H, m, H9), 2.74 (2H, t, *J* = 7.5 Hz, H5), 2.17 – 2.06 (2H, m, H7), 1.87 – 1.74 (2H, m, H6); **δ_C** (101 MHz, $CDCl_3$) 177.1 (C10), 163.8 (C1), 152.0 (C4), 137.7 (C8), 123.9 (C2), 115.6 (C9), 108.9 (C3), 33.2 (C7), 27.8 (C6), 26.8 (C5); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{10}H_{13}O_2$ 165.0910, found, 165.0910.

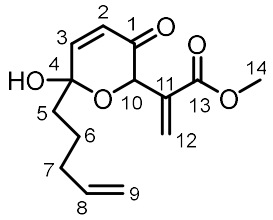
Methyl 2-[hydroxy[5-(pent-4-en-1-yl)furan-2-yl]methyl]acrylate (2.105)



A solution of hexamethylphosphoramide (2.5 mL, 14 mmol) in THF (30 mL) in a 100 mL flask was cooled to 0 °C and DIBAL-H (1.2M in toluene, 7.3 mL, 8.8 mmol) was added. The solution was stirred for 30 min and added methyl propiolate (0.65 mL, 7.3 mmol) and stirred for 1 h. To the resulting solution was added the aldehyde **2.104** (1.20 g, 7.31 mmol) and stirred for 4 h at RT. The reaction was quenched with 1M HCl (20 mL) and extracted with ether (3 × 20 mL) then the combined organic extracts were washed with 1M HCl (3 ×10 mL) and satd aq $NaHCO_3$ solution (10 mL) and dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by chromatography (pentane/EtOAc, 5:1) to give alcohol **2.105** as a colourless oil (1.61 g, 88%).

R_f 0.21 (pentane/EtOAc, 5:1); **IR** ν_{max}/cm^{-1} 3503w, 2952w, 1724s, 1439m, 1282m; **δ_H** (400 MHz, $CDCl_3$) 6.37 (1H, t, *J* = 1.0 Hz, H12), 6.12 (1H, dd, *J* = 3.0, 0.5 Hz, H3), 5.94 – 5.90 (2H, m, H2, H12′), 5.80 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, H8), 5.55 (1H, dd, *J* = 6.5, 1.0 Hz, H10), 5.08 – 4.92 (2H, m, H9), 3.76 (3H, s, H14), 2.96 (1H, d, *J* = 6.5 Hz, OH), 2.65 – 2.55 (2H, m, H5), 2.09 (2H, dtt, *J* = 8.0, 6.5, 1.5 Hz, H7), 1.79 – 1.64 (2H, m, H6); **δ_C** (101 MHz, $CDCl_3$) 166.6 (C13), 156.3 (C1), 152.2 (C4), 139.7 (C11), 138.2 (C8), 126.6 (C12), 115.0 (C9), 107.9 (C3), 105.7 (C2), 67.4 (C10), 52.0 (C14), 33.1 (C7), 27.4 (C6), 27.1 (C5); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{14}H_{18}O_4Na$ 273.1097, found, 273.1107.

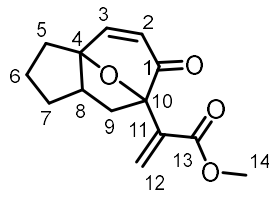
Methyl 2-[6-hydroxy-3-oxo-6-(pent-4-en-1-yl)-3,6-dihydro-2*H*-pyran-2-yl]acrylate (2.106)



A solution of furan alcohol **2.105** (1.48 g, 5.92 mmol) in DCM (70 mL) in a 250 mL flask was cooled to 0 °C, and MCPBA (75% w/w, 1.50 g, 6.52 mmol) was added. The reaction was stirred at 0 °C for 1.5 h. Satd aq $NaHCO_3$ solution (30 mL) was added and the mixture was extracted with DCM (3 × 20 mL); The combined organic extracts were washed with water (30 mL) and brine (15 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 2:1) to give dihydropyran **2.106** as a colourless oil and as a pair of diastereomers (1.44 g, 91%, dr = 10:1).

R_f 0.39 (pentane/EtOAc, 2:1); **IR** ν_{max}/cm^{-1} 3480w, 2952m, 1728s, 1642m, 1206s; **δ_H** (400 MHz, $CDCl_3$) (for major diastereomer) 6.80 (1H, d, *J* = 10.5 Hz, H2), 6.44 (1H, d, *J* = 1.0 Hz, H12), 6.14 (1H, d, *J* = 10.5 Hz, H3), 5.92 (1H, t, *J* = 1.0 Hz, H12′), 5.78 (1H, ddt, *J* = 17.0, 10.5, 6.5 Hz, H8), 5.38 (1H, d, *J* = 1.0 Hz, H10), 5.06 – 4.96 (2H, m, H9), 3.76 (3H, s, H14), 2.67 (1H, s, OH), 2.10 (2H, qt, *J* = 7.0, 1.5 Hz, H7), 1.87 (2H, ddt, *J* = 9.5, 6.0, 3.0 Hz, H5), 1.64 – 1.47 (2H, m, H6); **δ_C** (101 MHz, $CDCl_3$) (for major diastereomer) 193.5 (C1), 165.5 (C13), 146.8 (C2), 137.9 (C8), 136.5 (C11), 129.2 (C12), 127.3 (C3), 115.3 (C9), 94.9 (C4), 74.3 (C10), 52.1 (C14), 41.1 (C5), 33.4 (C7), 22.8 (C6); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{14}H_{18}O_5Na$ 289.1047, found, 289.1049.

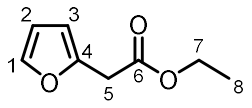
Methyl 2-[6-oxo-2,3,8,8a-tetrahydro-1H-3a,7-epoxyazulen-7(6*H*)-yl]acrylate (2.107)



A solution of dihydropyran **2.106** (0.27 g, 1.0 mmol) in dry DCM (10 mL) in a 50 mL flask was cooled to 0 °C and acetic anhydride (0.28 mL, 3.0 mmol), pyridine (0.12 mL, 1.5 mmol) and DMAP (97.7 mg, 0.800 mmol) were added. The mixture was stirred at 0 °C for 2 h and quenched with satd aq $CuSO_4$ solution (10 mL). The organic phase was washed with satd aq $NaHCO_3$ solution (10 mL), satd aq $CuSO_4$ solution (10 mL) and brine (10 mL) and dried over Na_2SO_4 and concentrated to obtain the crude acetate product (0.278 g, 0.9 mmol). The residue was dissolved in acetonitrile (15 mL) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.45 mL, 3.0 mmol) was added. The solution was warmed to 60 °C and stirred for 18 h. Acetic acid (0.50 mL, 8.7 mmol) was added and the mixture was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 5:1) to give cyclised product **2.107** as a yellow oil (14.2 mg, 5.7%).

R_f 0.42 (pentane/EtOAc, 5:1); **IR** ν_{max}/cm^{-1} 2972m, 1731m, 1694m, 1131m, 953s; **δ_H** (400 MHz, $CDCl_3$) 7.30 – 7.25 (1H, m, H2), 6.32 (1H, d, *J* = 1.0 Hz, H12), 6.03 (1H, d, *J* = 10.0 Hz, H3), 5.97 (1H, d, *J* = 1.0 Hz, H12′), 3.77 (3H, s, H14), 2.54 (1H, tdd, *J* = 8.5, 6.5, 3.0 Hz, H8), 2.48 (1H, dd, *J* = 13.0, 8.5 Hz, H9), 2.20 (1H, ddd, *J* = 13.0, 7.0, 4.5 Hz, H5), 2.12 (1H, dd, *J* = 13.0, 3.0 Hz, H9′), 2.07 – 1.93 (2H, m, H6, H7), 1.92 – 1.85 (1H, m, H5′), 1.84 – 1.73 (1H, m, H6′), 1.54 – 1.43 (1H, m, H7′); **δ_C** (101 MHz, $CDCl_3$) 196.1 (C1), 166.3 (C13), 155.7 (C2), 139.7 (C11), 126.7 (C3), 125.5 (C12), 92.1 (C10), 90.6 (C4), 52.1 (C14), 49.5 (C8), 39.5 (C9), 35.2 (C5), 33.5 (C7), 26.3 (C6); **HRMS** (ESI+) *m/z* $[M+K]^+$ calcd. for $C_{14}H_{16}O_4K$ 287.0680, found, 287.0681.

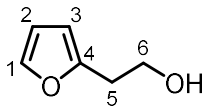
Ethyl 2-(furan-2-yl)acetate[16] (2.108)



To a solution of furan (30.0 mL, 412 mmol) in DMSO (100 mL) in a 250 flask was added ethyl iodoacetate (2.82 mL, 23.8 mmol) and $FeSO_4 \bullet 7H_2O$ (3.32 g, 11.9 mmol). The mixture was cooled to 0 °C and H_2O_2 (30 % wt in H_2O, 5.6 mL) added dropwise over 1.5 h. The solution was kept in a water bath for 18 h. Brine (100 mL) was added and the mixture was extracted with ether (3 × 50 mL); the combined organic extracts were washed with water (3 × 30 mL) and brine (2 ×20 mL) and dried over Na_2SO_4 and filtered through a short plug of silica. The filtrate was concentrated to give crude ester **2.108** as a pale yellow oil (2.98 g, 81%).

$\mathbf{R_f}$ 0.25 (pentane/EtOAc, 20:1); **IR** ν_{max}/cm^{-1} 1739s, 1312m, 1184m, 1032m, 750w; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.36 (1H, dd, *J* = 2.0, 1.0 Hz, H1), 6.33 (1H, dd, *J* = 3.0, 2.0 Hz, H2), 6.22 (1H, dt, *J* = 3.0, 1.0 Hz, H3), 4.18 (2H, q, *J* = 7.0 Hz, H7), 3.68 (2H, s, H5), 1.26 (3H, d, *J* = 7.0 Hz, H8); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 169.6 (C6), 147.9 (C4), 142.2 (C1), 110.6 (C2), 108.1 (C3), 61.3 (C7), 34.3 (C5), 14.3 (C8).

2-(Furan-2-yl)ethan-1-ol[17] (2.109)



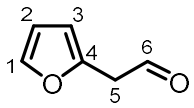
To a solution of ester **2.108** (2.70 g, 17.5 mmol) in THF (80 mL) was cooled to 0 °C and $LiAlH_4$ (1.33g, 35.0 mmol) added. The mixture was warmed to RT and stirred for 1 h. The reaction was cooled to 0 °C and added satd aq NH_4Cl solution (50 mL) slowly. The mixture was extracted with ether (3 × 50 mL); the combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 3:1) to give alcohol **2.109** as a colourless oil (1.73 g, 88%).

Alternative BuLi/ethyleneoxide method:

To a solution of furan (2.13 mL, 29.4 mmol) in THF (30 mL) in a 100 mL flask was cooled to 0 °C and BuLi (1.6 M in hexane, 18.4 mL, 29.4 mmol) added. The mixture was warmed to RT and stirred for 3 h. The solution was cooled to 0 °C and added ethylene oxide (2.5 ~ 3.3 M in THF, 9.0 mL, 27 mmol). The reaction was warmed to RT and stirred for 18 h. Satd aq NH_4Cl solution (30 mL) was added and the mixture was extracted with DCM (3 × 30 mL); the combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 3:1) to give alcohol **2.109** as a colourless oil (0.96 g, 29%).

R_f 0.20 (pentane/EtOAc, 3:1); **IR** ν_{max}/cm^{-1} 3374m, 2922w, 1050m, 735s; **δ_H** (400 MHz, $CDCl_3$) 7.34 (1H, dd, *J* = 2.0, 1.0 Hz, H1), 6.31 (1H, dd, *J* = 3.0, 2.0 Hz, H2), 6.11 (1H, dt, *J* = 3.0, 1.0 Hz, H3), 3.88 (2H, q, *J* = 6.0 Hz, H6), 2.91 (2H, t, *J* = 6.0 Hz, H5), 1.60 (1H, dt, *J* = 10.5, 4.0 Hz, OH); **δ_C** (101 MHz, $CDCl_3$) 153.0 (C4), 141.7 (C1), 110.4 (C2), 106.7 (C3), 61.3 (C6), 31.7 (C5).

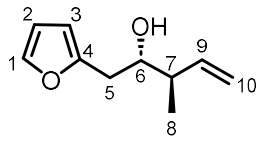
Furan-2-ylacetaldehyde[18] (2.110)



To a solution of alcohol **2.109** (3.24 g, 28.9 mmol) in DCM (150 mL) in a 500 mL flask was cooled to 0 °C and DMP (13.5 g, 31.8 mmol) added. The mixture was warmed to RT and stirred for 2 h. Satd aq $NaHCO_3$ solution (70 mL) and satd aq $Na_2S_2O_3$ solution (70 mL) were added and the mixture was stirred for 20 min. The organic phase was extracted with ether (3 × 30 mL) and dried over Na_2SO_4 and concentrated to give crude aldehyde **2.110** as a red oil (2.54 g, <80%) which is unstable on silica.

IR ν_{max}/cm^{-1} 2981m, 1736m, 1148m, 1015m, 744s; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.72 (1H, t, *J* = 2.0 Hz, H6), 7.41 (1H, dd, *J* = 2.0, 1.0 Hz, H1), 6.38 (1H, dd, *J* = 3.5, 2.0 Hz, H2), 6.25 (1H, dq, *J* = 3.5, 1.0 Hz, H3), 3.72 (2H, dd, *J* = 2.0, 1.0 Hz, H5); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 197.0 (C6), 146.5 (C4), 142.9 (C1), 110.9 (C2), 108.9 (C3), 43.0 (C5).

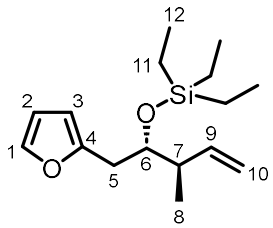
(2*S,3*R**)-1-(Furan-2-yl)-3-methylpent-4-en-2-ol (2.111)**



To a solution of $CrCl_2$ (0.25 g, 2.0 mmol) in dry THF (125 mL) in a 250 mL flask was added Mn powder (2.66 g, 48.5 mmol). The mixture was stirred at RT for 30 min. To this mixture was added the crude aldehyde **2.110** (2.54 g, <23.1 mmol), crotyl bromide (5.94 mL, 57.7 mmol) and chlorotrimethylsilane (8.8 mL, 69 mmol) and stirred at RT for 3.5 h. Water (60 mL) was added and the mixture was stirred further for 1 h. The mixture was extracted with ether (3× 30 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 5:1) to give alcohol **2.111** as a colourless oil (2.44 g, 51% over two steps) and as a single diastereomer.

R_f 0.60 (pentane/EtOAc, 3:1); **IR** ν_{max}/cm^{-1} 3469w, 2924w, 1011s, 919s, 734s; **δ_H** (400 MHz, $CDCl_3$) 7.34 (1H, dd, *J* = 2.0, 1.0 Hz, H1), 6.31 (1H, dd, *J* = 3.0, 2.0 Hz, H2), 6.12 (1H, dq, *J* = 3.0, 1.0 Hz, H3), 5.89 – 5.75 (1H, m, H9), 5.19 – 5.04 (2H, m, H10), 3.76 (1H, ddd, *J* = 8.5, 5.5, 4.0 Hz, H6), 2.86 (1H, ddd, *J* = 15.0, 4.0, 1.0 Hz, H5), 2.73 (1H, dd, *J* = 15.0, 8.5 Hz, H5′), 2.36 – 2.21 (1H, m, H7), 1.10 (3H, d, *J* = 7.0 Hz, H8); **δ_C** (101 MHz, $CDCl_3$) 153.1 (C4), 141.7 (C1), 139.8 (C9), 116.5 (C10), 110.5 (C2), 107.1 (C3), 73.5 (C6), 43.4 (C7), 33.4 (C5), 16.4 (C8); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{10}H_{15}O_2$ 167.1067, found, 167.1065.

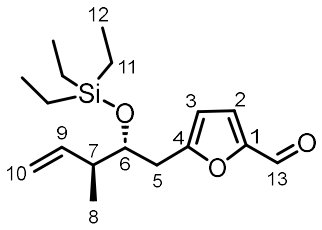
Triethyl[[(2*S,3*R**)-1-(furan-2-yl)-3-methylpent-4-en-2-yl]oxy]silane (2.113)**



A solution of alcohol **2.111** (2.44 g, 14.7 mmol) in dry DMF (100 mL) in a 250 mL flask was cooled to 0 °C and chlorotriethylsilane (4.9 mL, 29 mmol) and imidazole (2.50 g, 36.7 mmol) added. The mixture was stirred at 0 °C for 1 h. Satd aq NH_4Cl solution (60 mL) was added and the mixture was extracted with ether (3× 30 mL). The organic extracts were washed with water (50 mL) and brine (50 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give TES protected alcohol **2.113** as a colourless oil (3.67 g, 89%).

R_f 0.80 (pentane/EtOAc, 10:1); **IR** ν_{max}/cm^{-1} 2958w, 2878w, 1010m, 915m, 727s; **δ_H** (400 MHz, $CDCl_3$) 7.30 (1H, dd, *J* = 2.0, 1.0 Hz, H1), 6.27 (1H, dd, *J* = 3.0, 2.0 Hz, H2), 6.01 (1H, dd, *J* = 3.0, 1.0 Hz, H3), 5.91 – 5.76 (1H, m, H9), 5.10 – 4.96 (2H, m, H10), 3.95 (1H, ddd, *J* = 7.0, 6.0, 3.0 Hz, H6), 2.71 (2H, qd, *J* = 14.5, 6.5 Hz, H5), 2.32 – 2.21 (1H, m, H7), 1.04 (3H, d, *J* = 7.0 Hz, H8), 0.94 – 0.89 (9H, m, H12), 0.56 – 0.49 (6H, m, H11); **δ_C** (101 MHz, $CDCl_3$) 153.6 (C4), 141.0 (C1), 140.2 (C9), 115.3 (C10), 110.4 (C2), 106.9 (C3), 74.7 (C6), 43.3 (C7), 33.6 (C5), 15.9 (C8), 7.0 (C12), 5.1 (C11); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{16}H_{29}O_2Si$ 281.1931, found, 281.1896.

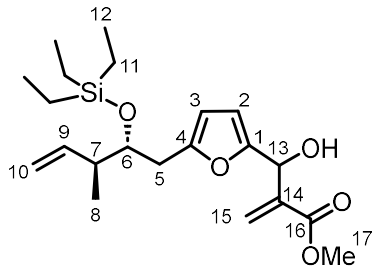
5-[(2*R,3*S**)-3-Methyl-2-[(triethylsilyl)oxy]pent-4-en-1-yl]furan-2-carbaldehyde (2.114)**



To a solution of substrate **2.113** (2.51 g, 9.52 mmol) in dry THF (100 mL) in a 250 mL flask was cooled to –78 °C and BuLi (1.6 M in hexane, 11.9 mL, 19.0 mmol) added. The mixture was warmed to –5°C and stirred for 45 min. The solution was cooled to –78 °C and added dimethylformamide (2.0 mL, 26 mmol) and stirred for 0.5 h. The solution was warmed to RT and stirred for 2 h. Satd aq NH_4Cl solution (60 mL) was added and the mixture was extracted with ether (3× 30 mL). The organic extracts were washed with water (30 mL) and brine (30 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give aldehyde **2.114** as a colourless oil (2.07 g, 71%).

R_f 0.41 (pentane/EtOAc, 10:1); **IR** ν_{max}/cm^{-1} 2959w, 1683s, 1519s, 1020m, 741s; **δ_H** (400 MHz, $CDCl_3$) 9.54 (1H, s, H13), 7.17 (1H, d, *J* = 3.5 Hz, H2), 6.28 (1H, dd, *J* = 3.5, 1.0 Hz, H3), 5.88 – 5.75 (1H, m, H9), 5.10 – 4.97 (2H, m, H10), 4.06 (1H, ddd, *J* = 7.5, 5.5, 3.5 Hz, H6), 2.79 (2H, dd, *J* = 6.5, 3.5 Hz, H5), 2.35 – 2.25 (1H, m, H7), 1.05 (3H, d, *J* = 7.0 Hz, H8), 0.88 (9H, t, *J* = 8.0 Hz, H12), 0.48 (6H, m, H11); **δ_C** (101 MHz, $CDCl_3$) 177.1 (C13), 161.5 (C4), 152.1 (C1), 139.8 (C9), 123.4 (C2), 115.6 (C10), 111.0 (C3), 74.1 (C6), 43.7 (C7), 33.6 (C5), 14.9 (C8), 7.0 (C12), 5.0 (C11); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{28}O_3SiNa$ 331.1700, found, 331.1700.

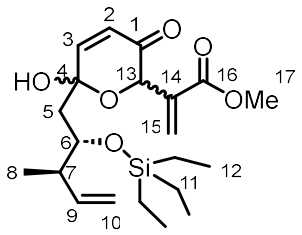
Methyl 2-[hydroxy[5-[(2*R,3*S**)-3-methyl-2-[(triethylsilyl)oxy]pent-4-en-1-yl]furan-2-yl]methyl]acrylate (2.115)**



A solution of HMPA (9.1 mL, 52 mmol) in THF (100 mL) in a 250 mL flask was cooled to 0 °C and DIBAL-H (1.0 M in hexane, 17.5 mL, 17.5 mmol) added and stirred for 30 min. Methyl propiolate (1.7 mL, 19 mmol) was added and the mixture was stirred at 0 °C for 2.5 h. A solution of the aldehyde **2.114** (2.16 g, 7.01 mmol) in dry THF (10 mL) was added and the mixture was warmed to RT and stirred for 18 h. The mixture was cooled to 0 °C and 1M HCl (30 mL) was added and the mixture was extracted with ether (3× 30 mL). The combined organic extracts were washed with 1M HCl solution (30 mL) and satd aq $NaHCO_3$ solution (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 6:1) to give alcohol **2.115** as a colourless oil and as a single diastereomer (2.19 g, 79%, not assigned).

R_f 0.35 (pentane/EtOAc, 6:1); **IR** ν_{max}/cm^{-1} 3488w, 2959m, 1727s, 1016s, 742s; **δ_H** (400 MHz, $CDCl_3$) 6.38 (1H, dt, *J* = 1.5, 1.0 Hz, H15), 6.13 (1H, d, *J* = 3.0 Hz, H2), 5.96 (2H, m, H3, H15′), 5.87 – 5.74 (1H, m, H9), 5.54 (1H, s, H13), 5.10 – 4.96 (2H, m, H10), 3.92 (1H, tdd, *J* = 7.0, 5.5, 3.5 Hz, H6), 3.76 (3H, s, H17), 2.92 (1H, s, OH), 2.75 – 2.57 (2H, m, H5), 2.25 (1H, dddd, *J* = 9.0, 4.5, 2.0, 1.0 Hz, H7), 1.03 (3H, d, *J* = 7.0 Hz, H8), 0.91 (9H, t, *J* = 8.0 Hz, H12), 0.55 – 0.45 (6H, m, H11); **δ_C** (101 MHz, $CDCl_3$) 166.6 (C16), 153.7 (C4), 152.7 (C1), 140.2 (C9), 139.7 (C14), 126.8 (C15), 115.3 (C10), 108.1 (C2), 107.9 (C3), 74.6 (C6), 67.6 (C13), 52.1 (C17), 43.4 (C7), 33.7 (C5), 15.8 (C8), 7.0 (C12), 5.1 (C11); **HRMS** (ESI+) *m/z* $[M+K]^+$ calcd. for $C_{21}H_{34}O_5SiK$ 433.1807, found, 433.1804.

Methyl 2-[6-hydroxy-6-[(2*S,3*R**)-3-methyl-2-[(triethylsilyl)oxy]pent-4-en-1-yl]-3-oxo-3,6-dihydro-2*H*-pyran-2-yl]acrylate (2.116)**



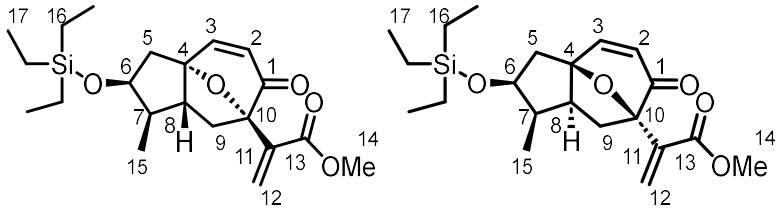
A solution of furan alcohol **2.115** (27.0 mg, 0.0685 mmol) in DCM (2 mL) in a 25 mL flask was cooled to 0 °C and MCPBA (75% w/w, 18.7 mg, 0.0814 mmol) was added. The reaction was stirred at 0 °C for 1.5 h. Satd aq $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 5:1) to give the first diastereomer as a colourless oil (10.0 mg, 33%).

R_f 0.35 (pentane/EtOAc, 5:1); **IR** ν_{max}/cm^{-1} 3465w, 2970m, 1730s, 1071s, 743s; **δ_H** (400 MHz, $CDCl_3$) 6.70 (1H, d, *J* = 10.5 Hz, H3), 6.42 (1H, d, *J* = 1.0 Hz, H15), 6.05 – 5.97 (1H, m, H2), 5.87 (1H, t, *J* = 1.0 Hz, H15′), 5.81 (1H, s, OH), 5.73 – 5.59 (1H, m, 9H), 5.46 (1H, d, *J* = 1.0 Hz, H13), 5.06 (2H, ddq, *J* = 14.5, 3.0, 1.5 Hz, H10), 4.53 (1H, ddd, *J* = 11.0, 4.0, 2.5 Hz, H6), 3.76 (3H, s, H17), 2.53 – 2.43 (1H, m, H7), 1.96 – 1.84 (1H, m, H5), 1.72 (1H, dd, *J* = 14.0, 2.5 Hz, H5′), 1.05 (3H, d, *J* = 7.0 Hz, H8), 0.96 (9H, t, *J* = 8.0 Hz, H12), 0.70 – 0.62 (6H, m, H11); **δ_C** (101 MHz, $CDCl_3$) 194.5 (C1), 165.7 (C16), 147.9 (C3), 139.6 (C9), 137.0 (C14), 128.6 (C15), 125.6 (C2), 115.5 (C10), 94.5 (C4), 74.2 (C13), 73.0 (C6), 52.2 (C17), 43.1 (C7), 37.8 (C5), 11.3 (C8), 6.8 (C12), 5.2 (C11); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{34}O_6SiNa$ 433.2017, found, 433.2006.

Further elution (pentane/EtOAc, 5:1) gave another diasteromer as a colourless oil (11.4 mg, 41%). **R_f** 0.25 (pentane/EtOAc, 5:1); **IR** ν_{max}/cm^{-1} 3480w, 2955m, 1730s, 1691m, 743s; **δ_H** (400 MHz, $CDCl_3$) 6.81 (1H, d, *J* = 10.5 Hz, H3), 6.42 (1H, d, *J* = 1.0 Hz, H15), 6.04 (1H, d, *J* = 10.5 Hz, H2), 5.92 (1H, d, *J* = 1.0 Hz, H15′), 5.76 – 5.65 (1H, m, H9), 5.47 (1H, d, *J* = 1.0 Hz, H13), 5.08 – 5.00 (2H, m, H10), 3.98 (1H, ddd, *J* = 7.0, 5.5, 3.0 Hz, H6), 3.75 (3H, s, H17), 2.69 – 2.61 (1H, m, H7), 2.05 (1H, dd, *J* = 14.5, 7.0 Hz, H5), 1.96 – 1.89 (1H, m, H5′), 1.01 – 0.91 (12H, m, H8, H12), 0.65 (6H, q, *J* = 8.0 Hz,

H11); δ_C (101 MHz, $CDCl_3$) 194.2 (C1), 165.7 (C16), 147.5 (C3), 140.7 (C9), 136.8 (C14), 129.0 (C15), 125.8 (C2), 115.6 (C10), 95.1 (C4), 74.4 (C13), 74.4 (C6), 52.2 (C17), 43.3 (C7), 40.8 (C5), 13.5 (C8), 7.0 (C12), 5.2 (C11); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{34}O_6SiNa$ 433.2017, found, 433.2006.

Methyl 2-[(1*R,2*S**,3a*R**,7*S**,8a*R**)-1-methyl-6-oxo-2-[(triethylsilyl)oxy]-2,3,8,8a-tetrahydro-1*H*-3a,7-epoxyazulen-7(6*H*)-yl]acrylate (2.117) and methyl 2-[(1*R**,2*S**,3a*S**,7*R**,8a*S**)-1-methyl-6-oxo-2-[(triethylsilyl)oxy]-2,3,8,8a-tetrahydro-1*H*-3a,7-epoxyazulen-7(6*H*)-yl]acrylate (2.118)**



A solution of dihydropyran **2.116** (0.80 g, 1.9 mmol) in dry DCM (30 mL) in a 150 mL flask was cooled to 0 °C and DMAP (47.6 mg, 0.390 mmol) and di-*tert*-butyldicarbonate (0.64 g, 2.9 mmol) added. The mixture was stirred for 1 h and then added triethylamine (1.0 mL, 7.3 mmol). The solution was warmed to RT and stirred for 2.5 h. Satd aq NH_4Cl solution (20 mL) was added and the mixture was extracted with ether (3 × 20 mL). The organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 3:1) to give the first diastereomer **2.117** as a pale yellow oil (0.39 g, 51%).

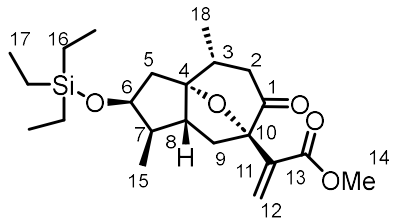
R_f 0.60 (pentane/EtOAc, 3:1); **IR** ν_{max}/cm^{-1} 2954w, 1733s, 1698s, 1046m, 742s; **δ_H** (400 MHz, $CDCl_3$) 7.28 – 7.23 (1H, m, H3), 6.31 (1H, d, *J* = 1.0 Hz, H12), 5.99 (1H, d, *J* = 9.5 Hz, H2), 5.94 (1H, d, *J* = 1.0 Hz, H12′), 4.28 (1H, t, *J* = 4.5 Hz, H6), 3.77 (3H, s, H15), 2.48 (1H, ddd, *J* = 11.0, 8.5, 3.0 Hz, H8), 2.40 – 2.35 (1H, m, H9), 2.33 (1H, dd, *J* = 10.0, 5.0 Hz, H5), 2.10 – 2.03 (2H, m, H5′, H9′), 1.76 (1H, dqd, *J* = 10.5, 7.0, 4.0 Hz, H7), 1.02 – 0.93 (12H, m, H15, H17), 0.64 – 0.55 (6H, m, H16); **δ_C** (101 MHz, $CDCl_3$) 195.6 (C1), 166.2 (C13), 157.1 (C3), 139.7 (C11), 125.9 (C2), 125.4 (C12), 91.6 (C10), 91.0 (C4), 79.0 (C6), 54.6 (C8), 52.1 (C14), 47.3 (C7), 45.7 (C5), 36.0 (C9), 12.7 (C15), 7.0 (C17), 5.0 (C16); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{32}O_5SiNa$ 415.1911, found, 415.1899.

Further elution (pentane/EtOAc, 5:1) gave another diasteromer **2.118** as a pale yellow oil (11.4 mg, 41%).

R_f 0.45 (pentane/EtOAc, 3:1); **IR** ν_{max}/cm^{-1} 2942w, 1733s, 1698s, 1010w, 744s; **δ_H** (600 MHz, $CDCl_3$) 7.20 (1H, d, *J* = 9.5 Hz, H3), 6.29 (1H, dd, *J* = 2.5, 1.0 Hz, H12), 5.98 – 5.91 (2H, m, H2, H12′), 4.34

(1H, ddd, J = 9.0, 7.5, 6.0 Hz, H6), 3.78 (3H, d, J = 2.0 Hz, H14), 2.55 (ddd, J = 9.0, 7.5, 4.0 Hz, H8), 2.37 (1H, dd, J = 14.0, 3.5 Hz, H9), 2.29 (1H, dd, J = 14.0, 9.0 Hz, H9′), 2.22 (1H, dd, J = 14.0, 7.5 Hz, H5), 2.19 – 2.09 (2H, m, H5′, H7), 0.96 (9H, t, J = 8.0 Hz, H17), 0.88 (3H, d, J = 7.5 Hz, H15), 0.60 (6H, q, J = 7.5 Hz, H16); $\boldsymbol{\delta_C}$ (151 MHz, $CDCl_3$) 195.7 (C1), 166.4 (C13), 156.9 (C3), 138.8 (C11), 125.9 (C2), 125.1 (C12), 90.7 (C10), 88.6 (C4), 76.8 (C6), 52.1 (C14), 50.0 (C8), 41.5 (C5), 40.1 (C7), 32.5 (C9), 9.7 (C15), 6.9 (C17), 4.9 (C16); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{32}O_5SiNa$ 415.1911, found, 415.1901.

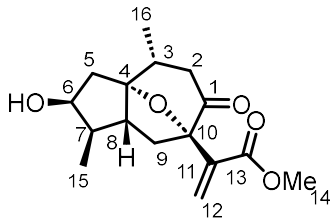
Methyl 2-[(1*R,2*S**,3a*R**,4*R**,7*S**,8a*R**)-1,4-dimethyl-6-oxo-2-[(triethylsilyl)oxy]hexahydro-1*H*-3a,7-epoxyazulen-7(4*H*)-yl)acrylate (2.119)**



A suspension of CuI (0.19 g, 1.0 mmol) in dry THF (25 mL) in a 100 mL flask was cooled to 0 °C and methyllithium (1.6 M in ether, 1.3 mL, 2.0 mmol) added. The solution was stirred for 30 min and a solution of substrate **2.117** (0.39 g, 1.0 mmol) in dry THF (2 mL) added. The mixture was stirred at 0 °C for 1 h. Satd aq NH_4Cl solution (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The organic extracts were washed with brine (10 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give product **2.119** as a colourless oil (0.23 g, 57%).

R_f 0.35 (pentane/EtOAc, 10:1); **IR** ν_{max}/cm^{-1} 3027w, 1731s, 1438m, 1035m, 743m; **δ_H** (400 MHz, $CDCl_3$) 6.27 (1H, d, *J* = 1.5 Hz, H12), 5.96 (1H, d, *J* = 1.5 Hz, H12′), 4.25 (1H, td, *J* = 4.5, 2.5 Hz, H6), 3.74 (3H, s, H14), 2.90 (1H, dd, *J* = 15.5, 7.5 Hz, H2), 2.73 (1H, dd, *J* = 14.0, 9.0 Hz, H9), 2.48 (1H, td, *J* = 9.0, 4.5 Hz, H8), 2.27 (1H, pd, *J* = 7.0, 1.5 Hz, H3), 2.17 – 2.05 (2H, m, H2′, H5), 1.86 (1H, dd, *J* = 14.5, 2.5 Hz, H5′), 1.76 (2H, ddd, *J* = 14.0, 9.5, 3.5 Hz, H7, H9′), 1.10 (3H, d, *J* = 7.0 Hz, H18), 1.00 – 0.92 (12H, m, H15, H17), 0.63 – 0.51 (6H, m, H16); **δ_C** (101 MHz, $CDCl_3$) 205.3 (C1), 166.2 (C13), 139.6 (C11), 124.9 (C12), 94.5 (C10), 91.4 (C4), 77.7 (C6), 53.3 (C8), 52.0 (C14), 48.1 (C7), 43.5 (C5), 42.5 (C3), 42.0 (C2), 41.1 (C9), 16.6 (C18), 13.1 (C15), 7.0 (C17), 5.0 (C16); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{22}H_{36}O_5SiNa$ 431.2224, found, 431.2238.

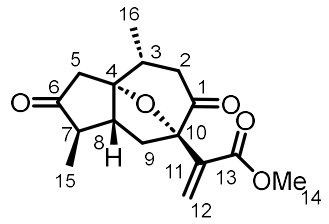
Methyl 2-[(1*R,2*S**,3a*R**,4*R**,7*S**,8a*R**)-2-hydroxy-1,4-dimethyl-6-oxohexahydro-1*H*-3a,7-epoxyazulen-7(4*H*)-yl]acrylate (2.120)**



A solution of ketone **2.119** (0.23 g, 0.57 mmol) in dry THF (10 mL) was cooled to 0 °C and TBAF (1.0 M in THF, 0.63 mL, 0.63 mmol) added. The mixture was warmed to RT and stirred for 1 h. Satd aq NH_4Cl solution (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The organic extracts were washed with brine (10 mL) and dried over Na_2SO_4 and concentrated to give crude product **2.120** (0.24 g) which is used in next step without further purification.

R_f 0.25 (pentane/EtOAc, 1:1); **IR** ν_{max}/cm^{-1} 3504w, 2921w, 1728s, 1203w, 1035m; **δ_H** (400 MHz, $CDCl_3$) 6.27 (1H, d, *J* = 1.5 Hz, H12), 5.97 (1H, d, *J* = 1.5 Hz, H12′), 4.29 (1H, ddd, *J* = 5.5, 4.0, 2.0 Hz, H6), 3.73 (3H, s, H14), 2.90 (1H, dd, *J* = 15.5, 7.0 Hz, H2), 2.75 (1H, dd, *J* = 14.0, 9.0 Hz, H9), 2.51 (1H, td, *J* = 9.5, 4.0 Hz, H8), 2.38 – 2.24 (1H, m, H3), 2.20 (1H, dd, *J* = 15.0, 5.0 Hz, H5), 2.12 (1H, dd, *J* = 15.5, 1.5 Hz, H2′), 1.93 (1H, dd, *J* = 15.0, 2.0 Hz, H5′), 1.88 – 1.82 (1H, m, H7), 1.77 (1H, dd, *J* = 14.0, 4.0 Hz, H9′), 1.10 (3H, d, *J* = 7.0 Hz, H22), 1.03 (3H, d, *J* = 7.0 Hz, H15); **δ_C** (101 MHz, $CDCl_3$) 204.8 (C1), 166.2 (C13), 139.5 (C11), 124.9 (C12), 94.8 (C10), 91.3 (C4), 77.7 (C6), 53.2 (C8), 52.0 (C14), 47.7 (C7), 42.9 (C5), 42.6 (C3), 41.9 (C2), 41.0 (C9), 16.5 (C22), 12.4 (C15); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{22}O_5Na$ 317.1360, found, 317.1358.

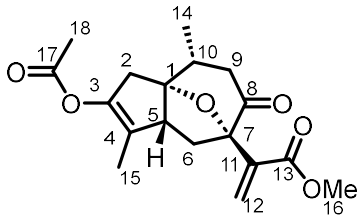
Methyl 2-[(1*R,3a*R**,4*R**,7*S**,8a*R**)-1,4-dimethyl-2,6-dioxohexahydro-1*H*-3a,7-epoxyazulen-7(4*H*)-yl]acrylate (2.121)**



A solution of oxalyl chloride (96 μL, 1.1 mmol) in dry DCM (10 mL) in a 50 mL flask was cooled to –78 °C and dimethylsulfoxide (0.12 mL, 1.7 mmol) added. The solution was stirred for 15 min and a solution of crude substrate **2.120** (0.24 g) in dry DCM (2 mL) added. The reaction was stirred at –78 °C for 15 min. To the reaction was added triethylamine (0.48 mL, 3.4 mmol) and the mixture stirred at –78 °C for 15 min then warmed to RT. The mixture was stirred for 2 h and satd. aq NH_4Cl solution (20 mL) was added. The mixture was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 1:1) to give diketone **2.121** as a colourless oil (0.15 g, 92% over two steps).

R_f 0.32 (pentane/EtOAc, 1:1); **IR** ν_{max}/cm^{-1} 2923m, 2850w, 1745s, 1731s, 1459m; **δ_H** (600 MHz, $CDCl_3$) 6.31 (1H, d, *J* = 1.5 Hz, H12), 6.00 (1H, d, *J* = 1.5 Hz, H12′), 3.76 (3H, s, H14), 3.06 (1H, dd, *J* = 15.0, 8.5 Hz, H9), 3.00 (1H, dd, *J* = 15.5, 7.5 Hz, H2), 2.82 (1H, dd, *J* = 19.5, 1.5 Hz, H5), 2.52 – 2.45 (1H, m, H8), 2.42 (1H, d, *J* = 19.5 Hz, H5′), 2.36 – 2.27 (1H, m, H3), 2.24 – 2.19 (1H, m, H7), 2.18 – 2.13 (1H, m, H2′), 2.05 (1H, dd, *J* = 15.0, 2.5 Hz, H9′), 1.15 (6H, m, H15, H16); **δ_C** (151 MHz, $CDCl_3$) 216.5 (C6), 202.9 (C1), 165.9 (C13), 138.8 (C11), 125.1 (C12), 89.5 (C10), 88.9 (C4), 53.7 (C7), 52.2 (C8), 52.1 (C14), 46.3 (C5), 43.7 (C9), 42.5 (C3), 41.0 (C2), 16.8 (C16), 13.2 (C15); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{16}H_{21}O_5$ 293.1384, found, 293.1382.

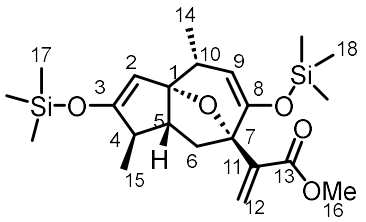
Methyl 2-[(3a*R,4*R**,7*S**,8a*R**)-2-acetoxy-1,4-dimethyl-6-oxo-5,6,8,8a-tetrahydro-3*H*-3a,7-epoxyazulen-7(4*H*)-yl]acrylate (43)**



To a solution of diketone **2.121** (10.0 mg, 0.0342 mmol) in acetic anhydride (1 mL) in a 25 mL flask was added $ZnCl_2$ (46.3 mg, 0.340 mmol) and the suspension was stirred at RT for 1h then warmed to 80 °C for 1 h. The mixture was cooled to RT and water (10 mL) was added. The aqueous phase was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 1:1) to give acetate **2.123** as a yellow oil (6.5 mg, 57%).

R_f 0.51 (pentane/EtOAc, 1:1); **IR** ν_{max}/cm^{-1} 2981m, 1750m, 1724s, 1219s, 1041m; **δ_H** (400 MHz, $CDCl_3$) 6.28 (1H, d, *J* = 1.5 Hz, H12), 5.98 (1H, d, *J* = 1.5 Hz, H12′), 3.75 (3H, s, H16), 3.24 (1H, ddt, *J* = 9.5, 5.0, 1.5 Hz, H5), 2.86 – 2.79 (2H, m, H2, H9), 2.74 (1H, dd, *J* = 14.0, 9.5 Hz, H6), 2.59 (1H, dquin, *J* = 16.5, 2.0 Hz, H2′), 2.34 (1H, pd, *J* = 7.0, 1.0 Hz, H10), 2.20 (1H, dd, *J* = 16.0, 1.0 Hz, H9), 2.16 (3H, s, H18), 1.84 (1H, ddd, *J* = 14.0, 5.0, 0.5 Hz, H6′), 1.59 – 1.53 (3H, m, H15), 1.12 (3H, d, *J* = 7.0 Hz, H14); **δ_C** (101 MHz, $CDCl_3$) 204.4 (C8), 168.8 (C17), 166.2 (C13), 141.2 (C3), 138.9 (C11), 125.4 (C12), 123.6 (C4), 89.8 (C7), 88.7 (C1), 53.4 (C5), 52.0 (C16), 41.9 (C9), 41.1 (C10), 39.4 (C2), 38.6 (C6), 20.9 (C18), 16.2 (C14), 10.4 (C15); HRMS (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{18}H_{22}O_6Na$ 357.1309, found, 357.1313.

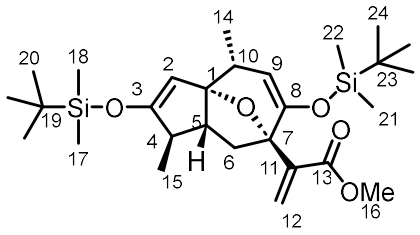
Methyl 2-[(1*R,3a*R**,4*R**,7*S**,8a*R**)-1,4-dimethyl-2,6-bis[(trimethylsilyl)oxy]-8,8a-dihydro-1*H*-3a,7-epoxyazulen-7(4*H*)-yl]acrylate (2.124)**



To a solution of diketone **2.121** (10.0 mg, 0.0342 mmol) in THF (2 mL) in a 25 mL flask was added chlorotrimethylsilane (21 μL, 0.17 mmol) and LHMDS (1.0 M in THF, 75 μL, 0.075 mmol) at –78 °C. The solution was stirred at –78 °C for 30 min then warmed to 0 °C for 1 h. The reaction was quenched with satd aq NH_4Cl solution (5 mL). The aqueous phase was extracted with ether (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give dienol ether **2.124** as a colourless oil (14.2 mg, 95%).

R_f 0.60 (pentane/EtOAc, 10:1); **IR** ν_{max}/cm^{-1} 2981m, 1733m, 740m, 654s; **δ_H** (400 MHz, $CDCl_3$) 6.18 (1H, d, *J* = 1.5 Hz, H12), 6.00 (1H, d, *J* = 1.5 Hz, H12′), 4.81 (1H, d, *J* = 1.5 Hz, H2), 4.48 (1H, d, *J* = 5.0 Hz, H9), 3.72 (3H, s, H16), 3.05 (1H, dd, *J* = 12.0, 8.5 Hz, H6), 2.37 – 2.31 (1H, m, H4), 2.07 (1H, ddd, *J* = 8.5, 7.0, 4.5 Hz, H5), 1.92 (1H, ddd, *J* = 13.5, 7.0, 4.0 Hz, H10), 1.77 (1H, dd, *J* = 12.0, 7.5 Hz, H6′), 1.12 (3H, d, *J* = 7.0 Hz, H14), 1.07 (3H, d, *J* = 7.0 Hz, H15), 0.23 (9H, s, H18), 0.14 (9H, s, H17); **δ_C** (101 MHz, $CDCl_3$) 167.0 (C13), 162.6 (C3), 154.1 (C8), 140.8 (C11), 125.5 (C12), 103.5 (C9), 101.6 (C2), 93.4 (C7), 84.3 (C1), 53.0 (C5), 51.6 (C16), 47.3 (C4), 47.2 (C6), 41.7 (C10), 19.7 (C15), 17.9 (C14), 0.2 (C17), 0.2 (C18); HRMS (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{22}H_{36}O_5Si_2Na$ 459.1994, found, 459.1979.

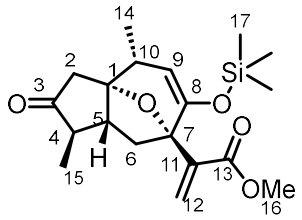
Methyl 2-[(1*R,3a*R**,4*R**,7*S**,8a*R**)-2,6-bis[(tert-butyldimethylsilyl)oxy]-1,4-dimethyl-8,8a-dihydro-1*H*-3a,7-epoxyazulen-7(4*H*)-yl]acrylate (2.125)**



To a solution of diketone **2.121** (11.0 mg, 0.0377 mmol) in THF (2 mL) in a 25 mL flask was added *tert*-butyldimethylsilyl chloride (33.4 mg, 0.222 mmol), LHMDS (1.0 M in THF, 0.11 mL, 0.11 mmol) and hexamethylphosphoramide (19 μL, 0.11 mmol) at –78 °C. The solution was stirred at –78 °C for 30 min then warmed to 0 °C for 1 h. The reaction was quenched with satd aq NH_4Cl solution (5 mL). The aqueous phase was extracted with ether (3 × 5 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over Na_2SO_4 and concentrated to give dienol ether **2.125** as a colourless oil (17.7 mg, 90%).

R_f 0.60 (pentane/EtOAc, 10:1); **IR** ν_{max}/cm^{-1} 2957w, 1717w, 739s, 669m, 642m; **δ_H** (400 MHz, C_6D_6) 6.34 (1H, d, *J* = 1.5 Hz, H12), 6.02 (1H, d, *J* = 1.5 Hz, H12′), 5.05 (1H, d, *J* = 1.5 Hz, H2), 4.57 (1H, d, *J* = 5.0 Hz, H9), 3.45 (3H, s, H16), 3.14 (1H, dd, *J* = 12.0, 8.5 Hz, H6), 2.47 – 2.37 (1H, m, H4), 2.16 (1H, ddd, *J* = 8.5, 7.0, 5.0 Hz, H5), 2.00 (1H, qd, *J* = 7.0, 5.0 Hz, H10), 1.92 (1H, dd, *J* = 12.0, 7.0 Hz, H6′), 1.38 (3H, d, *J* = 5.0 Hz, H14), 1.12 (3H, d, *J* = 7.0 Hz, H15), 0.95 (9H, s, H20), 0.94 (9H, s, H24), 0.18 (3H, s, H17), 0.16 (3H, s, H18), 0.12 (3H, s, H21), 0.10 (3H, s, H22); **δ_C** (101 MHz, C_6D_6) 166.2 (C13), 162.6 (C3), 154.9 (C8), 141.8 (C11), 126.0 (C12), 102.5 (C9), 102.1 (C2), 93.7 (C7), 84.9 (C1), 53.3 (C5), 51.1 (C16), 47.9 (C4), 47.5 (C6), 42.0 (C10), 25.9 (C20), 25.8 (C24), 19.9 (C15), 18.5 (C19), 18.5 (C23), 18.3 (C14), -4.4 (C17), -4.5 (C18), -4.7 (C21), -4.9 (C22); HRMS (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{28}H_{48}O_5Si_2Na$ 543.2933, found, 543.2927.

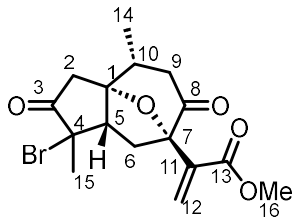
Methyl 2-[(1*R,3a*R**,4*R**,7*S**,8a*R**)-1,4-dimethyl-2-oxo-6-[(trimethylsilyl)oxy]-2,3,8,8a-tetrahydro-1*H*-3a,7-epoxyazulen-7(4*H*)-yl]acrylate (2.127)**



To a solution of di-trimethylsilyl enol ether **2.124** (16.4 mg, 0.0376 mmol) in THF (2 mL) in a 25 mL flask was added BF_3•OEt_2 (11 μL, 0.090 mmol) at –78 °C. The solution was stirred at –78 °C for 1 h then warmed to 0 °C for 1 h. Satd aq $NaHCO_3$ solution (10 mL) was added and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give mono enol ether **2.127** as a pale yellow oil (6.4 mg, 47%).

R_f 0.42 (pentane/EtOAc, 10:1); **IR** ν_{max}/cm^{-1} 2958m, 2926m, 1745s, 939m, 850s; **δ_H** (400 MHz, C_6D_6) 6.23 (1H, d, *J* = 2.0 Hz, H12), 6.07 (1H, d, *J* = 2.0 Hz, H12′), 4.41 (1H, d, *J* = 4.5 Hz, H9), 3.45 (3H, s, H16), 3.29 – 3.22 (1H, m, H6), 2.59 (1H, dd, *J* = 19.0, 1.5 Hz, H2), 2.18 (1H, d, *J* = 19.0 Hz, H2′), 1.95 (1H, td, *J* = 8.0, 5.0 Hz, H5), 1.89 – 1.84 (2H, m, H4, H6′), 1.59 (1H, qd, *J* = 6.5, 4.5 Hz, H10), 0.97 – 0.91 (6H, m, H14, H15), 0.14 (9H, s, H17); **δ_C** (101 MHz, C_6D_6) 215.9 (C3), 166.4 (C13), 155.1 (C8), 141.1 (C11), 124.5 (C12), 102.2 (C9), 86.9 (C7), 85.3 (C1), 53.4 (C5), 53.1 (C4), 51.2 (C16), 50.5 (C6), 46.3 (C2), 40.1 (C10), 18.4 (C14), 15.5 (C15), 0.0 (C17); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{19}H_{28}O_5SiNa$ 387.1598, found, 387.1604.

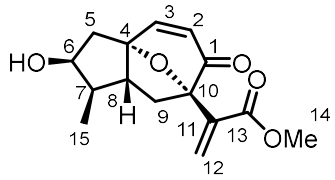
Methyl 2-[(1*S,3a*R**,4*R**,7*S**,8a*S**)-1-bromo-1,4-dimethyl-2,6-dioxohexahydro-1*H*-3a,7-epoxyazulen-7(4*H*)-yl]acrylate (2.130)**



To a solution of acetate **2.123** (4.2 mg, 0.013 mmol) in THF (2 mL) in a 25 mL flask was added a solution of *N*-bromosuccinimide (3.5 mg, 0.020 mmol) in THF (0.5 mL) at –78 °C. The solution was stirred at –78 °C for 20 min and warmed to RT. Water (5 mL) was added and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give bromide **2.130** as a colourless oil and as a single diastereomer (3.3 mg, 69%, not assigned).

R_f 0.15 (pentane/EtOAc, 2:1); **IR** ν_{max}/cm^{-1} 2957m, 2920m, 1752s, 1731s, 1038m; **δ_H** (400 MHz, $CDCl_3$) 6.36 (1H, d, *J* = 1.5 Hz, H12), 6.04 (1H, d, *J* = 1.5 Hz, H12′), 3.78 (3H, s, H16), 3.35 (1H, d, *J* = 19.5 Hz, H2), 2.99 (2H, m, H6, H9), 2.70 – 2.58 (2H, m, H5, H9′), 2.53 (1H, d, *J* = 19.5 Hz, H2′), 2.31 – 2.20 (1H, m, H10), 2.16 (1H, dd, *J* = 15.5, 1.0 Hz, H6′), 1.79 (3H, s, H15), 1.14 (3H, d, *J* = 7.0 Hz, H14); **δ_C** (176 MHz, $CDCl_3$) 206.9 (C3), 202.3 (C8), 166.1 (C13), 136.7 (C11), 126.0 (C12), 89.9 (C7), 87.4 (C1), 68.7 (C4), 56.0 (C5), 52.1 (C16), 43.1 (C10), 43.1 (C2), 40.8 (C6), 40.0 (C9), 25.6 (C15), 16.4 (C14); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{19}O_5BrNa$ 393.0308, found, 393.0310.

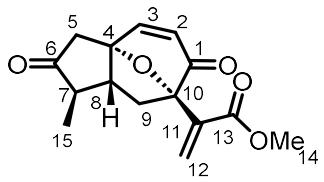
Methyl 2-[(1*R,2*S**,3a*R**,7*S**,8a*R**)-2-hydroxy-1-methyl-6-oxo-2,3,8,8a-tetrahydro-1*H*-3a,7-epoxyazulen-7(6*H*)-yl]acrylate (2.132)**



A solution of ketone **2.117** (0.22 g, 0.56 mmol) in dry THF (10 mL) was cooled to 0 °C and TBAF (1.0 M in THF, 0.63 mL, 0.63 mmol) added. The mixture was warmed to RT and stirred for 1 h. Satd aq NH_4Cl solution (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to obtain crude product **2.132** (0.25 g) which is used directly in next step without purification.

R_f 0.15 (pentane/EtOAc, 1:1); **IR** ν_{max}/cm^{-1} 3504w, 3053w, 1731s, 1694s, 1439m; **δ_H** (400 MHz, $CDCl_3$) 7.31 (1H, d, *J* = 9.5 Hz, H3), 6.31 (1H, d, *J* = 1.0 Hz, H12), 6.00 (1H, d, *J* = 9.5 Hz, H2), 5.95 (1H, d, *J* = 1.0 Hz, H12′), 4.34 (1H, dd, *J* = 5.0, 4.0 Hz, H6), 3.78 (3H, s, H14), 2.54 – 2.29 (3H, m, H5, H8, H9), 2.12 (2H, ddd, *J* = 17.5, 14.5, 2.0 Hz, H5′, H9′), 1.90 – 1.77 (1H, m, H7), 1.06 (3H, d, *J* = 7.0 Hz, H15); **δ_C** (101 MHz, $CDCl_3$) 195.5 (C1), 166.2 (C13), 156.6 (C3), 139.6 (C11), 126.0 (C2), 125.4 (C12), 91.3 (C10), 91.1 (C4), 78.6 (C6), 54.2 (C8), 52.1 (C14), 46.8 (C7), 44.6 (C9), 36.1 (C5), 12.1 (C15); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{15}H_{18}O_5Na$ 301.1047, found, 301.1055.

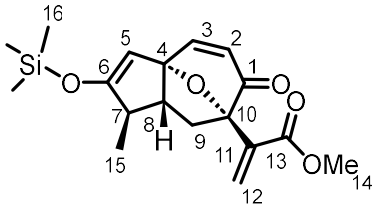
Methyl 2-[(1*R,3a*R**,7*S**,8a*R**)-1-methyl-2,6-dioxo-2,3,8,8a-tetrahydro-1*H*-3a,7-epoxyazulen-7(6*H*)-yl]acrylate (2.133)**



A solution of oxalyl chloride (96.5 μL, 1.14 mmol) in DCM (10 mL) in a 50 mL flask was cooled to –78 °C and dimethylsulfoxide (0.12 mL, 1.7 mmol) added. The solution was stirred for 15 min and a solution of crude substrate **2.132** (0.25 g) in DCM (2 mL) was added. The reaction was stirred at –78 °C for 15 min. To the reaction was added triethylamine (0.48 mL, 3.4 mmol) and the mixture stirred at –78 °C for 15 min then warmed to RT. The mixture was stirred for 2 h and satd aq NH_4Cl solution (20 mL) was added. The mixture was extracted with DCM (3 × 20 mL). The organic extracts were washed with brine (2 × 20 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 1:1) to give diketone **2.133** as a colourless oil (0.12 g, 78% over two steps).

R_f 0.40 (pentane/EtOAc, 1:1); **IR** ν_{max}/cm^{-1} 2954w, 1747s, 1727s, 1697s, 1073s; **δ_H** (400 MHz, $CDCl_3$) 7.15 (1H, d, *J* = 10.0 Hz, H3), 6.32 (1H, d, *J* = 1.0 Hz, H12), 6.09 (1H, d, *J* = 10.0 Hz, H2), 5.96 (1H, d, *J* = 1.0 Hz, H12′), 3.80 (3H, s, H14), 3.00 (1H, dd, *J* = 19.5, 1.0 Hz, H5), 2.73 (1H, dd, *J* = 14.5, 8.0 Hz, H9), 2.63 (1H, d, *J* = 19.5 Hz, H5′), 2.45 – 2.29 (2H, m, H8, H9′), 2.22 – 2.07 (1H, m, H7), 1.16 (3H, d, *J* = 7.0 Hz, H15); **δ_C** (101 MHz, $CDCl_3$) 215.6 (C6), 194.1 (C1), 166.0 (C13), 152.3 (C3), 138.9 (C11), 127.2 (C2), 125.2 (C12), 89.6 (C10), 85.4 (C4), 52.2 (C14), 51.6 (C8), 51.0 (C7), 46.3 (C5), 38.7 (C9), 13.0 (C15); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{17}O_5$ 277.1071, found, 277.1073.

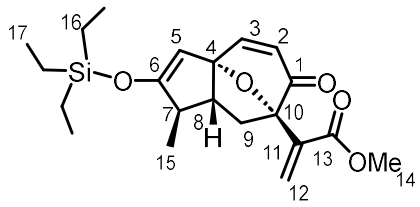
Methyl 2-[(1*R,3a*R**,7*S**,8a*R**)-1-methyl-6-oxo-2-[(trimethylsilyl)oxy]-8,8a-dihydro-1*H*-3a,7-epoxyazulen-7(6*H*)-yl]acrylate (2.135)**



To a solution of diketone **2.133** (10.0 mg, 0.0362 mmol) in THF (2 mL) in a 25 mL flask was added chlorotrimethylsilane (20 μL, 0.16 mmol) and LHMDS (1.0 M in THF, 43 μL, 0.043 mmol) at –78 °C. The solution was stirred at –78 °C for 30 min then warmed to 0 °C for 1 h. The reaction was quenched with satd aq NH_4Cl solution (10 mL). The aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give a mixture of trimethylsilyl enol ether **2.135** and substrate **2.133** (ratio 2:1) from which product **2.135** could be characterised by NMR analysis.

δ_H (400 MHz, C_6D_6) 6.69 (1H, d, *J* = 9.5 Hz, 3H), 6.27 (1H, d, *J* = 1.5 Hz, H12), 5.95 (1H, d, *J* = 1.5 Hz, H12′), 5.88 (1H, d, *J* = 9.5 Hz, H2), 4.75 (1H, d, *J* = 2.0 Hz, H5), 3.44 (3H, s, H14), 2.56 – 2.45 (1H, m, H9), 2.39 (1H, pd, *J* = 7.0, 2.0 Hz, H7), 2.11 (1H, m, H9′), 1.95 (1H, m, H8), 0.95 (3H, d, *J* = 7.0 Hz, H15), 0.09 (9H, s, H16); **δ_C** (101 MHz, C_6D_6) 194.9 (C1), 166.0 (C13), 165.1 (C6), 155.9 (C3), 141.0 (C11), 126.9 (C2), 124.1 (C12), 100.5 (C5), 91.8 (C10), 90.6 (C4), 55.3 (C8), 51.5 (C14), 47.2 (C7), 37.7 (C9), 17.2 (C15), -0.3 (C16).

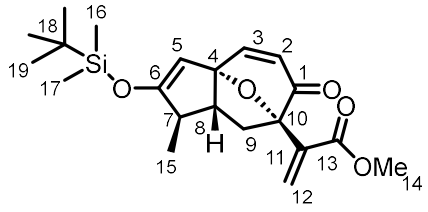
Methyl 2-[(1*R,3a*R**,7*S**,8a*R**)-1-methyl-6-oxo-2-[(triethylsilyl)oxy]-8,8a-dihydro-1*H*-3a,7-epoxyazulen-7(6*H*)-yl]acrylate (2.136)**



To a solution of diketone **2.133** (0.21 g, 0.75 mmol) in THF (10 mL) in a 50 mL flask was added chlorotriethylsilane (0.63 mL, 3.7 mmol) and the mixture cooled to –78 °C. KHMDS (1.0 M in THF, 1.5 mL, 1.5 mmol) was added and the mixture was stirred at –78 °C for 1 h. Satd aq $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give TES enol ether **2.136** as a colourless oil (0.23 g, 80%).

R_f 0.35 (pentane/EtOAc, 10:1); **IR** ν_{max}/cm^{-1} 2956m, 1735w, 1700w, 1073s, 740s; **δ_H** (400 MHz, C_6D_6) 6.69 (1H, d, *J* = 9.5 Hz, H3), 6.27 (1H, d, *J* = 1.5 Hz, H12), 5.95 (1H, d, *J* = 1.5 Hz, H12′), 5.87 (1H, d, *J* = 9.5 Hz, H2), 4.79 (1H, d, *J* = 2.0 Hz, H5), 3.45 (3H, s, H14), 2.53 (1H, dd, *J* = 14.0, 9.0 Hz, H9), 2.40 (1H, pd, *J* = 7.0, 2.0 Hz, H7), 2.13 (1H, dd, *J* = 14.0, 4.0 Hz, H9′), 1.96 (1H, ddd, *J* = 9.0, 6.5, 3.5 Hz, H8), 0.99 – 0.89 (12H, m, H15, H17), 0.64 – 0.56 (6H, m, H16); **δ_C** (101 MHz, C_6D_6) 194.9 (C1), 166.1 (C13), 165.3 (C6), 155.9 (C3), 141.1 (C11), 126.9 (C2), 124.0 (C12), 100.4 (C5), 91.8 (C4), 90.6 (C10), 55.3 (C8), 51.5 (C14), 47.2 (C7), 37.8 (C9), 17.3 (C15), 6.7 (C17), 5.0 (C16); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{21}H_{31}O_5Si$ 391.1935, found, 391.1939.

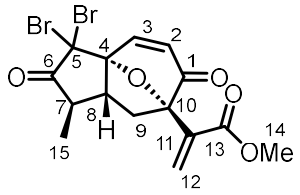
Methyl 2-[(1*R,3a*R**,7*S**,8a*R**)-2-[(tert-butyldimethylsilyl)oxy]-1-methyl-6-oxo-8,8a-dihydro-1*H*-3a,7-epoxyazulen-7(6*H*)-yl]acrylate (2.137)**



To a solution of diketone **2.133** (10.0 mg, 0.0362 mmol) in THF (2 mL) in a 25 mL flask was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (40 μL, 0.17 mmol) and cooled to –78 °C. KHMDS (1.0 M in THF, 50 μL, 0.050 mmol) was added and the mixture was stirred at –78 °C for 1 h. Satd aq $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The organic extracts were washed with brine (10 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give enol ether **2.137** as a colourless oil (6.2 mg, 44%).

R_f 0.70 (pentane/EtOAc, 2:1); **IR** ν_{max}/cm^{-1} 2981w, 1724m, 1265m, 688s; **δ_H** (400 MHz, C_6D_6) 6.68 (1H, dd, *J* = 9.5, 1.0 Hz, H3), 6.27 (1H, d, *J* = 1.5 Hz, H12), 5.95 (1H, d, *J* = 1.5 Hz, H12′), 5.88 (1H, d, *J* = 9.5 Hz, H2), 4.75 (1H, d, *J* = 2.0 Hz, H5), 3.44 (3H, s, H14), 2.51 (1H, dd, *J* = 14.0, 9.0 Hz, H9), 2.37 (1H, qd, *J* = 7.0, 2.0 Hz, H7), 2.12 (1H, dd, *J* = 14.0, 4.0 Hz, H9′), 1.95 (1H, ddd, *J* = 9.0, 6.5, 4.0 Hz, H8), 0.93 (3H, d, *J* = 7.0 Hz, H15), 0.91 (9H, s, H19), 0.06 (3H, s, H16), 0.05 (3H, s, H17); **δ_C** (101 MHz, C_6D_6) 194.9 (C1), 166.1 (C13), 165.2 (C6), 155.9 (C3), 141.0 (C11), 126.9 (C2), 124.1 (C12), 100.6 (C5), 91.9 (C10), 90.6 (C4), 55.3 (C8), 51.5 (C14), 47.2 (C7), 37.7 (C9), 25.6 (C19), 18.2 (C18), 17.2 (C15), -4.9 (C16), -5.0 (C17); HRMS (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{21}H_{31}O_5Si$ 391.1935, found, 391.1933.

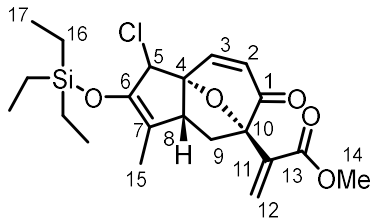
Methyl 2-[(1*R,3a*R**,7*S**,8a*R**)-3,3-dibromo-1-methyl-2,6-dioxo-2,3,8,8a-tetrahydro-1*H*-3a,7-epoxyazulen-7(6*H*)-yl]acrylate (2.141)**



To a solution of enol ether **2.136** (12.4 mg, 0.0358 mmol) in THF (2 mL) in a 25 mL flask was added a solution of *N*-bromosuccinimide (9.6 mg, 0.054 mmol) in THF (0.5 mL) at 0 °C. The solution was stirred at 0 °C for 1 h and warmed to RT. Satd aq $NaHCO_3$ solution (5 mL) and satd aq $Na_2S_2O_3$ solution (5 mL) were added and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 15:1) to give dibromo ketone **2.141** as a yellow oil (4.8 mg, 31%).

R_f 0.35 (pentane/EtOAc, 20:1); **IR** ν_{max}/cm^{-1} 2956w, 2917m, 1769s, 1728s, 1708s; **δ_H** (600 MHz, $CDCl_3$) 7.67 (1H, d, *J* = 10.0 Hz, H3), 6.30 (1H, d, *J* = 1.0 Hz, H12), 6.27 (1H, d, *J* = 10.0 Hz, H2), 5.90 (1H, d, *J* = 1.0 Hz, H12′), 3.83 – 3.75 (3H, m, H14), 2.92 – 2.83 (1H, m, H9), 2.75 (1H, td, *J* = 7.5, 1.0 Hz, H8), 2.56 – 2.49 (1H, m, H9′), 2.14 (1H, t, *J* = 7.5 Hz, H7), 1.47 (3H, d, *J* = 7.5 Hz, H15); **δ_C** (151 MHz, $CDCl_3$) 201.7 (C6), 192.3 (C1), 165.6 (C13), 145.8 (C3), 137.8 (C11), 129.9 (C2), 125.3 (C12), 89.9 (C4), 89.3 (C10), 64.0 (C5), 52.3 (C14), 48.7 (C8), 46.8 (C7), 40.3 (C9), 17.9 (C15); HRMS (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{15}H_{15}O_5{}^{79}Br_2$ 432.9281, found, 432.9292.

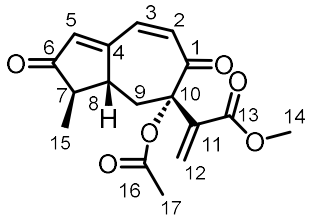
Methyl 2-[(3a*R,7*S**,8a*R**)-3-chloro-1-methyl-6-oxo-2-[(triethylsilyl)oxy]-8,8a-dihydro-3*H*-3a,7-epoxyazulen-7(6*H*)-yl]acrylate (2.140)**



To a solution of enol ether **2.136** (12.5 mg, 0.0361 mmol) in THF (2 mL) in a 25 mL flask was added *N*-chlorosuccinimide (4.8 mg, 0.0359 mmol). The solution was warmed to 40 °C and stirred for 30 min then cooled to RT. The mixture was concentrated then diluted with hexane (10 mL) and filtered. The filtrate was concentrated and the residue was purified by chromatography (pentane/EtOAc, 20:1) to give chloro enol ether **2.140** as a colourless oil and as a single diastereomer (2.5 mg, 16%, not assigned).

R$_f$ 0.15 (pentane/EtOAc, 20:1); **IR** ν_{max}/cm^{-1} 2957w, 1723m, 1050s, 739w; **δ_H** (400 MHz, C_6D_6) 7.47 (1H, d, *J* = 10.0 Hz, H3), 6.22 (1H, d, *J* = 1.5 Hz, H12), 5.89 (1H, d, *J* = 10.0 Hz, H2), 5.76 (1H, d, *J* = 1.5 Hz, H12′), 4.53 (1H, quin, *J* = 1.0 Hz, H5), 3.43 (3H, s, H14), 2.67 (1H, ddq, *J* = 9.0, 3.5, 1.5 Hz, H8), 2.33 (1H, dd, *J* = 14.0, 9.0 Hz, H9), 2.02 (1H, dd, *J* = 14.0, 3.5 Hz, H9′), 1.32 (3H, t, *J* = 1.5 Hz, H15), 0.94 (9H, t, *J* = 8.0 Hz, H17), 0.63 – 0.54 (6H, m, H16); **δ_C** (101 MHz, C_6D_6) 193.9 (C1), 174.9 (C6), 165.6 (C13), 150.3 (C3), 140.2 (C11), 127.1 (C2), 123.8 (C12), 121.1 (C7), 90.8 (C10), 86.9 (C4), 65.3 (C5), 53.2 (C8), 51.6 (C14), 34.1 (C9), 10.7 (C15), 6.8 (C17), 5.6 (C16); HRMS (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{21}H_{30}O_5ClSi$ 425.1546, found, 425.1554.

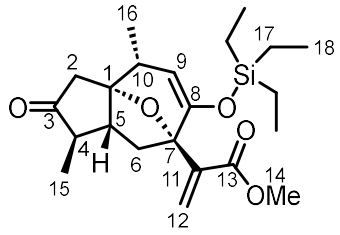
Methyl 2-[(3*R,3a*R**,5*S**)-5-acetoxy-3-methyl-2,6-dioxo-2,3,3a,4,5,6-hexahydroazulen-5-yl]acrylate (2.143)**



To a solution of enol ether **2.136** (60.0 mg, 0.153 mmol) in benzene (2 mL) in a 25 mL flask was added $ZnCl_2$ (1.0 g, 7.3 mmol) and acetic anhydride (0.29 mL, 3.07 mmol). The mixture was stirred at RT for 1 h then triethylamine (43 μL, 0.31 mmol) was added. The reaction was continued for 1 h and diluted with ether (20 mL). The organic phase was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 2:1) to give diketone **2.143** as a pale yellow oil (45.7 mg, 94%).

R_f 0.42 (pentane/EtOAc, 2:1); **IR** ν_{max}/cm^{-1} 2981s, 1738m, 1706m, 1381m, 1241m; **δ_H** (400 MHz, $CDCl_3$) 7.03 (1H, dt, *J* = 12.5, 1.0 Hz, H3), 6.50 (1H, s, H12), 6.32 (1H, d, *J* = 12.5 Hz, H2), 6.21 (1H, d, *J* = 2.0 Hz, H5), 5.95 (1H, s, H12′), 3.77 (3H, s, H14), 2.84 (1H, t, *J* = 12.5 Hz, H9), 2.79 – 2.69 (1H, m, H8), 2.61 – 2.54 (1H, m, H9′), 2.17 (1H, tt, *J* = 7.0, 3.5 Hz, H7), 2.09 (3H, s, H17), 1.21 (3H, d, *J* = 7.0 Hz, H15); **δ_C** (101 MHz, $CDCl_3$) 208.9 (C6), 196.2 (C1), 169.6 (C16), 168.4 (C4), 166.1 (C13), 140.8 (C11), 134.4 (C5), 134.0 (C2), 132.2 (C3), 129.8 (C12), 86.0 (C10), 52.7 (C14), 50.1 (C7), 45.4 (C8), 38.0 (C9), 21.3 (C17), 13.1 (C15); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{18}O_6Na$ 341.0996, found, 341.0999.

Methyl 2-[(1*R,3a*R**,4*R**,7*S**,8a*R**)-1,4-dimethyl-2-oxo-6-[(triethylsilyl)oxy]-2,3,8,8a-tetrahydro-1*H*-3a,7-epoxyazulen-7(4*H*)-yl]acrylate (2.145)**

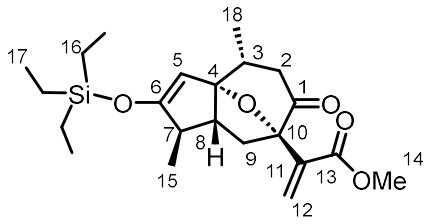


To a solution of diketone **2.121** (10.0 mg, 0.0342 mmol) in THF (2 mL) in a 25 mL flask was added chlorotriethylsilane (45 mL, 0.27 mmol) and the mixture cooled to –78 °C. KHMDS (1.0 M in THF, 0.10 mL, 0.10 mmol) was added and the mixture was stirred at –78 °C for 1 h. Satd aq $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give crude di TES enol ether **2.144** as a yellow oil (17.8 mg) that was used directly for next step without purification.

To a solution of crude product **2.144** (17.8 mg, 0.0342 mmol) in benzene (2 mL) in a 25 mL flask was added $ZnCl_2$ (50.0 mg, 0.367 mmol) and acetic anhydride (0.10 mL, 1.1 mmol). The mixture was stirred at RT for 1 h then triethylamine (50 μL, 0.36 mmol) was added. The reaction was continued for 18 h and diluted with ether (20 mL). The organic phase was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give mono TES enol ether **2.145** as a pale yellow oil (4.5 mg, 32% for two steps).

R_f 0.31 (pentane/EtOAc, 10:1); **IR** (film) ν_{max}/cm^{-1} 2958s, 2932m, 1745s, 1661w, 744s; **δ_H** (400 MHz, C_6D_6) 6.28 (1H, d, *J* = 2.0 Hz, H12), 6.04 (1H, d, *J* = 2.0 Hz, H12′), 4.43 (1H, d, *J* = 4.5 Hz, H9), 3.47 (3H, s, H14), 3.24 (1H, dd, *J* = 12.5, 8.5 Hz, H6), 2.59 (1H, dd, *J* = 19.0, 1.5 Hz, H2), 2.22 – 2.15 (1H, m, H2′), 1.97 (1H, td, *J* = 8.0, 5.0 Hz, H5), 1.92 – 1.83 (2H, m, H4, H6′), 1.64 – 1.57 (1H, m, H10), 1.04 – 0.88 (15H, m, H15, H16, H18), 0.70 – 0.62 (6H, m, H17); **δ_C** (176 MHz, C_6D_6) 215.9 (C3), 166.2 (C13), 155.2 (C8), 141.0 (C11), 125.0 (C12), 101.2 (C9), 87.0 (C1), 85.4 (C7), 53.4 (C5), 53.1 (C4), 51.1 (C14), 50.5 (C6), 46.3 (C2), 40.2 (C10), 18.5 (C16), 15.5 (C15), 6.9 (C18), 5.2 (C17); HRMS (ESI+) *m/z* $[M+K]^+$ calcd. for $C_{22}H_{34}O_5SiK$ 445.1807, found, 445.1799.

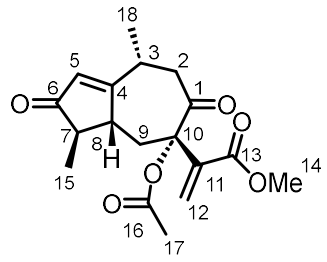
Methyl 2-[(1*R,3a*R**,4*R**,7*S**,8a*R**)-1,4-dimethyl-6-oxo-2-[(triethylsilyl)oxy]-5,6,8,8a-tetrahydro-1*H*-3a,7-epoxyazulen-7(4*H*)-yl]acrylate (2.152)**



A suspension of CuI (52.5 mg, 0.273 mmol) in THF (25 mL) in a 100 mL flask was cooled to 0 °C and methyllithium (1.6 M in ether, 0.34 mL, 0.54 mmol) added. The solution was stirred for 30 min and a solution of enol ether **2.136** (0.10 g, 0.27 mmol) in THF (3 mL) was added. The mixture was stirred at 0 °C for 1 h. Satd aq NH_4Cl solution (20 mL) was added and the mixture was extracted with ether (3 × 20 mL). The organic extracts were washed with brine (20 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 3:1) to give product **2.152** as a yellow oil (71.4 mg, 64%).

R_f 0.71 (pentane/EtOAc, 3:1); **IR** ν_{max}/cm^{-1} 2981s, 2887m, 1732m, 1684w, 1005m; **δ_H** (400 MHz, $CDCl_3$) 6.28 (1H, d, *J* = 1.5 Hz, H12), 5.96 (1H, d, *J* = 1.5 Hz, H12′), 4.79 (1H, d, *J* = 2.0 Hz, H5), 3.74 (3H, s, H14), 2.86 – 2.75 (2H, m, H2, H9), 2.43 (1H, qdd, *J* = 7.0, 5.0, 2.0 Hz, H7), 2.35 – 2.26 (1H, m, H2′), 2.23 (1H, ddd, *J* = 9.0, 6.0, 5.0 Hz, H8), 2.13 (1H, qt, *J* = 7.0, 3.5 Hz, H3), 1.90 (1H, dd, *J* = 13.5, 6.0 Hz, H9′), 1.19 – 1.16 (3H, m, H18), 1.13 (3H, d, *J* = 7.0 Hz, H15), 1.02 – 0.95 (9H, m, H17), 0.76 – 0.67 (6H, m, H16); **δ_C** (101 MHz, $CDCl_3$) 207.3 (C1), 166.2 (C13), 162.9 (C6), 139.3 (C11), 125.9 (C12), 100.0 (C5), 95.3 (C4), 90.0 (C10), 52.9 (C8), 52.0 (C14), 48.6 (C7), 42.4 (C2), 42.4 (C9), 41.9 (C3), 18.7 (C15), 17.5 (C18), 6.7 (C17), 4.9 (C16); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{35}O_5Si$ 407.2248, found, 407.2253.

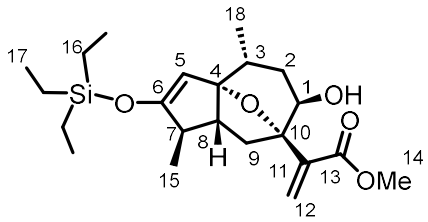
Methyl 2-[(3*R,3a*R**,5*S**,8*R**)-5-acetoxy-3,8-dimethyl-2,6-dioxo-2,3,3a,4,5,6,7,8-octahydroazulen-5-yl]acrylate (2.148)**



To a solution of substrate **2.152** (16.0 mg, 0.0393 mmol) in dry benzene (1 mL) in a 25 mL flask was added $ZnCl_2$ (0.50 g, 3.7 mmol) and acetic anhydride (0.10 mL, 1.1 mmol). The mixture was stirred at RT for 1 h then triethylamine (0.1 mL, 0.72 mmol) was added. The reaction was continued for 1 h and diluted with ether (20 mL). The organic phase was washed with water (10 mL) and brine (10 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 2:1) to give diketone **2.148** as a colourless oil (4.2 mg, 32%).

R_f 0.15 (pentane/EtOAc, 2:1); **IR** ν_{max}/cm^{-1} 2926w, 2850w, 1730s, 1711s, 1244m; **δ_H** (600 MHz, $CDCl_3$) 6.49 (1H, s, H12), 5.96 (1H, s, H5), 5.90 (1H, s, H12′), 3.80 (3H, s, H14), 3.05 (1H, t, *J* = 13.0 Hz, H2), 2.90 (1H, t, *J* = 10.0 Hz, H3), 2.70 (2H, m, H2′, H9), 2.59 (2H, m, H8, H9′), 2.11 (1H, dt, *J* = 10.0, 7.0 Hz, H7), 2.05 (3H, s, H17), 1.33 (3H, d, *J* = 6.5 Hz, H18), 1.18 (3H, d, *J* = 7.5 Hz, H15); **δ_C** (151 MHz, $CDCl_3$) 209.5 (C6), 204.6 (C1), 183.5 (C4), 169.7 (C16), 166.1 (C13), 139.8 (C11), 129.0 (C12), 127.4 (C5), 86.1 (C10), 52.6 (C14), 49.7 (C7), 48.4 (C8), 47.2 (C2), 38.8 (C9), 33.4 (C3), 21.3 (C17), 20.2 (C18), 14.6 (C15); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{18}H_{23}O_6$ 335.1489, found, 335.1490.

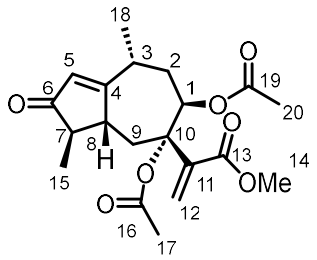
Methyl 2-[(1*R,3a*R**,4*R**,6*S**,7*S**,8a*R**)-6-hydroxy-1,4-dimethyl-2-[(triethylsilyl)oxy]-5,6,8,8a-tetrahydro-1*H*-3a,7-epoxyazulen-7(4*H*)-yl]acrylate (2.153)**



To a solution of substrate **2.152** (22.0 mg, 0.0541 mmol) in ether in a 25 mL flask was added $LiBH_4$ (2 M in THF, 81 μL, 0.16 mmol) dropwise at –78 °C. The resulting solution was stirred at -78 °C for 0.5 h. Satd aq NH_4Cl solution (10 mL) was added at –78 °C then the mixture was warmed to RT and extracted with ether (3 × 10 mL). The organic extracts were washed with brine (20 mL) and dried over Na_2SO_4 and concentrated to obtain pure product **2.153** as a yellow oil (24.0 mg) which could be used for the next step.

R_f 0.11 (pentane/EtOAc, 10:1); **IR** ν_{max}/cm^{-1} 2956m, 1633s, 1009s, 977s; **δ_H** (400 MHz, $CDCl_3$) 6.18 (1H, d, *J* = 1.5 Hz, H12), 6.09 (1H, d, *J* = 1.5 Hz, H12′), 4.75 (1H, d, *J* = 2.0 Hz, H5), 3.78 (3H, s, H14), 3.72 – 3.64 (1H, m, H1), 2.72 (1H, dd, *J* = 13.5, 9.5 Hz, H9), 2.41 – 2.31 (1H, m, H7), 2.04 (1H, ddd, *J* = 9.5, 6.0, 4.5 Hz, H8), 1.80 – 1.66 (3H, m, H2, H3), 1.52 (1H, ddd, *J* = 13.5, 4.5, 1.0 Hz, H9′), 1.17 – 1.12 (3H, m, H18), 1.05 (3H, d, *J* = 7.0 Hz, H15), 0.97 (9H, t, *J* = 8.0 Hz, H17), 0.73 – 0.66 (6H, m, H16); **δ_C** (101 MHz, $CDCl_3$) 169.6 (C13), 162.8 (C6), 144.2 (C11), 126.2 (C12), 100.8 (C5), 94.3 (C4), 87.6 (C10), 71.6 (C1), 54.0 (C8), 52.5 (C14), 48.9 (C7), 38.2 (C3), 36.2 (C9), 35.3 (C2), 18.0 (C15), 16.4 (C18), 6.7 (C17), 4.9 (C16); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{37}O_5Si$ 409.2405, found, 409.2415.

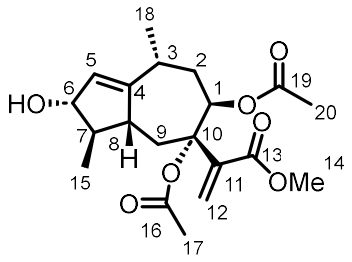
(3*R,3a*R**,5*S**,6*R**,8*R**)-5-(3-Methoxy-3-oxoprop-1-en-2-yl)-3,8-dimethyl-2-oxo-2,3,3a,4,5,6,7,8-octahydroazulene-5,6-diyl diacetate (2.156)**



To a solution of crude product **2.153** (9.3 mg, 0.022 mmol) in dry benzene (1 mL) in a 25 mL flask was added $ZnCl_2$ (0.40 g, 2.9 mmol) and acetic anhydride (100 μL,1.06 mmol). The mixture was stirred at RT for 1 h and then triethylamine (100 μL,0.717 mmol) was added. The mixture was stirred for 1 h and diluted with ether (20 mL). The organic phase was washed with water (10 mL) and brine (10 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (pentane/EtOAc, 3:1) to give product **2.156** as a colourless oil (5.0 mg, 58%).

R_f 0.25 (pentane/EtOAc, 1:1); **IR** ν_{max}/cm^{-1} 2981s, 2889m, 1744m, 1381m; **δ_H** (600 MHz, $CDCl_3$) 6.26 (1H, s, H12), 5.95 (1H, dd, *J* = 2.0, 1.0 Hz, H5), 5.67 (1H, s, H12′), 5.59 (1H, dd, *J* = 5.0, 2.0 Hz, H1), 3.70 (3H, s, H14), 2.88 (1H, dd, *J* = 15.5, 7.5 Hz, H9), 2.78 – 2.75 (1H, m, H8), 2.74 – 2.66 (1H, m, H3), 2.45 (1H, ddd, *J* = 15.5, 3.0, 1.0 Hz, H9′), 2.20 – 2.16 (1H, m, H7), 2.11 – 2.06 (1H, m, H2), 2.05 (3H, s, H20), 1.93 – 1.87 (1H, m, H2′), 1.87 (3H, s, H17), 1.27 (3H, d, *J* = 7.0 Hz, H18), 1.18 (3H, d, *J* = 7.5 Hz, H15); **δ_C** (151 MHz, $CDCl_3$) 210.5 (C6), 186.3 (C4), 170.2 (C16), 169.3 (C19), 165.3 (C13), 142.1 (C11), 125.5 (C5), 125.4 (C12), 82.0 (C10), 71.8 (C1), 52.2 (C14), 49.0 (C8), 48.8 (C7), 37.2 (C2), 31.2 (C9), 31.0 (C3), 21.7 (C17), 21.2 (C20), 20.0 (C18), 14.9 (C15); **HRMS** (ESI+) *m/z* $[M+H]^+$ calcd. for $C_{20}H_{27}O_7$ 379.1751, found, 379.1744.

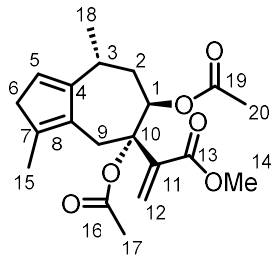
(2*S,3*R**,3a*R**,5*S**,6*R**,8*R**)-2-Hydroxy-5-(3-methoxy-3-oxoprop-1-en-2-yl)-3,8-dimethyl-2,3,3a,4,5,6,7,8-octahydroazulene-5,6-diyl diacetate (2.160)**



To a solution of the substrate **2.156** (8.3 mg, 0.022 mmol) in methanol (1 mL) in a 10 mL flask was added $CeCl_3$•$7H_2O$ (8.2 mg, 0.022 mmol) at 0 °C. $NaBH_4$ (0.8 mg, 0.022 mmol) was then added to the solution and the mixture was stirred at 0 °C for 1 h by which time the reaction was complete (TLC). Water (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product **2.160**, a colourless oil, (9.0 mg) was used directly for the next step without further purification.

R_f 0.25 (pentane/EtOAc, 1:1); **IR** ν_{max}/cm^{-1} 3465w, 2981s, 1740s, 1380m, 1237m; **δ_H** (600 MHz, C_6D_6) 6.23 (1H, s, H12), 5.91 (1H, dd, *J* = 5.0, 2.5 Hz, H1), 5.49 (1H, s, H12′), 5.30 (1H, q, *J* = 2.0 Hz, H5), 4.06 (1H, dq, *J* = 6.0, 2.0 Hz, H6), 3.33 (3H, s, H14), 2.61 (1H, dd, *J* = 15.0, 6.5 Hz, H9), 2.35 – 2.26 (2H, m, H3, H9′), 2.22 – 2.18 (1H, m, H8), 1.99 – 1.93 (2H, m, H2), 1.92 (3H, s, H17), 1.80 – 1.75 (1H, m, H7), 1.61 (3H, s, H20), 1.07 (3H, d, *J* = 7.0 Hz, H15), 1.02 (3H, d, *J* = 7.0 Hz, H18); **δ_C** (151 MHz, C_6D_6) 169.8 (C16), 168.7 (C19), 165.5 (C13), 153.3 (C4), 143.3 (C11), 124.9 (C12), 124.8 (C5), 82.8 (C10), 82.3 (C6), 72.6 (C1), 51.5 (C14), 50.6 (C7), 50.4 (C8), 37.5 (C2), 33.5 (C9), 28.9 (C3), 21.9 (C17), 20.5 (C20), 20.5 (C18), 17.1 (C15); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{20}H_{28}O_7Na$ 403.1727, found, 403.1727.

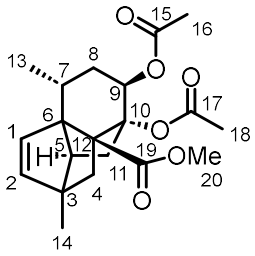
(5*S,6*R**,8*R**)-5-(3-Methoxy-3-oxoprop-1-en-2-yl)-3,8-dimethyl-2,4,5,6,7,8-hexahydroazulene-5,6-diyl diacetate (2.161)**



To a solution of crude alcohol **2.160** from the previous reaction (9.0 mg, <0.022 mmol) in benzene (1 mL) in a 10 mL flask was added Burgess reagent (10.4 mg, 0.0438 mmol) at RT. The resulting solution was warmed to 32 °C and stirred for 2 h. The reaction was then quenched by adding water (10 mL). The aqueous phase was extracted with ether (3 × 10 mL) then the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by chromatography (pentane/EtOAc, 10:1) to give product **2.161** as a colourless oil (7.1 mg, 90% over two steps).

R_f 0.80 (pentane/EtOAc, 2:1); **IR** ν_{max}/cm^{-1} 3232w, 3096m, 1746s, 1016m; **δ_H** (400 MHz, $CDCl_3$) 6.24 (1H, s, H12), 5.75 (1H, d, *J* = 2.0 Hz, H5), 5.73 (1H, s, H12′), 5.51 (1H, dd, *J* = 4.5, 2.5 Hz, H1), 3.71 (3H, s, H14), 3.40 (1H, ddd, *J* = 14.0, 1.5, 0.5 Hz, H9), 3.06 (1H, dq, *J* = 14.0, 1.5 Hz, H9′), 2.81 (2H, q, *J* = 2.0 Hz, H6), 2.74 (1H, ddt, *J* = 6.5, 4.5, 2.5 Hz, H3), 2.04 (3H, s, H17), 1.93 – 1.86 (2H, m, H2), 1.84 (3H, d, *J* = 1.5 Hz, H15), 1.76 (3H, s, H20), 1.20 (3H, d, *J* = 7.5 Hz, H18); **δ_C** (101 MHz, $CDCl_3$) 169.6 (C16), 169.2 (C19), 165.5 (C13), 153.3 (C4), 143.3 (C11), 140.8 (C8 or C7), 134.7 (C8 or C7), 125.2 (C12), 119.7 (C5), 81.3 (C10), 72.3 (C1), 52.0 (C14), 44.4 (C6), 37.0 (C2), 29.4 (C9), 26.9 (C3), 21.2 (C17), 21.0 (C20), 20.0 (C18), 13.5 (C15); **HRMS** (ESI+) *m/z* $[M+Na]^+$ calcd. for $C_{20}H_{26}O_6Na$ 385.1622, found, 385.1627.

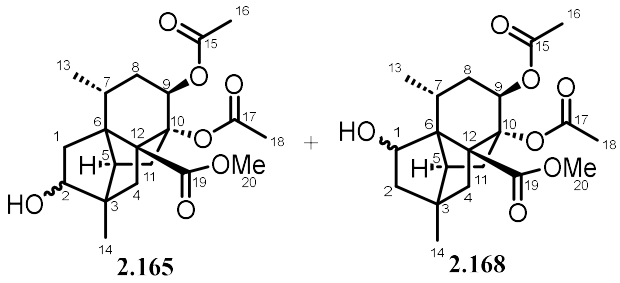
(4*R,6*R**,7*R**,8a*S**,9*S**)-9-(Methoxycarbonyl)-1,4-dimethyl-5,6,8,8a-tetrahydro-1*H*-3a,7,1-(epiethane[1,1,2]triyl)azulene-6,7(4*H*)-diyl diacetate (2.164)**



A solution of cyclopentadiene derivative **2.161** (6.2 mg, 0.017 mmol) in toluene (1 mL) in a pressure tube was heated to 160 °C for 3 h. The solution was cooled to RT and concentrated then the residue was purified by chromatography (pentane/EtOAc, 6:1) to give product **2.164** as a colourless oil (5.7 mg, 92%).

R$_f$ 0.11 (pentane/EtOAc, 6:1); **IR** ν_{max}/cm^{-1} 3115w, 2922m, 1745s, 1435m, 1006m; **δ_H** (600 MHz, $CDCl_3$) 5.98 (1H, d, *J* = 5.5 Hz, H2), 5.83 (1H, d, *J* = 5.5 Hz, H1), 5.77 (1H, dd, *J* = 4.0, 2.5 Hz, H9), 3.66 (3H, s, H20), 2.86 (1H, dquin, *J* = 13.0, 6.5 Hz, H7), 2.19 (1H, ddd, *J* = 15.0, 5.5, 1.0 Hz, H11), 2.06 – 2.00 (4H, m, H4, H18), 1.97 (3H, s, H16), 1.84 – 1.77 (2H, m, H5, H8), 1.70 – 1.62 (1H, m, H8′), 1.57 – 1.55 (1H, m, H11′), 1.13 – 1.07 (4H, m, H4′, H14), 0.97 (3H, d, *J* = 6.5 Hz, H13); **δ_C** (151 MHz, $CDCl_3$) 173.3 (C19), 170.9 (C17), 170.0 (C15), 141.3 (C2), 132.7 (C1), 90.7 (C10), 71.4 (C9), 65.6 (C6), 58.2 (C5), 57.2 (C12), 52.3 (C3), 51.4 (C20), 43.3 (C4), 34.9 (C8), 31.6 (C11), 25.4 (C7), 22.0 (C18), 21.1 (C16), 18.8 (C13), 15.2 (C14); **HRMS** (ESI+) *m/z* $[M+NH_4]^+$ calcd. for $C_{20}H_{30}NO_6$ 380.2068, found, 380.2071.

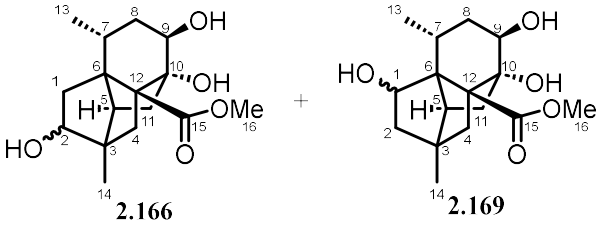
(4*R,6*R**,7*R**,8a*R**,9*S**)-2-Hydroxy-9-(methoxycarbonyl)-1,4-dimethylhexahydro-1*H*-3a,7,1-(epiethane[1,1,2]triyl)azulene-6,7(4*H*)-diyl diacetate (2.165) and (4*R**,6*R**,7*R**,8a*S**,9*S**)-3-hydroxy-9-(methoxycarbonyl)-1,4-dimethylhexahydro-1*H*-3a,7,1-(epiethane[1,1,2]triyl)azulene-6,7(4*H*)-diyl diacetate (2.168)**



To a solution of diacetate **2.164** (2.0 mg, 0.0055 mmol) in THF (0.5 mL) in a 5 mL flask was added a solution of BH_3•THF (1.0 M in THF, 0.10 mL, 0.1 mmol) at –78 °C. The solution was warmed to RT and stirred for 1 h. The reaction was then cooled to 0 °C and quenched with water (1 mL). Satd aq $NaBO_3$ solution (1 mL) was added and the mixture was warmed to RT and stirred for 1 h. The mixture was extracted with ether (4 × 3 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (pentane/EtOAc, 1:1) to give complex **2.165** and **2.168** as a colourless oil (1.8 mg, 86%). (*Appendix 22*)

R_f 0.15 (pentane/EtOAc, 1:1); **δ_H** (600 MHz, $CDCl_3$) selected peaks are reported here 5.77 – 5.65 (1H, m, H9), 4.40 – 4.31 (0.5 H, m, H2 in **2.165** and H1 in **2.168**), 4.25 – 4.07 (0.2 H, m, H2 in **2.165** and H1 in **2.168**), 3.76 – 3.64 (3H, m, H20), 3.60 – 3.51 (0.2H, m, H2 in **2.165** and H1 in **2.168**), 2.03 – 1.95 (6H, m, H16, H18); **HRMS** (ESI+) *m/z* $[M+NH_4]^+$ calcd. for $C_{20}H_{32}NO_7$ 398.2173, found, 398.2162.

Methyl (4*R,6*R**,7*R**,8a*R**,9*S**)-2,6,7-trihydroxy-1,4-dimethyloctahydro-1*H*-3a,7,1-(epiethane[1,1,2]triyl)azulene-9-carboxylate (2.166) and methyl (4*R**,6*R**,7*R**,8a*S**,9*S**)-3,6,7-trihydroxy-1,4-dimethyloctahydro-1*H*-3a,7,1-(epiethane[1,1,2]triyl)azulene-9-carboxylate (2.169)**



To a solution of alcohol **2.165** and **2.168** (1.0 mg, 0.0026 mmol) in methanol (0.5 mL) in a 5 mL flask was added sodium methoxide (5.0 mg, 0.093 mmol). The mixture was stirred at RT for 18 h and neutralised with Amberlyst® 15 (hydrogen form, 30.0 mg). The mixture was filtered and the filtrate was concentrated to give crude product **2.166** and **2.169** as a colourless oil (0.7 mg). (*Appendix 23*)

δ_H (400 MHz, $CDCl_3$) selected peaks are reported here 4.50 (1H, s, H2 in **2.166** and H1 in **2.169**), 4.19 – 4.07 (1H, m, H9), 3.60 (1.5 H, s, H16), 3.42 (1.5 H, s, H16).

References

[1] a) K. Walsh, H. F. Sneddon and C. J. Moody, *Org. Lett.* **2014**, *16*, 5224–5227; b) C. G. Francisco, R. Freire, R. Hernandez, D. Melian, J. A. Salazar and E. Suarez, *J. Chem. Soc., Perkin Trans. I* **1984**, *3*, 459–465.

[2] a) S.-S. Shen, V. Kartika, Y. S. Tan, R. D. Webster and K. Narasaka, *Tetrahedron Lett.* **2012**, *53*, 986–990; b) A. Hortmann and A. Ong, *J. Org. Chem.* **1970**, *35*, 4290–4292.

[3] M. Miyazawa, T. Wada and H. Kameoka, *J. Agric. Food Chem.* **1998**, *46*, 300–303.

[4] H. Sugiyama, F. Yokokawa and T. Shioiri, *Org. Lett.* **2000**, *2*, 2149–2152.

[5] L. Palais and A. Alexakis, *Chem. Eur. J.* **2009**, *15*, 10473–10485.

[6] M. Simon, K. Karaghiosoff and P. Knochel, *Org. Lett.* **2018**, *20*, 3518–3521.

[7] M. Leiva de Faria, R. de A. Magalhães, F. C. Silva, L. G. de O. Matias, M. A. Ceschi, U. Brocksom and T. J. Brocksom, *Tetrahedron: Asymmetry* **2000**, *11*, 4093–4103.

[8] L. D. C. Alves, A. L. Desiderá, K. T. De Oliveira, S. Newton, S. V. Ley and T. J. Brocksom, *Org. Biomol. Chem.* **2015**, *13*, 7633–7642.

[9] M. R. Harris, M. O. Konev and E. R. Jarvo, *J. Am. Chem. Soc.* **2014**, *136*, 7825–7828.

[10] F. J. Moreno-Dorado, F. M. Guerra, F. L. Manzano, F. J. Aladro, Z. a. D. Jorge and G. M. Massanet, *Tetrahedron Lett.* **2003**, *44*, 6691–6693.

[11] G. Blay, B. Garcia, E. Molina and J. R. Pedro, *Org. Lett.* **2005**, *7*, 3291–3294.

[12] J. Zong and J. Robertson, *Molecules* **2023**, *28*, 3900.

[13] X. Xie and S. S. Stahl, *J. Am. Chem. Soc.* **2015**, *137*, 3767–3770.

[14] H. Shimizu, H. Maeda and H. Nara, *Org. Process Res. Dev.* **2020**, *24*, 2772–2779.

[15] D. Kalaitzakis, E. Antonatou and G. Vassilikogiannakis, *J. Chem. Soc., Chem. Commun.* **2014**, *50*, 400–402.

[16] F. Loiseau, J.-M. Simone, D. Carcache, P. Bobal and R. Neier, *Monatsh. Chem.* **2007**, *138*, 121–129.

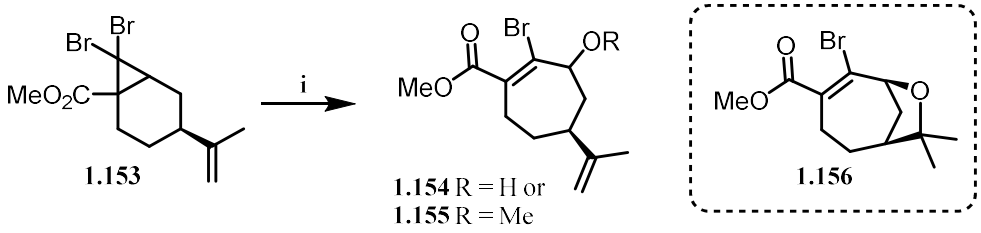
[17] E. G. Tse, L. Aithani, M. Anderson, et al. *J. Med. Chem.* **2021**, *64*, 16450–16463.

[18] A. S. K. Hashmi and M. Wölfle, *Tetrahedron* **2009**, *65*, 9021–9029.

Appendices

Appendices for Project I

Appendix 01: **Ring expansion of ester 1.153 into 1.155.**



1.153

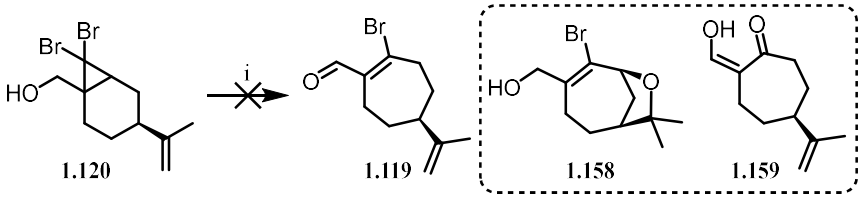
1.154 R = H or
1.155 R = Me

1.156

Entry	[Ag] (eq.)	Solvent	Temperature (°C)	result
1	-	CH_3CN	80	n.r.
2	-	toluene	110	n.r.
3	$AgBF_4$ (1.3)	DME:H_2O = 5:1	80	n.r.
4	Ag_2O+HBF_4 (1.2)	DME:H_2O = 4:1	80	3% **1.156**
5[a]	$AgBF_4$ (1.3)	acetone:H_2O = 4:1	130	decomposed
6[a]	$AgBF_4$ (2)	acetone:H_2O = 1:1	130	n.r.
7[a]	$AgBF_4$ (2)	DMF:H_2O = 4:1	130	n.r.
8	$AgNO_3$ (1.1)	MeOH	70	n.r.
9	$AgNO_3$ (1.5)	MeOH	70	n.r.
10[a]	$AgNO_3$ (2)	acetone:H_2O = 1:4	130	n.r.
11	AgOAc (1.5)	AcOH	130	n.r.
12[a]	$CuSO_4$•$5H_2O$ (1)	DMSO:H_2O = 1:1	130	n.r.

[a] In a sealed tube.

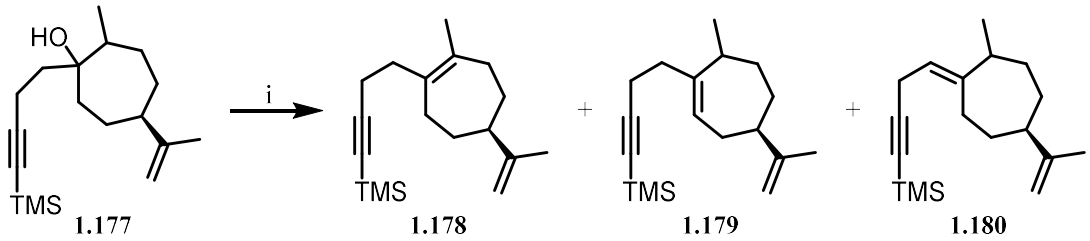
Appendix 02: **Attempted ring expansion of alcohol 1.120 into 1.119.**



Entry	[Ag] (eq.)	Solvent	Temperature (°C)	result
1	$AgNO_3$ (1.5)	DME	80	n.r.
2[a]	$AgNO_3$ (1.5)	acetone	80	n.r.
3	$AgNO_3$ (1.5)	MeOH	80	n.r.
4[a]	$AgNO_3$ (1.8)	H_2O	130	5% **1.158**
5	$AgNO_3$ (1.6)	DMF	135	n.r.
6[a]	$AgBF_4$ (1.5)	acetone	80	n.r.
7	$AgBF_4$ (1.5)	DMF	100	19% **1.159**
8	$AgBF_4$ (2)	DMF:H_2O = 10:1	100	n.r.
9[a]	$AgClO_4$ (1.5)	acetone:H_2O = 9:1	100	18% **1.158**
10[a]	$AgBF_4$ (2)	acetone:H_2O = 9:1	100	14% **1.158**
11[a]	$AgClO_4$ (1.5)	acetone:H_2O = 9:1	80	n.r.
12[a]	$AgClO_4$ (1.5)	acetone:H_2O = 7:3	100	32% **1.158**
13[a]	$AgClO_4$ (1.5)	acetone:H_2O = 1:1	100	24% **1.158**
14[a]	$AgClO_4$ (3)	acetone:H_2O = 7:3	100	28% **1.158**

[a] In a sealed tube.

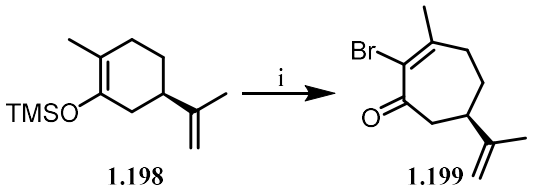
***Appendix 03*: Dehydration of alcohol 1.177 into substrate 1.178.**



1.177 **1.178** **1.179** **1.180**

Entry	conditions (i)	**1.178**:**1.179**:**1.180**
1	1.1 eq. $SOCl_2$,1.2 eq. pyridine, DCM, 40 °C, 2 h	31:43:26
2	1.1 eq. $SOCl_2$, 1.2 eq. pyridine, DCM, 0 °C, 0.5 h	0:62:38
3	1.1 eq. $SOCl_2$, 1.2 eq. pyridine, DCM, –30 °C, 20 h	33:40:26
4	1.1 eq. $SOCl_2$, 1.2 eq. pyridine, DCE, 70 °C, 20 h	decomposed
5	1.1 eq. $SOCl_2$, 1.2 eq. pyridine/collidine, DCM, 0 °C, 0.5 h	37:39:20
6	1.1 eq. $SOCl_2$, pyridine/collidine (1:1), RT, 20 h	59:29:12
7	1.1 eq. PPTS, DCM, RT, 20 h	32:42:25
8	1.1 eq. PPTS, DCM, 40 °C, 20 h	30:43:26

Appendix 04: **Study of the ring expansion step (1.198 to 1.199).**

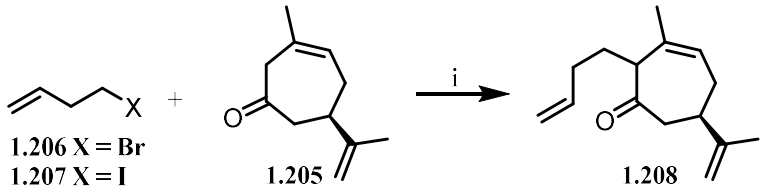


1.198 **1.199**

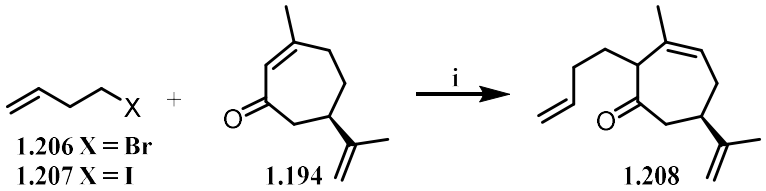
Entry	conditions (i)	yield
1	5 eq. $HCBr_3$, 6 eq. *t*-BuOK, hexane, –30 °C to RT, 18 h	14%
2	1.2 eq. $HCBr_3$, 3 eq. *t*-BuOK, hexane, –30 °C to RT, 18 h	25%
3[a]	1.2 eq. $HCBr_3$, 3 eq. *t*-BuOK, hexane, –30 °C to RT, 18 h	decomposed
4	1.2 eq. $HCBr_3$, 3 eq. KHMDS, THF, –78 °C to RT, 18 h	9%
5	3 eq. $HCBr_3$, 10 mol% *t*-BuOH, 1.1 eq. KHMDS, THF, –78 °C to RT, 18 h	n.r.
6	3 eq. $HCBr_3$,1.1 eq. *t*-BuOK (dropwise), hexane, –30 °C to RT, 18 h	n.r.
7	1 eq. $HCBr_3$, 2 eq. *t*-BuOK, hexane, –30 °C to RT, 18 h then 40 mol% TsOH	15%

[a] 8 mmol.

***Appendix 05*: Direct butenylation of enones 1.194 and 1.205.**

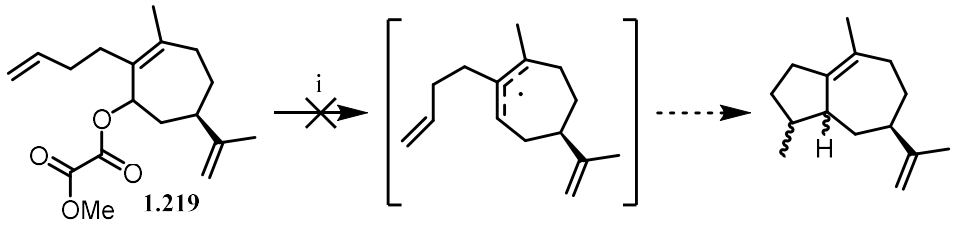


Entry	conditions (i)	yield
1	1.5 eq. **1.207**, 1.4 eq. *t*-BuOK, THF, RT, 18 h	25%
2	1.3 eq. **1.207**, 1.1 eq. *t*-BuOK, 12 eq. DMPU, DMF, RT, 18 h	21%
3	1.3 eq. **1.207**, 1.25 eq. LHMDS, THF, RT, 18 h	trace
4	1.3 eq. **1.207**, 1.2 eq. *t*-BuONa, THF, RT, 18 h	trace
5	1.5 eq. **1.207**, 1.2 eq. KHMDS, DMF, RT, 18 h	trace
6	1.5 eq. **1.207**, 1.25 eq. LHMDS, DMF, –30 °C to RT, 18 h	trace
7	1.3 eq. **1.206**, 1.2 eq. *t*-BuOK, DMF, RT, 18 h	16%
8	1.2 eq. *t*-BuOK, DMF, RT, 1 h, then 1.3 eq. **1.206**, 0 °C, 1 h	10%
9	1.3 eq. **1.206**, 1.2 eq. *t*-BuOK, *t*-BuOH, RT, 6 h	trace



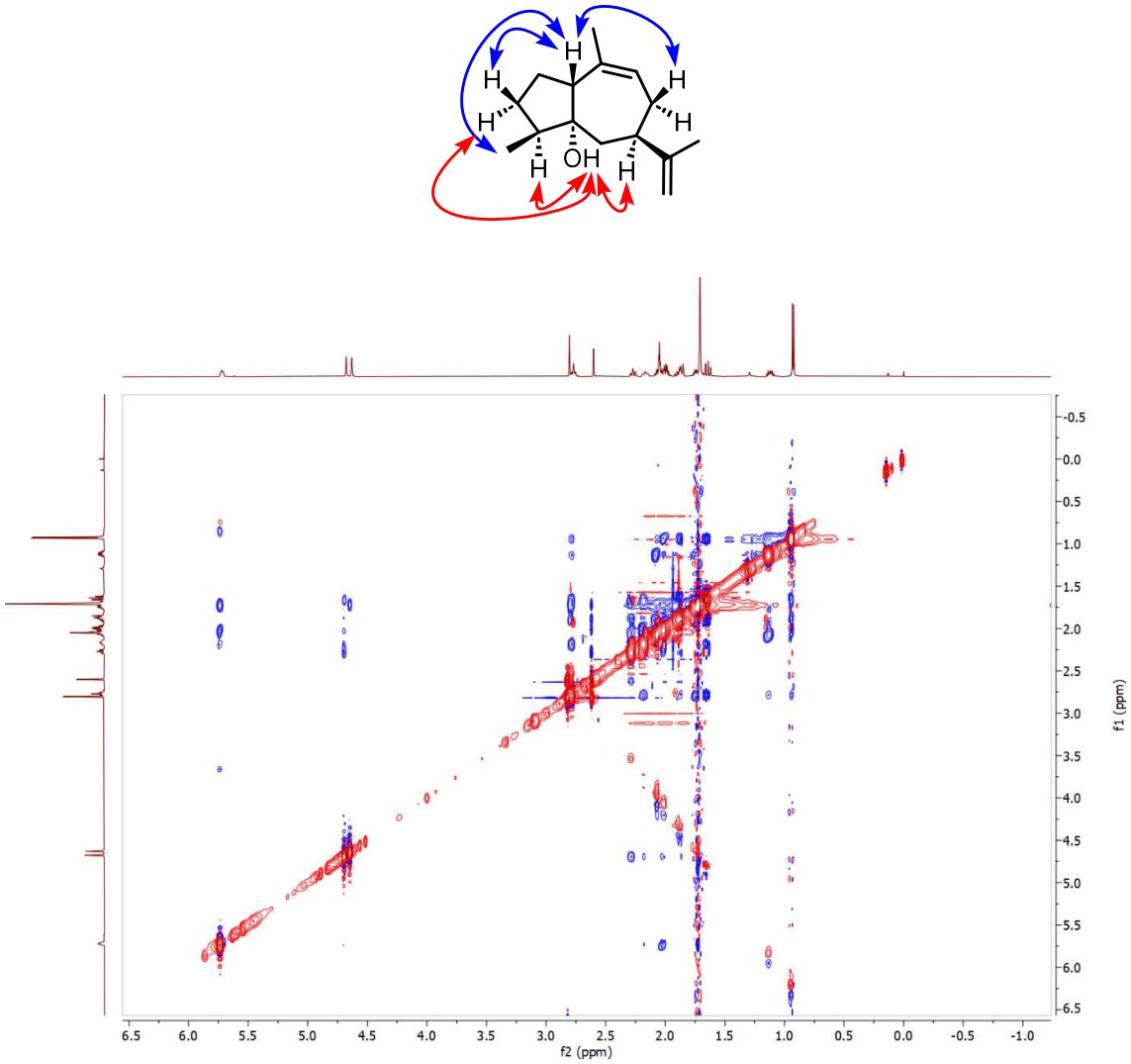
Entry	conditions (i)	yield
1	1.5 eq. **1.207**, 1.2 eq. *t*-BuOK, 30 eq. HMPA, THF, RT, 18 h	25%
2	1.2 eq. **1.206**, 1.1 eq. *t*-BuOK, 0.5 eq. NaI, THF, RT, 18 h	trace
3	2 eq. **1.207**, 2 eq. NaH, THF, RT to 60 °C, 3 h	11%
4	2 eq. **1.207**, 2 eq. NaH, THF, reflux, 48 h	trace
5	1.3 eq. **1.206**, 1.2 eq. KHMDS, 4.5 eq. HMPA, THF, –78 °C to RT, 18 h	trace
6	18 eq. **1.207**, 1.2 eq. KHMDS, THF, –78 °C to RT, 2 h	13%

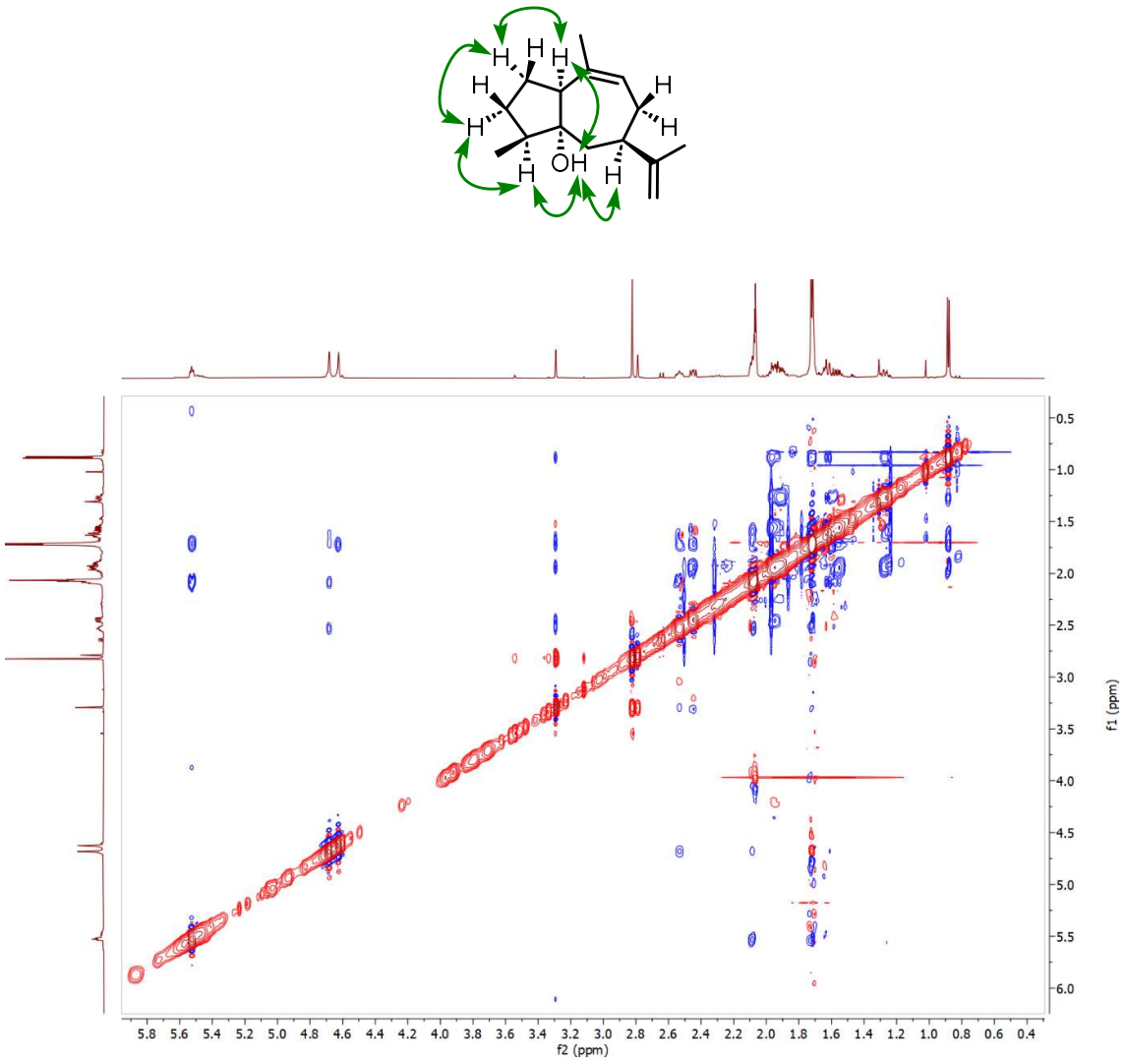
Appendix 06: **Radical cyclisation of methyl oxalyl ester 1.219.**



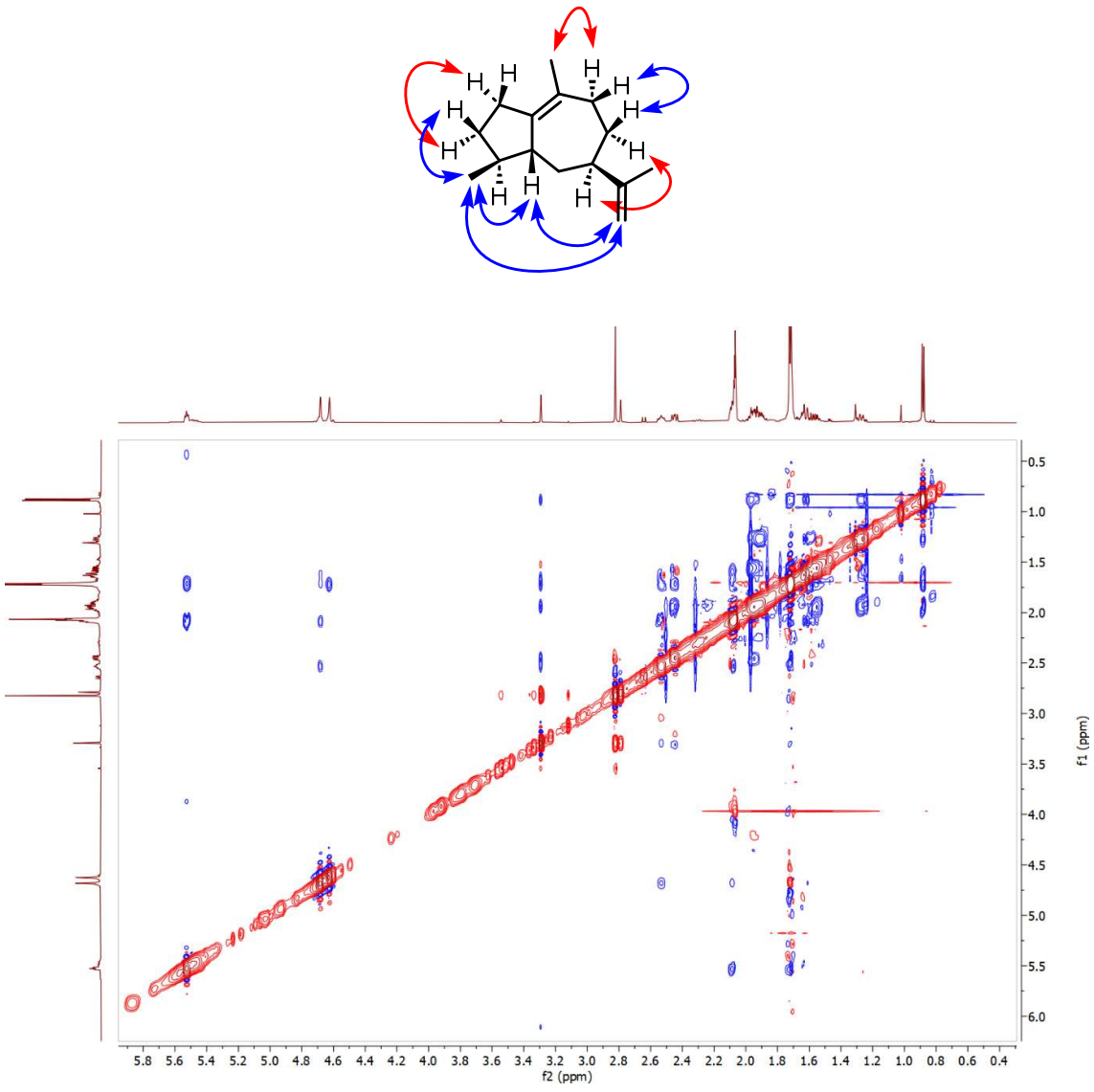
Entry	conditions (i)	result
1	2.5 eq. Bu_3SnH, 10 mol% AIBN, benzene, 80 °C, 2 h	n.r.
2	2.5 eq. Bu_3SnH, 10 mol% AIBN, toluene, 110 °C, 2 h	n.r.
3	2.5 eq. Bu_3SnH (quickly added), 10 mol% AIBN, benzene, 80 °C, 2 h	decomposed
4	2.5 eq. Zn, 2 eq. $MgCl_2$, 20 mol% $Fe(acac)_3$, CH_3CN, RT, 1 h	decomposed

Appendix 07: **NOESY Spectrum of compound 1.259 and 1.260.**

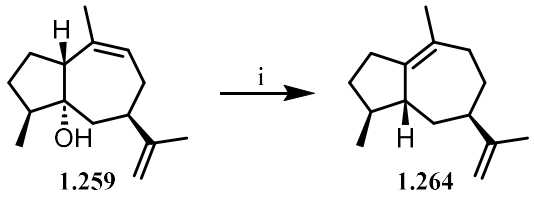



H
H
H
H
H
H
H
H
OH
H
5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4
f2 (ppm)
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
f1 (ppm)

Appendix 08: **NOESY Spectrum of compound 1.264.**



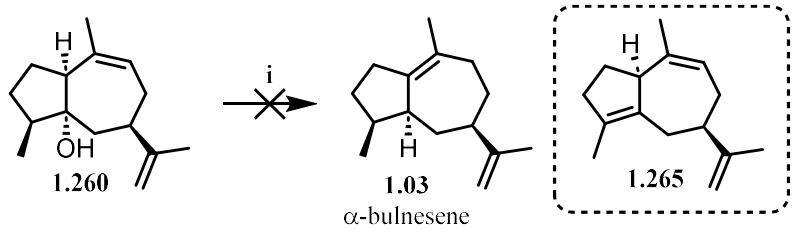
Appendix 09: **Reductive rearrangement of alcohol 1.259 into product 1.264.**



1.259 **1.264**

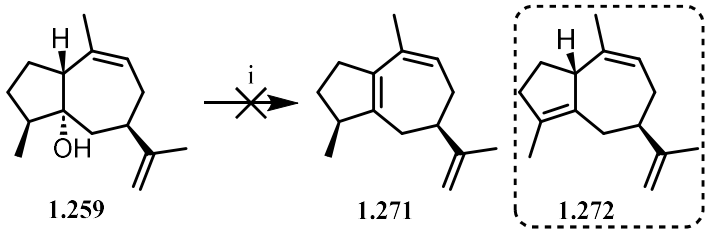
Entry	conditions (i)	result
1	1 eq. BF_3•OEt_2, DCM, –78 °C, 2.5 h then 0 °C, 1 h	complex
2	1 eq. BF_3•OEt_2, 1 eq. Et_3SiH, DCM, –78 °C to 0 °C, 1 h	**17%**
3	1 eq. BF_3•OEt_2, 2 eq. Et_3SiH, DCM, –46 °C to 0 °C, 1 h	**32%**
4	1 eq. BF_3•OEt_2, 2 eq. Et_3SiH, DCM, –78 °C to 0 °C, 1 h	**53%**
5	0.66 eq. BF_3•OEt_2, 2 eq. Et_3SiH, DCM, –78 °C to 0 °C, 1 h	**35%**
6	0.7 eq. BF_3•OEt_2, 6 eq. Et_3SiH, DCM, –78 °C to –10 °C, 1 h	**54%**
7	1 eq. BF_3•OEt_2, 2 eq. Et_3SiH, CH_3CN, –40 °C to 0 °C, 1 h	**29%**
8	5 mol% $InCl_3$, 2 eq. Ph_2SiHCl, DCM, RT, 1 h	complex

Appendix 10: **Attempted reductive rearrangement of alcohol 1.260 into product 1.03.**



Entry	conditions (i)	result
1	1 eq. BF_3•OEt_2, 2 eq. Et_3SiH, DCM, –78 °C to 0 °C, 1 h	complex
2	1 eq. BF_3•OEt_2, 2 eq. Et_3SiH, CH_3CN, –40 °C to RT, 1 h	**1.265 (23%)**
3	1 eq. BF_3•OEt_2, 3 eq. Et_3SiH, MeOH, –78 °C to RT, 2 h	n.r.
4	1 eq. BF_3•OEt_2, 4 eq. Et_3SiH, DCM, RT, 0.5 h	complex
5	1 eq. TfOH, 4 eq. Et_3SiH, CH_3CN, –35 °C, 1 h	**1.265**
6	1 eq. TfOH, 4 eq. Et_3SiH, DCM, –78 °C to 0 °C, 1 h	decomposed
7	1 eq. TfOH, 4 eq. Et_3SiH, DMPU, 0 °C to 50 °C, 1.5 h	n.r.
8	36 eq. BF_3•OEt_2, 400 eq. Et_3SiH, –78 °C to 0 °C, 1 h	decomposed
9	5 mol% $InCl_3$, 2 eq. Ph_2SiHCl, DCM, RT, 1 h	complex
10	40 mol% $B(C_6F_5)_3$, 1 eq. Et_3SiH, toluene, RT, 18 h	n.r.

Appendix 11: **Attempted elimination of alcohol 1.259 into diene 1.271.**

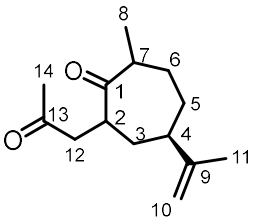


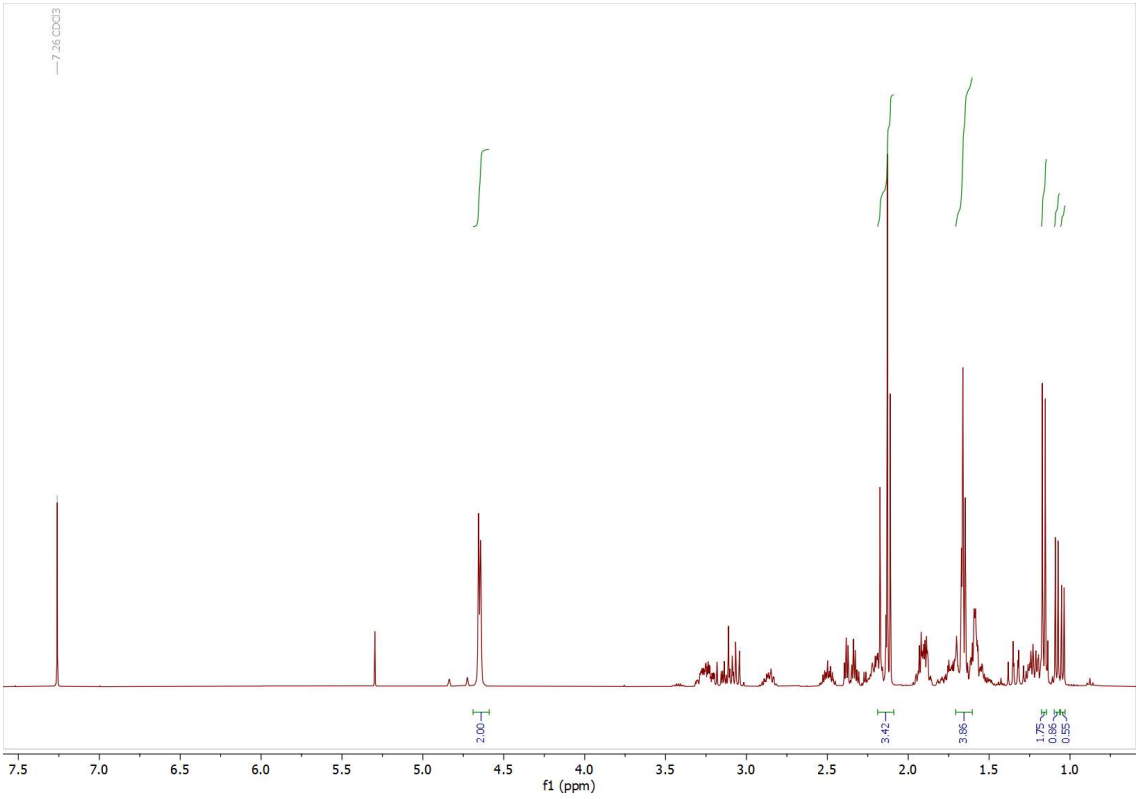
1.259 **1.271** **1.272**

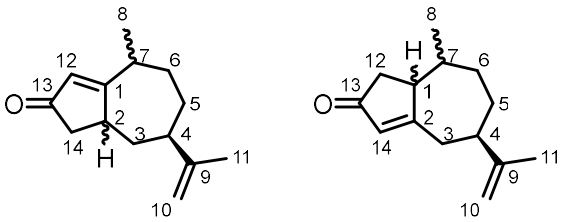
Entry	conditions (i)	result
1	2 eq. Burgess reagent, THF, RT, 2 h	87% **1.272**
2	3 eq. $SOCl_2$, 5 eq. 2,4,6-collidine, 5 eq. pyridine, DCM, 0 °C, 0.5 h	complex
3	20 eq. $SOCl_2$, pyridine, 0 °C, 0.5 h	decomposed
4	20 eq. $SOCl_2$, pyridine, –40 °C, 0.5 h	decomposed
5	3 eq. $SOCl_2$, 5 eq. 2,4,6-collidine, 5 eq. pyridine, DCM, –78 °C, 2 h	**1.272**
6	5 eq. MsCl, 5 eq. DMAP, 5 eq. Et_3N, DCM, 0 °C to RT, 2.5 h	n.r.
7	10 eq. MsCl, pyridine, 0 °C, 5 h	n.r.
8	3 eq. TFAA, 50 mol% DMAP, 3 eq. pyridine, DCM, RT, 18 h	n.r.
9	10 eq. $ZnCl_2$, Ac_2O, RT, 1 h	decomposed
10	2 eq. MsCl, 3 eq. KHMDS, THF, –78 °C to 0 °C, 1 h	n.r.
11	1.5 eq. MsCl, 3 eq. KH, THF, 0 °C, 1 h	n.r.
12	1 eq. Martin Sulfurane, DCM, RT, 2 h	n.r.

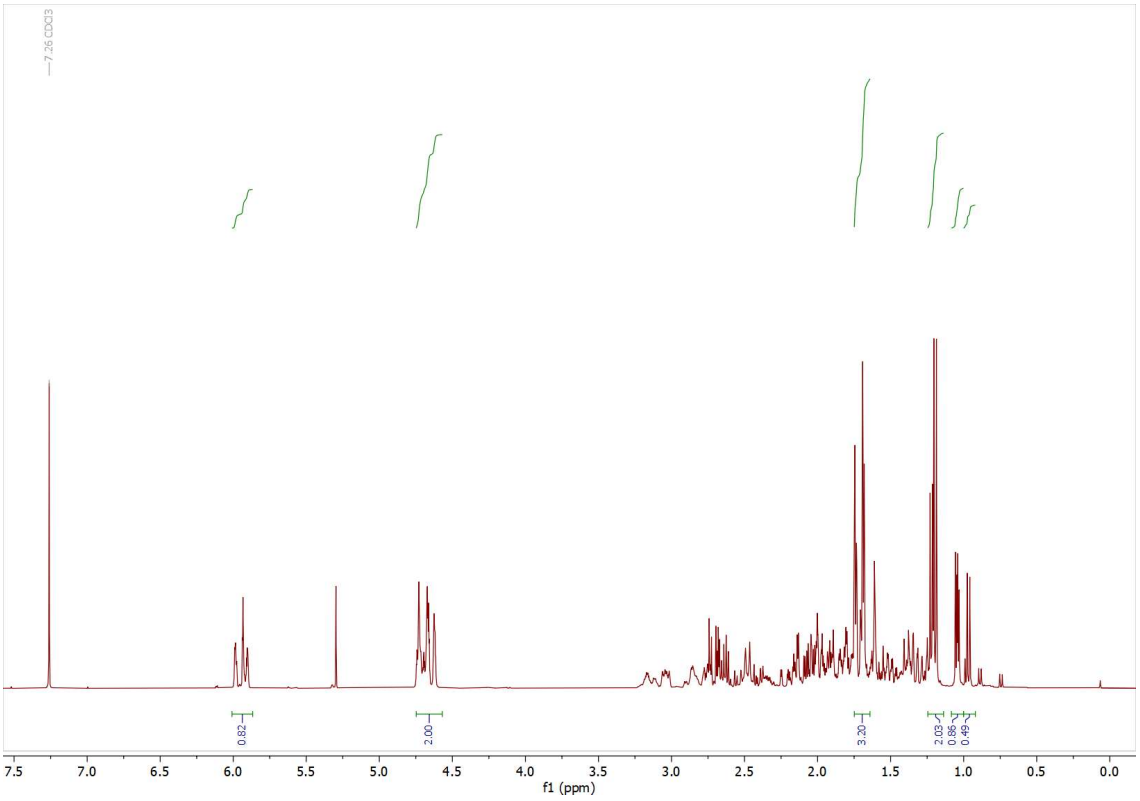
Appendices for Project II

Appendix 12: ^{1}H-NMR spectra of diketone 2.51 and enone 2.50.

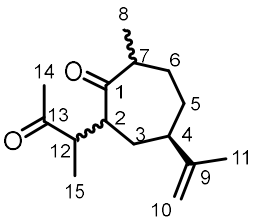


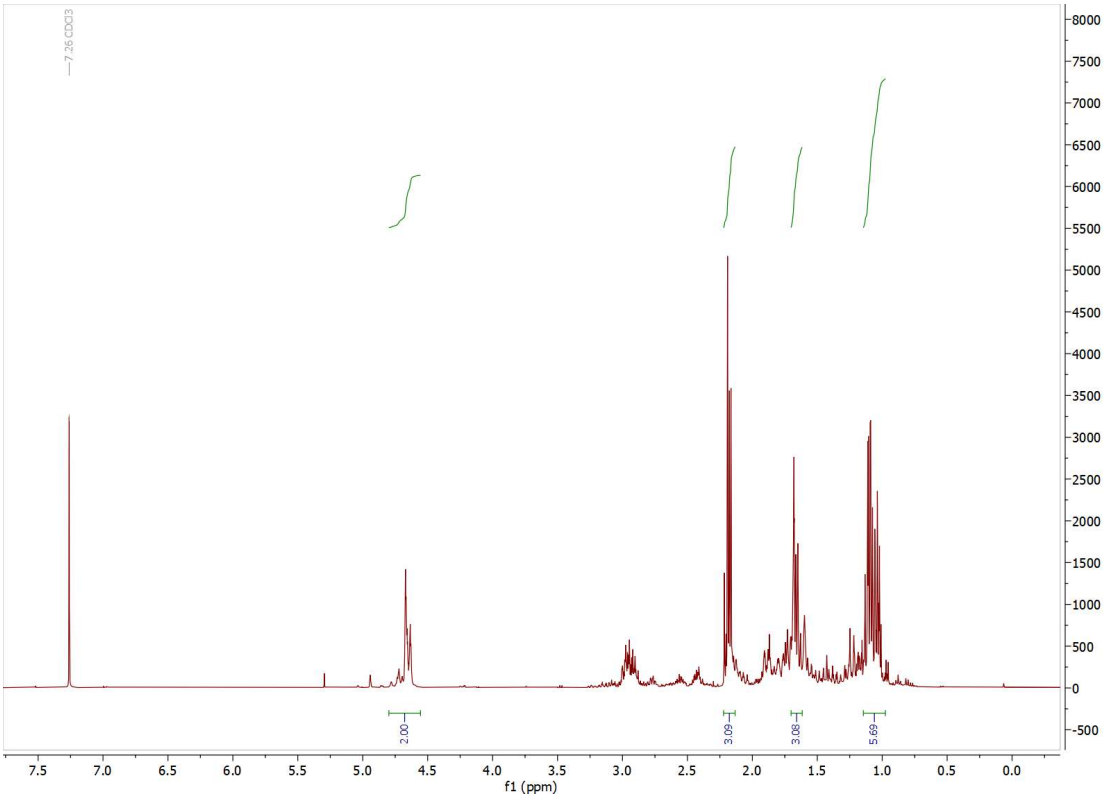


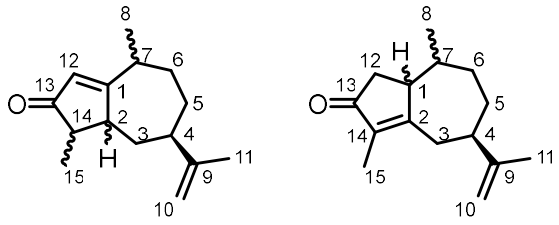

8
12
7
6
13
1
5
O
2
3
4
14
H
11
9
10
8
H
12
7
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13
1
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O
2
3
4
14
11
9
10

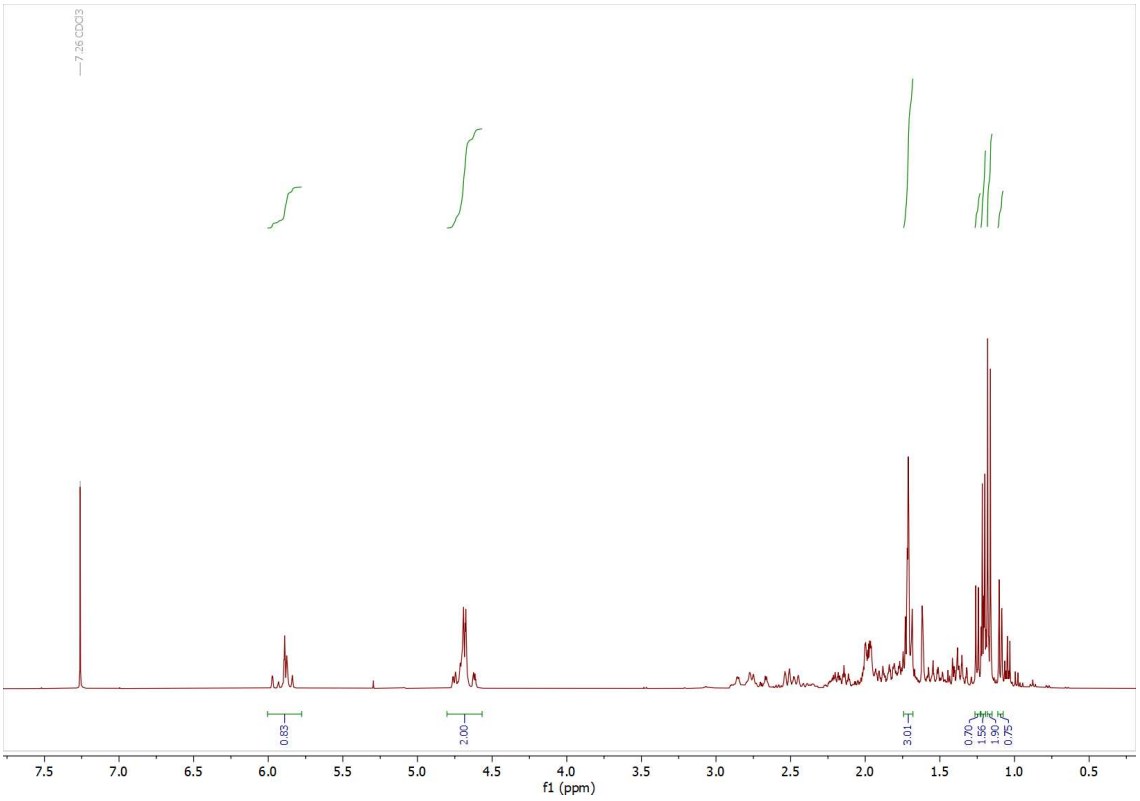

7.26 CDCl3
0.82
2.00
3.20
2.03
0.86
0.49
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

Appendix 13: **^{1}H-NMR spectrum of diketone 2.61, enone 2.57 and 2.62.**

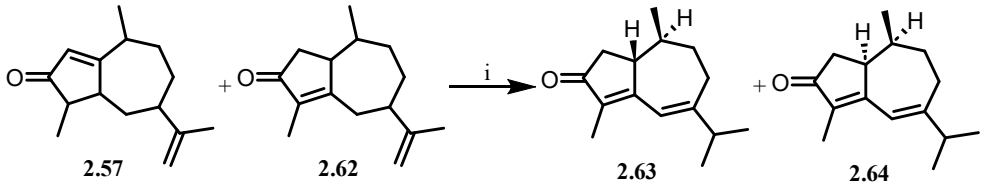





8
12
7
6
13
1
O
5
14
2
3
4
H
11
15
9
10
8
12
H
7
6
13
1
O
5
14
2
3
4
11
15
9
10


7.26 CDCl3
0.83
2.00
3.01
0.70
1.56
1.90
0.75
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

Appendix 14: **Attempted IMDA reaction of 2.57 and 2.62.**



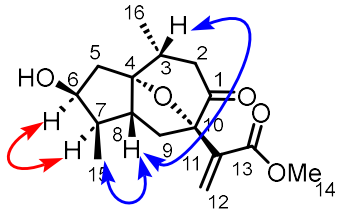
2.57 **2.62** **2.63** **2.64**

Entry	conditions (i)	Result
1[a]	10 eq. TMSCl, 10 eq. Et_3N, 10 eq. $ZnCl_2$, toluene, 160 °C, 18 h	complex
2	10 eq. TMSCl, 10 eq. Et_3N, 10 eq. $ZnCl_2$, benzene, 85 °C, 5 h	complex
3	10 eq. TMSCl, 10 eq. Et_3N, toluene, 120 °C, 5 h	n.r.
4	5 eq. TESCl, 2 eq. LHMDS, THF, –78 °C, 1 h	n.r.
5	1 eq. TESOTf, 30 eq. NaH, benzene, 85 °C, 1 h	n.r.
6	10 eq. TMSOTf, 30 eq. NaH, benzene, 85 °C, 1 h	complex
7	5 eq. TMSOTf, 5 eq. Et_3N, DCM, RT, 2 h	complex
8	11 eq. Ac_2O, 146 eq. $ZnCl_2$, benzene, RT, 1 h	n.r.
9	11 eq. Ac_2O, 146 eq. $ZnCl_2$, benzene, RT, 18 h	decomposed
10	2.5 eq. $TMSNTf_2$, 1.5 eq. Et_3N, benzene, 85°C, 18 h	complex
11	5 eq. $TMSNTf_2$, 4.5 eq. Et_3N, toluene, 110 °C, 1 h	21% **2.63**, 12% **2.64**

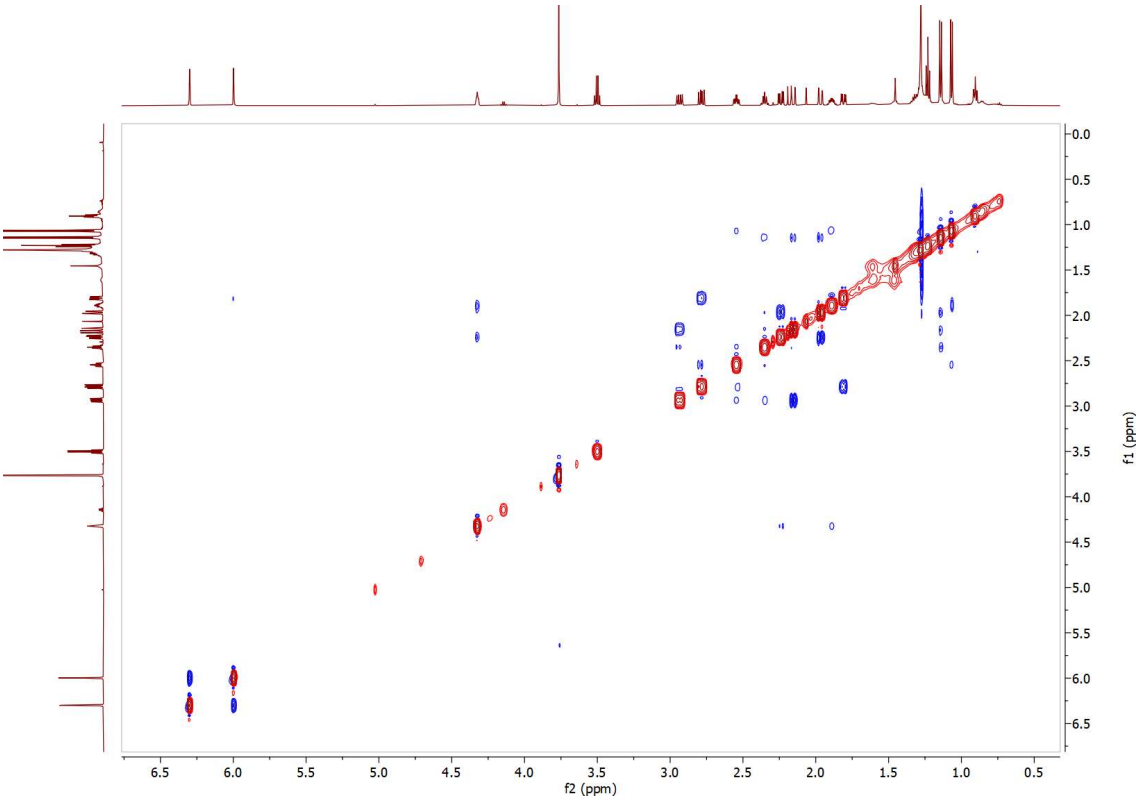
[a] In a sealed tube.

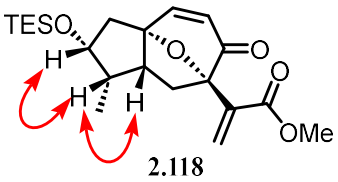
Appendix 15: **NOESY spectrum of compound 2.118 and 2.120.**

The configuration of compound **2.117** and **2.119** was confirmed from the correlations in the NOESY spectrum of its derivative **2.120**.

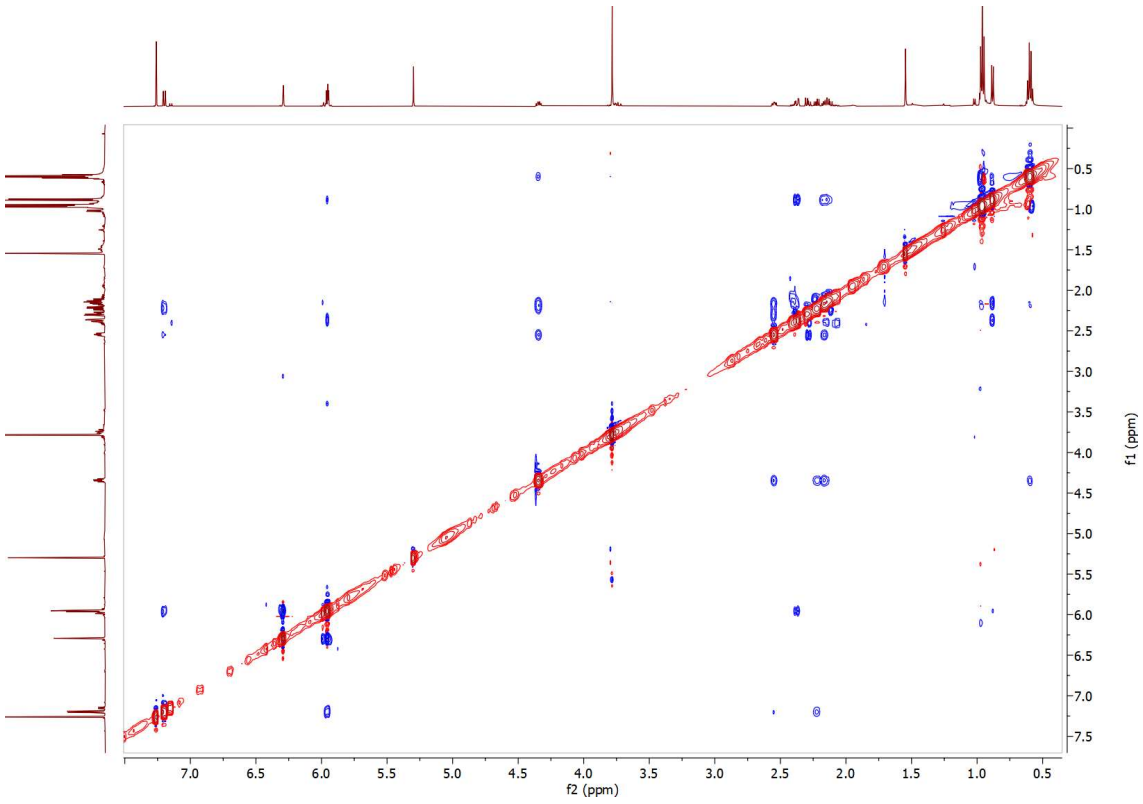


2.120

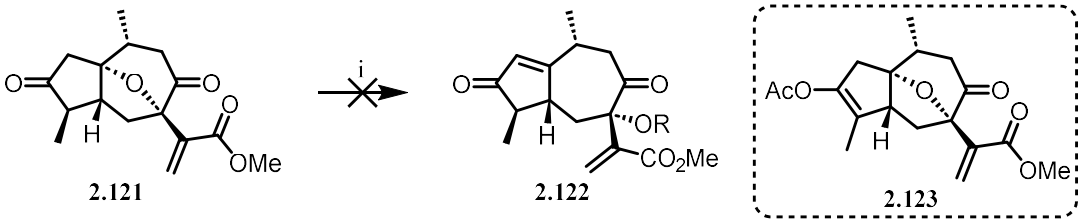




2.118



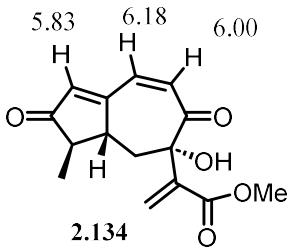
Appendix 16: **Attempted oxa-bridge cleavage of diketone 2.121 into enone 2.122.**



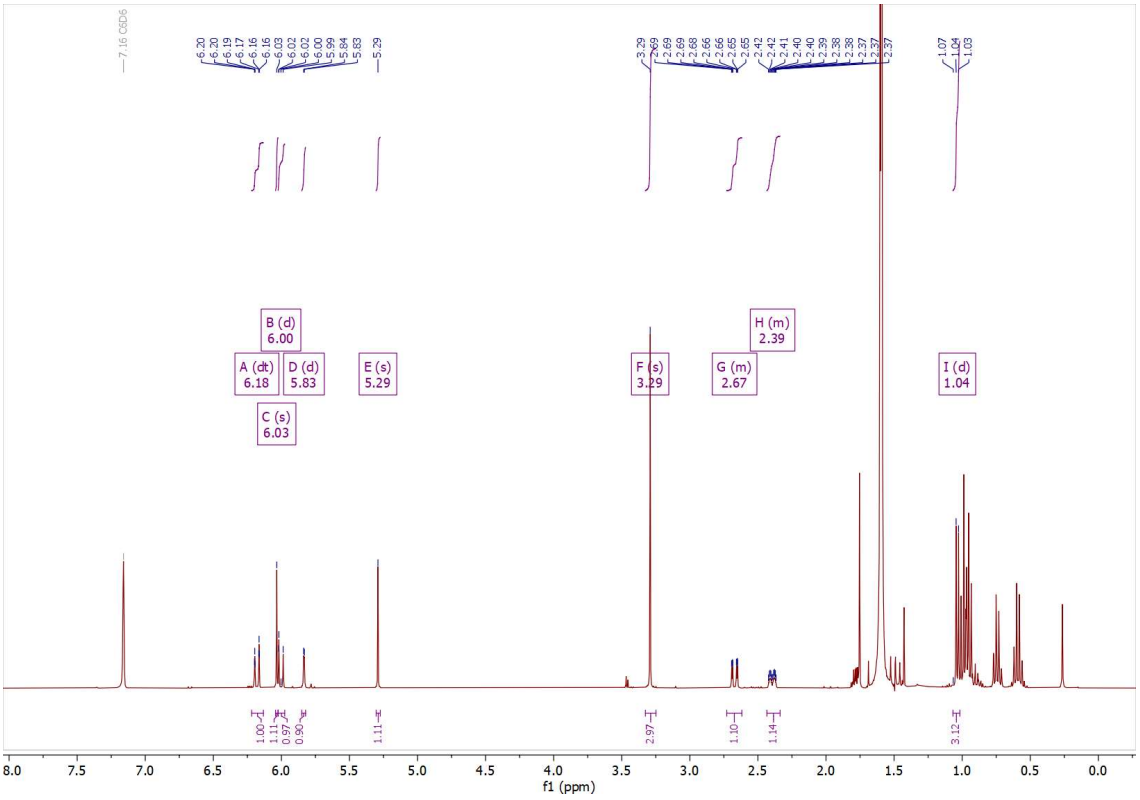
2.121 2.122 2.123

Entry	conditions (i)	Result
1	1 eq. LHMDS, THF, –78 °C	n.r.
2	3 eq. LHMDS, THF, –78 °C to RT	decomposed
3	5 eq. NaOMe, MeOH, RT	n.r.
4	5 eq. NaOMe, MeOH, 70 °C	decomposed
5	50 mol% DBU, DCM, RT	n.r.
6	75 mol% BF_3•OEt_2, DCM, 0 °C	n.r.
7	1 eq. *p*-TsOH, dioxane, 60 °C	n.r.
8	4 eq. *p*-TsOH, dioxane, 60 °C	n.r.
9	3 eq. TMSOTf, 1.2 eq. LHMDS, THF, –78 °C	complex
10	3 eq. TBSOTf, 5 eq. DBU, THF, RT to 70 °C	n.r.
11	8 eq. Et_3N, 4 eq. Ac_2O, THF, 70 °C	n.r.
12	1 eq. PPTS, 5 eq. Ac_2O, toluene, 120 °C	decomposed
13	10 eq. $ZnCl_2$, Ac_2O (as solvent), RT	n.r.
14	10 eq. $ZnCl_2$, Ac_2O (as solvent), 80 °C	57% of **2.123**

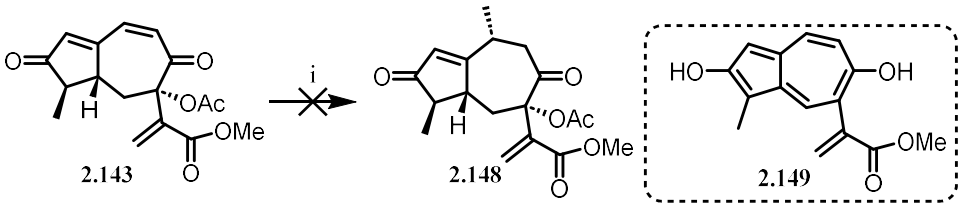
Appendix 17: **^{1}H NMR spectrum of reaction intermediate 2.134.**



2.134

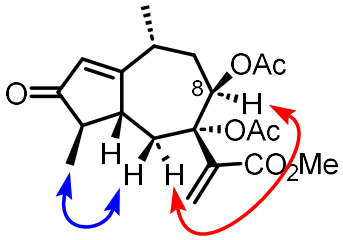


Appendix 18: **Attempted methyl addition to dienone 2.143 leading to enone 2.148.**

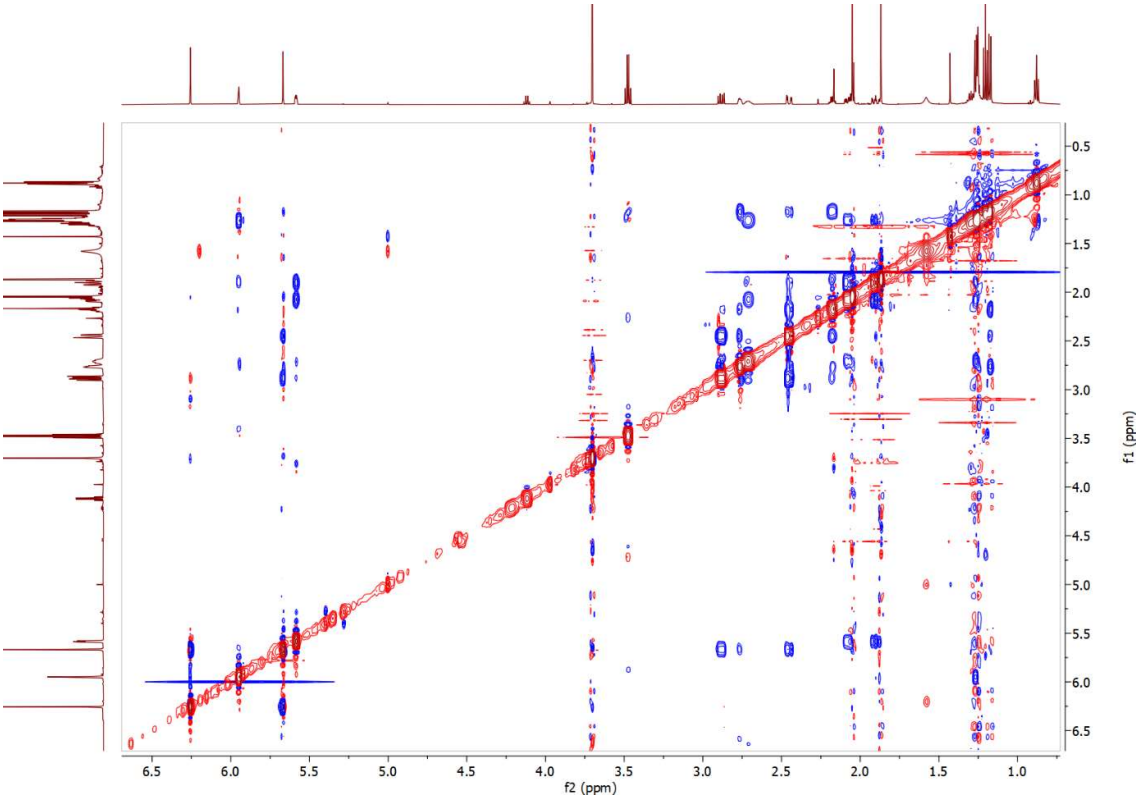


Entry	conditions (i)	Result
1	1 eq. Me_2CuLi, THF, 0 °C	**2.143** and **2.149**
2	2.5 eq. Me_2CuLi, THF, 0 °C	**2.149**
3	1 eq. $CuBr•SMe_2$, 1 eq. TMSCl, 2 eq. MeLi, THF, 0 °C	n.r.
4	1 eq. CuI•LiCl, 1 eq. TMSCl, 2 eq. MeLi, THF, 0 °C	n.r.
5	1 eq. Me_2CuLi, 1 eq. $BF_3•OEt_2$, THF, –78 °C	decomposed
6	1 eq. MeMgBr, DCM, 0 °C	decomposed

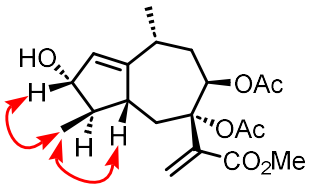
Appendix 19: **NOESY spectrum of compound 2.156.**



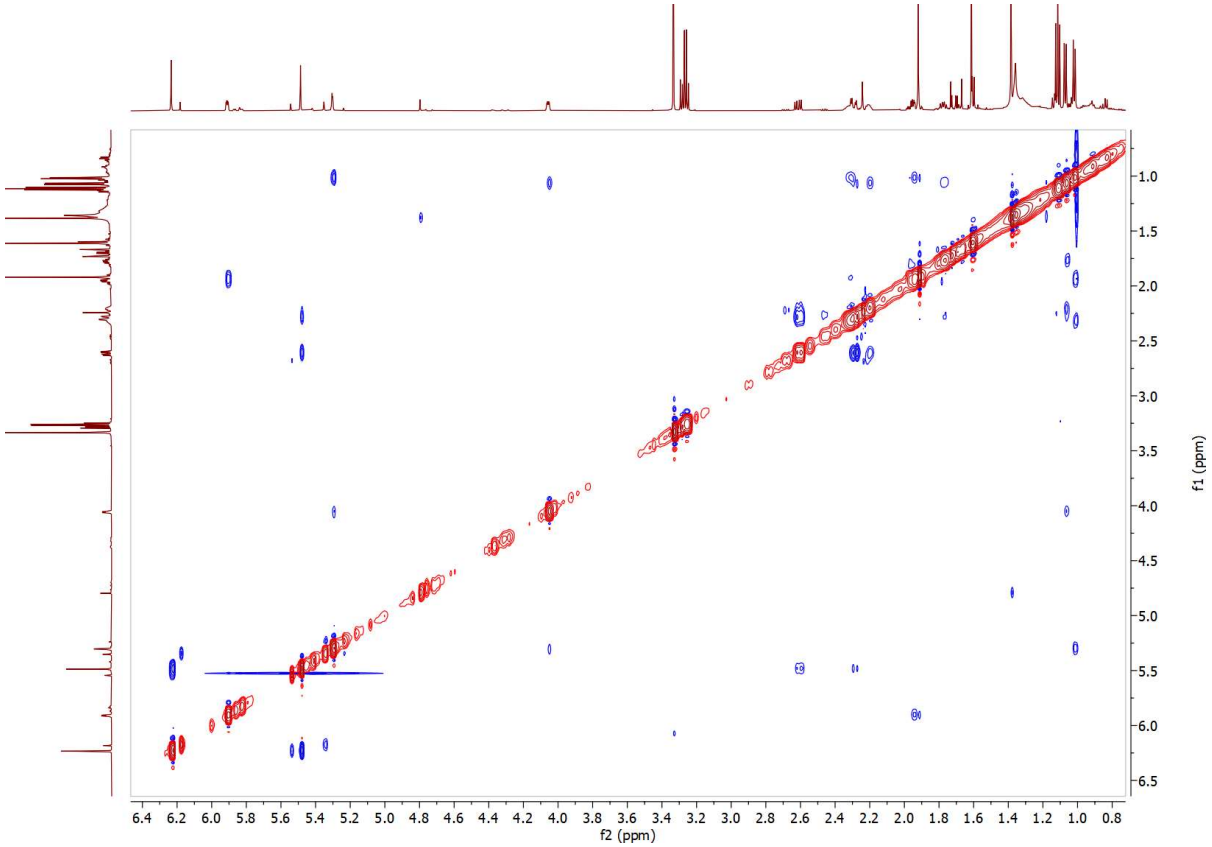
2.156
Key NOE correlations



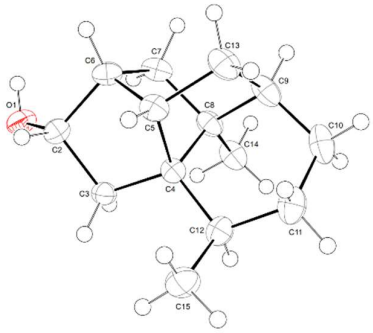
Appendix 20: **NOESY spectrum of compound 2.160.**



2.160
Key NOE correlations

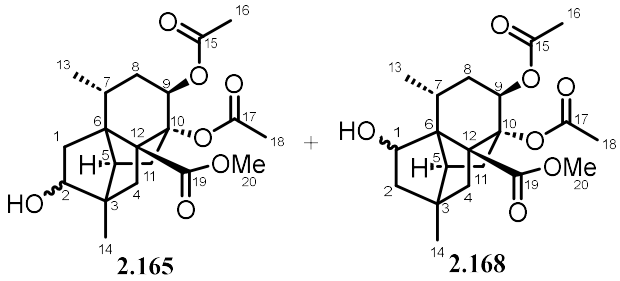


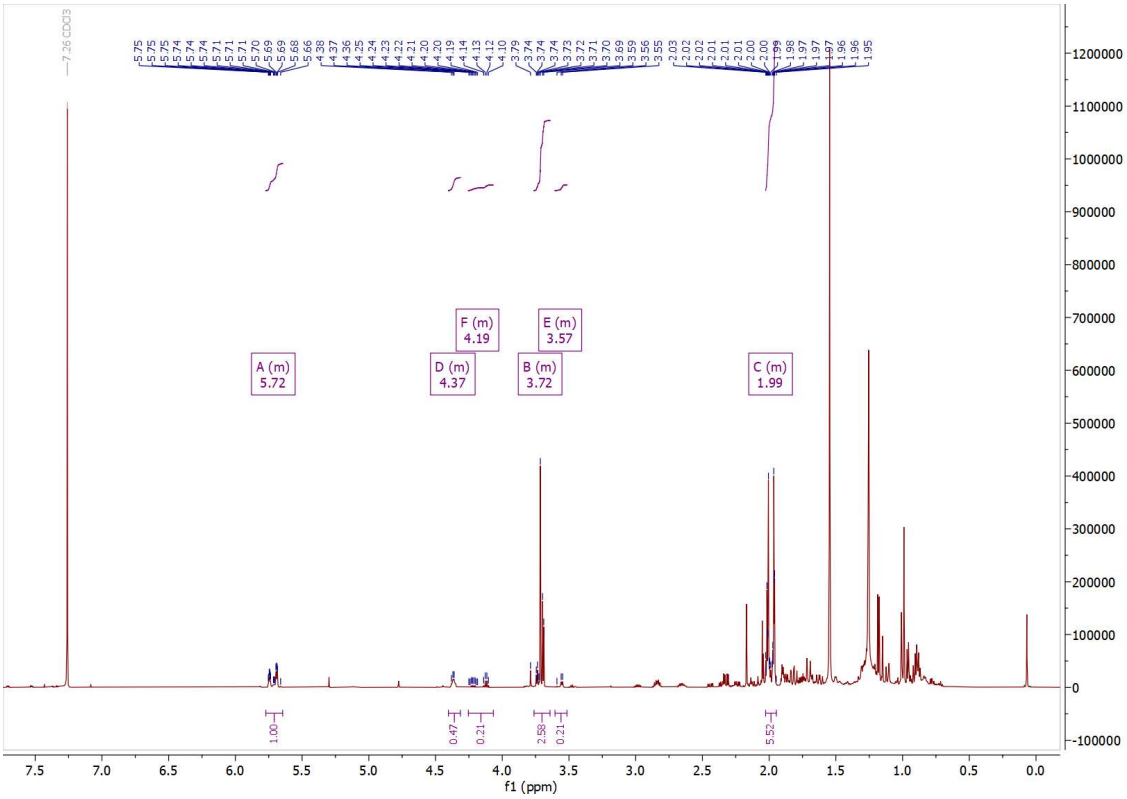
Appendix 21: **Single crystal X-ray data for alcohol 2.56**



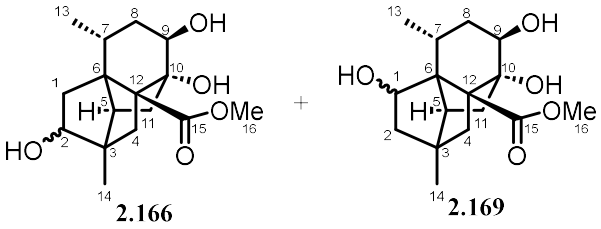
Empirical formula	C14 H22 O
Formula weight	206.33
Temperature	150 K
Wavelength	1.54184Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 11.65800(10) Å α= 90°. b = 13.89720(10) Å β= 90°. c = 21.91580(10) Å γ = 90°.
Volume	3550.66(4) $Å^3$
Z	12
Density (calculated)	1.158 Mg/m^3
Absorption coefficient	0.533 mm^{-1}
F(000)	1368
Crystal size	0.22 x 0.11 x 0.05 mm^3
Theta range for data collection	3.766 to 76.200°.
Index ranges	-14<=h<=14, -17<=k<=17, -26<=l<=27
Reflections collected	81289
Independent reflections	7412 [R(int) = 0.036]
Completeness to theta = 76.200°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.97 and 0.80
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7412 / 0 / 407
Goodness-of-fit on F^2	1.0011
Final R indices [I>2sigma(I)]	R1 = 0.0291, wR2 = 0.0773
R indices (all data)	R1 = 0.0305, wR2 = 0.0787
Absolute structure parameter	-0.05(4)
Largest diff. peak and hole	0.07 and -0.07 $e.Å^{-3}$

Appendix 22: **^{1}H-NMR spectra of alcohol 2.165 and 2.168.**





Appendix 23: **^{1}H-NMR spectra of alcohol 2.165 and 2.168.**



2.166 + **2.169**

