Rhodium-Catalysed [(3+2)+2] Carbocyclisation of Heteroatom-Substituted Alkenes and Synthetic Studies Towards (+)-Repin

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Abstract

The stereoselective construction of fused 5,7-bicycles has attracted considerable attention due to the ubiquity of this motif in complex biologically active sesquiterpene lactones (dehydrocostus lactone, helenalin). Transition metal-catalysed carbocyclisation reactions represent a highly attractive approach towards the construction of functionalised cyclic and polycyclic molecules. Generation of 5- and 7-membered rings from strained 3-membered cycles has emerged as a particularly effective strategy, which is complementing more traditional pericyclic reactions. The description of the transition metal-catalysed carbocyclisation reactions of alkylidenecyclopropanes (ACPs) is provided in the introductory review, which seeks to highlight the evolution of these processes and their application in the context of the construction of 7-membered rings. Despite the numerous advantages that are afforded by this approach, the methods, that allow the synthesis of the suitably functionalised carbocycles for the synthesis of complex natural products, are still rare.

Chapter 2 describes our work on the cycloaddition reactions of functionalised olefins, which resulted in the development of highly regio- and diastereoselective rhodium-catalysed [(3+2)+2] carbocyclisation of vinyl silanes with various monosubstituted alkynes. The transformation provides silylated *cis*-fused 5,7-bicyclic systems, which can be further modified in a number of ways. We have demonstrated that selective oxidation of the silyl group affords C6 hydroxylated 5,7-bicycles – a motif reminiscent of guaianolide and pseudoguaianolide natural products. We anticipate that the methodology outlined herein will find significant application in target directed synthesis.

Chapter 3 provides an account of our synthetic efforts towards guaianolide (+)-repin. Rhodium-catalysed [(3+2)+2] carbocyclisation was successfully employed for the construction of the *cis*-fused 5,7-bicyclic system at the core of the molecule. In the course of these studies we developed an effective strategy for the functionalisation of the 7-membered ring through a series of oxidative transformations. The lactone moiety was introduced *via* substrate-controlled radical reaction of bromohydrin with silyl ketene acetal and constitutes the first application of these reaction conditions to bromohydrins for the direct synthesis of lactones. We believe that our strategy towards the tricyclic core of repin could also find application in related natural products, providing a general entry to the guaianolide family of compounds.

Acknowledgements

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Chapter 3: Total Synthesis of Repin

List of Abbreviations

Å	angstrom
Ac	acetyl
acac	acetylacetonato
ACP	alkylidenecyclopropane
AIBN	2,2`-azobis(2-methylpropionitrile)
AN	acrylonitrile
APT	attached proton test
Ar	aryl
bipy	bipyridine
Bn	benzyl
^{n}Bu	*n*-butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl
c	concentration
°C	degrees Celsius
cod	1,5-cyclooctadiene
mCPBA	3-chloroperbenzoic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
δ	chemical shift
DBN	1,5-diazabicyclo[4.3.0]non-5-ene

DFT	density functional theory
DIBAL-H	di-*iso*-butylaluminium hydride
DIPEA	*N*,*N*-di-*iso*-propylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
ds	diastereoselectivity
E	entgegen
ee	enantiomeric excess
ESI	electrospray ionisation
eq.	equation
Et	ethyl
equiv.	equivalent
FTIR	Fourier transform infrared spectroscopy
EWG	electron withdrawing group
g	gram
GC	gas chromatography
h	hours
Hex	hexyl

HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant
L_n	ligand set
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	molar
M^n	metal with an oxidation state n
MCP	methylenecyclopropane
Me	methyl
mg	milligram
MHz	megahertz
mL	millilitre
mmol	millimol
MOM	methoxymethyl
MS	molecular sieves
NHC	N-heterocyclic carbene
N	normal
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine

NMO	*N*-methylmorpholine-*N*-oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	nucleophile
PDC	pyridinium dichromate
Ph	phenyl
pin	pinacolato
pKa	logarithmic acid dissociation constant
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulphonate
Py	pyridine
^{i}Pr	*iso*-propyl
^{n}Pr	*n*-propyl
RT	room temperature
SOMO	singly occupied molecular orbital
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TES	triethylsilyl

THF	tetrahydrofuran
TIPS	tri-*iso*-propylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	toluenesulfonyl
UV	ultraviolet
Z	zusammen
$[\alpha]_D^t$	specific rotation at temperature *t* and wavelength of sodium D line
μL	microlitre

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Chapter 1

Transition Metal-Mediated Synthesis of 5- and 7-Membered Carbocycles from Methylene- and Alkylidenecyclopropanes

1.1. Introduction

Transition metal-catalysed carbocyclisation reactions have gained increased attention in recent years as an important class of transformations that facilitate selective and efficient construction of cyclic structures that are difficult to access in other ways.[1] These reactions usually employ even-numbered unsaturated π-components such as alkenes, alkynes and dienes for the synthesis of 4-, 6,- or 8-membered rings but require odd-numbered building blocks for the preparation of 5- or 7-membered carbocycles. One of the strategies employed in the latter case relies on the ability of transition metals to oxidatively insert into strained three-membered rings. The strain energy contained within a cyclopropane ring is 27.5 kcal/mol compared to its acyclic counterpart propane. Further increase of the strain energy can be obtained by changing hybridisation state of one of the carbon atoms to sp^2, as in methylenecyclopropane (**1.1**) (MCP) – 40.9 kcal/mol (Fig. 1.1). This high ring strain energy is responsible for the unique properties that MCPs and alkylidenecyclopropanes (ACPs) possess in the presence of transition metals. Another way to look at the cyclopropane ring is in terms of molecular orbitals. The bonds between carbon atoms in cyclopropane bear a significant p orbital character and hence are suitable for overlap with adjacent π electrons of the double bond, as in the case of vinylcyclopropanes (VCPs), forming a new system with unique properties.[2]

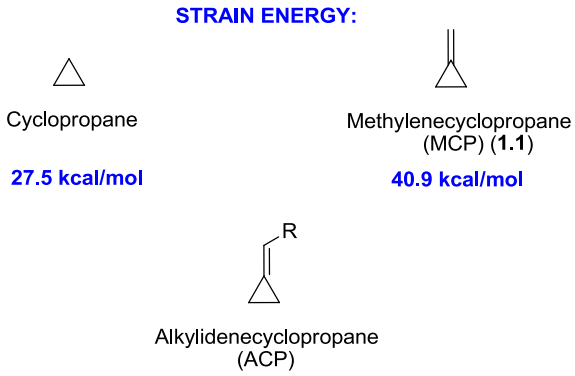
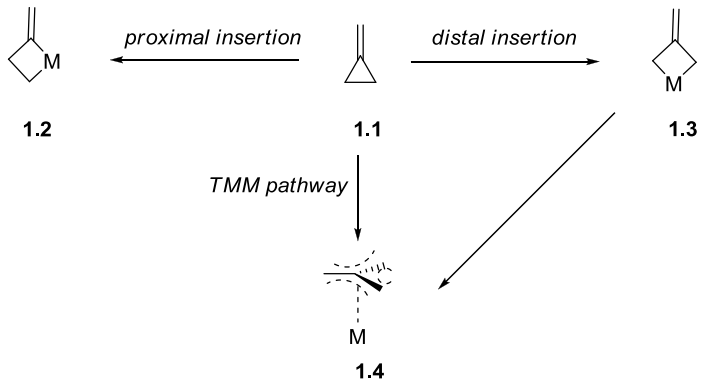


Figure 1.1. Strain energies of three-membered rings.

There are several modes of ring opening of MCP by transition metals. The metal can insert into either the proximal or the distal bond of MCP affording regioisomeric metallacycles **1.2** and **1.3**, respectively (Scheme 1.1). The third possibility is the formation of symmetrical transition metal-trimethylenemethane (TMM) complex **1.4** that can occur either directly or through the intermediacy of **1.3**. Each of the above mentioned species can then serve as a three carbon unit in a variety of cycloadditions.



Scheme 1.1. Possible modes of MCP ring cleavage by transition metals.

There is a vast number of reactions involving MCPs and the chemistry of these useful building blocks has been highlighted in a number of extensive reviews.[3] The main target of this chapter is to show how transition metal-mediated reactions of

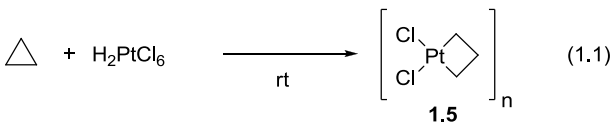
MCPs and ACPs can be applied for the construction of 7-membered carbocyclic rings,- a motif, which is often difficult to access by other means. This area of application of MCPs and ACPs is relatively new and relies heavily on the knowledge gained earlier. Therefore, the first half of the chapter will provide the necessary background on the carbocyclisation chemistry of MCPs and ACPs in the presence of transition metals by highlighting the early works that contributed most to the understanding of the mechanisms and the scope of these reactions. Carbocyclisation reactions of vinylcyclopropanes (VCPs) will not be covered in this review because VCPs constitute a distinctively different class of compounds with its own unique mode of reactivity.[4,5]

1.2. Methylenecyclopropanes

1.2.1. First Investigations: Intermolecular Cycloaddition and the Nature of Reactive Species

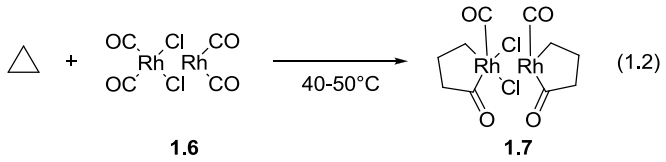
1.2.1.1. Metal Insertion into Simple Cyclopropanes

Transition metal-mediated chemistry of strained 3-membered rings can be dated back to 1955, when an important observation was made by Tipper, who discovered that when a dilute solution of chloroplatinic acid in acetic anhydride was treated with cyclopropane, a brown solid with the empirical formula $PtCl_2C_3H_6$ readily precipitated.[6] This complex was later shown to be a chloride-bridged polymer built from dichloro(trimethylene)platinum(IV) (**1.5**) (eqn. 1.1).[7]



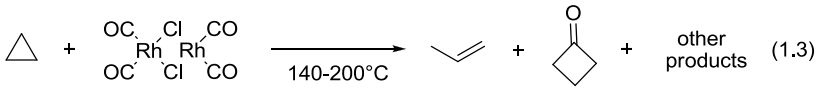
1.5 (1.1)

The ability of transition metals to insert into cyclopropane ring was also demonstrated by Wilkinson *et al.* Dicarbonylchlororhodium(I) dimer (**1.6**) was used to affect ring cleavage, and the product of the reaction was dimeric complex **1.7** (eqn. 1.2).[8]



1.6 **1.7**

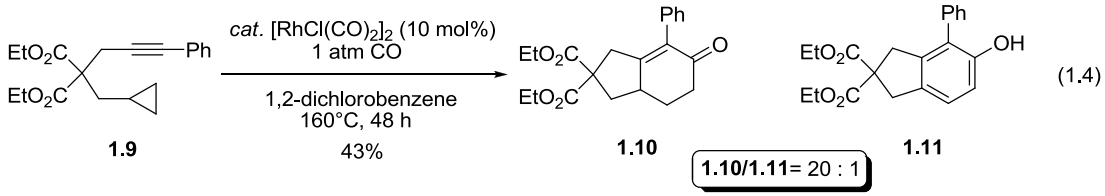
When cyclopropane was treated with a catalytic amount of **1.6** at much higher temperatures (140-200°C) under CO pressure a complex mixture of products was obtained. The main component was propylene, which is the isomerisation product of cyclopropane resulting from the β-hydride elimination of the metallacyclobutane. Trace amounts of cyclobutanone (**1.8**) could also be detected, which was presumably formed from **1.7** in a reductive elimination reaction (eqn. 1.3).[9]



1.6 up to 51% **1.8** up to 4%

The tendency of metalacyclobutanes to undergo β-hydride elimination forming alkenes was also reported for platinum complexes.[10] This feature has resulted in a limited number of methodologies employing simple cyclopropanes. Successful examples involve intramolecular reactions where a π-component coordinates to the metal and undergoes insertion reaction prior to β-hydride elimination. For example, this was the principle underlying the synthesis of bicycle[4.3.0]nonenones from 4-pentynyl cyclopropanes developed by Narasaka and Koga.[11] Treatment of **1.9** with dicarbonylchlororhodium(I) dimer (**1.6**) in 1,2-dichlorobenzene at 160°C under CO

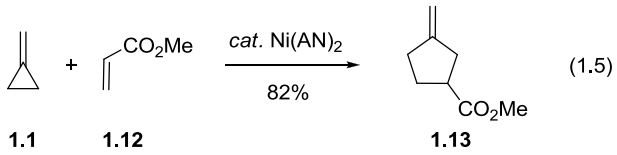
atmosphere resulted in formation of cyclohexanone **1.10** in moderate yield accompanied by trace amounts of oxidation product **1.11** (eqn. 1.4).



(1.4)

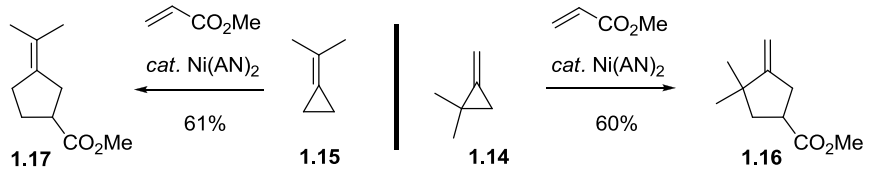
1.2.1.2. Nickel-Catalysed [3+2] Cycloaddition of Methylenecyclopropanes

On the contrary to the metallacycles derived from simple cyclopropanes, metallacycles formed by metal insertion into MCP ring do not undergo β-hydride elimination easily. This makes it possible to intercept these intermediates by various π-components. The first example of the use of MCP as a three-carbon synthon in transition metal-catalysed carbocyclisation was reported by Noyori *et al.* in 1970.[12] MCP **1.1** was treated with an excess of methyl acrylate (**1.12**) in the presence of bis(acrylonitrile)nickel(0) to furnish **1.13** in 82% yield (eqn. 1.5).



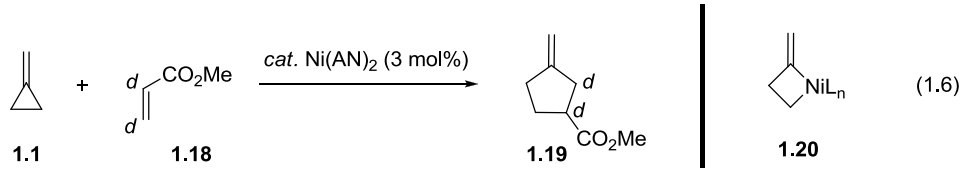
(1.5)

The initial assumption that the reaction proceeds through the intermediacy of the Ni-TMM complex was ruled out by the authors based on the results of reactions of substituted MCPs. When subjected to the nickel catalyst in the presence of methyl acrylate, 2,2-dimethylmethylenecyclopropane (**1.14**) and isopropylidene-cyclopropane (**1.15**) afforded cyclopentanes **1.16** and **1.17** respectively (Scheme 1.2). If a TMM complex were involved as the intermediate, these two reactions should give the same adduct or an identical mixture of isomers.

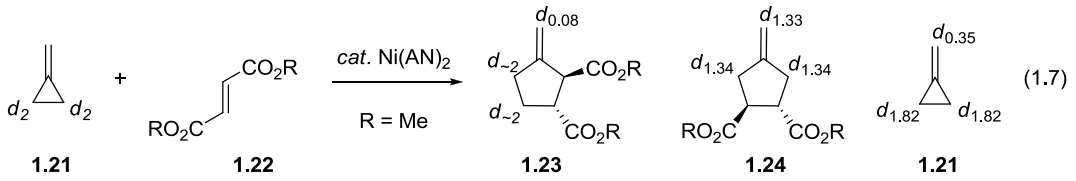


Scheme 1.2. Selective reactions of substituted MCPs.

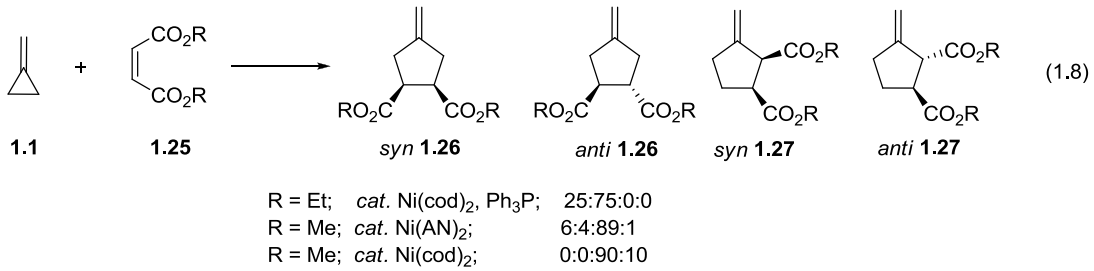
Later deuterium labelling experiments were conducted in order to determine whether a proximal or distal cyclopropane bond cleavage was operating. Reaction of **1** with methyl 2,3-dideuteroacrylate (**1.18**) in the presence of $Ni(AN)_2$ afforded cycloadduct **1.19** in 70% yield (eqn. 1.6). The positions of deuterium labels allowed to establish unambiguously that a proximal bond cleavage with the formation of **1.20** operated in this case.[13]



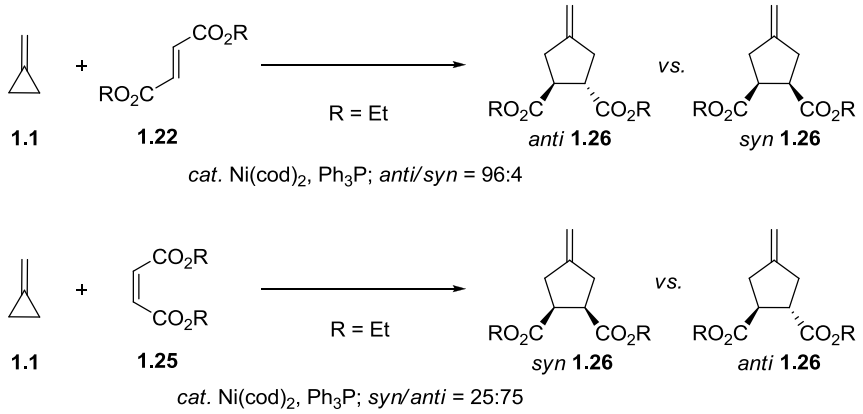
However, it must be said that the mode of ring cleavage seems to be strongly dependent on the nature of reacting olefin, since when a 1,2-disubstituted alkene was employed, it was found that a competing TMM pathway was also important.[14] When deuterated MCP **1.21** was reacted with fumarate **1.22** (R=Me) in the presence of $Ni(AN)_2$, a 38:62 mixture of cycloadducts **1.23** and **1.24** was formed (eqn. 1.7). The first compound corresponded to the proximal cleavage of the cyclopropane and its deuterium atoms were mainly located on two original carbon atoms. Product **1.24**, on the other hand, had deuterium atoms completely scrambled over three carbon atoms indicating that the cleavage of cyclopropane made all carbon atoms equivalent. Some deuterium scrambling in the recovered starting material was also observed suggesting some sort of equilibrium between MCP and ring opened TMM-species.



Additionally, the exact nature of the nickel catalyst is important in determining the product distribution. A good example is the reaction of MCP **1.1** with maleates **1.25**: in the presence of $Ni(cod)_2/PPh_3$[15] only the products resulting from the distal ring opening are formed, whereas using $Ni(AN)_2$ leads to a mixture of both distal and proximal products[13], and only proximal products are formed when $Ni(cod)_2$ is used (eqn. 1.8).[16]

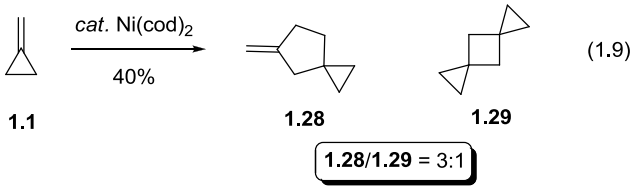


The last equation also demonstrates the general lack of stereospecificity in the cycloadditions of maleates and fumarates, which seems to be the subject to thermodynamic control. For example, when dialkyl fumarate **1.22** (R=Et) was treated with $Ni(cod)_2$ and triphenylphosphine in the presence of MCP **1.1**, carbocyclisation product **1.26** was formed as a mixture of *anti/syn* isomers in a ratio of 96:4. When dialkyl maleate **1.25** (R=Et) was subjected to the same conditions, cycloaddition product **1.26** was isolated as a *syn/anti* mixture in a 1:3 ratio, with the expected *syn* isomer now being the minor component (Scheme 1.3).[15] The isomerisation of starting material could take place prior to the carbocyclisation process. However, Noyori has observed only 1.5% isomerisation of dimethyl maleate into fumarate when the starting material was recovered from a $Ni(AN)_2$-catalysed reaction.



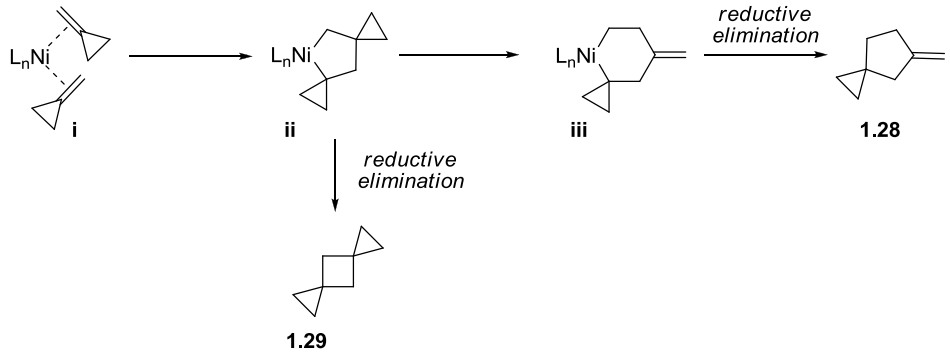
Scheme 1.3. Different stereochemical outcome in cycloadditions of fumarates and maleates.

The reaction mechanism for the nickel-catalysed [3+2] carbocyclisation proposed by Noyori *et al*. involved the formation of a nickelacyclobutane in the initial step (*vide supra*). A different mechanistical hypothesis, which did not involve direct formation of nickelacyclobutane, was proposed by Binger *et al.* In 1972, he reported that upon treatment with $Ni(cod)_2$ at temperatures as low as −15°C, MCP **1.1** could be oligomerised to afford a mixture that predominately consisted of dimers **1.28** and **1.29** (eqn. 1.9).[17]



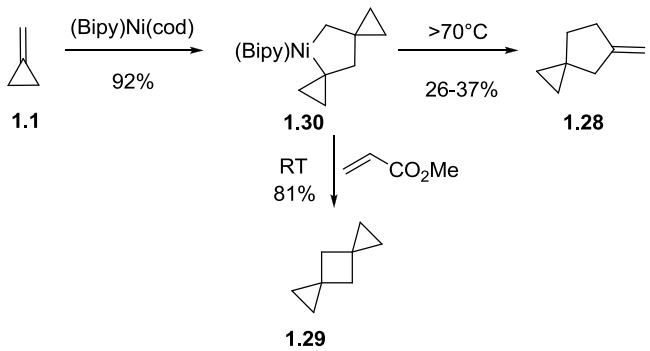
In order to explain these observations it was suggested that both compounds could form *via* initial coordination of two alkenes to the metal centre to give **i** followed by the formation of metallacycle **ii** (Scheme 1.4). Cyclopropylmethyl-butenyl rearrangement of **ii** would then lead to **iii**, which after reductive elimination would yield cyclopentene **1.28**. Premature reductive elimination from intermediate **ii** would

lead to the other observed product – cyclobutane **1.29**.



Scheme 1.4. Alternative mechanism not involving direct insertion into the proximal bond.

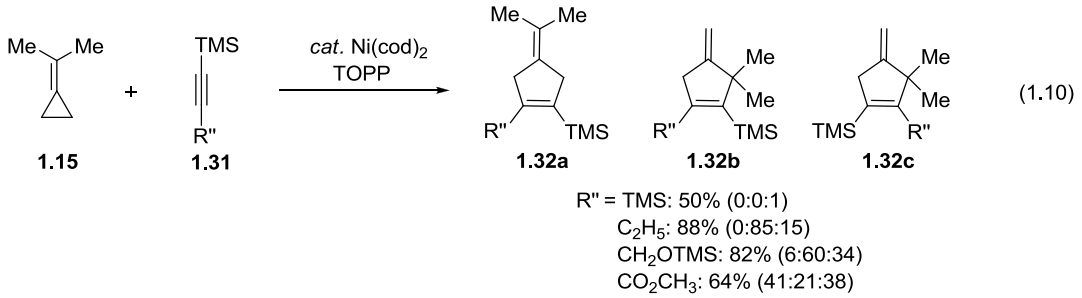
In order to support the above hypothesis, nickel metallacycle **1.30** was synthesised from MCP **1.1** and (2,2'-bipyridine)(1,5-cyclooctadienyl)nickel (Scheme 1.5). The complex was isolated and characterised spectroscopically. It was demonstrated that upon treatment with methyl acrylate, cyclobutane **1.29** was formed *via* reductive elimination. When complex **1.30** was heated neat or in suspension above 70°C, considerable decomposition was observed alongside with the formation of cyclopentane **1.28** in 26-37% yield.[18]



Scheme 1.5. Experimental evidence for the alternative mechanism with Ni catalyst.

Later, in 1985, Binger *et al*. were the first to show that MCPs can also engage in

reactions with alkynes. The reaction was catalysed by $Ni(cod)_2$ modified with (*o*-phenylphenyl)phosphite (TOPP) and afforded 4-methylene-1-cyclopentenes **1.32**.[19] The reaction worked best with alkynylsilanes **1.31** with another substituent R`` being -TMS, -alkyl, $-CO_2Me$ or $-CH_2OTMS$ (eqn. 1.10).



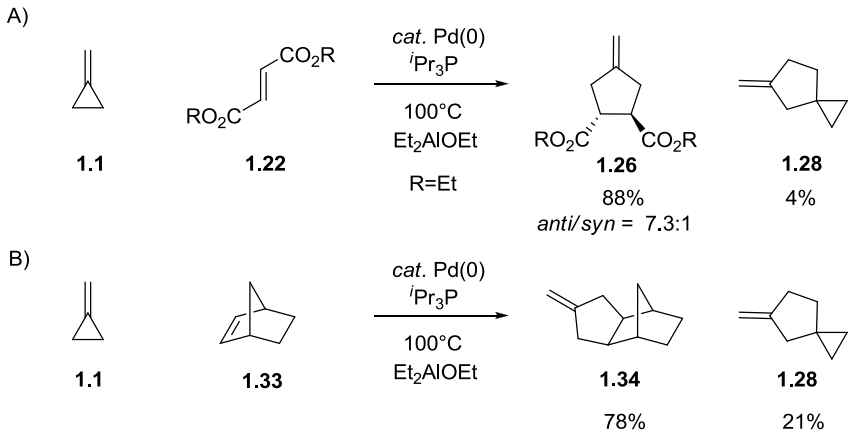
(1.10)

1-Alkynes and dialkylacetylenes were poor substrates because of the side reactions such as cotrimerisation and oligomerisation. Surprisingly, irrespective of the number or type of the substituents in the two reactants, the reaction took place *via* distal bond cleavage of MCP **1.15** giving products **1.32a**, **1.32b** and **1.32c**. This is in contrast with the previously discussed nickel-catalysed cycloaddition of MCP **1.1** and electron-deficient alkenes. There was also a high tendency for the formation of methylenecyclopentanes with the methyl groups at the σ-position to the methylene group (e.g. reaction of **1.15** and **1.31** (R''=CH_2OTMS) afforded **1.32a**/**1.32b**/**1.32c** = 6:60:34). The regioselectivity of the process was generally low and mixtures of regioisomers were formed in the reactions with unsymmetrical alkynes.[19]

1.2.1.3. Palladium-Catalysed [3+2] Cycloaddition of Methylenecyclopropanes

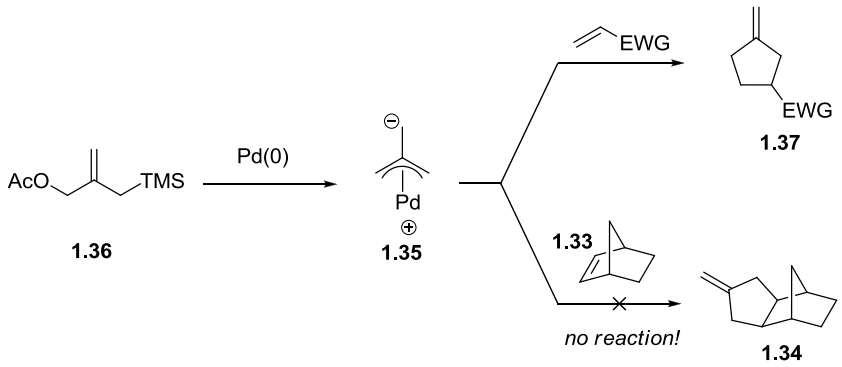
In 1977, Binger and Schuchardt reported that palladium(0) catalysts are also capable of effecting [3+2] cycloaddition of MCP **1.1** and alkenes. For example, the reaction of **1.1** with fumarate **1.22** (R=Et) in the presence of bis(pentanedionato)palladium, triisopropylphosphine and ethoxydiethylaluminum afforded cyclopentene **1.26**

(R=Et) in 88% yield and trace amounts of homodimer **1.28** (Scheme 1.6, A). It is worth noting that the formation of the homodimer was a competing reaction in all cases, with some substrates affording more of the homodimer than of the desired product. Only the products resulting from the distal insertion were observed and experiments with 1-methyl-2-methylenecyclopropane led to the scrambling of the methyl group, which led the authors to assume that the reaction proceeds *via* Pd-TMM complexes.[20]



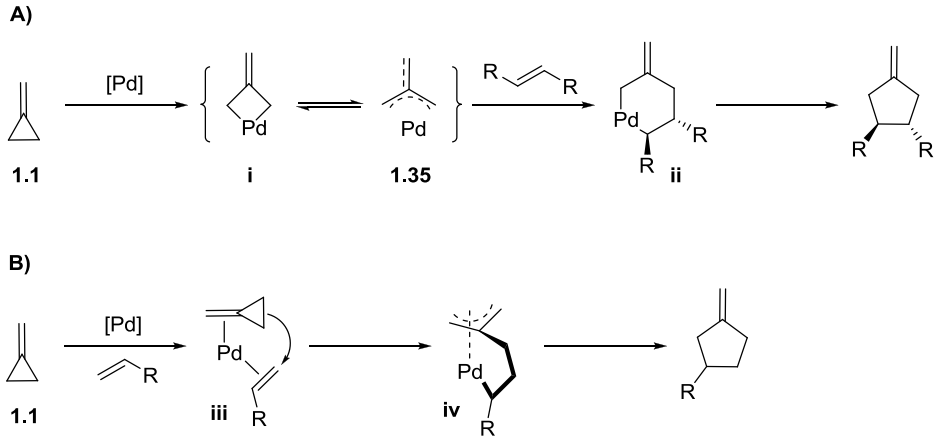
Scheme 1.6. Pd-Catalysed reactions of MCP with electron-rich and electron-poor olefins.

It was also demonstrated for the first time that under palladium catalysis MCP **1.1** can engage in the cycloaddition reaction with electron-rich olefins, such as norbornene (**1.33**) to afford cycloadduct **1.34** in good yield (Scheme 1.6, B). This was in stark contrast with the cycloadditions of Pd-TMM complex **1.35** derived from 2-acetoxymethyl-3-allyltrimethylsilane (**1.36**) that engaged in the reactions only with electron-deficient olefins (Scheme 1.7).[21]



Scheme 1.7. Reactivity of Pd-TMM complex generated from 2-acetoxymethyl-3-allyltrimethylsilane.

This difference led Trost to propose that the Pd-catalysed cycloadditions of MCPs did not involve the formation of the TMM complex but proceeded directly through intermediates **iii** and **iv** (Scheme 1.8, B).[22] Binger opposed this idea by providing a series of experimental evidence for the stepwise process consisting of palladium insertion into the distal bond of the MCP to give **i** and isomerisation to the TMM-like species **1.35** (Scheme 1.8, A).[23]



Scheme 1.8. Proposed modes of reactivity of MCP in Pd-catalysed [3+2] cycloadditions.

1.2.1.4. Summary

The seminal studies mentioned in this section demonstrated that Pd- and Ni-catalysed reactions of MCPs with alkenes and alkynes can serve as convenient and straightforward routes to cyclopentanoids. Different modes of reactivity were observed for Pd and Ni catalysts, with the former delivering the products corresponding to the distal cyclopropane bond cleavage and the latter furnishing products with the selectivity strongly dependant on the nature of the catalyst. "Naked" nickel catalysts (e.g. $Ni(cod)_2$) are more likely to give the products of the proximal cyclopropane bond cleavage, whereas catalysts modified with phosphine ligands will lead to the products of the distal bond cleavage. The intermediacy of the Pd-TMM species in Pd-catalysed cycloadditions of MCPs has caused considerable debate. Experimental work done by Binger *et al.* provided some evidence in support of those intermediate.

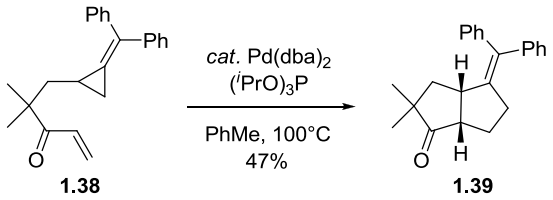
1.2.2. Further Developments: First Intramolecular Examples and Stereochemical Studies

1.2.2.1. Intramolecular [3+2] Cycloaddition of MCPs with Alkenes

A large number of reactions mentioned in the previous section suffer either from the formation of homodimerisation products or from poor regioselectivity. A way to get around these problems was to render reactions *intra*molecular, which would ensure that both reaction components are in close proximity to each other at all times and are aligned in the desired fashion.

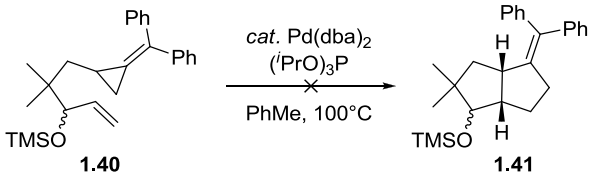
In 1988, Motherwell *et al.* reported the first example of the intramolecular reaction of MCP.[24] Treatment of enone **1.38** with bis(dibenzylideneacetone)palladium and

triisopropyl phosphite at 110°C afforded bicycle **1.39** in 47% (eqn. 1.11). The product is formed by a distal cleavage of the cyclopropane ring by palladium catalyst.



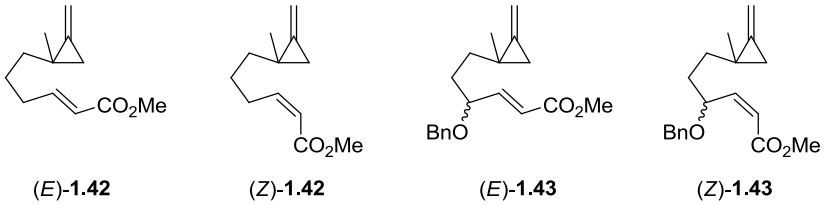
1.38 **1.39** (1.11)

A noteworthy feature is the successful use of an acyclic enone as a π-component, since in the case of *inter*molecular reaction, molecules such as acrolein, which can adopt a *cisoid* conformation, were reported to act as strongly binding ligands for Pd(0) and inhibit its reaction with alkylidene cyclopropane.[25] The electron-deficient nature of the olefin was crucial for the success of the reaction since the substrate **1.40**, possessing a TMS-protected secondary alcohol instead of a ketone, failed to afford cycloadduct **1.41** under identical reaction conditions (eqn. 1.12).[26]



1.40 **1.41** (1.12)

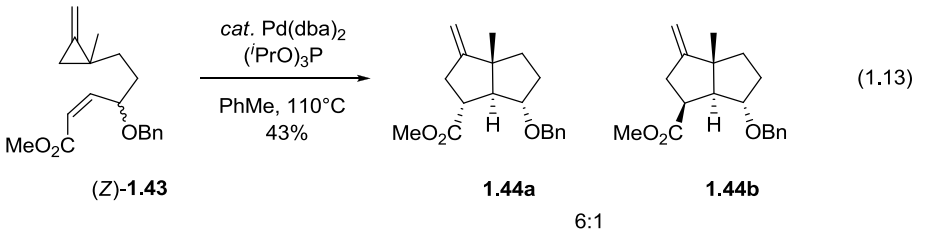
Interesting results were obtained when an EWG was attached to the other end of the double bond as in two isomeric acrylates (*E*)-**1.42** and (*Z*)-**1.42** and their analogues bearing a benzyloxy group in the tether, (*E*)-**1.43** and (*Z*)-**1.43** (Fig. 1.2).



(*E*)-**1.42** (*Z*)-**1.42** (*E*)-**1.43** (*Z*)-**1.43**

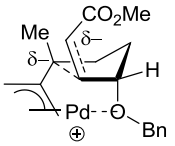
Figure 1.2. Acrylates for the intramolecular [3+2]carbocyclisation.

Both (*E*)-**1.42** and (*Z*)-**1.42** failed to afford any bicyclic products under standard conditions delivering complex mixtures of dienes resulting from the ring opening of MCP. Interestingly, when substrate (*Z*)-**1.43** was subjected to the same reaction conditions, bicyclic adducts **1.44a** and **1.44b** were isolated in 43% yield and 6:1 ratio (eqn. 1.13). Under identical conditions, (*E*)-**1.43** failed to yield any bicyclic products.[27]



(*Z*)-**1.43** **1.44a** **1.44b** 6:1 (1.13)

The authors proposed a model which explained the peculiar effect the benzyloxy group had on the reactivity of (*Z*)-**1.43**. According to their model, an oxidative insertion of palladium into the distal bond of MCP leads to the formation of the palladium-TMM intermediate **1.45** in which the ester group is pointing away from the metal (Fig. 1.3). The ether oxygen then adopts a pseudo-axial orientation in **1.45** and stabilises this intermediate by coordinating to the metal. This interaction also brings the reaction partners together and assists in the formation of cycloadducts.

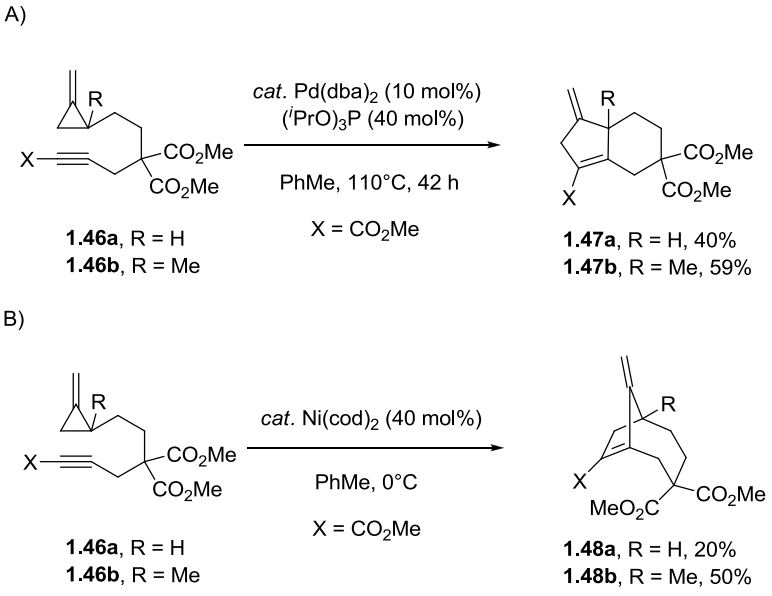


1.45

Figure 1.3. Model involving coordination of benzyloxy oxygen to palladium during reaction.

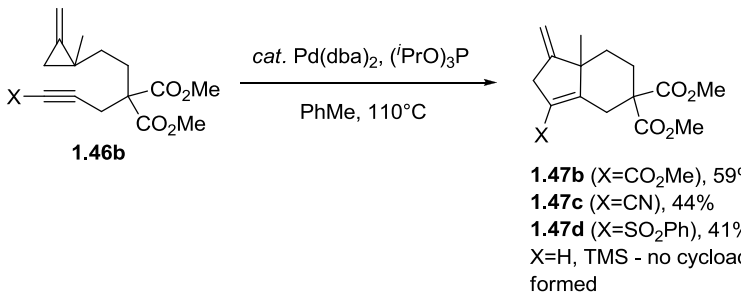
1.2.2.2. Intramolecular [3+2] Cycloaddition of MCPs with Alkynes

Other classes of substrates studied by Motherwell were methylenecyclopropanes possessing an acetylenic moiety. Esters **1.46a** and **1.46b** were treated with a palladium(0) catalyst in the presence of triisopropyl phosphite in toluene at 110°C to afford bicyclic products **1.47a** and **1.47b** in 40% and 59% yield, respectively (Scheme 1.9, A). Once again only the products corresponding to the distal cleavage of MCP were observed under Pd(0) catalysis. Interestingly, the use of the same substrates in a nickel(0)-catalysed reaction resulted in a formation of different cycloadducts **1.48a** and **1.48b** originating through the selective cleavage of the proximal bond of MCP (Scheme 1.9, B).[28]



Scheme 1.9. The influence of the metal nature on the regioselectivity of MCP cleavage.

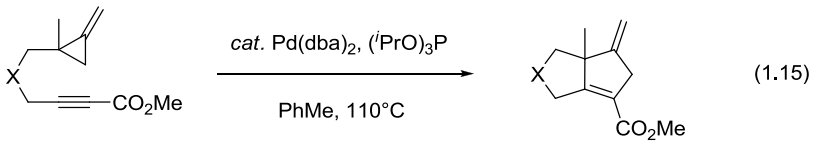
Investigation of the scope of the reaction by Motherwell *et al.* showed an electron-withdrawing group on the alkyne to be necessary for the transformation to take place. Terminal and TMS-protected acetylenes failed to afford desired cycloadducts under these conditions (eqn. 1.14).[29] Interestingly, earlier Lautens *et al.* reported an example of the cycloaddition of -CH_2OH substituted acetylene under identical contidions, which proceeded in 85% yield.[30] This could mean that the absence of reactivity of terminal and TMS-protected olefins has other origins than the simple electronic properties of these groups.



(1.14)

The nature and the length of the tether can play a tremendous role in determining the

reactivity of the substrates in the carbocyclisation reactions. When substrate **1.49a**, possessing an all-carbon tether, was subjected to the Pd-catalysed conditions, cycloadduct **1.50a** was formed in 54% yield (eqn. 1.15). The similar substrate **1.49b** possessing an oxygen atom in the tether delivered a complex mixture of products derived from the opening of methylenecyclopropane to conjugated dienes. Moreover, when the all-carbon tether was extended to 5 carbon atoms no cycloadducts could be isolated probably due to unfavourable transannular interactions on the way to the hydroazulene skeleton.[29]



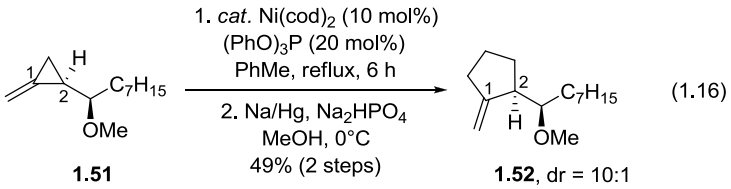
(1.15)

1.49a, X=CH_2
1.49b, X=O

1.50a, X=CH_2, 54%
1.50b, X=O, decomposition

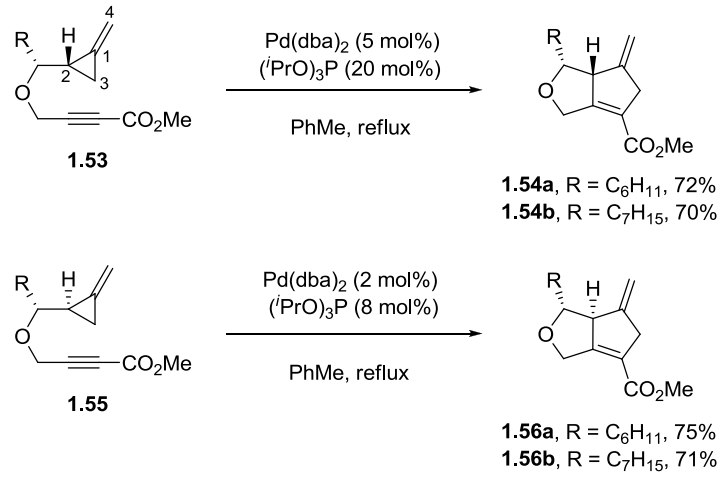
1.2.2.3. Stereochemical Aspects of Metal-Catalysed [3+2] Cycloaddition of MCPs

The question of stereochemical integrity in transition metal catalysed cycloadditions of substituted MCPs was first investigated by Lautens *et al.*[30] When single isomer **1.51** was subjected to phenyl vinyl sulfone in the presence of $Ni(cod)_2$ modified with triphenylphosphite, a mixture of cycloadducts was isolated. Desulfonylation by sodium amalgam in methanol afforded **1.52** in 49% yield over two steps (eqn. 1.16). It was established that a 10:1 mixture of diastereomers at C-2 was produced, which was not in agreement with the previously established mode of MCP ring cleavage by nickel catalysts. If the reaction would take place exclusively at a proximal bond, as expected for nickel, no epimerisation should be observed.



(1.16)

In contrast, palladium catalysts usually react at a distal bond of MCP and epimerisation could be expected in this case *via* interconversion of σ-allyl (or π-allyl) species. However, when single isomers **1.53** and **1.55** were subjected to $Pd_2(dba)_3$ modified with triisopropyl phosphite, intramolecular cycloaddition took place to afford bicycles **1.54** and **1.56** as the only products of the reaction (Scheme 1.10). The reactions proceeded in an identical fashion and were equally stereospecific. X-Ray analysis of the derivative of **1.56a** showed that this cycloaddition was not only stereospecific but proceeded with the overall retention of stereochemistry, suggesting that a mechanism must involve either a stereospecific double inversion or a double retention.

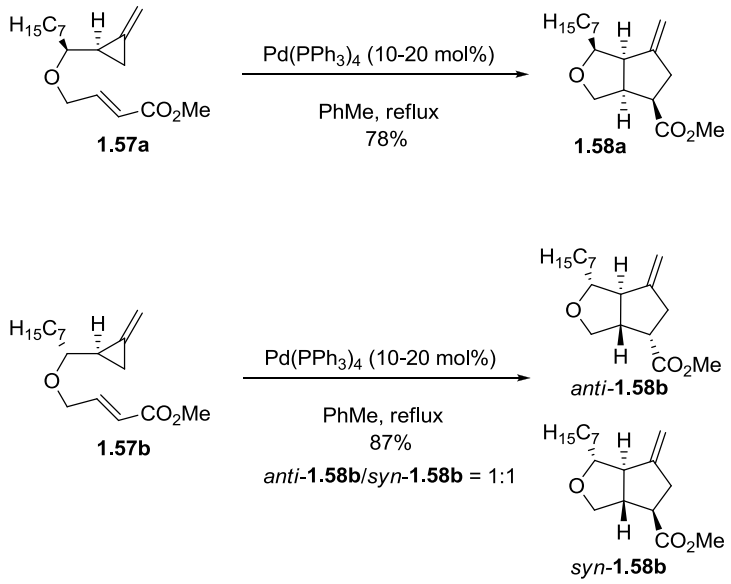


Scheme 1.10. Stereospecific intramolecular cycloaddition.

When compound **1.53** deuterated at C3 was subjected to cycloaddition conditions, complete scrambling between C3 and C4 was observed. Surprisingly, when the reaction was stopped at 18% conversion, no scrambling was observed in the

recovered starting material, indicating that the metal insertion step is irreversible. This is in contrast with the observations made by Noyori (*vide supra*) for the nickel-catalysed intermolecular process.

Further insights into the stereochemical course of intramolecular palladium-catalysed [3+2] cycloadditions were gained by studying acrylates **1.57a** and **1.57b**. Surprisingly, it was established that different diastereomers of the starting material resulted in different stereochemistry at the ring junction (*cis vs. trans*). Thus, when **1.57a** was treated with $Pd(PPh_3)_4$ in refluxing toluene, *cis*-fused cycloadduct **1.58a** was isolated as a single diastereomer in 78% yield (Scheme 1.11). When diastereomeric substrate **1.57b** was subjected to the same reaction conditions, only *trans*-fused products (*anti*-**1.58b** and *syn*-**1.58b**), that are epimeric at EWG bearing carbon, were obtained. The fact that the integrity of the alkene geometry was not preserved in the course of the reaction suggests that an equilibrium was established at some point that allowed the epimerisation at the carbon bearing EWG to occur.[31]



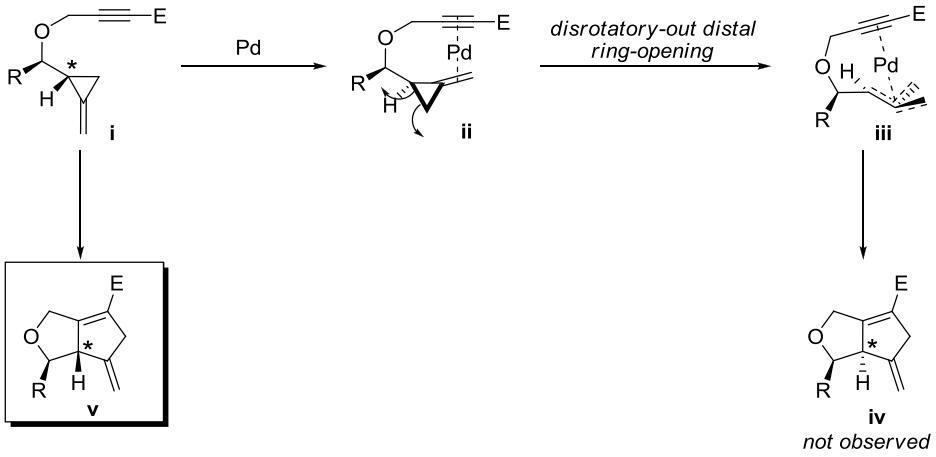
Scheme 1.11. Cis vs. trans fused bicycle formation depending on the stereochemistry of the starting material.

Pd-TMM complex **1.59** or metalacycle **1.60** have been proposed as intermediates during the insertion of Pd into the distal bond of MCP in the course of intramolecular [3+2] cycloaddition (Fig. 1.4).

1.59 **1.60**

Figure 1.4. Proposed intermediates resulting from the insertion of Pd into MCP.

Experiments with the stereochemically defined MCPs have led Lautens *et al.* to an interesting conclusion. The metal insertion into the distal bond of MCP **i** is preceded by the coordination of palladium to the alkyne and the exocyclic methylene group as in **ii**. Based on the literature precedents on the formation of metal-TMM complexes from MCPs, if a Pd-TMM intermediate **iii** was to be involved in the intramolecular [3+2] cycloaddition, it would have to be generated from **ii** in a disrotatory-out ring-opening where the 2,3-σ bond undergoing reaction would bend away from the Pd.[32] The following cycloaddition then would deliver the product **iv** with the net inversion of stereochemistry at C*, which was not observed (Scheme 1.12).



Scheme 1.12. Stereochemical outcome of disrotatory-out ring-opening of MCP by palladium.

Since it is currently accepted that migratory insertion proceeds with a retention of configuration at the migrating carbon atom,[33] the only way to explain the overall retention of the stereochemistry in the performed experiments is to exclude the direct formation of Pd-TMM species in favour of palladocyclobutane **1.60**.

1.2.2.4. Summary

The studies on the intramolecular [3+2] cycloaddition performed by Motherwell, Lautens and others helped to solve several problems associated with the [3+2] cycloadditions previously, such as homodimerisation of MCPs and regioselectivity issues. It was established that intramolecular cycloadditions of MCPs proceed with the retention of the stereochemistry at the cyclopropane ring. Direct formation of Pd-TMM species from MCPs was shown to be unlikely. It was also disclosed that the nature of the tether plays an important role in determining the reactivity of a given substrate. The particular effect a tether will exert on the reactivity seems to be hard to predict theoretically.

1.3. Alkylidenecyclopropanes

1.3.1. First Example

In the previous section the stereochemical aspects of the intramolecular [3+2] cycloaddition were discussed. It must be pointed out that despite the fact that chiral nonracemic MCPs can be successfully employed in these reactions, the preparation of substrates in enantiopure form is not trivial requiring multi-step reaction sequences.[30] This fact has contributed to the development of the intramolecular cycloaddition chemistry of alkylidenecyclopropanes (ACPs), which are achiral and hence more easily accessible. In essence ACPs are MCPs with a substituent moved from the cyclopropane ring to the terminus of the double bond. Early papers describing intermolecular reactions of intermediates of the type **1.61** (Fig. 1.5), still referred to them as MCPs. We will apply the same convention and use the term ACP only in the context of the intramolecular reactions.

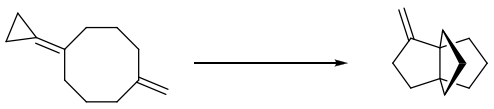
1.61

R^1 = H, Alkyl, Aryl
R^2 = Alkyl, Aryl

Figure 1.5. Substituted MCP.

In 1988, Nakamura *et al.* demonstrated that ACP **1.62** can engage in [(3+2)] transannular ring closure to afford propellane **1.63** (eqn. 1.17). The authors proposed that a nickel catalyst might cleave the proximal bond of ACP generating an intermediate topologically incapable of cyclisation, but in reality the reaction proceeded well with $Ni(cod)_2/PPh_3$, affording the desired propellane skeleton in 74% yield (GC yield).[34] The palladium catalyst, as expected, proved to be even more

effective allowing for isolation of the target compound in 98% yield.



1.62 **1.63** (1.17)

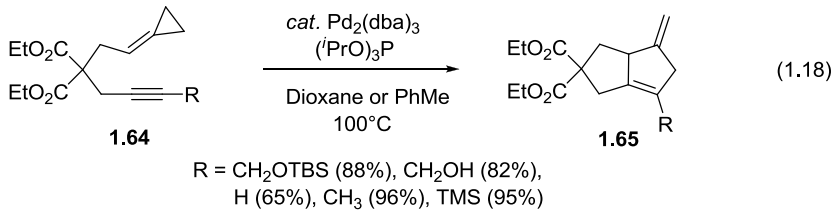
cat. $Ni(cod)_2/PPh_3$ - 74%
PhMe, 110°C

cat. $PdCl_2(Ph_3P)_2$ - 98%
DIBAL, PhMe, 130°C

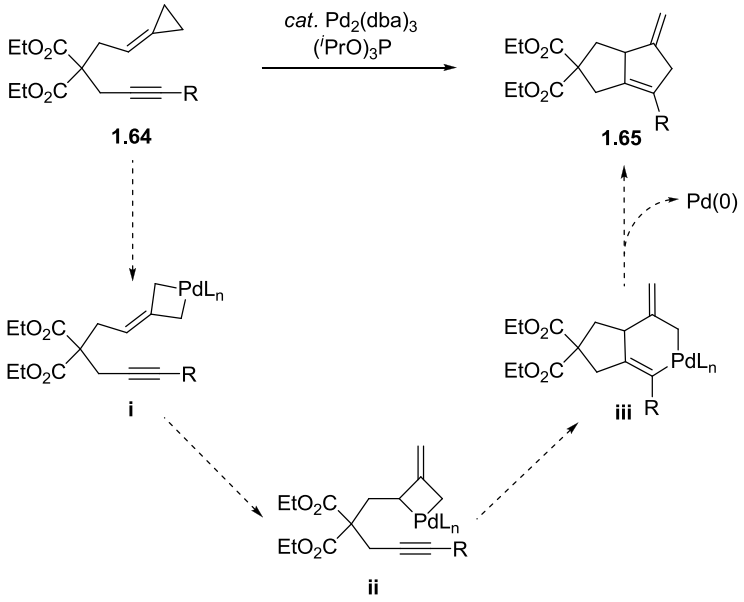
The result obtained by Nakamura and co-workers contrasts with failed attempts previously reported by Motherwell to obtain carbocyclisation products with unactivated alkenes (eqn. 1.12, *vide supra*). The reduced conformational freedom of **1.62** was suggested by Motherwell to be the major reason for the difference in reactivity between **1.40** and **1.62**.[26]

1.3.2. Intramolecular [3+2] Cycloaddition with Alkynes

In 2003, Mascareñas *et al.* showed that the ACP-based approach can be extended to more general systems in order to access common polycyclic motifs. It was demonstrated that when alkylidenecyclopropanes (ACPs) such as **1.64** are treated with $Pd_2(dba)_3$ modified with $P(OiPr)_3$, cycloadducts **1.65** are isolated in good to excellent yields (eqn. 1.18).[35] The reaction tolerates different substituents on the triple bond and even encumbered TMS-acetylene **1.64** (R=TMS) reacted readily to afford bicyclic product in excellent yields (95%). However, strongly electron-withdrawing groups on the triple bond ($R=CO_2Bn$) seemed to inhibit the reaction completely. Interestingly, this was a reverse of the trend observed by Motherwell *et al.* in the intramolecular reactions of MCPs (*vide supra*).

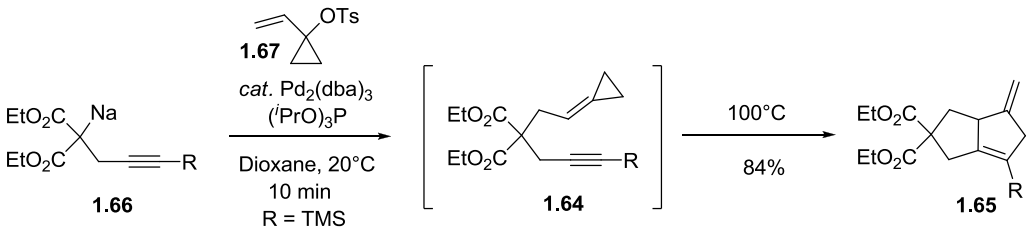


The reaction was believed to proceed *via* initial distal bond cleavage of cyclopropane ring of **1.64** to give palladocyclobutane **i**, possibly followed by rearrangement to **ii** (Scheme 1.13). Alkyne insertion into Pd-C bond in **i** or **ii** gives palladocycle **iii** which after reductive elimination furnishes **1.65** and regenerates the catalyst.



Scheme 1.13. Proposed reaction mechanism of Pd-catalysed cycloaddition of ACPs.

A noteworthy feature of this process is the simplicity and versatility of substrate preparation since no chirality is embedded in ACPs (in contrast to alkyl substituted MCPs) and precursors can be assembled by palladium-catalysed allylic alkylation (AA) of an appropriate nucleophile. Since both reactions employed the same catalyst, the substrate synthesis and the carbocyclisation could be carried out in one pot starting from nucleophile **1.66** and tosylate **1.67** by adjusting the reaction temperature (Scheme 1.14).

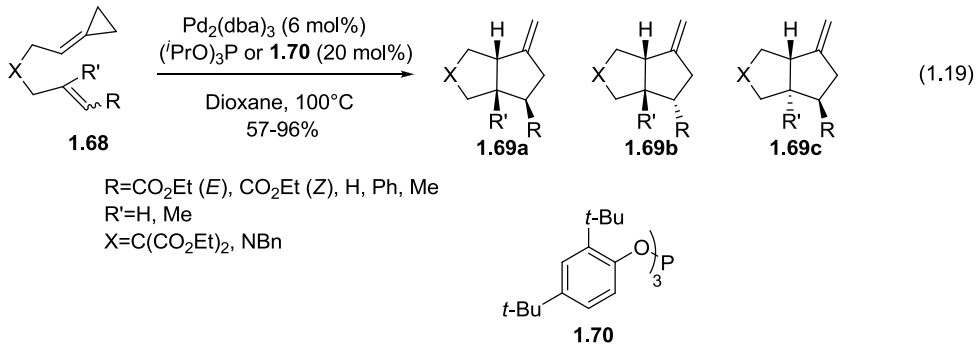


Scheme 1.14. One-pot AA and carbocyclisation reactions.

Later, Mascareñas *et al.* reported that [3+2] cycloaddition of ACPs and alkynes could also be affected by ruthenium-based Grubbs I catalyst. This transformation was more sensitive to steric hindrance of the alkyne in comparison to the palladium-catalysed process. Thus, TMS-substituted **1.64** failed to afford any product under ruthenium catalysis. The authors suggested that the active catalytic species could be a non-carbene derivative formed from a catalyst precursor at high reaction temperatures.[36]

1.3.3. Intramolecular [3+2] Cycloaddition with Alkenes

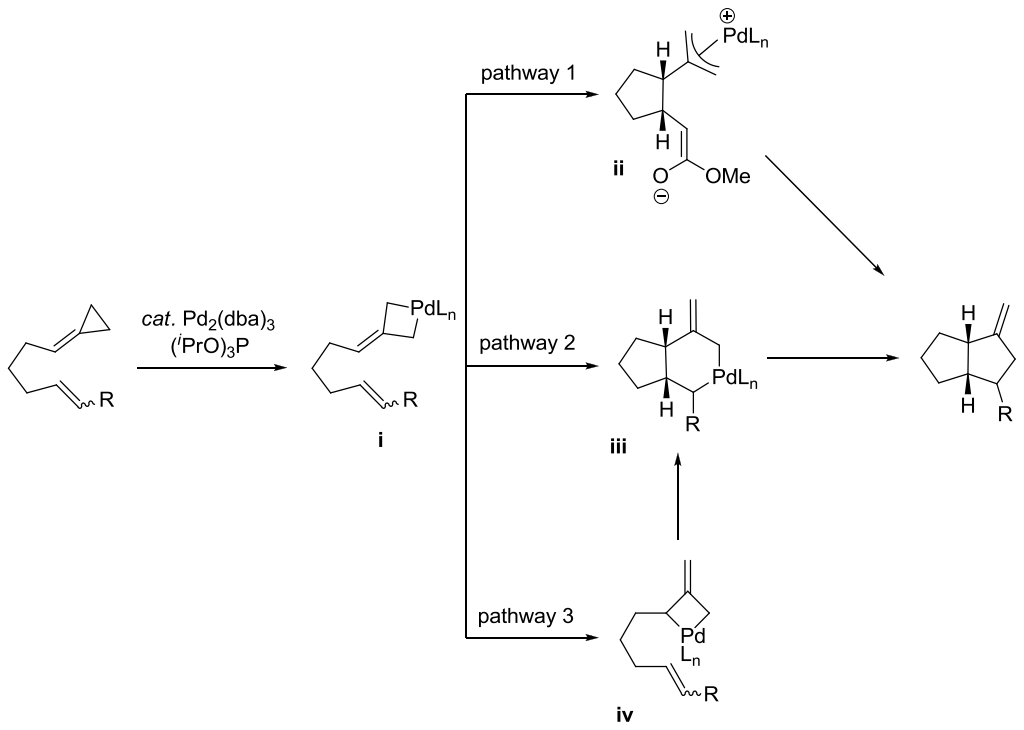
In 2006, Mascarneñas *et al.* extended their palladium-catalysed carbocyclisation methodology to include alk-5-enylidenecyclopropanes **1.68**, which allowed generation of more sophisticated bicyclic systems, bearing up to three stereogenic centres (eqn. 1.19). The reaction took place in the presence of a palladium catalyst modified with an appropriate phosphite, and generated bicycles **1.69a, 1.69b** and **1.69c** in good to excellent yields with product ratios strongly depending on a structure of the precursor and the ligand employed.[37]



(1.19)

Several interesting features of this transformation are worth noting. First of all, the authors established that both geometrical isomers of ACP **1.68** (R=CO_2Et, R`=H) lead to the same product **1.69a** (R=$CO_2$Et, R`=H) in 74% for (*E*) and 72% for (*Z*) isomer under Pd/(^{i}PrO)$_3$P conditions. When the reaction was run to partial conversion, the recovered starting material showed no isomerisation of the alkene, indicating that the stereochemistry of the product must be a consequence of the reaction mechanism. Surprisingly, when a bulky tris(2,4-di-*tert*-butylphenyl)phosphite (**1.70**) was used as a ligand instead of (^{i}PrO)$_3$P in the reaction of *(Z)*-**1.68** (R=CO_2Et, R`=H), epimers **1.69b** and **1.69c** were obtained in 87% yield and 5.3:1 ratio. The same bulky ligand was necessary to drive the reaction in case of substrates with unactivated alkenes (R=H, Ph). Based on these results and on DFT calculations, the authors proposed that different reaction mechanisms are operating in the presence of (^{i}PrO)$_3$P and tris(2,4-di-*tert*-butylphenyl)phosphate (**1.70**) ligands. Initially, two low-energy pathways were proposed that consist either of a concerted pallada-ene reaction from **i** to **iii** (Scheme 1.15, pathway 2) or a stepwise process involving the zwitterionic intermediate **ii** (pathway 1). However, subsequent computational studies established that whereas in the presence of (^{i}PrO)$_3$P, the reaction probably does takes place *via* pathway 1, and that the third pathway most likely operates in the case of bulky tris(2,4-di-*tert*-butylphenyl)phosphite. This route involves the isomerisation of **i** to methylenepalladacyclobutane **iv** *via* a Pd-TMM-

type transition state followed by carbometallation and reductive elimination to give the product. Pathway 1 explains the lack of stereospecificity observed in the reaction of (*Z*)-**1.68** (R=CO_2Et, R`=H) with (^{i}PrO)$_3$P ligand. The zwitterionic pathway may operate only for activated alkenes and in other cases pathway 3 must be operating, explaining why alkenes lacking activating groups require tris(2,4-di-*tert*-butylphenyl)phosphite for conversion.[38]



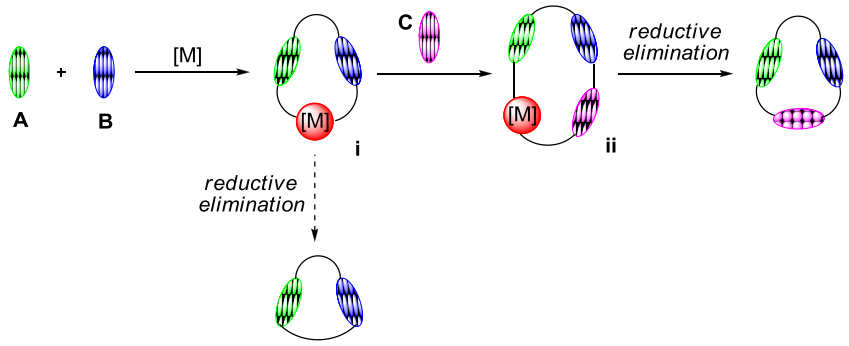
Scheme 1.15. Three pathways proposed for the mechanism of [3+2] carbocyclisation of alk-5-enylidenecyclopropanes.

Thus, Mascareñas and others have demonstrated that easily accessible ACPs can be successfully employed instead of MCPs in the intramolecular [3+2] cycloadditions delivering policyclic ring systems with high efficiency. Computational studies (DFT) have provided additional evidence for the palladium insertion into the distal bond of the cyclopropane and generation of a palladocyclobutane, which only after isomerisation provides the intermediate capable of cycloaddition.

1.4. Methylene- and Alkylidenecyclopropanes in the Synthesis of 7-Membered Rings

1.4.1. Requirements for a Metal-Catalysed Multicomponent Carbocyclisation

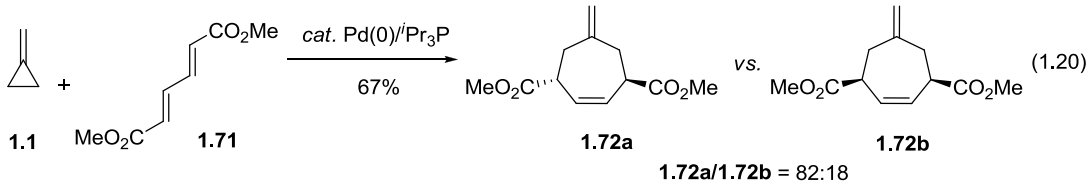
Transition metal-catalysed reactions of MCPs and ACPs find their application in various areas of organic synthesis. Of particular importance are reactions which utilise those building blocks as three-carbon units for the construction of 7-membered rings. These reactions are based on the introduction of an extra π-component **C** into the processes that were discussed earlier and that involved only two π-components **A** and **B**. A necessary prerequisite for this type of transformation is the stability of the intermediate metallacycle **i** towards premature reductive elimination (Scheme 1.16). If this condition is fulfilled, then theoretically, an insertion of an additional π-component can take place to generate a larger metallacycle **ii**, which then can furnish desired 7-membered ring after reductive elimination.



Scheme 1.16. Principle scheme of metal-catalysed multicomponent carbocyclisation.

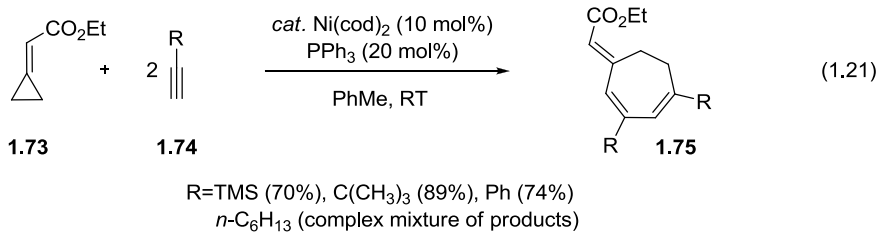
The very first example of such transformations was mentioned by Binger *et al.* as an unpublished result. MCP **1.1** was reacted with dimethyl muconate (**1.71**) in the presence of palladium(0) modified with triisopropylphosphine to afford

diastereomeric 5-methylenecycloheptenes **1.72a** and **1.72b** instead of expected five-membered carbocycle (eqn. 1.20).[25] This result highlighted the potential of MCP **1.1** as a precursor for the synthesis of seven-membered rings and showed that conjugated π-components possess unique mode of reactivity under transition metal catalysis.



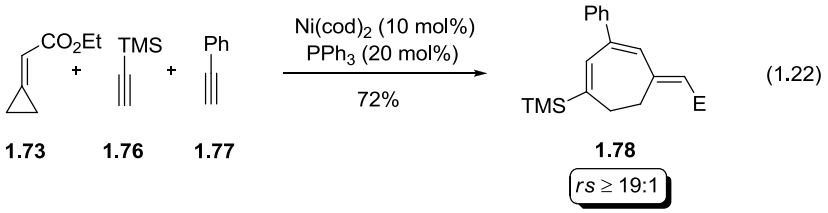
1.4.2. Nickel-Catalysed Intermolecular [3+2+2] Cycloaddition Reaction

In 2004, Saito *et al*. were the first to report the fully intermolecular [3+2+2] carbocyclisation reaction. The authors demonstrated that cyclopropylideneacetate **1.73** could be coupled with various terminal alkynes **1.74** in a highly regio- and stereoselective manner to afford substituted seven-membered rings **1.75** (eqn. 1.21).[39] The steric properties of the substituent on the alkyne played a key role in determining the yields of the products with bulky substituents (e.g. $C(CH_3)_3$) affording the best results. It was shown that a carbomethoxy group on **1.73** was crucial for obtaining the cycloadducts, since octylidenecyclopropane proved completely unreactive and only dimerisation and oligomerisation of alkyne took place.



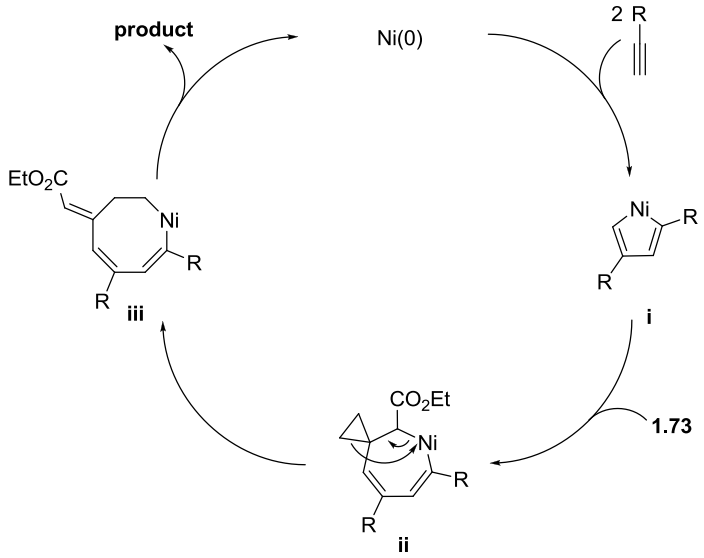
The reaction was further developed to a three-component coupling of

cyclopropylideneacetates with two different terminal alkynes. For example, when a mixture of cyclopropylideneacetate **1.73**, trimethylsilylacetylene (**1.76**) and phenylacetylene (**1.77**), was added slowly to the nickel catalyst derived from $Ni(cod)_2$ and triphenylphosphine, cycloheptatriene **1.78** was obtained in 72% yield as a single regio- and stereoisomer (eqn. 1.22). The remarkable regioselectivity was achieved by employing an excess of the less reactive bulky trimethylsilyl substituted alkyne.[40]



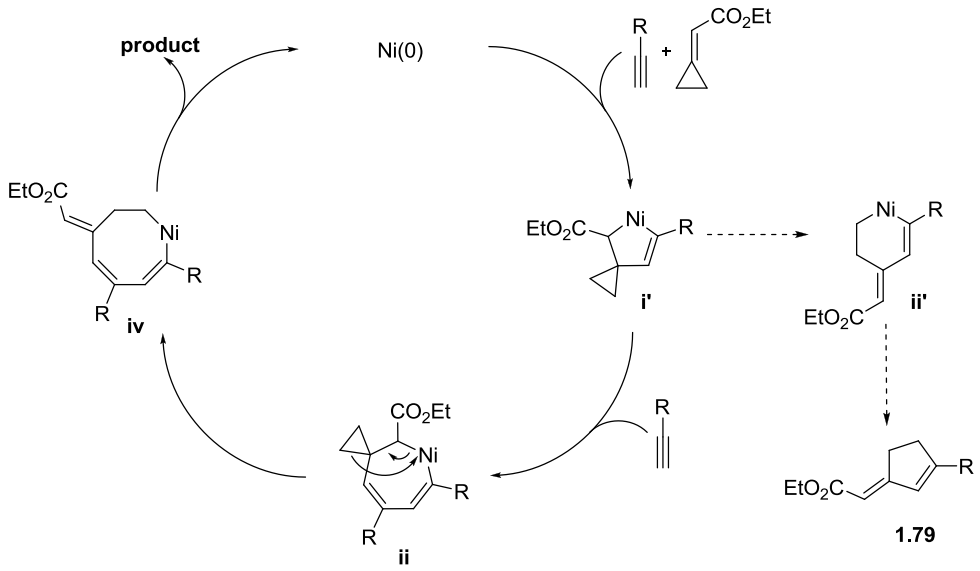
(1.22)

The proposed mechanism of the reaction differs from those discussed earlier in that the transformation is not initiated by the oxidative insertion of the metal into three-membered ring. Initially, the authors proposed that the formation of nickelacyclopentadiene **i** takes place first (Scheme 1.17). Insertion of cyclopropylidene acetate would lead to nickelacycloheptadiene **ii**, which after β-alkyl elimination could furnish metallacycle **iii**. Reductive elimination of the nickel (0) species would then furnish the product.



Scheme 1.17. Proposed catalytic cycle for the Ni-catalysed [3+2+2] cycloaddition: path A.

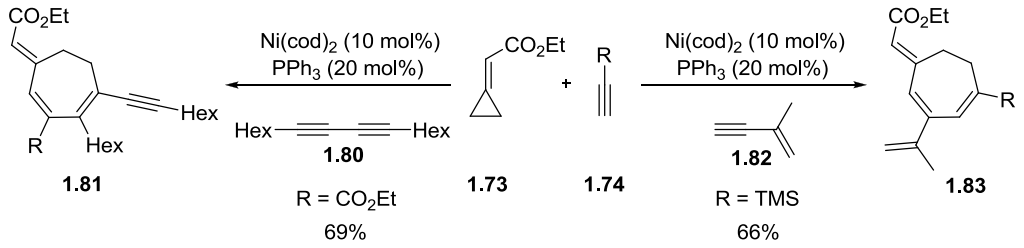
The alternative mechanism with the oxidative addition between one alkyne molecule and cyclopropylideneacetate taking place first was initially ruled out on a basis of the assumption that an intermediate **i'** would be prone to rearrangement to **ii'**, which after reductive elimination would deliver cyclopentene **1.79**, whereas no such product was observed in the reaction (Scheme 1.18).



Scheme 1.18. Proposed catalytic cycle for the Ni-catalysed [3+2+2] cycloaddition: path B.

However, recent computational studies revealed that both reaction pathways are feasible and depend on the nature of the alkyne. Normal alkynes, such as alkyl acetylenes favour path B over path A, and the regioselectivity is determined by the bulkiness of the alkyne at the second acetylene insertion step. The use of strongly electron-deficient alkynes favours path A with the formation of nickelacyclopentadiene becoming a regio-determining step.[41]

Further expansion of the scope of the transformation included the three-component reactions of cyclopropylideneacetate **1.73** with 1,3-diynes[42] and enynes[43] to furnish diversely substituted cycloheptatrienes. For example when a mixture of **1.73**, 7,9-hexadiyne (**1.80**) and sterically unhindered ethyl propiolate (**1.74**, R=CO_2Et) was slowly added to the catalyst solution cycloadduct **1.81** was formed selectively in 69% yield. On the contrary, in order to effect the selective cycloaddition with enyne **1.82**, electron-rich bulky TMS-acetylene had to be used to achieve sufficient differentiation between two alkyne partners (Scheme 1.19).

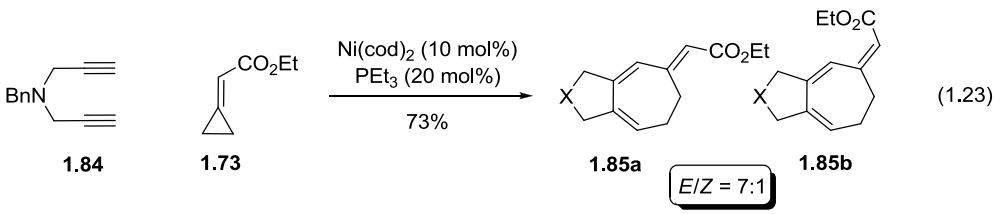


Scheme 1.19. Ni-Catalysed [3+2+2] cycloadditions with diynes and enynes.

It was demonstrated that in the cycloaddition of diynes, the use of heteroatom-substituted alkynes, such as ynol ethers and ynamines, was feasible, which allowed for the preparation of structures bearing functional groups that could potentially be used for further modification of the cycloadducts.[44]

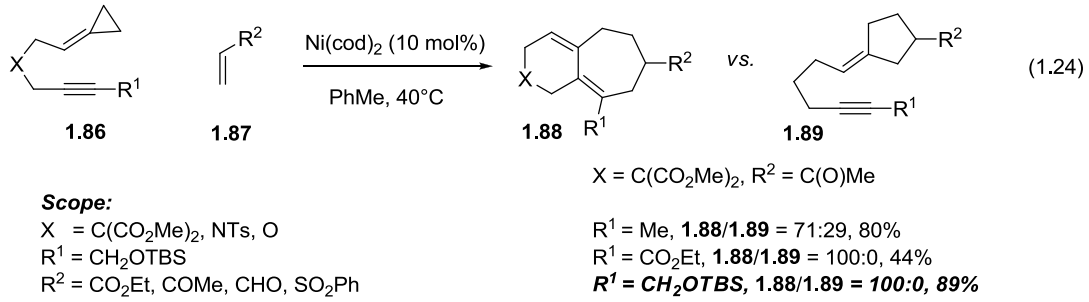
1.4.3. Nickel-Catalysed [3+(2+2)] and [(3+2)+2] Cycloaddition Reactions

The same basic transformation was also accomplished in an intramolecular fashion for the construction of 7,6- and 7,5-fused bicycloheptatrienes. For example, treatment of diyne **1.84** and cyclopropylideneacetate **1.73** with a nickel catalyst afforded bicycloheptatrienes **1.85a** and **1.85b** in good yield as a 7:1 mixture (*E*/*Z* isomers) (eqn. 1.23). In this case two alkyne components are tethered and no regioselectivity issues arise in the formation of metalacycle.[45] However, the reaction affords mixtures of *E/Z* isomers in most cases and is very sensitive to the length and the nature of the tether, requiring different ligands for individual cases.

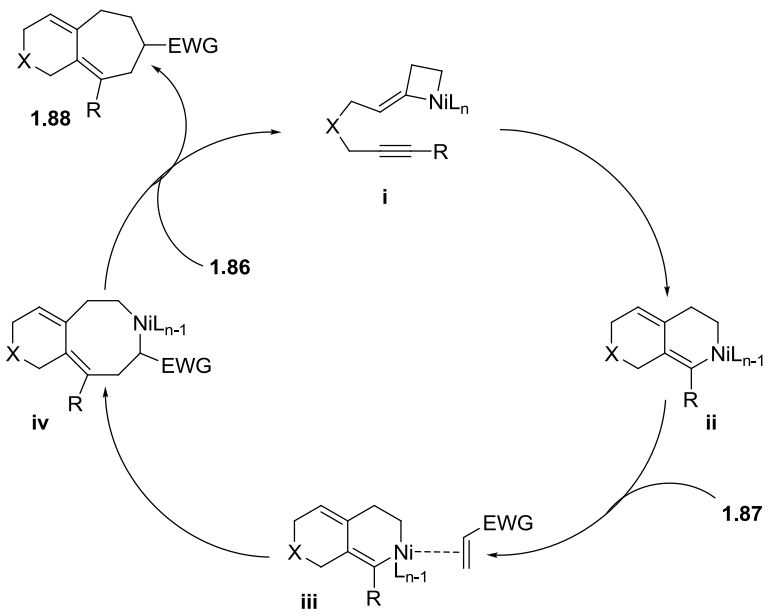


In 2010 Mascareñas *et al*. used a related approach for the construction of the 7,6-fused cycloheptadienes by means of a nickel-catalysed [(3+2)+2] cycloaddition of

alkylidenecyclopropanes **1.86** with activated alkenes **1.87**.[46] Instead of two tethered alkynes used by Saito, the authors employed an alkyne tethered to an ACP. The reaction was catalysed by $Ni(cod)_2$ and afforded 6,7-bicyclic products **1.88** resulting from the formal cleavage of the cyclopropane proximal bond (eqn. 1.24).



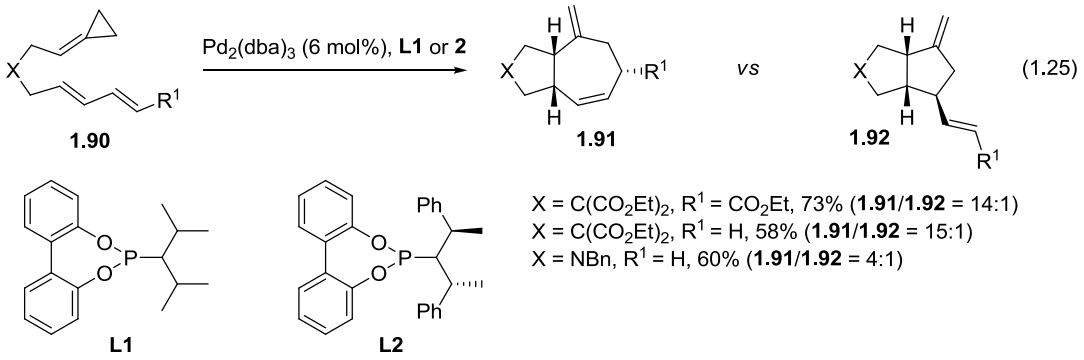
Initial results with **1.86** (R^1=Me, X=$C(CO_2Me)_2$) provided modest selectivities for the preferential formation of the [(3+2)+2] product **1.88** over [3+2] products **1.89** (formed *via* premature reductive elimination). Interestingly, an electron-withdrawing ester group on the alkyne (R^1=CO_2Me) improved the selectivity significantly, albeit the yield remained moderate. Finally, the *tert*-butyldimethylsilyl protected hydroxymethyl group allowed to obtain the desired 6,7-bicycle in good yield and with excellent selectivity. Unfortunately, the authors do not provide any explanation regarding the effect the CH_2OTBS group has on the relative rates of insertion and premature reductive elimination. The reaction showed considerable generality, with nitrogen and oxygen tethered substrates providing similar results. DFT calculations suggested that the reaction is initiated by the insertion of nickel into proximal ACP bond to give **i** followed by the formation of the six- membered metallacycle **ii** (Scheme 1.20). Coordination of the activated alkene and insertion into the Ni-C(sp^2) bond affords intermediate **iv** which produces the final product upon reductive elimination.



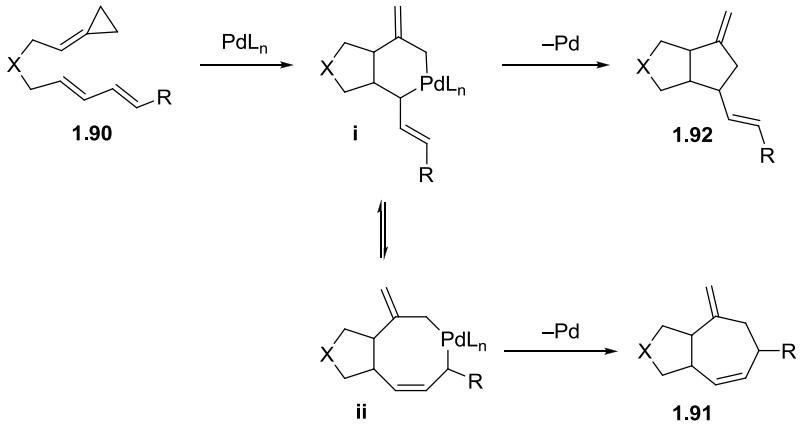
Scheme 1.20. Mechanism of the Nickel-Catalysed [(3+2)+2] Cycloaddition

1.4.4. Palladium-Catalysed [(4+3)] Cycloaddition Reaction

In 2007, Mascareñas *et al*. reported the first intramolecular metal-catalysed [(4+3)] cycloaddition reaction of alkylidenecyclopropanes and dienes. Treatment of precursors **1.90** with 6 mol% $Pd_2(dba)_3$ and 24 mol% of phosphoramidite **L1** or **L2** afforded 5,7-bicycles **1.91** with excellent diastereoselectivity, albeit with varying yields (eqn. 1.25).[47] Moderate enantioinduction (47% *ee*) was observed when chiral ligand **L2** was employed in the cyclisation of **1.89** (X=C(CO_2Et)$_2$, R^1=CO_2Et). The selectivity of the reaction (7-membered **1.90** *vs*. 5,5-bicyclic **1.91**) was highly influenced by the nature of the ligand and the type of the tether, however, even under the optimized conditions it proved impossible to suppress completely the formation of the 5,5-bicycles resulting from the premature reductive elimination (eqn. 25).



A reaction mechanism involving the insertion of the metal into the distal ACP bond followed by the formation of the six-membered palladocycle **i** was proposed (Scheme 1.21). Isomerisation to the palladocyclooctane intermediate **ii** and reductive elimination result in the formation of the 5,7-bicycle whereas reductive elimination of **i** results in the formation of the 5,5-bicycle.

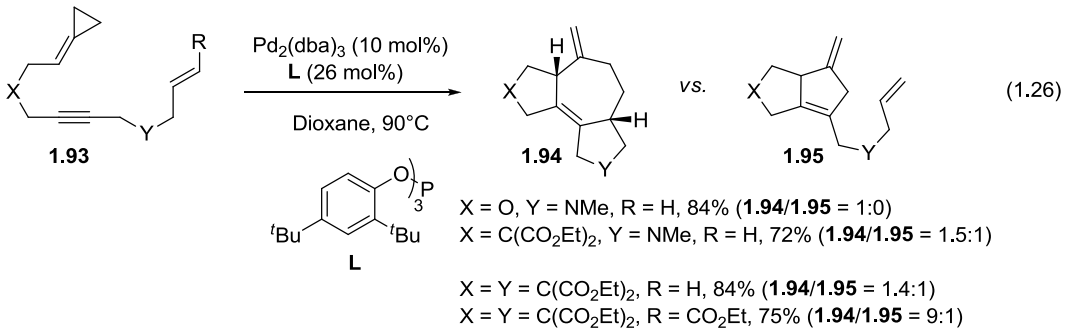


Scheme 1.21. Mechanism of the Palladium-Catalysed [(4+3)] Cycloaddition.

1.4.5. Palladium-Catalysed [(3+2+2)] Cycloaddition Reaction

In 2010, an impressive Pd-catalysed fully intramolecular [(3+2+2)] carbocyclisation reaction of ACPs was disclosed by Mascareñas *et al*. The process allowed for the construction of fused 5,7,5-tricyclic systems **1.94** in a diastereoselective fashion starting from linear precursors **1.93**. The reaction employed a phosphite ligand and was effective for different tethers, but suffered significantly from a competing side

reaction, namely the formation of 5,5-bicycle **1.95** (eqn. 1.26).[48] The chemoselectivity depended strongly on the nature of the linkers X and Y in **1.93**. For example whereas the ACP **1.93** (X=O, Y=NMe or NTs) provided exclusive formation of **1.94**, closely related substrate **1.93** (X=C(CO_2Et)$_2$, Y=NMe) with a different tether provided only a 1.5:1 selectivity for the formation of tricyclic product. It was also noticed that when an electron-withdrawing CO_2Et group was attached to an alkene unit an increase in selectivity favouring the 5,7,5-product was observed. This was explained by the increased coordination ability of the electron-deficient alkene, which favours the second carbometallation step.

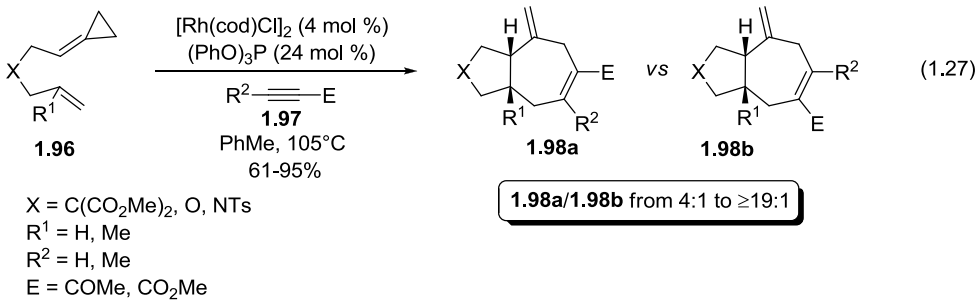


1.4.6. Rhodium-Catalysed [(3+2)+2] Cycloaddition Reaction

1.4.6.1. Scope and Selectivity

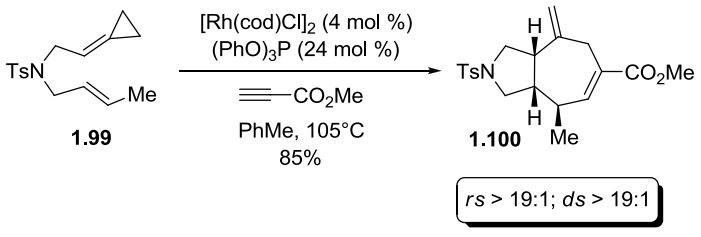
In 2008, Evans and Inglesby reported a [(3+2)+2] carbocyclisation reaction between tethered ACPs **1.96** and activated alkynes **1.97** (eqn. 1.27).[49] The reaction took place at 105^{o}C in toluene and was catalysed by a complex derived from [Rh(cod)Cl]$_2$ and triphenylphosphite. The carbocyclisation was highly efficient and diastereoselective, and afforded 5,7-bicyclic products **1.98a** and **1.98b** selectively with none of the 5,5-products being observed. The reaction worked equally well for substrates with different tethers, however, the yields for substrates with the oxygen linker were slightly lower due to the inherent volatility of the precursor ACPs. The reaction was

regioselective and favoured the formation of bicycle **1.98a** over bicycle **1.98b** in all cases. The level of regiocontrol varied with the degree of the electron-withdrawing ability of the substituent on the alkyne (E) with COMe > CO_2Me > CO_2NR_2.



(1.27)

Another intriguing feature of this reaction was the ability to employ 1,1-disubstituted alkenes as substrates, which permitted the introduction of quaternary carbon stereogenic centres. Interestingly, in the case of 1,2-disubstituted olefin, *Z*-isomer provided a complex mixture resulting from a competitive β-hydride elimination pathway, whereas *E*-olefin **1.99** afforded desired bicycle **1.100** with excellent diastereoselectivity (eqn. 1.28). The ability to employ *E*-alkenes with the concomitant formation of products with up to three new stereogenic centres makes this reaction a very promising tool for the construction of cycloheptane-containing natural products.

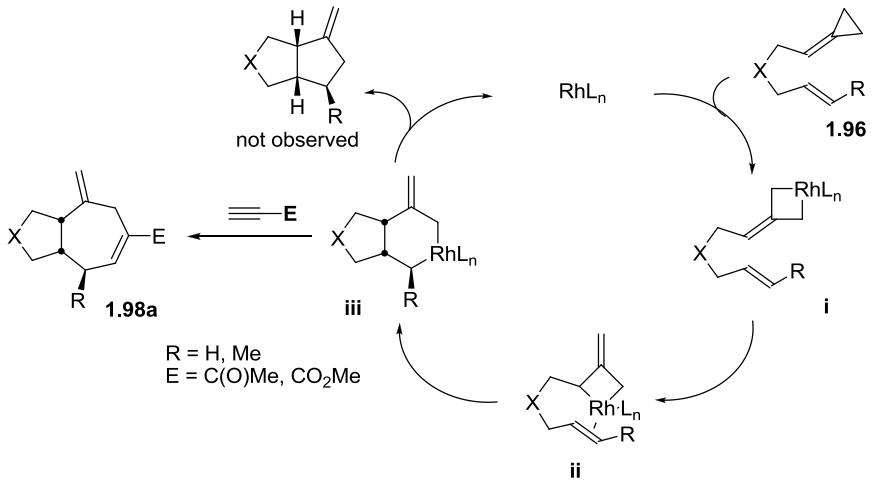


(1.28)

1.4.6.2. Mechanistical Considerations

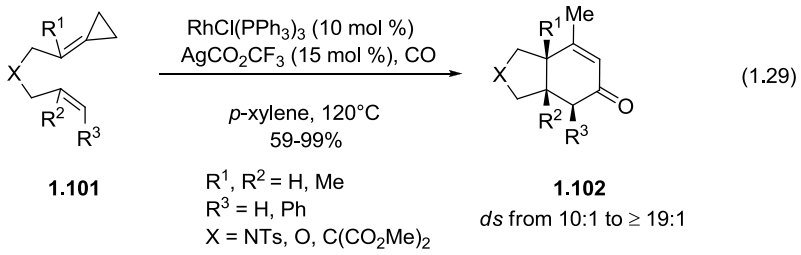
The initially proposed mechanism of the reaction mirrored previously described mechanisms for the palladium-catalysed transformations. The reaction was thought

to begin with rhodium metal inserting into the ACP distal bond to give **i**, which then rearranges to give **ii** (Scheme 1.22). Alkene insertion into rhodium-carbon bond affords metallocycle **iii**, which after alkyne insertion and reductive elimination provides the desired product. It is important to stress that the 5,5-bicyclic products resulting from competing reaction pathway are not observed under these conditions, which can be attributed to the slower sp^3-sp^3 reductive elimination when compared to sp^2-sp^3 elimination.[50] This promotes alkyne insertion to provide a more favourable (sp^2-sp^3) reductive elimination.



Scheme 1.22. Initially proposed mechanism of the Rh-catalysed [(3+2)+2] carbocyclisation.

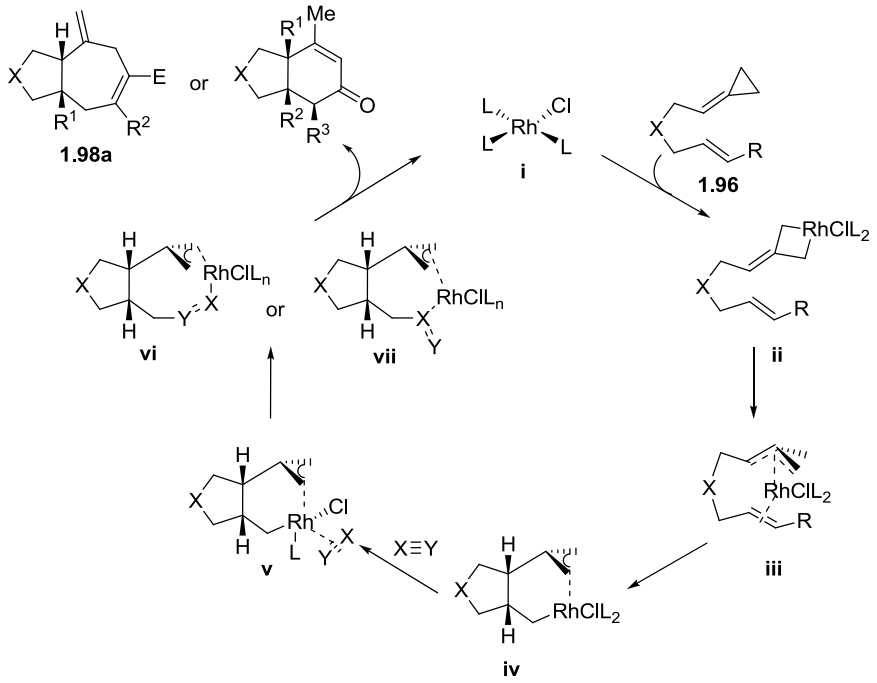
Recently, in 2012, a novel rhodium-catalysed [(3+2)+1] carbocyclisation was reported. It was shown that ACPs **1.101** can be successfully transformed into *cis*-fused bicyclohexenones **1.102** in the presence of cationic rhodium catalyst in great yields and with excellent diastereoselectivities (eqn. 1.29).[51]



(1.29)

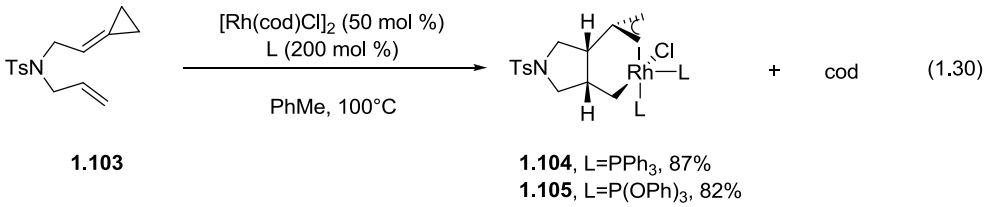
The work featured detailed computational studies of the process, which shed further light on the general mechanism of rhodium-catalysed processes involving ACPs. Based on the results of the calculations a modified mechanism for the rhodium-catalysed [(3+2)+2] and [(3+2)+1] carbocyclisations emerged. It was established that the formation of initial complex between metal and ACP is followed by oxidative addition to give square-pyramidal rhodacyclobutane **ii** (Scheme 1.23). The alternative pathway involving oxidative addition into proximal C-C bond was ruled out as being too energetically demanding. The most intriguing feature of the calculations was the finding that complex **ii** unexpectedly rearranges to the Rh-trimethylenemethane complex **iii**, which was proposed to be the resting state of the catalytic cycle. This event is followed by a stereoselective carbometalation of a pendant vinyl moiety to furnish *cis*-fused bicycle **iv**. The insertion of the vinyl group is most likely the rate-determining step of the catalytic cycle. The energy of the transition state TS1 leading to *cis* product was calculated to be ~7 kcal/mol lower than the energy of the alternative transition state TS2 leading to *trans* bicycle. In the TS1 the tether maintains its chair-type envelope structure, while in TS2 the conformation of the tether changes to a twisted boat. This difference in the conformation accounts for the lower activation energy required for the *syn* alignment of the two hydrogen atoms. After this carbometalation step an insertion of a third π-component takes place preceded by its coordination to the metal centre. Migratory insertion of the carbonyl or alkyne gives intermediates **vi** or **vii**, respectively, which

after reductive elimination yield desired bicyclic products.



Scheme 1.23. Unified catalytic cycle of Rh-catalysed [(3+2)+n] carbocyclisation.

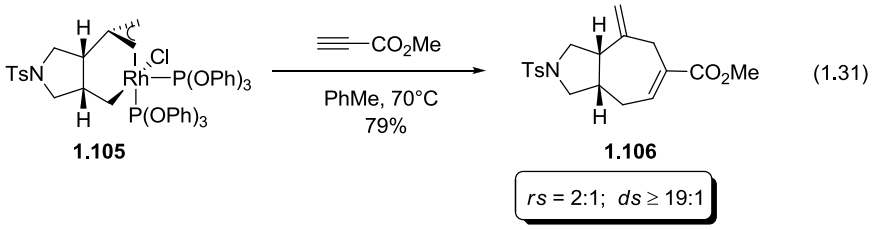
To gain further insights into the mechanism of the Rh-catalysed [(3+2)+2] carbocyclisation, elegant work on the isolation of intermediate metallacycles was carried out by Evans and Inglesby. Thus, treatment of ACP **1.103** with a stoichiometric amount of rhodium(I) catalyst, derived from $[Rh(cod)Cl]_2$ and PPh_3, allowed the isolation of the new rhodium metallacycle **1.104** in 87% yield as an air-stable solid (eqn. 1.30).[52] The corresponding triphenylphosphite complex **1.105** was prepared in an analogous manner in 82% yield. The complex **1.104** was studied by NMR and X-ray crystallography, which revealed that it contains a 6-coordinate 18-electron rhodium atom with a distorted monocapped octahedral geometry and η^3-allyl binding mode.



1.103

1.104, L=PPh_3, 87%
1.105, L=$P(OPh)_3$, 82%

In order to prove the relevance of the complex **1.105** in the rhodium-catalysed [(3+2)+2] carbocyclisation the metallacycle was treated with methyl propiolate. The product bicycle **1.106** was obtained in 79% yield with the same regio- and diastereoselectivity as in a catalytic version (eqn. 1.31). Interestingly, the reaction took place at lower temperature than was necessary for the formation of the complex, confirming that formation of metallacycle is a rate-limiting step of the reaction (*vide supra*).



1.105

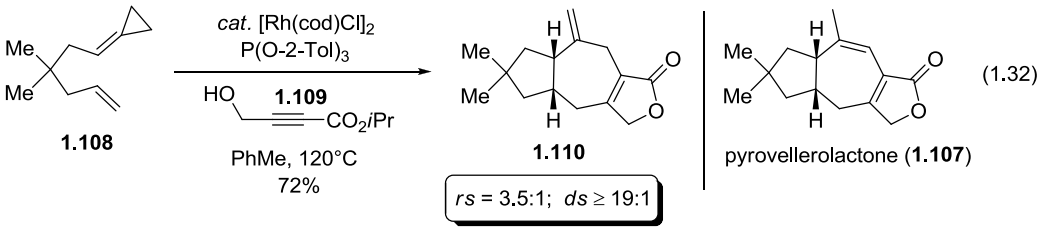
1.106

rs = 2:1; *ds* ≥ 19:1

1.4.6.3. Practical Applications

Advances that were achieved in recent years in the field of transition metal-catalysed synthesis of 7-membered rings employing MCPs and ACPs have established this approach as a powerful strategy towards the title structures. Together with [5+2] cycloadditions of VCPs these reactions provide a direct and flexible solution to the synthesis of different mono- and bicyclic structures containing 7-membered rings. Rhodium-catalysed [(3+2)+2] cycloaddition has already been successfully employed in the context of natural products preparation for the short and concise synthesis of pyrovellerolactone (**1.107**).[53] The key step involved gram- scale reaction of ACP **1.108** with acetylenic ester **1.109** to afford tricyclic lactone **1.110** in 72% yield and

with 3.5:1 regioselectivity (eqn. 1.32).



This result highlights very well how effective transition metal-catalysed 7-membered ring formation from ACP can be, when applied towards the right target. It must be pointed out, however, that there is a need for further development in this area in order to include more complex substrates that would lead to more advanced cycloadducts.

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Chapter 2

Rhodium-Catalysed [(3+2)+2] Carbocyclisation of Heteroatom-Substituted Alkylidenecyclopropane Containing Olefins

2.1. Introduction

The following chapter describes the development of a rhodium-catalysed [(3+2)+2] carbocyclisation of heteroatom-substituted olefins for the synthesis of the C6-oxygenated guaianolide skeleton. These studies have resulted in the highly regio- and diastereoselective carbocyclisation reaction of trialkoxysilyl-substituted alkylidenecyclopropanes (ACPs) with monosubstituted alkynes. This reaction represents the first example of a metal-catalysed higher-order carbocyclisation of vinylsilane, which allows the selective formation of a secondary alcohol.

2.2. Target Definition

Guaianolides are a class of natural products that contain a tricyclic 5,7,5-ring system, and belong to a large subgroup of naturally occurring sesquiterpene lactones that exhibit significant biological activity. The core structure of the guaianolides **2.1** is derived from guaiane (**2.2**), a natural product with a *cis*-fused 5,7-bicyclic hydroazulene ring system (Fig. 2.1). The *cis*-ring juncture is a distinctive feature, which is also found in the majority of the 5,7,5-tricyclic guaianolides. The γ-butyrolactone ring is *trans*-annulated in approximately 85% of all known guaianolide natural products.[1]

Figure 2.1. Core structure of 5,7,5-tricyclic guaianolides.

We envisaged that the *cis*-fused 5,7-bicyclic ring system, which is at the core of guaianolide natural products, could be conveniently accessed through the rhodium-catalysed [(3+2)+2] carbocyclisation developed in our group.[2] However, examination of the basic guaianolide structure **2.1** also reveals several potential challenges that could arise if we were to employ this strategy. First of all, control of the stereochemical outcome of the carbocyclisation step could present problems, since there have been no previous studies on the diastereoselectivity of this process. Hence, it remained to be seen how the pre-existing chiral centre contained within the substrate would influence the absolute configuration at the bridge of the cycloadduct. Another critical task would be the functionalisation of the 7-membered ring, especially at C6, which bears an oxygen atom in many guaianolide natural products, for example estafiatin (**2.3**), dehydrocostus lactone (**2.4**), and repin (**2.5**) (Fig. 2.2).

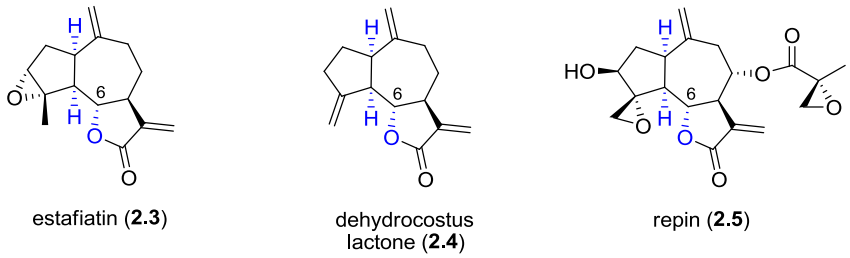
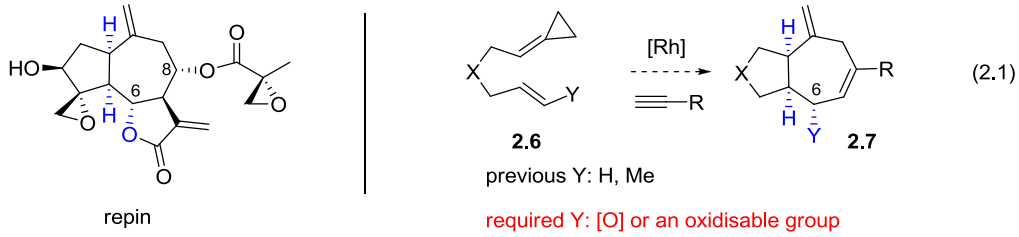


Figure 2.2. Representative C-6 hydroxylated guaianolides

Prior to this work, all of the cycloadducts obtained in rhodium-catalysed [(3+2)+2] carbocyclisation were either unsubstituted at the corresponding position or bore a

methyl substituent. One approach to the introduction of the C6-hydroxyl group would involve a carbocyclisation reaction to afford the C6-unsubstituted product followed by oxygenation. We, however, were more excited to pursue a different route, that is designing a substrate that would deliver the oxygen functionality directly or in a masked form (eqn. 2.1). This meant that a potential cyclisation substrate **2.6** should possess an oxygen atom or an oxidisable group attached directly to the *trans*-alkene (based on the work by Inglesby and Evans).[2]



(2.1)

2.3. Rhodium-Catalysed [(3+2)+2] Carbocyclisation of Vinyl Acetates

2.3.1. Electronic Properties of Vinyl Acetates

Our work commenced with an examination of substituents that would be tolerated in the rhodium-catalysed [(3+2)+2] carbocyclisation. An oxygen atom attached directly to an sp^2 carbon atom makes the double bond much more electron-rich when compared to an unsubstituted olefin. We had some concerns about whether such an electron-rich double bond would efficiently insert into the Rh-C bond during the formation of the rhodacycle, as the following example highlights how the nature of the reacting olefin influences the mode of hydrometallation/carbometallation events. 1-Hexene undergoes selective 1,2-insertion with nickel(II) hydride complexes containing amido diphosphine ligands (Fig. 2.3). In contrast, styrene and methyl acrylate insert into the Ni-H bond in an exclusively 2,1-manner.[3] It was suggested that the migrating hydrogen atom bears a partial negative charge, while on the *β*-

carbon atom there is a build up of partial positive charge. The regioselectivity of insertion is consistent with the electron-releasing character of *n*-butyl group and electron-withdrawing nature of phenyl and ester substituents. The alkene arranges itself in the way that allows a substituent to stabilise the transition state.[3]

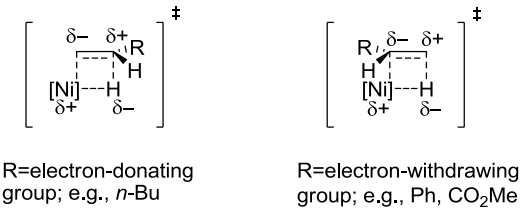


Figure 2.3. Four-membered cyclic transition states which contain electron-donating or electron-withdrawing substituents.

The rhodium-catalysed [(3+2)+2] carbocyclisation is an intramolecular reaction where the length of the tether allows only one mode of alkene insertion. As a consequence, the oxygen at the termini of the double bond inevitably causes the "wrong" polarisation of the alkene, forcing the reaction to occur *via* a less energetically favourable pathway. This led us to choose a vinyl acetate as the starting material for the cycloaddition, based predominantly on the reduced electron-donating ability of the vinyl acetate **2.8** when compared to another viable substrate – the enol ether **2.9** (Fig. 2.4).

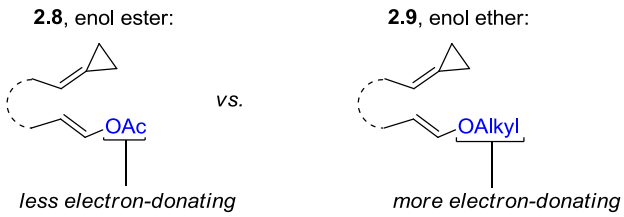
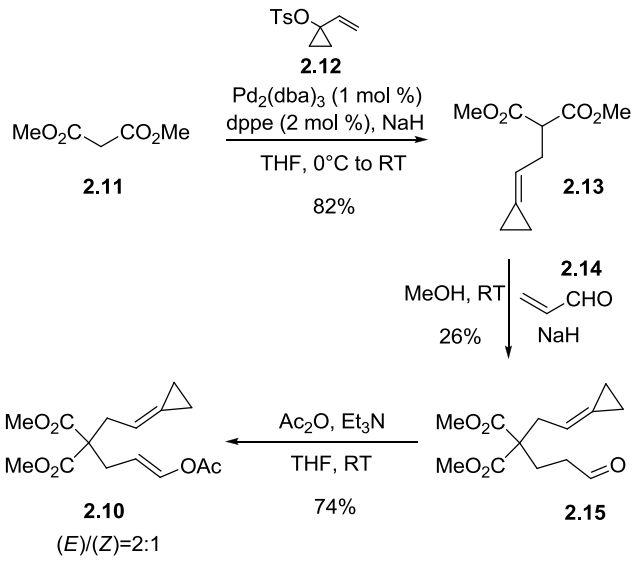


Figure 2.4. Relative electron-donating ability of enol ester vs. enol ether.

2.3.2. Synthesis of Vinyl Acetates and their Reactivity in the Rhodium-Catalysed [(3+2)+2] Carbocyclisation

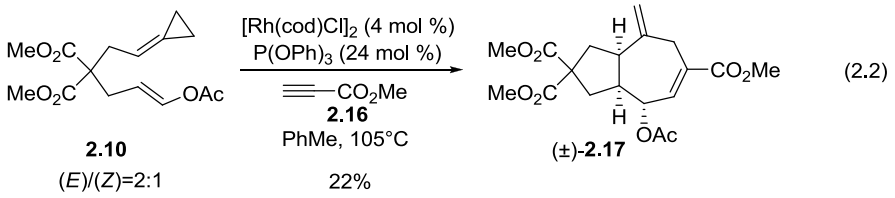
To verify our hypothesis, we decided to prepare and test the malonate derivative **2.10**. Dimethyl malonate (**2.11**) was subjected to the palladium-catalysed allylic alkylation with 1-vinylcyclopropyl tosylate (**2.12**) to provide the ACP **2.13** (Scheme 2.1). This intermediate then underwent 1,4-addition with acrolein (**2.14**) to afford the aldehyde **2.15** in low yield. Finally, enolisation of **2.15** in the presence of acetic anhydride delivered the desired enol acetate **2.10** as a 2:1 mixture of *E*- and *Z*-isomers.



Scheme 2.1. Synthesis of malonate **2.10**.

Gratifyingly, when **2.10** was subjected to the rhodium-catalysed [(3+2)+2] carbocyclisation with methyl propiolate (**2.16**), the 5,7-bicycle **2.17** was obtained as a single regio- and stereoisomer, albeit in low yield (22%) and with poor conversion (30%) (eqn. 2.2). Decomposition of the starting material under the reaction conditions was also observed leading to the formation of multiple unidentified side products. Surprisingly, despite the fact that a mixture of *E* and *Z*-olefins was

subjected to the reaction conditions, only one discrete cycloaddition product was isolated. It was known from the work of Inglesby and Evans that *Z*-olefins react sluggishly in a [(3+2)+2] carbocyclisation and that they decompose under the reaction conditions.[2] Based on this we rationalised that the *Z*-vinyl acetate is either decomposed under the reaction conditions or isomerised to the *E*-olefin. However, in order to study the reaction in more detail we required a single isomer of the vinyl acetate starting material.

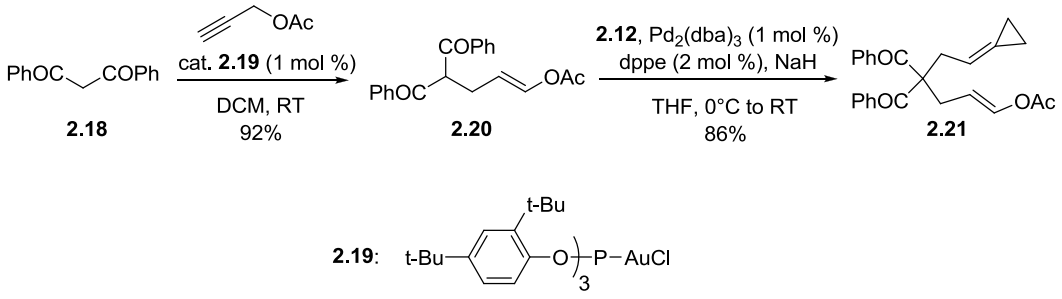


(2.2)

Unfortunately, most often the methods for the selective synthesis of vinyl acetates that involve the direct addition of carboxylic acids across a triple bond either lack selectivity or afford the *Z*-isomer predominantly, and a product of Markovnikov addition is often a by-product.[4-8] We, on the other hand, required access to *E*-vinyl acetates, since only in case of the *E*-isomer would the relative configuration of the resulting stereotriad correspond to the stereochemistry of natural guaianolides. Vinyl esters can be synthesised stereospecifically from vinyl boronates[9] and vinyl potassium trifluoroborates,[10] but these approaches are more laborious than the direct addition of acids to alkynes. After careful examination of the available literature, we decided to rely on a methodology developed by Echavarren, which involves the treatment of 1,3-diketones with substituted and unsubstituted propargyl acetates in the presence of gold catalysts.[11]

Enol acetate **2.21** was synthesised in two steps starting from the commercially available diketone **2.18** (Scheme 2.3). The gold-catalysed reaction of **2.18** with

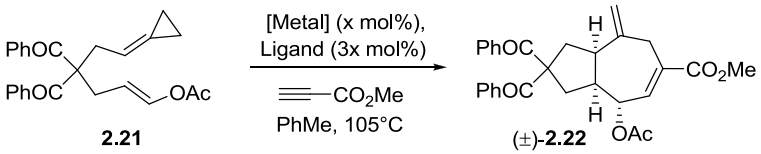
propargyl acetate afforded the *E*-enol acetate **2.20** as a single isomer in 92% yield. Compound **2.20** was then subjected to the palladium-catalysed allylic alkylation with 1-vinylcyclopropyl tosylate **2.14** to afford the requisite precursor **2.21** in excellent yield. However, this approach does not work with dimethyl malonate due to the failure of the gold-catalysed transformation. Most likely, the malonate ester is not acidic enough to engage in the reaction with propargyl acetate.



Scheme 2.2. Synthesis of enol acetate **2.21**.

Gratifyingly, treatment of the vinyl acetate **2.21** with methyl propiolate in the presence of $[Rh(cod)Cl]_2$ and triphenyl phosphite furnished the desired bicycle (±)-**2.22** as a single regio- and diastereoisomer, albeit in a very low yield of 21% and with poor conversion (Table 2.1, entry 1). The yield was improved by starting the reaction with a low concentration of alkyne and adding the remaining alkyne *via* syringe pump over 2.5 hours (entry 2 *vs* entry 1). A higher catalyst loading (8%) was necessary in order to increase the conversion but even then the reaction failed to go to completion (Table 2.1, entry 3). Attempts to further optimise the reaction conditions demonstrated that other ligands and catalysts were inferior to the original system (entries 4-9).

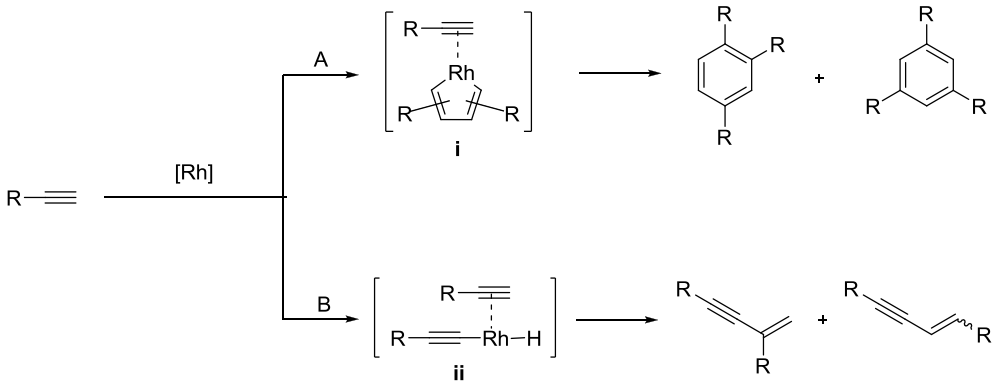
Table 2.1. Optimisation of the cycloaddition of **2.21**.



Entry[a]	Ligand	Catalyst	Metal %	Conver. (Yield)[b]
1[c]	$(PhO)_3P$	$[Rh(cod)Cl]_2$	8 mol %	31% (21%)
2	$(PhO)_3P$	$[Rh(cod)Cl]_2$	8 mol %	66% (51%)
3	$(PhO)_3P$	$[Rh(cod)Cl]_2$	16 mol%	83% (65%)
4	$(CF_3CH_2O)_3P$	"	"	17%
5	$(^{i}PrO)_3P$	"	"	34%
6	$(2\text{-}MeC_6H_4O)_3P$	"	"	50%
7	$(2,4\text{-di-}^{t}BuC_6H_3O)_3P$	"	"	no reaction
8	$(PhO)_3P$	$[Rh(cod)_2]SbF_6$	"	no reaction
9	$(PhO)_3P$	$[Ir(cod)Cl]_2$	"	no reaction

a) All reactions were carried as follows: 0.5 eq. alkyne was initially added to the reaction mixture and the remaining 4.5 eq. was added by syringe pump over the course of 2.5 h. After the addition the mixture was allowed to stir for a further 2 h before cooling to RT. b) Conversion was determined by ^{1}H-NMR and refers to the ratio between the starting material and the product. Numbers in parentheses are the isolated yields. c) All 5.0 eq. of alkyne was present at the beginning.

It is known that rhodium catalysts, both cationic and neutral, are able to induce various reactions of monoynes, such as cyclotrimerisation through a metallacyclopentadiene **i** (Scheme 2.3, path A) and dimerisation through C-H activation (Scheme 2.3, path B).[12,13] We hypothesise that maintaining a low alkyne concentration in the reaction mixture reduces the rate of these side reactions, which would otherwise compete effectively with the slow [(3+2)+2] carbocyclisation process and lead to ageing of the catalyst and consumption of the alkyne reagent.



Scheme 2.3. Rhodium-catalysed reactions of monoynes.

The relative stereochemistry of the product (±)-**2.22** was established *via* X-ray analysis of the corresponding alcohol (±)-**2.23** (Fig. 2.5). The hydroxyl group resides on the same face of the molecule as the bridgehead hydrogen atoms, which is consistent with the previous studies of Evans and Inglesby.[2]

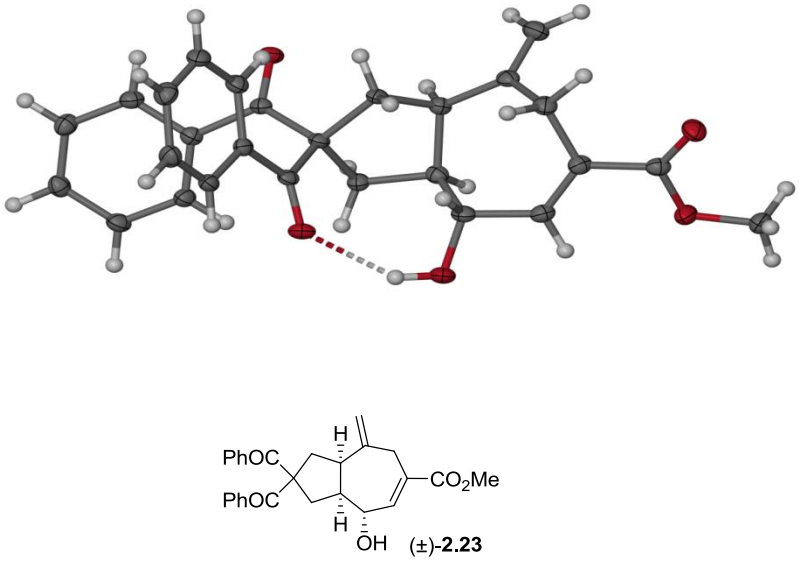
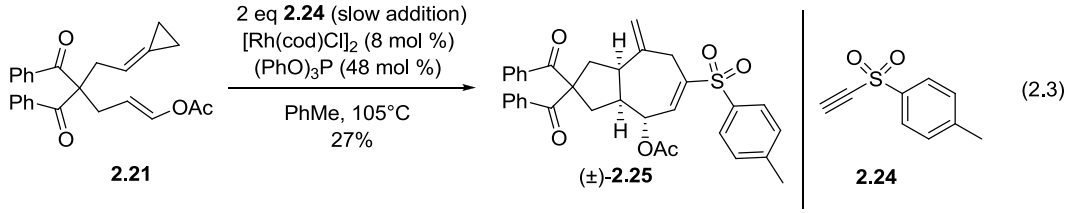


Figure 2.5 X-Ray Structure of (±)-**2.23**.

While the reaction of enol acetates with methyl propiolate was successful in furnishing the C6-hydroxylated bicyclic scaffold found in guaianolide natural products, it also introduced an additional carbon atom attached to C8 which is absent

in sesquiterpene lactones. Envisioning the possible application of this chemistry to the total synthesis of guaianolides, we elected to test the reaction with an alkyne bearing an activating group that would be easier to cleave than the previously employed methyl carboxylate. Ethynyl sulfone **2.24** was considered a viable option since reductive removal of the sulfone functionality is a well established transformation.[14] Gratifyingly, subjection of **2.21** and **2.24** to the rhodium-catalysed carbocyclisation reaction afforded the desired compound (±)-**2.25**, albeit in low yield and with a number of side products (eqn. 2.3). An insoluble brown precipitate was formed in the reaction, which was attributed to the polymerisation of ethynyl sulfone.



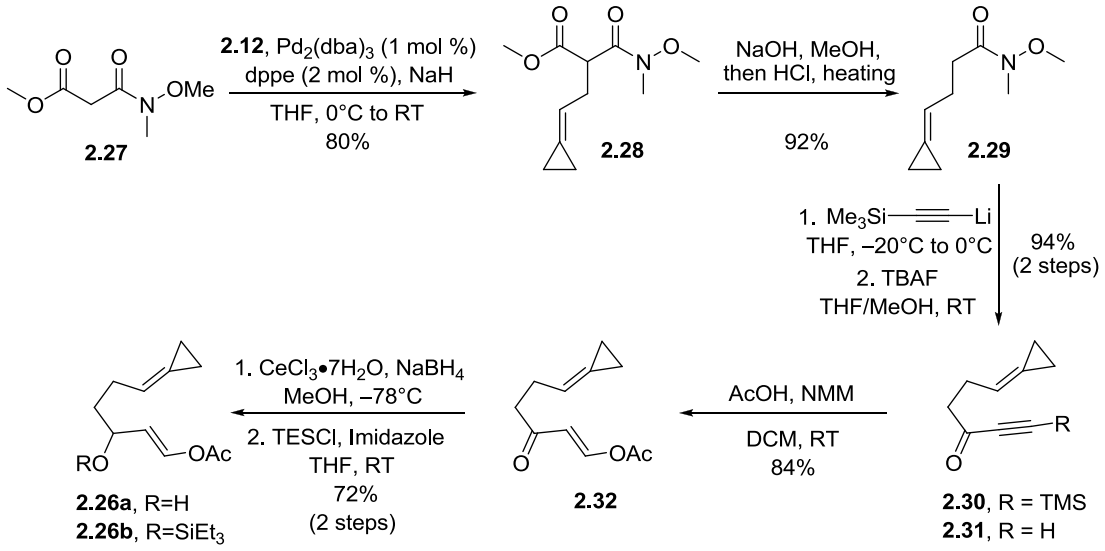
(2.3)

After obtaining encouraging results with the substrate **2.21**, we were disappointed to learn that with the enol acetate **2.10** the reaction fails to afford increased product yields even under our best conditions. Higher catalyst loadings and slow addition of the alkyne only resulted in a minor yield increase (27% vs. 22%). It remains unclear why the yield in this case was so much lower than in the reaction of **2.21**. One explanation could involve the Thorpe-Ingold effect[15,16] with the larger phenyl groups of **2.21** being more effective in bringing the two reacting parts of the molecule together.

2.3.3. Stereochemistry of the Cycloaddition with Vinyl Acetates

The fact that the reactions of both **2.21** and **2.10** fail to go to completion and that considerable decomposition is observed in both reactions, demonstrates that the

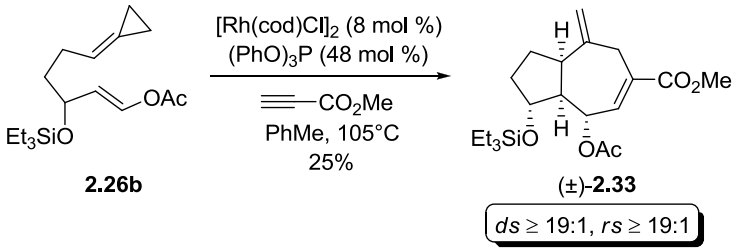
highly polarised double bond of the enol acetate makes the reaction much more sluggish. Our brief optimisation of the reaction conditions indicated that developing a catalytic system that could overcome this inherent lack of reactivity is not straightforward. Despite this, we believed it was important to study the reaction in more detail, particularly in terms of the diastereoselectivity, as transition metal-catalysed carbocyclisation reactions of enol acetates are rare and new insights in this field are of high value. Scheme 2.5 outlines the synthesis of the secondary alcohol **2.26a** – an enol acetate possessing a stereogenic centre. The synthesis began with a palladium-catalysed allylic alkylation reaction of tosylate **2.12** with *N*-methoxy-*N*-methylamide **2.27** (Scheme 2.4). Ester **2.28** was decarboxylated to give amide **2.29**. Treatment with lithium trimethylsilylacetylide afforded **2.30**, which after deprotection gave ynone **2.31**. Treatment of **2.31** with acetic acid in the presence of NMM[17] furnished the enone **2.32**, which was reduced under Luche conditions[18] to afford the alcohol **2.26a** and silyl-protected to afford **2.26b**.



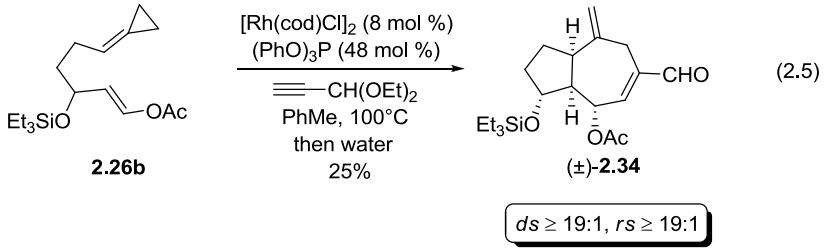
Scheme 2.4. Preparation of the cyclisation substrate **2.26b**.

To our surprise, treatment of **2.26b** with methyl propiolate produced the bicycle (±)-

2.33 in 25% yield as a *single* regio- and diastereoisomer (eqn. 2.4). The same high degree of regio- and diastereoselectivity was observed in a reaction of **2.26b** with 3,3-diethoxyprop-1-yne, which furnished the aldehyde (±)-**2.34** upon hydrolysis (eqn. 2.5).

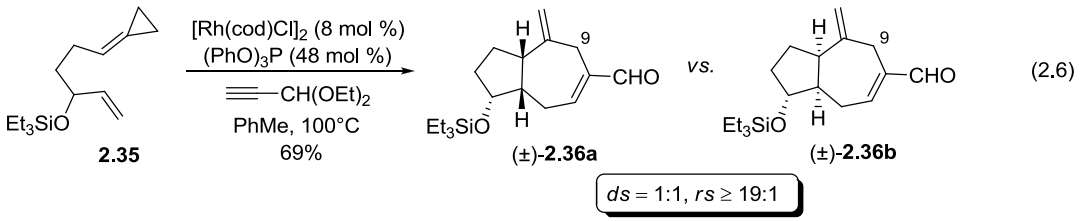


(2.4)



(2.5)

When the analogous substrate **2.35**, which lacks the enol acetate moiety, was subjected to the reaction with the acetal, the reaction proceeded with much higher efficiency affording the desired product in 69% yield. However, to our surprise, no stereoinduction from the secondary alcohol was observed in this case with the diastereomers (±)-**2.36a** and (±)-**2.36b** being formed in a 1:1 ratio (eqn. 2.6).



(2.6)

It is necessary to point out here that in every [(3+2)+2] carbocyclisation reaction, a substrate bearing a stereogenic centre and an unsymmetrical alkyne can form four different products. The exact product distribution depends on the diastereoselectivity

of the process and the regioselectivity of the alkyne insertion. It is critical to be able to distinguish the mixture of regioisomers from the mixture of the diastereomers. In the case of products derived from monosubstituted alkynes the two *bis*-allylic protons at C9 are indicative. Figure 2.6 shows the ^{1}H NMR signals of both diastereomeric products from equation 2.6. In both cases we observe an AB splitting pattern, which corresponds to the depicted regioisomer. If the other regioisomer was present then we would observe an ABX splitting for both protons because of the extra interaction with the olefinic proton.

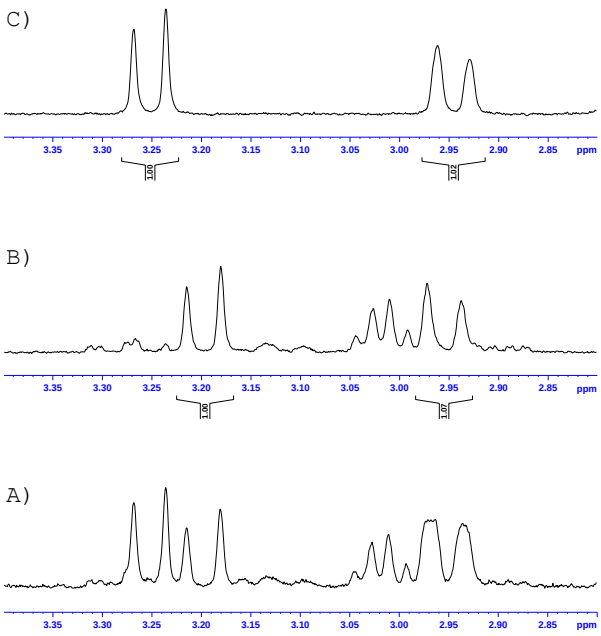


Figure 2.6 Determination of the nature of regioselectivity from ^{1}H NMR spectrum : A – crude reaction mixture, B – diastereomer **2.36b**, C – diastereomer **2.36a**.

Although the exact origin of the difference in diastereoselectivity between an enol acetate and an unsubstituted olefin is unknown, we propose that the coordination of the enol acetate moiety to the metal centre may play a role. It is known that vinyl acetate can complex to transition metals in a chelating manner.[19] It is possible that a

similar interaction is taking place in the course of the rhodium-catalysed [(3+2)+2] carbocyclisation, leading to a conformational change prior to the crucial carbometallation event (Fig. 2.7).

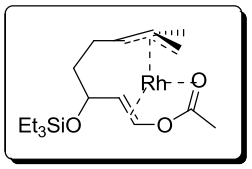
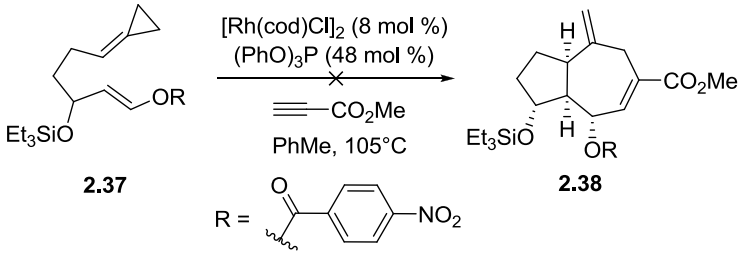


Figure 2.7 Proposed complexation of enol acetate to the metal centre.

It is worth noting that the reaction seems to be quite sensitive to steric hindrance. The bulkier substrate **2.37** (*p*-nitrobenzoyl analogue of **2.26b**) failed to afford any of the product **2.38** when subjected to the carbocyclisation conditions with methyl propiolate (eqn. 2.7). However, although we believe that the steric bulk of this substrate plays a key role in this case, electronic effects cannot be excluded.



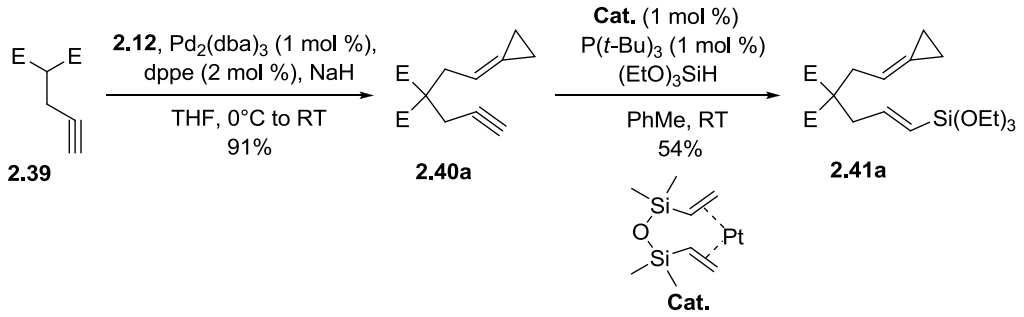
(2.7)

We have established that the rhodium-catalysed carbocyclisation of enol acetates is diastereoselective. However, the yield of this process has generally been shown to be disappointing and significant decomposition of the starting material is generally observed under the reaction conditions. This could happen either through hydrolysis of the sensitive enol acetate moiety, or through side reactions of the initially formed rhodium-TMM species[20,21] that fails to react quickly enough with the electron rich alkene.

2.4. Rhodium-Catalysed [(3+2)+2] Carbocyclisation of Vinyl Silanes

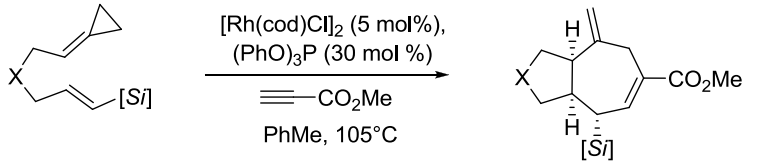
2.4.1. Synthesis of Vinyl Silanes and their Reactivity in the Rhodium-Catalysed [(3+2)+2] Carbocyclisation

At this point, we decided to trial an alternative approach, namely the use of a surrogate of oxygen in the form of an oxidisable group. Silicon based groups seemed especially appealing due to the wide range of oxidation reactions they can undergo.[22,23] We also assumed that the electronic properties of the vinyl silane would be more similar to those of a normal double bond than an enol acetate. This would potentially result in better reactivity and improved stability of the substrates under the reaction conditions. After a thorough examination of a number of potential candidates we chose triethoxysilyl- and dimethylphenylsilyl-groups as the most promising. The synthesis of the triethoxysilyl substrate is depicted in Scheme 2.6. Palladium-catalysed allylic alkylation of the commercially available **2.39** afforded the ACP **2.40a** in excellent yield. Vinyl silane **2.41a** was synthesised by hydrosilylation of the corresponding alkyne **2.40a** in the presence of a Karstedt's platinum catalyst[24] (Scheme 2.5). It must be noted here that the vinyl silane **2.41a** has limited stability on silica gel, meaning that its purification must be carried out quickly and whilst employing minimum amounts of adsorbent.



Scheme 2.5. Preparation of vinylsilane **2.41a**.

When subjected to the standard rhodium-catalysed [(3+2)+2] carbocyclisation conditions in the presence of methyl propiolate, vinyl silane **2.41a** was transformed into cycloadduct (±)-**2.42a** in 63% yield. The reaction proceeded with excellent regio- and diastereoselectivity to afford (±)-**2.42a** with the all *syn* arrangement of bridgehead hydrogens and silyl group (eqn. 2.8). It is noteworthy that the product is perfectly stable on silica gel and can be purified without any particular precautions. It was established by Evans and Inglesby[25] that under identical reaction conditions, the corresponding dimethylphenylsilane afforded the cycloadduct with the same selectivity, albeit in lower yield (eqn. 2.8). Therefore, the triethoxysilyl group was chosen for the oxygen surrogate in the following study.



(2.8)

2.41a, X = $C(CO_2Me)_2$, [*Si*] = $Si(OEt)_3$
2.43, X = $C(CO_2Me)_2$ [*Si*] = $SiMe_2Ph$

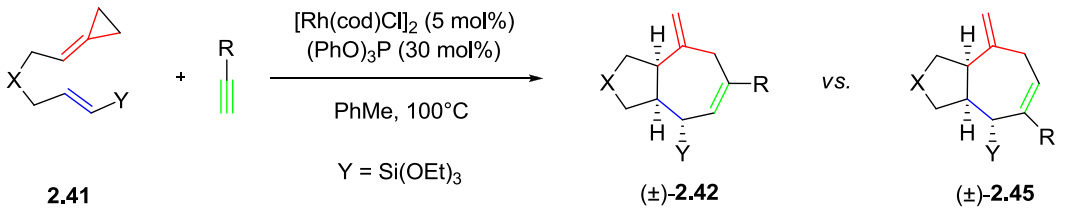
(±)-**2.42a** (63%), [*Si*] = $Si(OEt)_3$
(±)-**2.44** (53%), [*Si*] = $SiMe_2Ph$
ds ≥ 19:1, *rs* ≥ 19:1

2.4.2. Reaction Scope

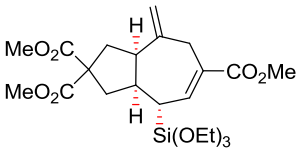
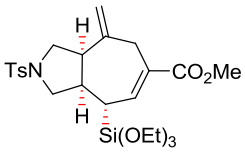
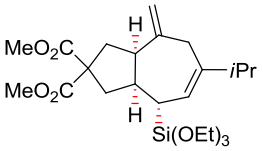
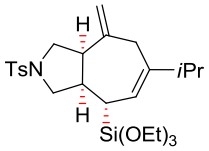
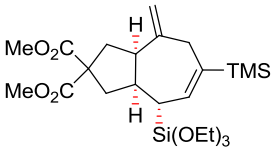
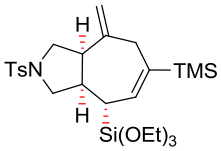
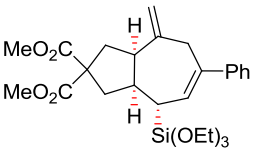
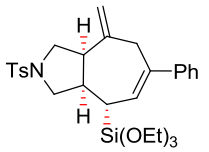
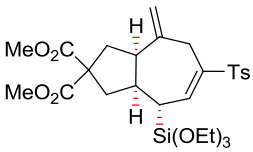
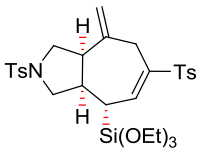
As the next step, we needed to examine the carbocyclisation of vinyl silanes in order to determine the scope of this reaction. Table 2.2 outlines the results of the carbocyclisation of carbon- and nitrogen-tethered ACP triethoxysilane **2.41** with a variety of monosubstituted alkynes. The reaction of the ACP **2.41a** (X=$C(CO_2Me)_2$) with isopropylacetylene afforded regioisomeric cycloadducts (±)-**2.42b**/(±)-**2.45b** in a 4:1 ratio favouring (±)-**2.42b** (Table 2.2, entry 2). This result is of high importance because previously it was unknown whether alkynes without electron-withdrawing activating groups are able to participate in the rhodium-catalysed [3+2+2] carbocyclisation. Methyl propiolate, trimethylsilylacetylene and phenylacetylene all

afforded excellent regio- and diastereoselectivity for (±)-**2.42a,** (±)-**2.42c**, and (±)-**2.42d**, respectively, albeit the latter required a slightly elevated temperature (entries 1, 3, and 4). Interestingly, the cycloadducts from the reaction with trimethylsilylacetylene contain two different silyl moieties thereby making them particulary versatile intermediates, which can be further elaborated into an array of functional groups.

Table 2.2. Highly regio- and diastereoselective [(3+2)+2] carbocyclisation reaction.



2.41 (±)-**2.42** (±)-**2.45**

	2.41a X=C(CO_2Me)$_2$		**2.41b** X=NTs	
1[a]		(±)-**2.42a**, 63% *rs ≥ 19:1, ds ≥ 19:1*	6		(±)-**2.42e**, 30%[e] *rs ≥ 19:1, ds ≥ 19:1*
2		(±)-**2.42b**, 73% *rs = 4:1, ds ≥ 19:1*	7		(±)-**2.42f**, 73% *rs = 5:1, ds ≥ 19:1*
3		(±)-**2.42c**, 61% *rs ≥ 19:1, ds ≥ 19:1*	8		(±)-**2.42g**, 73% *rs ≥ 19:1, ds ≥ 19:1*
4		(±)-**2.42d**, 81%[b] *rs ≥ 19:1, ds ≥ 19:1*	9		(±)-**2.42h**, 81%[b] *rs ≥ 19:1, ds ≥ 19:1*
5		(±)-**2.42d** not isolated[c] *rs ≥ 19:1, ds ≥ 19:1*	10		(±)-**2.42i** not isolated[c] *rs ≥ 19:1, ds ≥ 19:1*

[a]All reactions were carried out with 0.2 mmol of ACP in toluene (0.1 M) at 100°C utilizing 5 mol % of [Rh(cod)Cl]$_2$, 30 mol % P(OPh)$_3$, and 5 equiv. of alkyne. Isolated yields are reported. Regio- and diastereoselectivities were determined by ^{1}H NMR on the crude reaction mixtures. [b]Reaction performed at 120°C in *p*-xylene. [c]Conversion of 50% could only be achieved by the slow addition of alkyne in (10 h). [d]Only 50% conversion was achieved.

The reaction is also somewhat general with respect to the ACP, with the sulfonamide-tethered **2.41b** (X=NTs) affording the corresponding cycloadducts (±)-

2.42e-h with similar yields and selectivities (entries 5-8), albeit with the exception of (±)-**2.42e**. Unfortunately, both substrates failed to react with ethynyl sulfone **2.24**. Partial conversion could be achieved by very slow addition of the sulfone (syringe pump, overnight) but it turned out to be a highly unpractical process. To confirm the relative stereochemistry of cycloadducts, bicycle (±)-**2.42g** was studied by X-ray crystallography. As expected, the all *syn* arrangement of bridgehead hydrogen atoms and silyl substituent was observed (Fig. 2.8). All other compounds were assigned by analogy based on coupling constants in ^{1}H NMR.

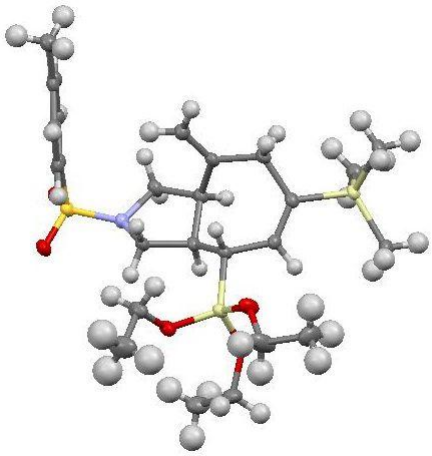
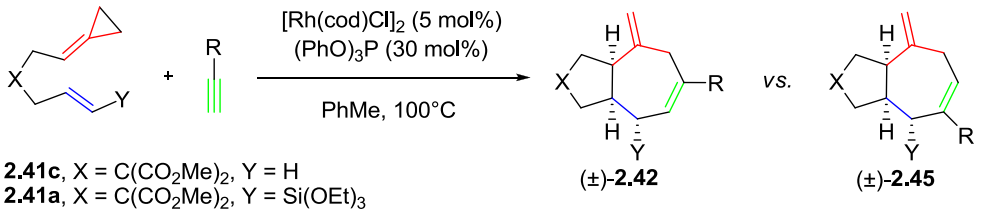


Figure 2.8 X-Ray structure of cycloadduct (±)-**2.42g**.

Since the majority of the alkynes were previously unknown to act as partners in rhodium-catalysed [(3+2)+2] carbocyclisation, we decided to compare the results of our vinyl silane cycloaddition with analogous reaction of unsubstituted ACPs. It turned out that although **2.41c** (X=C(CO_2Me)$_2$, Y=H) did react with isopropylacetylene and trimethylsilylacetylene, the mixtures of regioisomers (±)-**2.42** and (±)-**2.45** were produced in a 1:1 ratio in both cases (Table 2.3, enties 1, 2, Y=H). Interestingly, when malonate **2.41c** (X=C(CO_2Me)$_2$, Y=H) was reacted with ethynyl sulfone, full conversion could be achieved, and the bicyclic product was isolated in

79% yield with 2:1 selectivity in favour of isomer (±)-**2.42l** (entry 3, Y=H). The addition of sulfone by syringe pump is crucial, since the reaction fails to afford product in high yields if the sulfone is added at the beginning of the reaction. Interestingly, disubstituted alkynes lacking activating groups, such as 5-trimethylsilylpent-4-ynol, failed to react with **2.41c** (X=C(CO_2Me)$_2$, Y=H). Most likely disubstituted alkynes are too sterically hindered and fail to coordinate to rhodium centre and/or insert into Rh-C bond.

Table 2.3 Rhodium-catalysed [(3+2)+2] cycloadditions of unsubstituted olefins vs cycloadditions of vinyl silanes.



2.41c, X = C(CO_2Me)$_2$, Y = H
2.41a, X = C(CO_2Me)$_2$, Y = Si(OEt)$_3$

(±)-**2.42** (±)-**2.45**

Entry[a]	R	Yield, Y=H	Regioselectivity, Y=H	Yield, Y=Si(OEt)$_3$	Regioselectivity, Y=Si(OEt)$_3$
1	-*i*Pr	80%	**2.42j/2.45j** = 1:1	73%	≥ 4:1
2	-TMS	79%	**2.42k/2.45k** = 1:1	61%	≥ 19:1
3	-Ts	79%[b]	**2.42l/2.45l** = 2:1	n.i.	≥ 19:1
4	-Ph	78%	**2.42m/2.45m**= 1:4	81%	≥ 19:1
5	-CO_2Me	50%	**2.42n/2.45n** = 2:1	63%	≥ 19:1

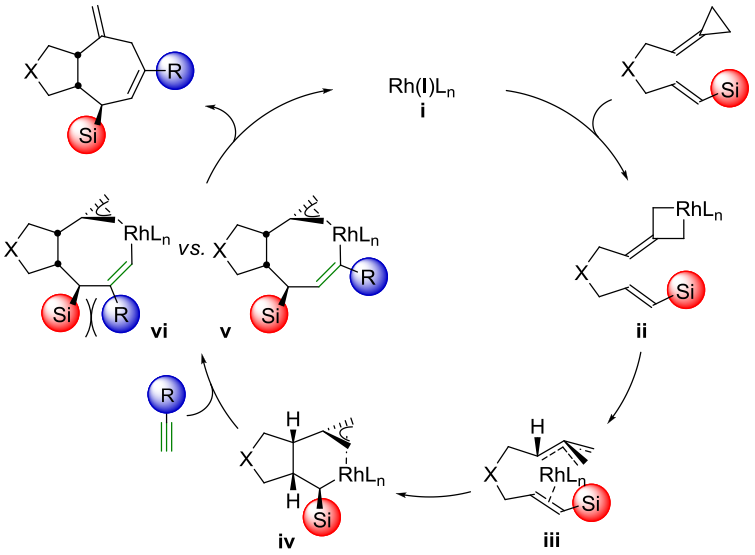
[a]All reactions of unsubstituted olefin were carried with 0.2 mmol ACP in toluene (0.1 M) at 100°C utilizing 5 mol % of [Rh(cod)Cl]$_2$, 30 mol % P(OPh)$_3$, and 5 equiv. of alkyne. Isolated yields are reported. Regioselectivities were determined by ^{1}H NMR on the crude reaction mixtures. [b]Full conversion could only be achieved by slow addition of alkyne (4 h).

The regioselectivity in the above examples was in stark contrast with the results obtained previously for the triethoxysilane **2.41a** (X=C(CO_2Me)$_2$, Y=Si(OEt)$_3$) that reacted with isopropylacetylene and trimethylsilylacetylene with 4:1 and ≥19:1 regioselectivity, respectively (Table 2.3, entries 1, 2, Y=Si(OEt)$_3$ *vs.* Y=H). Same

dramatic improvement in regioselectivity was observed in reactions of ethynylsulfone and methyl propiolate (entries 3, 5, Y=Si(OEt)$_3$ *vs.* Y=H). Additionally, the selectivity for the phenylacetylene cycloadduct is remarkable with **2.41a** (X=C(CO$_2$Me)$_2$, Y=Si(OEt)$_3$) which affords regioisomer (±)-**2.42** with ≥19:1 selectivity, whereas it was established earlier that **2.41c** (X=C(CO$_2$Me)$_2$, Y=H) reacts with phenylacetylene affording the opposite regioisomer with 4:1 selectivity.[26] The fact that phenylacetylene facilitates a reversal in the normal mode of regioselectivity is consistent with insertion occuring with electronic control. The reversal in regioselectivity between R=CO$_2$Me and Ph is attributed to the direction of polarisation.[27] This shows that triethoxysilyl group is able to override the inherent electronic preference for alkyne insertion.

2.4.3. Proposed Mechanism

Scheme 2.6 outlines the proposed catalytic cycle, which delineates the origin of regiocontrol in this process. Oxidative addition of the metal into the distal bond of the cyclopropane, followed by rearrangement to the TMM species **iii** provides the resting state for this transformation.[21] This is followed by rate-limiting stereospecific carbometallation of the alkene to afford **iv** as a single diastereoisomer. We believe that the steric bias of the triorganosilyl group [*Si*] controls the orientation of alkyne insertion to minimise steric interaction with the substituent on the alkyne (R), thereby favouring the formation of **v** (*vs* **vi**). Reductive elimination of the rhodium(III) intermediate **v** regenerates the active rhodium(I) species to afford the desired carbocycle **2.42** with excellent regio- and diastereoselectivity. Interestingly, we are unaware of any examples of higher-order carbocyclisation reactions of this type with vinylsilanes.

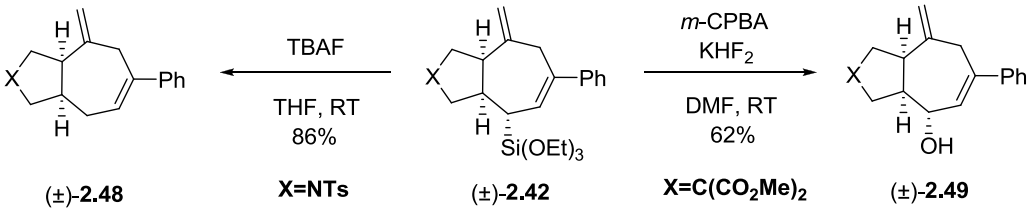


Scheme 2.6 Proposed catalytic cycle of the rhodium-catalysed [(3+2)+2] carbocyclisation reaction of vinylsilanes.

2.4.4. Elaboration of the Reaction Products

A great improvement in the selectivity of alkyne insertion was observed with vinylsilanes when compared to unsubstituted alkenes, which led us to idea that the triethoxysilyl group could also be viewed as an auxiliary guiding these processes. We envisaged that bicyclic products obtained in the carbocyclisation reactions could be further modified by cleaving the C-Si bond to afford the same products as those without silane, albeit with significantly improved selectivities. Moreover, oxidation of silanes to alcohols can be carried out providing an access to C6 hydroxylated 5,7-bicycles, a motif present in many sesquiterpene natural products.[1] Indeed, treatment of (±)-**2.42h** (X=NTs) with TBAF, furnished (±)-**2.48** in 86% yield as a single regio- and diastereoisomer, which circumvents the problems associated with simple monosubstituted alkynes (Scheme 2.7). It is crucial that the reaction is carried out at room temperature since elevated temperatures resulted in partial migration of the endocyclic double bond. Alternatively, Tamao oxidation[22] of the triethoxysilyl group

in (±)-**2.42d** (X=C($CO_2Me)_2$) furnished the secondary alcohol (±)-**2.49** in 62% yield, which maps onto the stereotriad in the C-6 hydroxylated sequiterpenes.



Scheme 2.7 Removal and oxidation of the triethoxysilyl group in the trialkoxysilyl-substituted bicycloheptadienes.

2.5. Conclusion

In summary, we have developed the first highly regio- and diastereoselective rhodium(I)-catalysed [(3+2)+2] carbocyclisation reaction of triethoxysilyl-substituted ACPs with monosubstituted alkynes. It was shown for the first time that not only activated alkynes but also simple alkyl- or silyl-substituted alkynes are competent reaction partners. The vinylsilane dramatically improves the regioselective insertion of both activated and unactivated alkynes. Furthermore, the silyl group can either serve as a traceless controller of regioselectivity or a secondary alcohol surrogate. Additionally, this study provides a deeper understanding of the reaction mechanism of the rhodium-catalysed [(3+2)+2] carbocyclisation reaction, in which alkyne insertion occurs *via* electronically and sterically controlled processes. Finally, these developments are likely to be employed in related [m+n+o] carbocyclisation reactions.

2.6. Experimental

2.6.1. General Information

All reactions were carried out under an argon atmosphere with anhydrous solvents unless stated otherwise. All commercially available reagents were purchased and used as received. Anhydrous DCM, Et_2O, benzene and toluene were obtained by passing solvents through activated alumina columns in a Grubbs purification system (*PureSolv MD-6* of *Innovative Technology Inc.*). Anhydrous THF was obtained by distillation from benzophenone ketyl. All compounds were purified by flash chromatography using silica gel 60Å (40-63 μm, *Aldrich*) and gave spectroscopic data consistent with being ≥ 95% the assigned structure. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60-F_{254} aluminium plates (*Merck*); visualised using UV light and by treatment with a $KMnO_4$ or anisaldehyde dip, followed by heating. Optical rotations ($[\alpha]_D^{20}$) were measured on a *Perkin-Elmer Model 343 plus* polarimeter with a sodium lamp (D line, 589 nm) at ambient temperature (indicated in ºC as superscript) using a 1 mL quartz cell of 100 mm length; solution concentrations (*c*) are given in g/100 mL. IR spectra were recorded on a *Perkin-Elmer FT-IR Spectrum 100* (ATR) spectrometer; wavenumbers (ν) are given in cm^{-1}; and the abbreviations w (weak, < 30%), m (medium, 30-65%), s (strong, >65%) and br (broad) are used to describe the relative intensities of the IR absorbance bands. Mass spectra were obtained through the Chemistry Department Mass Spectrometry Service, University of Liverpool or the EPSRC National Mass Spectrometry Service, Swansea. High resolution chemical ionization (CI) and electrospray ionisation (ESI) mass spectra were recorded on a *Fisons Trio-1000* or *LTQ Orbitrap*, and *Micromass LTC* mass spectrometers, respectively. ^{1}H NMR and ^{13}C NMR spectra were recorded on a *Bruker Avance DRX-500* spectrometer in

$CDCl_3$ (unless stated otherwise) at ambient temperature; chemical shifts (δ) are given in ppm and calibrated using the signal of residual undeuterated solvent as internal reference (δ_H = 7.26 ppm and δ_C = 77.16 ppm). ^{1}H NMR data are reported as follows: chemical shift (multiplicity, coupling constant, integration). Coupling constants (*J*) are reported in Hz and apparent splitting patterns are designated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad), app. (apparent) and the appropriate combinations. ^{13}C NMR spectra with complete proton decoupling were described with the aid of an APT sequence, separating methylene and quaternary carbons (e, even), from methyl and methine carbons (o, odd).

2.6.2. General Procedures

A. General procedure for the hydrosilylation of alkynes with triethoxysilane.

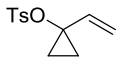
Tri-tert-butylphosphine (1.0 M in Toluene, 4.0 µL, 4.0 µmol) was added to a solution of platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane (2% wt in xylenes, 0.071 mL, 3.2 µmol) in Toluene (12 mL) at RT and the resulting mixture was stirred for 5 min. To this solution was added a solution of Substrate (0.32 mmol) in Toluene (4+4 mL) followed by triethoxysilane (0.065 mL, 0.35 mmol). The resulting dark mixture was stirred at RT overnight, filtered through the plug of silica gel (washed with Et_2O) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether).

B. General procedure for the rhodium-catalysed [(3+2)+2] carbocyclization reaction of vinyl silanes.

A solution of the ACP (0.20 mmol), alkyne (1.00 mmol), $[Rh(cod)Cl]_2$ (0.01 mmol), and triphenylphosphite (0.06 mmol) in toluene (2 mL) was back-filled under vacuum with argon. The reaction vessel was placed in pre-heated oil bath (100°C) and stirred

for ca. 16 h. The reaction was cooled to ambient temperature and concentrated in vacuo to afford the crude product. The crude residue was purified by flash chromatography (silica gel, eluting with diethyl ether/hexanes).

2.6.3. Experimental Procedures: Rhodium-Catalysed [(3+2)+2] Carbocyclisation of Vinyl Acetates



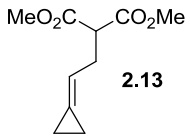
2.12

1-Vinylcyclopropyl 4-methylbenzenesulfonate (2.12)

Tosylate **2.12** was prepared in 3 steps in 77% yield starting from commercially available ethyl 3-chloropropanoate according to the procedure used by Evans *et al.* (2014)[28] in 86% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79-7.76 (m, 2H), 7.34-7.31 (m, 2H), 5.89 (dd, *J*=17.1, 10.8 Hz, 1H), 5.10 (d, *J*=17.1 Hz, 1H), 5.01 (d, *J*=10.7 Hz, 1H), 2.44 (s, 3H), 1.36-1.34 (m, 2H), 0.94-0.91 (m, 2H).

IR (neat) 1596 (w), 1348 (s), 1164 (s), 1089 (m), 949 (s), 820 (s), 703 (s) cm^{-1}.



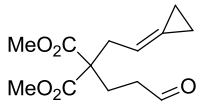
2.13

***Dimethyl 2-(2-cyclopropylideneethyl)malonate (2.13)*[29]**

Dimethyl malonate (1.20 mL, 10.5 mmol) was added dropwise to a suspension of sodium hydride (0.185 g, 60% wt, 4.62 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 15 mins. 1-Vinylcyclopropyl 4-methylbenzenesulfonate (**2.12**) (1.00 g, 4.20 mmol) was added to a solution of $Pd_2(dba)_3$ (0.038 g, 0.042 mmol) and dppe (0.033 g, 0.084 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred for 40 mins at room temperature and then slowly added to anion solution *via* syringe. The resulting yellow suspension

was stirred for 2 h, quenched with water and extracted several times with EtOAc. The combined organic fractions were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:40 → 1:5) afforded **2.13** (0.685 g, 82%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76-5.72 (m, 1H), 3.73 (s, 6H), 3.57 (t, *J* = 7.7 Hz, 1H), 2.80-2.76 (m, 2H), 1.05-1.02 (m, 4H).



2.15

Dimethyl 2-(2-cyclopropylideneethyl)-2-(3-oxopropyl)malonate (2.15)

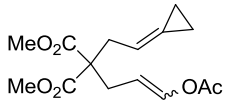
Sodium hydride (60% wt, 0.013 g, 0.33 mmol) and acrolein (**2.14**) (0.20 ml, 3.0 mmol) were added successively to a solution of malonate **2.13** (0.429 g, 2.16 mmol) in MeOH (11 ml) at 0°C whereupon the yellow colour appeared which faded after the mixture was stirred at RT for 20 h. Then the same amounts of sodium hydride and acrolein were added (yellow colour reappeared) and the mixture was stirred at RT for 24 h. The reaction mixture was quenched by the addition of AcOH (100 µl, 1.73 mmol) and concentrated *in vacuo*. Brine was added to the residue and the mixture was extracted with Et_2O (3 x 20 ml). Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:8 → 1:4→ 1:2 → 1:1) afforded **2.15** (0.143 g, 26%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (t, *J*=1.3 Hz, 1H), 5.62-5.57 (m, 1H), 3.72 (s, 6H), 2.79 (dm, *J*=7.3 Hz, 2H), 2.50-2.46 (m, 2H), 2.21-2.18 (m, 2H), 1.11-1.06 (m, 2H), 1.02-0.97 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.96 (o), 171.59 (e), 127.19 (e), 111.65 (o), 57.06 (e), 52.70 (o), 39.39 (e), 36.18 (e), 25.17 (e), 3.16 (e), 2.02 (e).

IR (neat) 2955 (w), 1724 (s), 1435 (m), 1198 (s), 1102 (m), 1000 (w), 755 (w) cm^{-1}.

HRMS (CI (Ammonia), $[M+H]^+$) calculated for $C_{13}H_{19}O_5$ 255.1227, found 255.1235.



2.10

E/*Z* = 2:1

(E)-Dimethyl 2-(3-acetoxyallyl)-2-(2-cyclopropylideneethyl)-malonate (2.10)

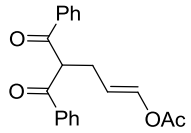
DMAP (6.7 mg, 0.055 mmol) was added to a solution aldehyde **2.15** (0.140 g, 0.550 mmol), triethylamine (0.23 ml, 1.7 mmol) and acetic anhydride (0.12 ml, 1.3 mmol) in THF (4 ml) and the resulting mixture was stirred at RT for 2 days. The reaction mixture was quenched with water and extracted with Et_2O (3x10 ml). The combined organic extracts were washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:8 → 1:4→ 1:2) afforded **2.10** (0.127 g, 74%, a 2:1 mixture of *E/Z* isomers) as a yellow oil.

Only the ^{1}H NMR data for the *E* isomer are given. ^{13}C NMR could not be resolved unambiguously.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (dt, *J*=12.4, 1.4 Hz, 1H), 5.60-5.55 (m, 1H), 5.30 (dt, *J*=12.6, 8.2 Hz, 1H), 3.72 (s, 6H), 2.80-2.75 (m, 2H), 2.57 (dd, *J*=8.1, 1.3 Hz, 2H), 2.10 (s, 3H), 1.11-1.04 (m, 2H), 1.03-0.95 (m, 2H).

IR (neat) 2955 (w), 1731 (s), 1436 (w), 1370 (w), 1285 (w), 1199 (s), 1101 (m), 1051 (m), 934 (m), 755 (w) cm^{-1}.

HRMS (CI (Ammonia), $[M+H]^+$) calculated for $C_{15}H_{21}O_6$ 297.1333, found 297.1343.

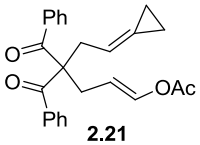


2.20

***(E)-4-Benzoyl-5-oxo-5-phenylpent-1-enyl acetate (2.20)*[11]**

Propargyl acetate (0.30 mL, 3.0 mmol) and diketone **2.18** (0.94 g, 4.2 mmol) were dissolved in DCM (8 mL) and slowly added to a suspension of chloro[tris(2,4-di-*tert*-butylphenyl)phosphite]gold (**2.19**) (0.046 g, 0.060 mmol) in DCM (4 mL) at room temperature. The reaction mixture was stirred overnight, filtered through a plug of silica gel and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:20 → 1:5) afforded **2.20** (0.89 g, 92%) as a green oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95-7.93 (m, 4H), 7.59-7.56 (m, 2H), 7.47-7.44 (m, 4H), 7.43 (d, *J* = 12.5 Hz, 1H), 5.51 (dt, *J* = 12.4, 7.9 Hz, 1H), 5.23 (t, *J* = 6.7 Hz, 1H), 2.82-2.79 (m, 2H), 2.08 (s, 3H).



2.21

(E)-4,4-Dibenzoyl-6-cyclopropylidenehex-1-enyl acetate (2.21)

A solution of enol acetate **2.20** (0.121 g, 0.370 mmol) in THF (1 mL) was added dropwise to a suspension of sodium hydride (0.015 g, 60% wt, 0.37 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at room temperature for 15 mins. 1-Vinylcyclopropyl 4-methylbenzenesulfonate (**2.12**) (0.081 g, 0.34 mmol) was added to a solution of $Pd_2(dba)_3$ (0.0031 g, 0.0034 mmol) and dppe (0.0027 g, 0.0068 mmol) at room temperature. The mixture was stirred for 40 mins and added *via* cannula to the anion solution. The resulting mixture was stirred at room temperature for 2.5 h, quenched with water and extracted several times with EtOAc. The

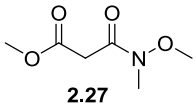
combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:20 → 1:5) afforded **2.21** (0.113 g, 86%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85-7.83 (m, 4H), 7.47-7.45 (m, 2H), 7.35-7.32 (m, 4H), 6.83 (d, *J* = 12.4 Hz, 1H), 5.45-5.42 (m, 1H), 5.12 (dt, *J* = 12.4, 8.3 Hz, 1H), 3.09 (d, *J* = 7.5 Hz, 2H), 2.91 (d, *J* = 8.3 Hz, 2H), 2.07 (s, 3H), 0.97-0.95 (m, 2H), 0.64-0.61 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.97 (e), 167.95 (e), 138.14 (o), 136.54 (e), 133.40 (o), 129.17 (o), 128.94 (o), 127.50 (e), 111.11 (o), 108.07 (o), 67.15 (e), 36.04 (e), 31.78 (e), 20.86 (o), 3.15 (e), 1.93 (e).

IR (neat) 2981 (w), 1755 (m), 1659 (s), 1597 (w), 1447 (m), 1205 (s), 1105 (m), 903 (m), 727 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{25}H_{24}O_4Na$ 411.1572, found 411.1577.

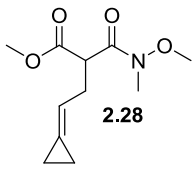


2.27

***Methyl 3-(methoxy(methyl)amino)-3-oxopropanoate (2.27)*[30]**

Amide **2.27** was prepared starting from commercially available methyl malonylchloride according to the procedure used by Helmchen *et al.* (2008). Purification of crude amide by bulb to bulb distillation (140 ^oC, 2 Torr) afforded compound **2.27** (5.12 g, 72.3%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.71 (s, 3H), 3.51 (s, 2H), 3.22 (s, 3H).



2.28

Methyl 4-cyclopropylidene-2-(methoxy(methyl)carbamoyl) butanoate (2.28)

Amide **2.27** (0.242 g, 1.50 mmol) was dissolved in THF (2 mL) and slowly added to

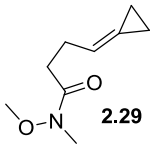
a suspension of sodium hydride (0.044 g, 60% wt, 1.1 mmol) in THF (4 mL) at 0 °C. The reaction mixture was stirred at room temperature for 15 mins. 1-Vinylcyclopropyl 4-methylbenzenesulfonate (**2.12**) (0.238 g, 1.00 mmol) was added to a solution of $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol) and dppe (8.0 mg, 0.020 mmol) in THF (4 mL) at rt. The reaction mixture was stirred at room temperature for 40 mins and then slowly added to the anion solution *via* syringe. The resulting yellow solution was stirred at room temperature for 4 h, quenched with water and extracted several times with EtOAc. The combined organic fractions were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with ethyl acetate/petroleum ether 1:10 → 1:1) afforded **2.28** (0.188 g, 83%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79-5.75 (m, 1H), 3.86 (t, *J* = 7.7 Hz, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.20 (s, 3H), 2.78-2.75 (m, 2H), 1.05-0.99 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 124.34 (e), 114.36 (o), 61.47 (o), 52.43 (o), 48.53 (o), 32.62 (o), 31.08 (e), 2.54 (e), 2.01 (e).

IR (neat) 2980 (w), 2952 (w), 1739 (s), 1663 (s), 1436 (m), 1162 (s), 986 (m) cm^{-1}.

HRMS (ES, $[M+Na]^+$) calculated for $C_{11}H_{17}NNaO_4$ 250.1055, found 250.1059.



2.29

4-Cyclopropylidene-N-methoxy-N-methylbutanamide (2.29)

An aqueous solution of NaOH (82 mL, 2N) was added to a solution of ester **2.28** (5.82 g, 25.6 mmol) in MeOH (250 mL). The reaction mixture was stirred at room temperature for 1.5 h, acidified to pH=1 with 2N HCl and extracted several times with DCM. The aqueous phase was saturated with solid NaCl and extracted with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4

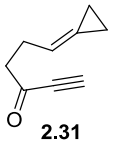
and concentrated *in vacuo*. Several crystals of 2,6-di-*tert*-butyl-4-methylphenol were added to the crude residue and the mixture was heated at 160 °C for 1 h. After cooling to room temperature the crude residue was filtered through a plug of silica gel (50 mL silica gel, washed with DCM) to afford amide **2.29** (3.98 g, 92%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79-5.83 (m, 1H), 3.68 (s, 3H), 3.18 (s, 3H), 2.62-2.56 (m, 2H), 2.54-2.48 (m, 2H), 1.05-1.01 (m, 4H).

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

IR (neat) 2978 (w), 1660 (s) 1413 (m), 1384 (m), 1176 (m), 994 (m) cm^{-1}.

HRMS (APCI, $[M+H]^+$) calculated for $C_9H_{16}NO_2$ 170.1176, found 170.1174.



2.31

***6-Cyclopropylidenehex-1-yn-3-one (2.31)*[31]**

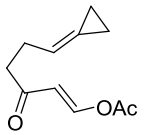
A solution of *n*BuLi (18.7 mL, 2.5 M in hexanes, 46.7 mmol) was added dropwise to a solution of trimethylsilylacetylene (6.73 mL, 47.9 mmol) in THF (240 mL) at −30 °C. The reaction mixture was stirred for 5 mins followed by 10 mins at 0 °C. The reaction mixture was cooled to −20 °C and a solution of amide **2.29** (4.056 g, 24.00 mmol) in THF (10 mL) was added slowly. The resulting mixture was stirred at −20 °C for 30 mins and at 0 °C for 2 h. The reaction mixture was quenched with 1N HCl and extracted several times with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was dissolved in THF (340 mL) and MeOH (9.6 mL) and cooled to −78 °C. To this solution TBAF (9.6 mL, 1.0 M in THF, 9.6 mmol) was added slowly and the resulting mixture was stirred at −78 °C for 30 min and poured into ice/10% HCl

mixture. The mixture was extracted several times with Et_2O and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:40 → 1:20) afforded **2.31** (3.048 g, 95%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78-5.75 (m, 1H), 3.22 (s, 1H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.57-2.53 (m, 2H), 1.06-1.00 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 187.19 (e), 122.96 (e), 115.60 (o), 81.53 (e), 78.55 (e), 44.85 (e), 26.10 (e), 2.29 (e), 2.14 (e).

IR (neat) 3258 (w), 2981 (w), 2092 (m), 1678 (s), 1105 (m) cm^{-1}.



2.32

(E)-6-Cyclopropylidene-3-oxohex-1-enyl acetate (2.32)

NMM (1.19 mL, 10.8 mmol) was added to a solution of ynone **2.31** (0.97 g, 7.2 mmol) and acetic acid (0.41 mL, 7.2 mmol) in DCM (70 mL) at room temperature. The reaction mixture was stirred for 3 h, quenched with saturated NH_4Cl and extracted several times with DCM. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:20 → 1:5) afforded vinylogous ester **2.32** (1.12 g, 84%) as a yellow oil.

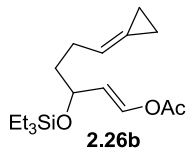
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 12.8 Hz, 1H), 6.02 (d, *J* = 12.8 Hz, 1H), 5.80-5.76 (m, 1H), 2.72 (t, *J* = 7.4 Hz, 2H), 2.53-2.48 (m, 2H), 2.23 (s, 3H), 1.02-1.01 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.54 (e), 167.27 (e), 148.60 (o), 122.44 (e), 116.43 (o), 114.29 (o), 40.21 (e), 26.44 (e), 20.81 (o), 2.17 (e), 2.15 (e).

IR (neat) 2980 (w), 1773 (s), 1669 (m), 1625 (m), 1370 (m), 1187 (s), 1123 (s), 951

(m) cm^{-1}.

HRMS (CI (Ammonia), $[M+H]^+$) calculated for $C_{11}H_{14}O_3$ 195.1016, found 195.1020.



2.26b

(E)-6-Cyclopropylidene-3-(triethylsilyloxy)hex-1-enyl acetate (2.26b)

Cerium(III) chloride heptahydrate (58.1 mg, 0.150 mmol) was added to a solution of vinylogous ester **2.32** (30.2 mg, 0.150 mmol) in MeOH (1.5 mL) at −78 °C. Sodium borohydride (9.9 mg, 0.26 mmol) was added and the reaction mixture was stirred at −78 °C for 10 min. After dilution with Et_2O the mixture was quenched with saturated NH_4Cl and extracted several times with Et_2O. Combined organic extracts were dried over Na_2SO_4, filtered through a plug of silica gel and concentrated *in vacuo*. Crude residue was dissolved in THF (7 mL). To this solution imidazole (0.073 g, 1.1 mmol) and chlorotriethylsilane (0.12 mL, 0.71 mmol) were added at 0 °C and the resulting mixture was stirred at room temperature for 2.5 h, quenched with saturated NH_4Cl and extracted several times with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:40 → 1:20) afforded silyl ether **2.26b** (0.214 g, 72%) as a colourless oil.

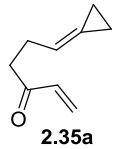
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 12.5, 0.7 Hz, 1H), 5.77-5.72 (m, 1H), 5.43 (dd, *J* = 12.5, 7.8 Hz, 1H), 4.15 (app q, *J* = 6.8 Hz, 1H), 2.22-2.16 (m, 2H), 2.13 (s, 3H), 1.76-1.69 (m, 1H), 1.66-1.59 (m, 1H), 1.02-1.00 (m, 4H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.59 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.23 (e), 136.25 (o), 121.60 (e), 118.00 (o), 117.72 (o), 69.70 (o), 38.37 (e), 27.76 (e), 20.91 (o), 6.97 (o), 5.06 (e), 2.27 (e), 2.14 (e).

IR (neat) 2890 (m), 1759 (s), 1674 (w), 1370 (m), 1215 (s) cm^{-1}.

HRMS (ES, $[M+Na]^+$) calculated for $C_{17}H_{30}O_3SiNa$ 333.1862, found 333.1863.

*Synthesis of (6-Cyclopropylidenehex-1-en-3-yloxy)triethylsilane (**2.35**):*

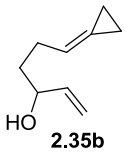


2.35a

6-Cyclopropylidenehex-1-en-3-one (2.35a)

Vinylmagnesium bromide (2.9 ml 1.0 M in THF, 2.9 mmol) was added to a solution of Weinreb amide **2.29** (0.248 g, 1.47 mmol) in THF (15 ml) at −78°C. The reaction mixture was allowed to warm to RT and stirred for additional 45 min (TLC control). The reaction mixture was quenched with sat. NH_4Cl solution and extracted with EtOAc (3x15 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:10) afforded enone **2.35a** (0.146 g, 73%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (dd, *J* = 17.7, 10.6 Hz, 1H), 6.23 (dd, *J* = 17.7, 1.2 Hz, 1H), 5.83 (dd, *J* = 10.6, 1.1 Hz, 1H), 5.81-5.77 (m, 1H), 2.77 (t, *J* = 7.4 Hz, 2H), 2.53-2.48 (m, 2H), 1.02-1.00 (m, 4H).



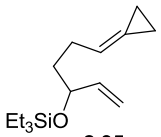
2.35b

6-Cyclopropylidenehex-1-en-3-ol (2.35b)

Cerium(III) chloride heptahydrate (0.290 g, 0.780 mmol) and sodium borohydride (0.0380 g, 1.01 mmol) were added successively to a solution of enone **2.35a** (0.106 g, 0.780 mmol) in MeOH (5 ml) at −78°C. After the mixture was stirred for 15 min it was diluted with Et_2O (10 ml) and quenched with sat. NH_4Cl solution. The resulting mixture was allowed to warm to RT and extracted with Et_2O (3x15 ml). The

combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was taken in DCM/water 8:1 (40 mL), the layers were separated and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:20 → 1:10 → 1:5) afforded alcohol **2.35b** (0.064 g, 60%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 16.8, 10.4, 6.1 Hz, 1H), 5.81-5.76 (m, 1H), 5.23 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.12 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.17-4.12 (m, 1H), 2.32-2.23 (m, 2H), 1.73-1.67 (m, 2H), 1.52 (d, *J* = 4.3 Hz, 1H), 1.04-1.02 (m, 4H).



2.35

(6-Cyclopropylidenehex-1-en-3-yloxy)triethylsilane (2.35)

Chlorotriethylsilane (79 µl, 0.47 mmol) was added to a solution of alcohol **2.35b** (0.059 g, 0.43 mmol) and imidazole (0.049 g, 0.73 mmol) in THF (4.3 ml) at RT. The reaction mixture was stirred for 1.5 h, quenched with sat. NH_4Cl solution and extracted with Et_2O (3x10 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 0:100 → 1:100 → 1:50) afforded silyl ether **2.35** (0.104 g, 96%) as a yellow oil.

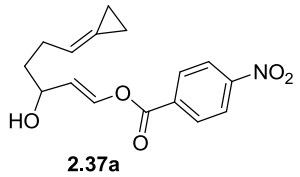
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.0, 10.3, 6.4 Hz, 1H), 5.78-5.74 (m, 1H), 5.14 (d, *J* = 17.1 Hz, 1H), 5.03 (d, *J* = 10.3 Hz, 1H), 4.11 (q, *J* = 6.4 Hz, 1H), 2.27-2.15 (m, 2H), 1.72-1.57 (m, 2H), 1.03-1.00 (m, 4H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.6 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.82 (o), 121.31 (e), 118.06 (o), 113.90 (e), 73.86 (o), 37.83 (e), 27.77 (e), 7.01 (o), 5.10 (e), 2.23 (e), 2.13 (e).

IR (neat) 2954 (m), 2877 (m), 1413 (w), 1238 (w), 1083 (m), 1005 (s), 740 (s) cm^{-1}.

HRMS (CI (Ammonia), $[M+H]^+$) calculated for $C_{15}H_{29}OSi$ 253.1982, found 253.1990.

*Synthesis of (E)-6-Cyclopropylidene-3-(triethylsilyloxy)hex-1-enyl 4-nitrobenzoate (**2.37**):*



2.37a

(E)-6-Cyclopropylidene-3-hydroxyhex-1-enyl 4-nitrobenzoate (2.37a)

N-Methylmorpholine (0.23 ml, 2.1 mmol) was added to a solution of enyne **2.31** (0.186 g, 1.39 mmol) and 4-nitrobenzoic acid (0.232 g, 1.39 mmol) in DCM (14 ml) at RT. The reaction mixture was stirred for 4 h, quenched with sat. NH_4Cl solution and extracted with DCM (3x15 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was dissolved in MeOH (10 ml) and cooled to −78°C. Cerium(III) chloride heptahydrate (0.517 g, 1.39 mmol) and sodium borohydride (0.068 g, 1.8 mmol) were added successively to the solution and the resulting mixture was stirred for 15 min before being diluted with Et_2O (10 ml) and quenched with sat. NH_4Cl solution. The resulting mixture was allowed to warm to RT and extracted with Et_2O (3x15 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was taken in DCM/water 8:1 (40 mL), the layers were separated and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:6 → 1:3 → 1:1.5) afforded alcohol **2.37a** (0.187 g, 44%) as a yellow oil.

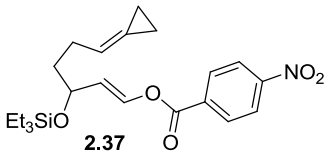
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34-8.32 (m, 2H), 8.29-8.26 (m, 2H), 7.54 (dd, *J* =

12.4, 1.0 Hz, 1H), 5.82-5.77 (m, 1H), 5.74 (dd, *J* = 12.4, 7.6 Hz, 1H), 4.33-4.28 (m, 1H), 2.33-2.29 (m, 2H), 1.87-1.72 (m, 2H), 1.64 (d, *J* = 4.0 Hz, 1H), 1.06-1.04 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.98 (e), 151.01 (e), 137.04 (o), 134.43 (e), 131.24 (o), 123.86 (o), 122.43 (e), 119.29 (o), 117.24 (o), 69.19 (o), 37.00 (e), 27.94 (e), 2.40 (e), 2.17 (e).

IR (neat) 3388 (w), 2923 (w), 1732 (s), 1526 (s), 1347 (m), 1262 (s), 1104 (m), 931 (m), 871 (m), 716 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{16}H_{17}NO_5Na$ 326.1004, found 329.0997.



2.37

(E)-6-Cyclopropylidene-3-(triethylsilyloxy)hex-1-enyl 4-nitrobenzoate (2.37)

Chlorotriethylsilane (97 µl, 0.58 mmol) was added dropwise to a solution of alcohol **2.37a** (0.176 g, 0.58 mmol) and imidazole (0.059 g, 0.87 mmol) in THF (6 ml) at 0°C. The reaction mixture was stirred at this temperature for 1 h, quenched with sat. NH_4Cl solution and extracted with Et_2O (3x10 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:80 → 1:40 → 1:20) afforded silyl ether **2.37** (0.188 g, 78%) as a yellow oil.

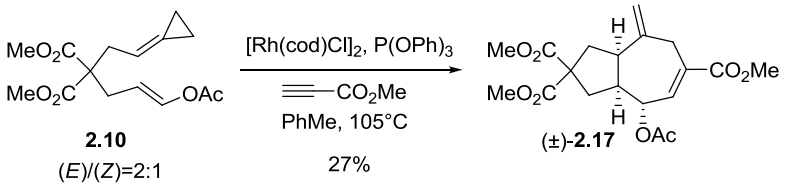
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34-8.31 (m, 2H), 8.29-8.26 (m, 2H), 7.74 (dd, *J* = 12.3, 1.1 Hz, 1H), 5.79-5.75 (m, 1H), 5.70 (dd, *J* = 12.3, 7.3 Hz, 1H), 4.27 (q, *J* = 6.4 Hz, 1H), 2.27-2.21 (m, 2H), 1.82-1.66 (m, 2H), 1.04-1.02 (m, 4H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.63 (q, *J* = 7.7 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.03 (e), 150.98 (e), 136.19 (o), 134.64 (e), 131.23 (o), 123.82 (o), 121.76 (e), 119.96 (o), 117.62 (o), 69.49 (o), 38.31 (e), 27.68 (e),

6.99 (o), 5.08 (e), 2.29 (e), 2.17 (e).

IR (neat) 2954(m), 1736 (s), 1531 (s), 1347 (m), 1264 (s), 1104 (s), 1014 (s), 932 (m), 718 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{22}H_{31}NO_5SiNa$ 440.1869, found 440.1866.



(3aR*,8R*,8aS*)-Trimethyl 8-acetoxy-4-methylene-3,3a,4,-5,8,8a-hexahydroazulene-2,2,6(1H)-tricarboxylate ((±)-2.17)

$[Rh(cod)Cl]_2$ (9.8 mg, 0.020 mmol) and triphenylphosphite (31 µL, 0.12 mmol) were heated in toluene (0.5 mL) at 105 °C for 10 mins before solution of enol acetate **2.10** (0.074 g, 0.25 mmol) in toluene (1.0 mL) was added followed by methyl propiolate (21 µL, 0.25 mmol). A solution of methyl propiolate (84 µL, 1.0 mmol) in toluene (1.0 mL) was added *via* syringe pump for 2.5 h. After the addition the mixture was stirred at 105 °C for additional 12 h, cooled to room temperature and directly applied to the column. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:10 → 1:5 → 1:2 → 1:1) afforded (±)-**2.17** (0.025 g, 27%) as a yellow oil.

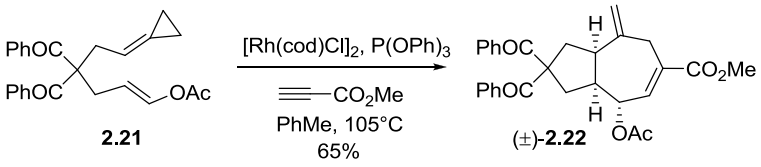
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (dt, *J* = 3.4, 1.7 Hz, 1H), 5.39 (dq, *J* = 11.5, 2.3 Hz, 1H), 5.07 (s, 1H), 4.94 (s, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.32 (dt, *J* = 18.2, 1.9 Hz, 1H), 3.10 (d, *J* = 18.0 Hz, 1H), 2.90 (q, *J* = 9.4 Hz, 1H), 2.70 (dtd, *J*=11.4, 9.2, 7.2 Hz, 1H), 2.54 (ddd, *J* = 13.8, 7.4, 1.8 Hz, 1H), 2.46 (ddd, *J* = 13.6, 7.1, 1.8 Hz, 1H), 2.36 (dd, *J* = 13.8, 10.1 Hz, 1H), 2.09 (s, 3H), 2.01 (dd, *J* = 13.6, 8.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.41 (e), 171.97 (e), 170.53 (e), 167.16 (e), 143.85

(e), 142.48 (o), 130.27 (e), 113.41 (e), 72.70 (o), 59.22 (e), 53.05 (o), 53.02 (o), 52.22 (o), 45.94 (o), 44.39 (o), 38.69 (e), 37.48 (e), 37.31 (e), 21.16 (o).

IR (neat) 2953 (w), 1731 (s), 1434 (m), 1227 (s), 1165 (m), 1024 (m), 936, (w), 910 (w), 731 (w) cm^{-1}.

HRMS (CI (Ammonia), $[M+NH_4]^+$) calculated for $C_{19}H_{28}O_8N$ 398.1809, found 398.1827.



(3aR*,8R*,8aS*)-Methyl 8-acetoxy-2,2-dibenzoyl-4-methylene-1,2,3,3a,4,5,8,8a-octahydroazulene-6-carboxylate ((±)-2.22)

$[Rh(cod)Cl]_2$ (6.9 mg, 0.014 mmol) and triphenylphosphite (22 µL, 0.084 mmol) were heated in toluene (1 mL) at 105 °C for 10 mins before solution of enol acetate **2.21** (68.0 mg, 0.175 mmol) in toluene (1 mL) was added followed by methyl propiolate (8 µL, 0.09 mmol). A solution of methyl propiolate (70 µL, 0.79 mmol) in toluene (1.5 mL) was added *via* syringe pump for 2.5 h. After the addition the mixture was stirred at 105 °C for additional 1.5 h, cooled to room temperature and directly applied to the column. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:40 → 1:1) afforded (±)-**2.22** (53.9 mg, 65%) as a pale yellow solid.

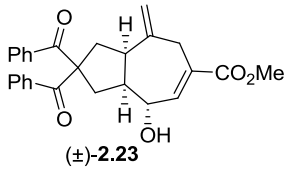
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.80 (m, 4H), 7.43-7.40 (m, 2H), 7.33-7.29 (m, 4H), 6.68 (dt, *J* = 3.3, 1.6 Hz, 1H), 5.35 (ddt, *J* = 11.4, 3.4, 1.8 Hz, 1H), 5.03 (s, 1H), 4.93 (s, 1H), 3.73 (s, 3H), 3.28 (dt, *J* = 17.7, 1.7 Hz, 1H), 3.16 (d, *J* = 17.7 Hz, 1H), 3.01 (q, *J* = 8.5 Hz, 1H), 2.89 (dd, *J* = 13.9, 7.6 Hz, 1H), 2.80-2.64 (m, 3H), 2.55 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.07 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.51 (e), 197.88 (e), 170.56 (e), 167.15 (e), 144.36

(e) 142.95 (o), 136.09 (e), 135.20 (e), 133.43(o), 133.39 (o), 130.43 (e), 129.52 (o), 129.45 (o), 128.79 (o), 128.76 (o), 113.40 (e), 72.71 (o), 69.22 (e), 52.22 (o), 46.04 (o), 45.42 (o), 38.34 (e), 37.71 (e), 37.40 (e), 21.22 (o).

IR (neat) 2949 (w), 1743 (m), 1717 (s), 1663 (s), 1597 (w), 1448 (w), 1232 (s), 1025 (m), 909 (m), 731 (m) cm^{-1}.

HRMS (ES, $[M+Na]^+$) calculated for $C_{29}H_{28}O_6Na$ 495.1784, found 495.1784.



(±)-**2.23**

(3aR*,8R*,8aS*)-Methyl 2,2-dibenzoyl-8-hydroxy-4-methylene-1,2,3,3a,-4,5,8,8a-octahydro-azulene-6-carboxylate ((±)-2.23)

Potassium carbonate (0.8 mg, 0.006 mmol) was added to a solution of acetate (±)-**2.22** (0.027 g, 0.057 mmol) in MeOH (1.5 mL) at room temperature. The reaction mixture was stirred at for 3 h. After removal of MeOH *in vacuo*, water (2 mL) was added and the mixture was extracted with DCM several times. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:10 → 1:2) afforded (±)-**2.23** (0.017 g, 69%) as a yellow solid.

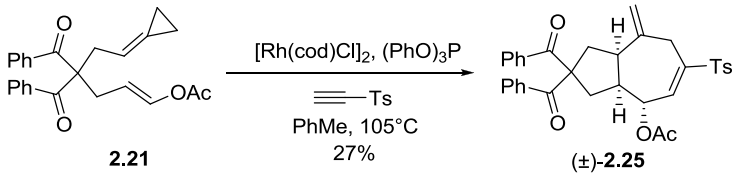
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85-7.80 (m, 4H), 7.46-7.41 (m, 2H), 7.35-7.30 (m, 4H), 7.00 (d, *J* = 3.1 Hz, 1H), 4.93 (s, 1H), 4.83 (s, 1H), 4.21 (dm, *J* = 10.9 Hz, 1H), 3.75 (s, 3H), 3.50 (d, *J* = 4.2 Hz, 1H), 3.33 (dd, *J* = 13.6, 7.6 Hz, 1H), 3.21-3.03 (m, 4H), 2.49 (dtd, *J* = 10.8, 6.8, 2.2 Hz, 1H), 2.27 (app t, *J* = 12.3 Hz, 1H), 2.17 (dd, *J* = 14.3, 6.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.56 (e), 197.73 (e), 167.49 (e), 146.72 (o), 144.77 (e), 135.49 (e), 135.36 (e), 133.79 (o), 133.44 (o), 130.20 (e), 129.64 (o), 129.34 (o), 128.87 (o), 128.81 (o), 113.58 (e), 68.48 (e), 68.06 (o), 52.13 (o), 48.96 (o), 48.28

(o), 38.48 (e), 37.56 (e), 34.92 (e).

IR (neat) 3512 (br), 2923 (w), 1710 (m), 1659 (s), 1597 (m), 1447 (m), 1240 (s), 902 (m), 734 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{27}H_{26}O_5Na$ 453.1678, found 453.1685.



2.21 (±)-**2.25**

(3aS*,4R*,8aR*)-2,2-Dibenzoyl-8-methylene-6-tosyl-1,2,3,3a,4,7,8,8a-octahydroazulen-4-yl acetate ((±)-2.25)

$[Rh(cod)Cl]_2$ (0.0069 g, 0.014 mmol) and triphenylphosphite (22 µL, 0.084 mmol) were stirred in toluene (1 mL) at 105 °C for 10 mins. Alkylidenecyclopropane **2.21** (0.068 g, 0.18 mmol) and 1-(ethynylsulfonyl)-4-methylbenzene (**2.24**) (0.016 g, 0.088 mmol) were added. A solution of 1-(ethynylsulfonyl)-4-methylbenzene (**2.24**) (0.047 g, 0.26 mmol) in toluene (1.5 mL) was added *via* syringe pump for 2.5 h. After the addition the reaction mixture was stirred at 105 °C for additional 2.5 h, cooled to room temperature and directly applied to the column. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:40 → 1:1) afforded bicycle (±)-**2.25** (0.028 g, 28%) as a yellow solid.

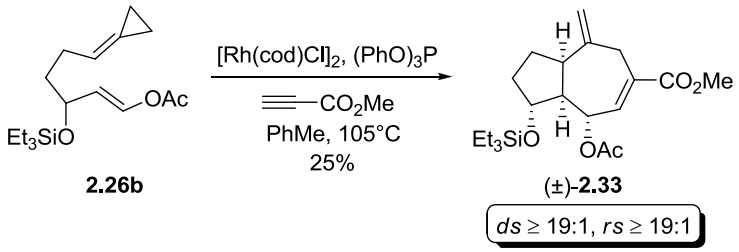
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.72 (m, 6H), 7.44-7.40 (m, 2H), 7.35-7.28 (m, 6H), 6.83-6.81 (m, 1H), 5.31 (d, *J* = 11.3 Hz, 1H), 4.89 (s, 1H), 4.79 (s, 1H), 3.09-3.01 (m, 2H), 2.94-2.77 (m, 3H), 2.69-2.62 (m, 2H), 2.55-2.50 (m, 1H), 2.45 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.32 (e), 197.68 (e), 170.40 (e), 144.70 (e), 142.66 (e), 141.33 (o), 139.96 (e), 135.95 (e), 135.70 (e), 135.06 (e), 133.51 (o), 133.47 (o), 130.09 (o), 129.50 (o), 129.43 (o), 128.81 (o), 128.79 (o), 128.39 (o), 114.39 (e),

71.98 (o), 69.10 (e), 46.13 (o), 45.07 (o), 37.97 (e), 37.56 (e), 36.30 (e), 27.78 (o), 21.14 (o).

IR (neat) 2926 (w), 1736 (s), 1662 (s), 1596 (m), 1448 (m), 1231 (s), 1149 (s), 1044 (m), 934 (m), 813 (m), 706 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{34}H_{32}O_6SNa$ 591.1817, found 591.1835.



(1R*,3aR*,8S*,8aS*)-Methyl 8-acetoxy-4-methylene-1-(triethylsilyloxy)-1,2,3,3a,4,5,8,8a-octahydroazulene-6-carboxylate ((±)-2.33)

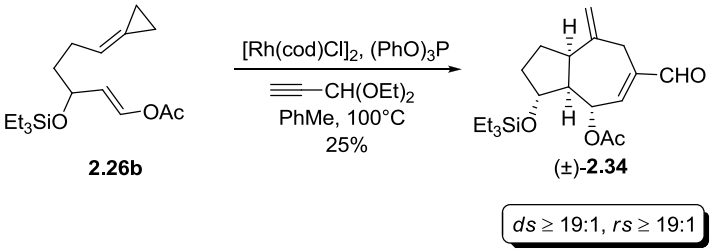
$[Rh(cod)Cl]_2$ (7.9 mg, 0.016 mmol) and triphenylphosphite (25 µL, 0.096 mmol) were heated in toluene (1 mL) at 105 °C for 10 mins before solution of silyl ether **2.26b** (62.0 mg, 0.200 mmol) in toluene (1 mL) was added followed by methyl propiolate (18 µL, 0.20 mmol). A solution of methyl propiolate (72 µL, 0.80 mmol) in toluene (1.5 mL) was added *via* syringe pump for 2.5 h. After the addition the mixture was stirred at 105 °C for additional 1 h, then cooled to room temperature and directly applied to the column. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:40 → 1:1) afforded bicycle (±)-**2.33** (20.0 mg, 25%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, *J* = 2.5 Hz, 1H), 5.36 (d, *J* = 11.8 Hz, 1H), 4.92 (s, 1H), 4.84 (s, 1H), 4.12-4.09 (m, 1H), 3.74 (s, 3H), 3.26 (d, *J* = 16.8 Hz, 1H), 3.10-3.05 (m, 2H), 2.38 (ddd, *J* = 11.7, 8.3, 2.1 Hz, 1H), 2.11 (s, 3H), 2.03-1.94 (m, 2H), 1.80-1.72 (m, 1H), 1.63-1.57 (m, 1H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.58 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.60 (e), 167.26 (e), 145.36 (e), 142.82 (o), 131.35 (e), 113.03 (e), 75.78 (o), 71.01 (o), 54.95 (o), 52.22 (o), 45.60 (o), 36.19 (e), 34.02 (e), 27.68 (e), 21.25 (o), 6.27 (o), 5.00 (e).

IR (neat) 2953 (m), 2876 (w), 1744 (m), 1717 (s), 1645 (w), 1370 (w), 1224 (s), 1020 (m), 728 (m) cm^{-1}.

HRMS (ES, $[M+Na]^+$) calculated for $C_{21}H_{34}O_5SiNa$ 417.2073, found 417.2078.



2.26b (±)-**2.34**

(3R*,3aS*,4S*,8aR*)-6-Formyl-8-methylene-3-(triethylsilyloxy)-1,2,3,3a,4,7,8,8a-octahydroazulen-4-yl acetate ((±)-2.34)

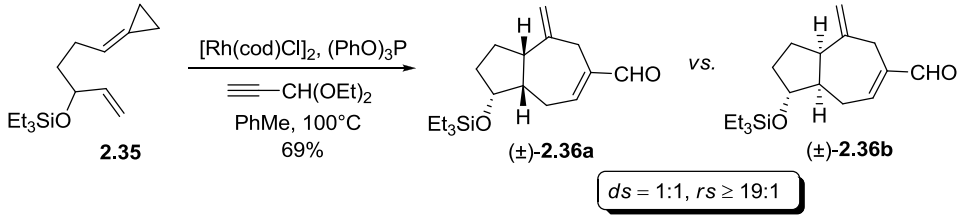
$[Rh(cod)Cl]_2$ (3.9 mg, 0.0080 mol) and triphenylphosphite (13 µL, 0.048 mol) were heated in toluene (1 mL) at 105 °C for 10 min before a solution of silyl ether **2.26b** (31.0 mg, 0.100 mol) in toluene (0.7 mL) was added followed by 3,3-diethoxyprop-1-yne (43 µL, 0.30 mol). The reaction mixture was stirred at 105 °C overnight, cooled to room temperature and directly applied to the column. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:40 → 1:10) afforded bicycle (±)-**2.34** (12.0 mg, 33%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 6.38 (dt, *J* = 2.7, 1.2 Hz, 1H), 5.44 (d, *J* = 11.5 Hz, 1H), 4.90 (s, 1H), 4.85 (t, *J* = 1.5 Hz, 1H), 4.15-4.13 (m, 1H), 3.20 (d, *J* = 16.8 Hz, 1H), 3.10 (app. q, *J* = 8.4 Hz, 1H), 2.95 (d, *J* = 17.0 Hz, 1H), 2.43 (ddd, *J* = 11.2, 8.2, 2.4 Hz, 1H), 2.15 (s, 3H), 2.07-1.98 (m, 2H), 1.80-1.72 (m, 1H), 1.66-1.61 (m, 1H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.59 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 193.06 (o), 170.63 (e), 153.12 (o), 145.04 (e), 141.86

(e), 113.26 (e), 75.73 (o), 71.22 (o), 54.91 (o), 45.71 (o), 34.08 (e), 32.98 (e), 27.42 (e), 21.22 (o), 6.98 (o), 5.01 (e).

IR (neat) 2953 (m), 2913 (m), 1743 (s), 1691 (s), 1646 (w), 1232 (s), 1019 (s), 743 (m) cm^{-1}.



Alkene **2.35** (0.032 g, 0.13 mmol) and 3,3-diethoxyprop-1-yne (55 µl, 0.38 mmol) were added to a prestirred (5 min at 105°C) solution of $[Rh(cod)Cl]_2$ (5.0 mg, 0.010 mmol) and $(PhO)_3P$ (16 µl, 0.060 mmol) and stirred at this temperature for 6 h. Water (0.15 ml) was added and the resulting mixture was cooled to RT and stirred overnight. The mixture was applied directly on a column. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:40 → 1:10) afforded diastereomeric aldehydes (±)-**2.36a** and (±)-**2.36b** in 1:1 ratio and in 83% combined yield.

(1R*,3aS*,8aS*)-4-Methylene-1-(triethylsilyloxy)-1,2,3,3a,4,5,8,8a-octahydroazulene-6-carbaldehyde ((±)-2.36a)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 6.78 (dd, *J* = 8.0, 3.4 Hz, 1H), 4.88 (s, 1H), 4.78 (t, *J* = 1.8 Hz, 1H), 4.22 (q, *J* = 6.8 Hz, 1H), 3.25 (d, *J* = 16.3 Hz, 1H), 2.95 (d, *J* = 16.3 Hz, 1H), 2.77 (app. q, *J* = 8.0 Hz, 1H), 2.55 (dd, *J* = 14.8, 8.1 Hz, 1H), 2.33-2.21 (m, 2H), 1.96-1.74 (m, 3H), 1.66-1.58 (m, 1H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 194.27 (o), 154.93 (o), 147.17 (e), 143.61 (e), 112.19 (e), 74.99 (o), 46.79 (o), 46.35 (o), 32.78 (e), 32.53 (e), 25.38 (e), 24.20 (e), 6.99 (o), 4.95 (e).

IR (neat) 2954 (m), 1685 (s), 1641 (m), 1111 (m), 1003 (m), 892 (m), 821 (w), 724 (s) cm^{-1}.

HRMS (CI (Ammonia), $[M+H]^+$) calculated for $C_{18}H_{30}O_2Si$ 307.2088, found 307.2094.

(1R*,3aR*,8aR*)-4-Methylene-1-(triethylsilyloxy)-1,2,3,3a,4,5,8,8a-octahydroazulene-6-carbaldehyde ((±)-2.36b)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 6.69 (t, *J* = 6.0 Hz, 1H), 4.86 (s, 1H), 4.80 (s, 1H), 3.81 (q, *J* = 6.1 Hz, 1H), 3.20 (d, *J* = 17.1 Hz, 1H), 3.02 (q, *J* = 8.8 Hz, 1H), 2.96 (d, *J* = 17.2 Hz, 1H), 2.37-2.33 (m, 2H), 2.24-219 (m, 1H), 2.05-1.89 (m, 2H), 1.66-1.54 (m, 2H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.58 (q, *J* = 7.8 Hz, 6H).

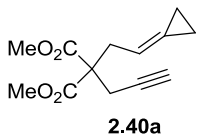
^{13}C NMR (125 MHz, $CDCl_3$) δ 194.29 (o), 152.97 (o), 147.13 (e), 143.32 (e), 112.59 (e), 78.94 (o), 50.14 (o), 46.68 (o), 34.59 (e), 33.62 (e), 26.05 (e), 26.30 (e), 6.96 (o), 4.98 (e).

IR (neat) 2953 (m), 1686 (s), 1643 (m), 1237 (w), 1113 (m), 1005 (m), 893 (w), 742 (s) cm^{-1}.

HRMS (CI (Ammonia), $[M+H]^+$) calculated for $C_{18}H_{30}O_2Si$ 307.2088, found 307.2091.

2.6.4. Experimental Procedures: Rhodium-Catalysed [(3+2)+2] Carbocyclisation of Vinyl Silanes

Preparation of vinyl triethoxysilanes:



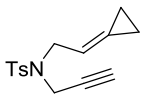
2.40a

***Dimethyl 2-(2-cyclopropylideneethyl)-2-(prop-2-ynyl)malonate (2.40a)*[32]**

ACP **2.40a** was prepared according to the procedure used by de Meijere et al. (1990)[32] in 91% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59-5.54 (m, 1H), 3.74 (s, 6H), 2.96 (d, *J* = 7.5 Hz, 2H), 2.79 (d, *J* = 2.7 Hz, 2H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.10-1.01 (m, 4H).

IR (neat) 3286 (w), 2955 (w), 1732 (s), 1436 (m), 1287 (m), 1198 (s), 1088 (m) cm^{-1}.



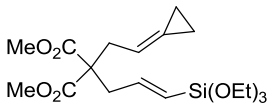
2.40b

***N-(2-Cyclopropylideneethyl)-4-methyl-N-(prop-2-ynyl)benzenesulfonamide (2.40b)*[33]**

2.40b was prepared according to the procedure used by de Meijere et al. (1994)[33] in 85% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76-7.73 (m, 2H), 7.31-7.28 (m, 2H), 5.72-5.68 (m, 1H), 4.08 (d, *J* = 2.4 Hz, 2H), 3.98 (d, *J* = 6.9 Hz, 2H), 2.43 (s, 3H), 1.97 (t, *J* = 2.5 Hz, 1H), 1.13-1.04 (m, 4H).

IR (neat) 3257 (w), 2984 (w), 2115 (w), 1329 (s), 1156 (s), 1034 (m), 892 (s), 714 (m) cm^{-1}.



2.41a

(E)-Dimethyl 2-(2-cyclopropylideneethyl)-2-(3-(triethoxysilyl)-allyl)malonate (2.41a)

2.41a was prepared from **2.40a** according to the general procedure A in 51% yield.

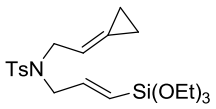
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (dt, *J* = 18.6, 7.1 Hz, 1H), 5.62-5.57 (m, 1H), 5.50 (dt, *J* = 18.6, 1.3 Hz, 1H), 3.79 (q, *J* = 7.0 Hz, 6H), 3.70 (s, 6H), 2.78 (d, *J*=7.4 Hz, 2H), 2.73 (dd, *J* = 7.1, 1.3 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 9H), 1.09-1.06 (m, 2H), 1.01-0.98 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (e), 147.0 (o), 126.9 (e), 124.9 (o), 111.8 (o),

58.6 (e), 57.9 (e), 52.6 (o), 39.9 (e), 35.3 (e),18.4 (o), 3.1 (e), 2.0 (e).

IR (neat) 2975 (w), 2885 (w), 1735 (s), 1620 (w), 1438 (w), 1232 (m), 1099 (s), 1074 (s), 957 (m), 780 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{19}H_{32}O_7SiNa$ 423.1815, found 423.1817.



2.41b

(E)-N-(2-Cyclopropylideneethyl)-4-methyl-N-(3-(triethoxysilyl)-allyl)benzenesulfonamide (2.41b)

2.41b was prepared from **2.40b** according to the general procedure A in 47% yield.

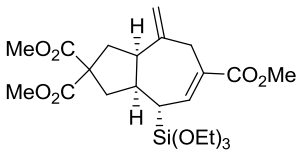
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.18 (dt, *J* = 18.8, 5.6 Hz, 1H), 5.60-5.56 (m, 1H), 5.50 (dt, *J* = 18.8, 1.5 Hz, 1H), 3.93 (d, *J* = 6.8 Hz, 2H), 3.85 (dd, *J* = 5.5, 1.4 Hz, 2H), 3.77 (q, *J* = 7.0 Hz, 6H), 2.42 (s, 3H), 1.20 (t, *J* = 7.0 Hz, 9H), 1.06-1.03 (m, 2H), 0.99-0.96 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8 (o), 143.3 (e), 137.7 (e), 129.8 (o), 127.7 (e), 127.3 (o), 123.2 (o), 112.7 (o), 58.6 (e), 51.4 (e), 48.8 (e), 21.7 (o), 18.4 (o), 2.6 (e), 2.0 (e).

IR (neat) 2974 (w), 2885 (w), 1621 (w), 1343 (m), 1159 (s), 1076 (s), 960 (m), 782 (m), 717 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{21}H_{33}NO_5SiSNa$ 462.1746, found 462.1762.

All rhodium-catalysed carbocyclisation reactions of vinyl triethoxysilanes 2.41a and 2.41b were carried out according to the general procedure B.



(±)-**2.42a**

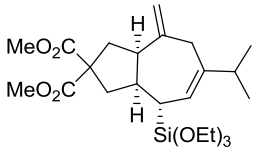
(3aR*,8R*,8aS*)-Trimethyl 4-methylene-8-(triethoxysilyl)-3,3a,4,5,8,8a-hexahydroazulene-2,2,6(1H)-tricarboxylate ((±)-2.42a)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 7.7, 1.6 Hz, 1H), 4.92 (s, 1H), 4.80 (s, 1H), 3.82 (q, *J* = 7.0 Hz, 6H), 3.73 (s, 3H), 3.72 (s, 3H), 3.72 (s, 3H), 3.32 (d, *J* = 17.8 Hz, 1H), 3.17 (d, *J* = 17.9 Hz, 1H), 3.02 (dt, *J* = 8.9, 5.5 Hz, 1H), 2.64 (dd, *J* = 14.5, 8.6 Hz, 1H), 2.58-2.51 (m, 1H), 2.32 (dd, *J* = 12.7, 5.6 Hz, 1H), 2.29 (dd, *J* = 14.5, 5.3 Hz, 1H), 2.14 (app. t, *J* = 7.7 Hz, 1H), 2.08 (app. t, *J* = 13.0 Hz, 1H), 1.21 (t, *J* = 7.0 Hz, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1 (e), 172.6 (e), 168.2 (e), 147.0 (e), 140.7 (o), 130.2 (e), 112.8 (e), 59.4 (e), 59.0 (e), 52.9 (o), 52.9 (o), 52.0 (o), 46.2 (o), 42.6 (o), 39.8 (e), 38.1 (e), 36.3 (e), 27.8 (o), 18.3 (o).

IR (neat) 2975 (w), 2890 (w), 1733 (s), 1709 (s), 1642 (w), 1435 (m), 1258 (vs), 1164 (s), 1101 (s), 1080 (vs), 960 (m), 734 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{23}H_{36}O_9SiNa$ 507.2026, found 507.2041.



(±)-**2.42b**

(3aR*,8R*,8aS*)-Dimethyl 6-isopropyl-4-methylene-8-(triethoxysilyl)-3,3a,4,5,8,8a-hexahydroazulene-2,2(1H)-dicarboxylate ((±)-2.42b)

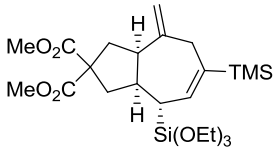
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (dd, *J* = 7.1, 1.6 Hz, 1H), 4.94 (s, 1H), 4.74 (s,

1H), 3.81 (q, *J* = 7.0 Hz, 6H), 3.73 (s, 3H), 3.72 (s, 3H), 3.02 (d, *J* = 18.1 Hz, 1H), 2.90 (dt, *J* = 8.7, 4.9 Hz, 1H), 2.81 (d, *J* = 18.1 Hz, 1H), 2.57 (dd, *J* = 14.7, 8.8 Hz, 1H), 2.51-2.44 (m, 1H), 2.40 (dd, *J* = 13.1, 5.7 Hz, 1H), 2.33 (dd, *J* = 14.8, 4.8 Hz, 1H), 2.19 (sept, *J* = 6.9 Hz, 1H), 1.96 (app. t, *J* = 12.8, 1H), 1.84 (dd, *J* = 10.8, 7.0 Hz, 1H), 1.21 (t, *J* = 7.0 Hz, 9H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5 (e), 172.9 (e), 148.9 (e), 145.3 (e), 119.7 (o), 109.8 (e), 60.0 (e), 58.7 (e), 52.8 (o), 52.8 (o), 45.8 (o), 44.8 (o), 39.5 (e), 38.7 (e), 36.9 (e), 36.7 (o), 24.1 (o), 21.9 (o), 21.6 (o), 18.4 (o).

IR (neat) 2971 (w), 2885 (w), 1734 (s), 1639 (w), 1435 (w), 1259 (m), 1165 (m), 1102 (s), 1078 (vs), 957 (m), 776 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{24}H_{40}O_7SiNa$ 491.2441, found 491.2458.



(±)-**2.42c**

(3aR*,8R*,8aS*)-Dimethyl 4-methylene-8-(triethoxysilyl)-6-(trimethylsilyl)-3,3a,4,5,8,8a-hexahydroazulene-2,2(1H)-dicarboxylate ((±)-2.42c)

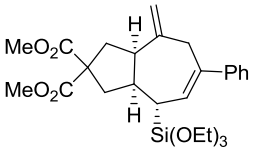
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (app. dt, *J*=6.9, 1.6 Hz, 1H), 4.85 (s, 1H), 4.72 (s, 1H), 3.81 (q, *J* = 7.0 Hz, 6H), 3.72 (s, 6H), 3.00 (d, *J* = 17.7 Hz, 1H), 2.97-2.93 (m, 1H), 2.93 (dt, *J* = 8.4, 5.0 Hz, 1H), 2.58 (dd, *J* = 14.6, 8.5 Hz, 1H), 2.51-2.44 (m, 1H), 2.37-2.31 (m, 2H), 2.05 (app. t, *J* = 12.8 Hz, 1H), 2.05-2.01 (m, 1H), 1.21 (t, *J* = 7.0 Hz, 9H), 0.04 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5 (e), 172.9 (e), 149.3 (e), 140.6 (e), 135.8 (o), 110.0 (e), 59.7 (e), 58.8 (e), 52.8 (o), 52.8 (o), 46.5 (o), 43.4 (o), 39.4 (e), 39.2 (e), 37.6 (e), 27.8 (o), 18.4 (o), −1.8 (o).

IR (neat) 2973 (w), 2888 (w), 1734 (s), 1640 (w), 1435 (w), 1247 (s), 1165 (m),

1102 (s), 1078 (vs), 957 (m), 833 (s), 780 (m), 748 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{24}H_{42}O_7Si_2Na$ 521.2367, found 521.2379.



(±)-**2.42d**

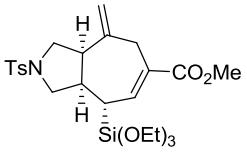
(3aR*,8R*,8aS*)-Dimethyl 4-methylene-6-phenyl-8-(triethoxysilyl)-3,3a,4,5,8,8a-hexahydroazulene-2,2(1H)-dicarboxylate ((±)-2.42d)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.28 (m, 4H), 7.23-7.20 (m, 1H), 5.97 (dd, *J* = 7.3, 2.0 Hz, 1H), 5.03 (s, 1H), 4.84 (s, 1H), 3.84 (q, *J* = 7.0 Hz, 6H), 3.74 (s, 3H), 3.73 (s, 3H), 3.48 (d, *J* = 18.1 Hz, 1H), 3.31 (d, *J* = 18.0 Hz, 1H), 3.07 (app. dt, *J* = 8.7, 5.3 Hz, 1H), 2.64-2.56 (m, 1H), 2.62 (dd, *J* = 14.5, 8.9 Hz, 1H), 2.45 (dd, *J* = 13.1, 5.7 Hz, 1H), 2.39 (dd, *J* = 14.6, 5.1 Hz, 1H), 2.08 (dd, *J* = 10.0, 7.5 Hz, 1H), 2.06 (app. t, *J* = 12.9 Hz, 1H), 1.22 (t, *J* = 7.0 Hz, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2 (e), 172.8 (e), 147.9 (e), 144.1 (e), 139.2 (e), 128.2 (o), 126.7 (o), 126.4 (o), 125.9 (o), 110.8 (e), 59.8 (e), 58.8 (e), 52.8 (o), 52.7 (o), 45.9 (o), 44.4 (o), 42.0 (e), 39.0 (e), 37.2 (e), 25.4 (o), 18.4 (o).

IR (neat) 2974 (w), 2887 (w), 1732 (s), 1644 (w), 1435 (w), 1248 (m), 1164 (m), 1100 (s), 1074 (s), 957 (m), 777 (m), 756 (m), 697 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{27}H_{38}O_7SiNa$ 525.2285, found 525.2291.



(±)-**2.42e**

(3aR*,8S*,8aR*)-Methyl 4-methylene-2-tosyl-8-(triethoxysilyl)-1,2,3,3a,4,5,8,8a-octahydrocyclohepta[c]pyrrole-6-carboxylate ((±)-2.42e)

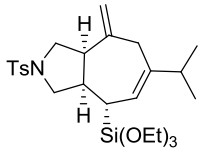
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H),

6.92 (dd, *J* = 7.6, 1.8 Hz, 1H), 4.86 (s, 1H), 4.50 (s, 1H), 3.79 (q, *J* = 7.0 Hz, 6H), 3.70 (s, 3H), 3.55 (dd, *J* = 10.1, 7.4 Hz, 1H), 3.45 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.33 (dd, *J* = 10.5, 2.2 Hz, 1H), 3.28 (d, *J* = 18.3 Hz, 1H), 2.97-2.92 (m, 3H), 2.49 (ddt, *J* = 10.4, 9.2, 7.5 Hz, 1H), 2.44 (s, 3H), 1.93 (app. t, *J* = 8.3 Hz, 1H), 1.20 (t, *J* = 7.0 Hz, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9 (e),145.0 (e),143.5 (e),139.8 (o),133.9 (e),131.3 (e),129.8 (o), 127.7 (o), 112.1 (e), 59.1 (e), 52.1 (e), 52.1 (o), 51.6 (e), 45.7 (o), 42.0 (o), 36.1 (e), 25.2 (o), 21.7 (o), 18.4 (o).

IR (neat) 2975 (w), 2890 (w), 1709 (m), 1645 (w),1598 (w), 1346 (m), 1259 (m),1160 (s),1074 (vs), 960 (m), 779 (m), 732 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{25}H_{37}NO_7SiSNa$ 546.1958, found 546.1962.



(±)-**2.42f**

(3aR*,8S*,8aR*)-6-iso-Propyl-4-methylene-2-tosyl-8-(triethoxysilyl)-1,2,3,3a,4,5,8,8a-octahydrocyclohepta[c]pyrrole ((±)-2.42f)

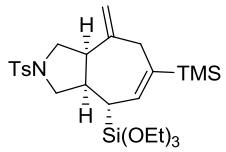
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.34 (dd, *J* = 7.0, 2.0 Hz, 1H), 4.82 (s, 1H), 4.40 (s, 1H), 3.77 (q, *J* = 7.0 Hz, 6H), 3.58 (dd, *J* = 10.3, 7.2 Hz, 1H), 3.37 (d, *J* = 4.6 Hz, 2H), 2.90 (d, *J* = 18.7 Hz, 1H), 2.85 (app. t, *J* = 10.5 Hz, 1H), 2.84 2.81 (m, 1H), 2.76 (d, *J* = 18.6 Hz, 1H), 2.42 (s, 3H), 2.37 (app. tt, *J* = 11.0, 7.5 Hz, 1H), 2.16 (sept, *J* = 6.8 Hz, 1H), 1.66 (dd, *J* = 11.3, 7.1 Hz, 1H), 1.92 (t, *J* = 7.0 Hz, 9H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5 (e), 146.1 (e), 143.3 (e), 134.2 (e), 129.7 (o),127.7 (o),118.9 (o),109.6 (e), 58.8 (e), 51.5 (e), 51.3 (e), 45.3 (o), 43.7 (o), 38.5

(e), 36.7 (o), 22.6 (o), 21.8 (o), 21.7 (o), 21.5 (o),18.4 (o).

IR (neat) 2972 (m), 2888 (w),1640 (w), 1489 (w), 1347 (m), 1162 (s), 1102 (s), 1080 (vs), 959 (m), 812 (w), 776 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{26}H_{41}NO_5SiSNa$ 530.2372, found 530.2375.



(±)-**2.42g**

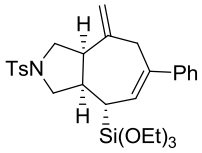
(3aR*,8R*,8aR*)-4-Methylene-2-tosyl-8-(triethoxysilyl)-6-(trimethylsilyl)-1,2,3,3a,4,5,8,8a-octahydrocyclohepta[c]pyrrole ((±)-2.42g)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.83 (dd, *J* = 6.8, 1.7 Hz, 1H), 4.74 (s, 1H), 4.45 (s, 1H), 3.77 (q, *J* = 7.0 Hz, 6H), 3.52 (dd, *J* = 10.1, 7.3 Hz, 1H), 3.42 (dd, *J* = 10.4, 7.4 Hz, 1H), 3.33 (dd, *J* = 10.4, 2.2 Hz, 1H), 2.93 (app. t, *J* = 10.3 Hz, 1H), 2.89-2.86 (m, 1H), 2.88 (d, *J* = 17.3 Hz, 1H), 2.75 (d, *J* = 17.9 Hz, 1H), 2.43 (s, 3H), 2.41 (app. tt, *J* = 10.0, 7.4 Hz, 1H), 1.86 (dd, *J* = 9.3, 6.5 Hz, 1H), 1.19 (t, *J* = 7.0 Hz, 9H), 0.00 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0 (e), 143.3 (e), 141.2 (e), 134.8 (o), 134.1 (e), 129.8 (o), 127.7 (o), 110.1(e), 58.9 (e), 52.1 (e), 51.6 (e), 46.0 (o), 42.3 (o), 38.2 (e), 26.2 (o), 21.7 (o), 18.4 (o), −1.9 (o).

IR (neat) 2974 (w), 2888 (w), 1642 (w), 1599 (w), 1348 (m), 1247 (w), 1163 (s), 1102 (s), 1080 (vs), 960 (w), 835 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{26}H_{43}NO_5Si_2SNa$ 560.2298, found 560.2286.



(±)-**2.42h**

(3aR*,8S*,8aR*)-4-Methylene-6-phenyl-2-tosyl-8-(triethoxysilyl)-1,2,3,3a,4,5,8,8a-

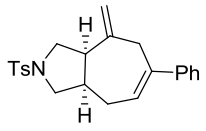
octahydrocyclohepta[c]pyrrole ((±)-2.42h)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.30-7.20 (m, 5H), 5.86 (dd, *J* = 7.3, 2.1 Hz, 1H), 4.91 (s, 1H), 4.47 (s, 1H), 3.81 (q, *J* = 7.0 Hz, 6H), 3.64 (dd, *J* = 10.3, 7.3 Hz, 1H), 3.45 (dd, *J* = 10.5, 7.2 Hz, 1H), 3.40 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.32 (d, *J* = 18.7 Hz, 1H), 3.25 (d, *J* = 18.5 Hz, 1H), 3.02 (dt, *J* = 7.4, 1.5 Hz, 1H), 2.94 (app. t, *J* = 10.5 Hz, 1H), 2.51 (app. tt, *J* = 10.7, 7.5 Hz, 1H), 2.44 (s, 3H), 1.90 (dd, *J* = 10.9, 7.4 Hz, 1H), 1.21 (t, *J* = 7.0 Hz, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9 (e), 143.7 (e), 143.4 (e), 140.0 (e), 133.9 (e), 129.8 (o), 128.3 (o), 127.7 (o), 127.0 (o), 125.9 (o), 125.5 (o), 110.6 (e), 59.0 (e), 51.7 (e), 51.4 (e), 45.5 (o), 43.4 (o), 41.1 (e), 23.7 (o), 21.7 (o), 18.5 (o).

IR (neat) 2974 (w), 2887 (w), 1645 (w), 1597 (w), 1490 (m), 1346 (m), 1161 (s), 1077 (vs), 958 (s), 813 (m), 755 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{29}H_{39}NO_5SiSNa$ 564.2216, found 564.2209.



(±)-**2.48**

(3aR*,8aR*)-4-Methylene-6-phenyl-2-tosyl-1,2,3,3a,4,5,8,8a-octahydrocyclohepta[c]pyrrole ((±)-2.48)

TBAF (0.37 mL, 0.37 mmol, 1 M in THF) was added to a stirred solution of silane **2.42h** (40.0 mg, 0.0740 mmol) in anhydrous THF (1.4 mL) at room temperature. The reaction mixture was stirred for ca. 45 min and then partitioned between water and diethyl ether. The combined organic phases were washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude product. Purification by flash column chromatography (silica gel, eluting with 30% diethyl ether/ hexanes) afforded (±)-**2.48** (24.0 mg, 86%) as a colourless oil.

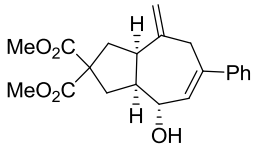
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H),

7.31-7.22 (m, 5H), 5.84 (dd, *J* = 7.0, 6.1 Hz, 1H), 4.92 (s, 1H), 4.67 (s, 1H), 3.56 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.49 (dd, *J* = 9.9, 7.0 Hz, 1H), 3.31 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.25 (d, *J* = 17.8 Hz, 1H), 3.21 (d, *J* = 17.6 Hz, 1H), 3.06 (app. q, *J* = 7.8 Hz, 1H), 3.03 (dd, *J* = 10.0, 4.9 Hz, 1H), 2.57 (dddt, *J* = 11.0, 7.6, 4.5, 3.1 Hz, 1H), 2.45 (s, 3H), 2.17 (ddd, *J* = 15.9, 10.9, 5.1 Hz, 1H), 2.03 (ddd, *J* = 15.4, 7.8, 3.1 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4 (e), 143.6 (e), 143.2 (e), 140.4 (e), 133.4 (e), 129.8 (o), 128.4 (o), 127.8 (o), 127.1 (o), 125.8 (o), 125.6 (o), 113.2 (e), 53.7 (e), 50.5 (e), 47.6 (o), 41.0 (o), 39.6 (e), 28.4 (e), 21.7 (o).

IR (neat) 3028 (w), 2937 (w), 1645 (w), 1481 (w), 1341 (s), 1161 (s), 1092 (m), 1045 (m), 904 (m), 815 (m), 663 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{23}H_{25}NO_2SNa$ 402.1504, found 402.1493.



(±)-**2.49**

(3aR*,8R*,8aS*)-Dimethyl 8-hydroxy-4-methylene-6-phenyl-3,3a,4,5,8,8a-hexahydroazulene-2,2(1H)-dicarboxylate ((±)-2.49)

mCPBA (13.0 mg, 0.0740 mmol) was added to a stirred solution of **2.42d** (34.0 mg, 0.0680 mmol) and KHF_2 (106.0 mg, 1.353 mmol) in anhydrous DMF (0.7 mL) at room temperature. The reaction mixture was stirred for ca. 6 h (TLC control) and then partitioned between water and diethyl ether. The combined organic phases were washed with saturated $NaHCO_3$ solution, water, saturated NaCl solution, dried (Na_2SO_4), and concentrated *in vacuo* to afford the crude product. Purification by flash chromatography (silica gel, eluting with 40-60% diethyl ether/petroleum ether) afforded (±)-**2.49** (15.1 mg, 62%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.36 (m, 2H), 7.33-7.30 (m, 2H), 7.27-7.24 (m,

1H), 5.95 (dt, *J* = 3.0, 1.4 Hz, 1H), 4.98 (s, 1H), 4.87 (s, 1H), 4.29-4.27 (m, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.34 (d, *J* = 16.7 Hz, 1H), 3.23 (d, *J* = 16.3 Hz, 1H), 3.02-2.97 (m, 1H), 2.68 (dd, *J* = 13.9, 7.8 Hz, 1H), 2.56-2.50 (m, 1H), 2.48 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.37 (d, *J* = 5.7 Hz, 1H), 2.33 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.28 (dd, *J* = 13.8, 10.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 (e), 172.7 (e), 145.8 (e), 142.7 (e), 138.0 (e), 133.2 (o), 128.5 (o), 127.3 (o), 126.0 (o), 112.4 (e), 69.6 (o), 58.9 (e), 53.2 (o), 53.1 (o), 49.2 (o), 46.5 (o), 40.9 (e), 37.5 (e), 37.1 (e).

IR (neat) 3708 (w), 3681 (w), 3444 (w), 2952 (m), 2866 (w), 1727 (s), 1644 (w), 1435 (m), 1256 (vs), 1202 (m), 1052 (s), 1033 (s), 897 (m), 732 (m), 698 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{21}H_{24}O_5Na$ 379.1521, found 379.1520.

2.7. References

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Chapter 3

Total Synthesis of Repin

3.1. Introduction

The following chapter describes the results of our synthetic studies towards the first total synthesis of repin. The application of the rhodium-catalysed [(3+2)+2] carbocyclisation led to the novel strategy for the preparation of 5,6-bicyclic core found in numerous natural products, and resulted in a highly novel synthesis of the tricyclic structure of repin.

Throughout the chapter the following notation is used for all prepared compounds: chiral *racemic* structures with multiple stereocentres have numbers ending with **r** to signify that only the relative stereochemistry is represented.

3.2. Repin Background

3.2.1. Isolation and Structure Determination of Repin

Repin (**3.1**) is a sesquiterpene lactone isolated together with acroptilin (**3.2**) from *Acroptilon repens* (Russian knapweed) by Evstratova *et al.* (Fig. 3.1).[1]

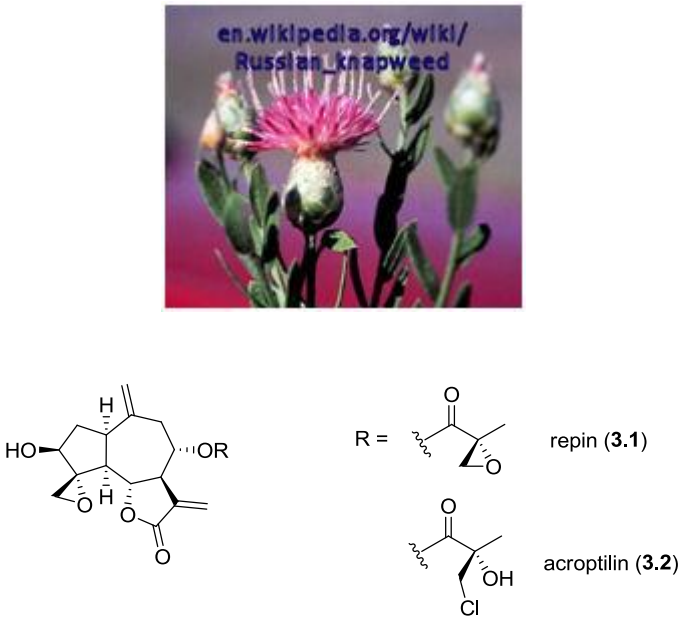


Figure 3.1. Acroptilon repens (Russian knapweed): natural source of repin (**3.1**) and acroptilin (**3.2**).

Initial chemical and spectroscopic studies carried out by Evstratova *et al.* revealed the basic structure of repin (Fig. 3.2).[2] Both acroptilin and repin share the same core structure and belong to the guaianolide subclass of the sesquiterpene lactone family of natural products. Based on the ^{1}H NMR coupling constants the authors determined the relative configuration around the seven-membered ring: each of the protons H_5, H_6, H_7 and H_8 was believed to be in a *trans* relationship to its neighbours (Fig. 3.2). To determine the configuration at C3 bearing a hydroxyl group, the spectra of repin with paramagnetic salt (europium tris(dipivalomethanate)) were recorded. Based on a large downfield shift observed for H_1 and H_6 protons ($\Delta\delta$ 0.7 and 0.4 ppm), the authors concluded that the hydroxy group and H_1 and H_6 protons reside on the same plane of the 5,7-bicyclic ring system. The same rationale was used to determine the position of the methylene group of the oxirane ring, which was assigned to be *trans* to the hydroxy group according to europium induced shifts.

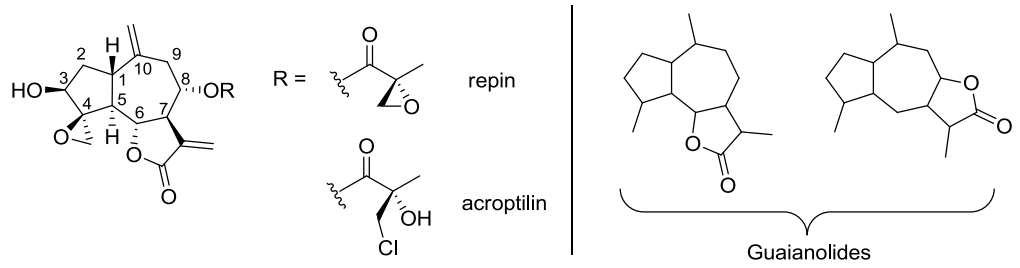
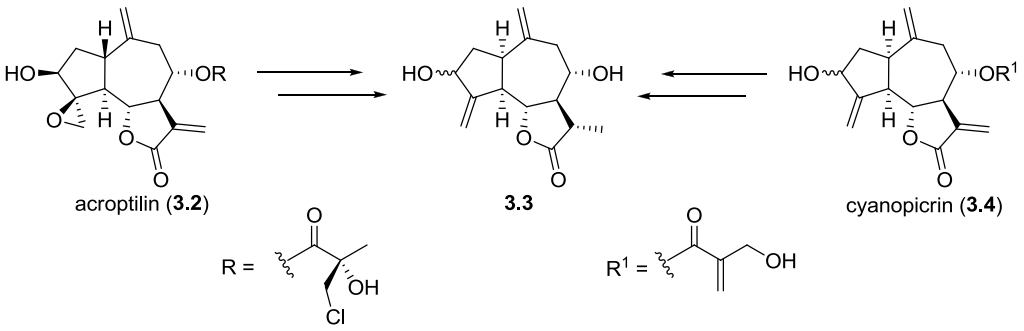


Figure 3.2. Initial stereochemistry assignment of repin by Evstratova et al.

In 1976, a study by Gonzalez *et al.* cast doubt on the original stereochemical assignment.[3] Their conclusions were based on the interconversions between sesquiterpene lactones from the same family. They demonstrated that acroptilin could be transformed into lactone **3.3**, and that the same lactone could be obtained by the selective reduction of cynaropicrin (**3.4**), the absolute configuration of which at the previously mentioned stereocentres had been rigorously established (Scheme 3.1).



Scheme 3.1. Demonstration of the relationship between acroptilin and cyanopicrin by Gonzalez et al.

The ability to prepare lactone **3.3** from both cynaropicrin (**3.4**) and acroptilin (**3.2**) demonstrates that the stereochemistry around seven-membered ring of both molecules is the same.

In 1982, Stevens revised the structures of repin and acroptilin and concluded that

repin was best depicted as the structure having the hydroxy group at C3 and the epoxide oxygen atom in a *trans* relationship to each other.[4] The unambigous confirmation of the stereochemical configuration of repin was disclosed in 1990, when Stevens *et al.* published an X-ray structure of the natural product (Fig. 3.3).[5] It was demonstrated that repin possesses the absolute configuration 1*R*, 3*S*, 4*S*, 5*S*, 6*S*, 7*S*, 8*S*, 17*R*, the same as that of acroptilin. The formation of acroptilin from repin involves opening of the epoxide to the epichlorohydrin with retention of absolute configuration.

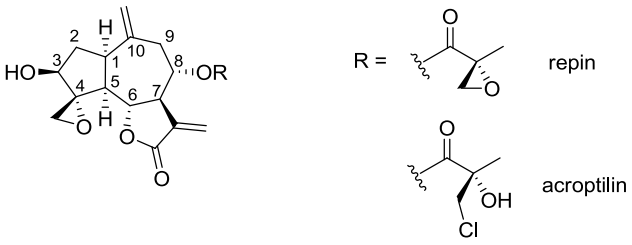


Figure 3.3. Structures of repin and acroptilin as confirmed by X-ray analysis.

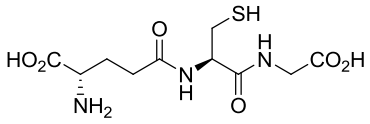
3.2.2. Biological Activity of Repin

Acroptilon repens (*Centaurea repens*, Russian knapweed) is a fast growing perennial weed of the family Asteraceae, that is rapidly becoming a major problem in many parts of United States.[5] Russian knapweed has been implicated as the causative agent of a nervous system disease in horses, called equine nigropallidal encephalomalacia (ENE), a disorded associated with signs and symptoms similar to those of Parkinson's disease (PD) in humans.[6]

Repin cytotoxicity was examined by Choi *et al.* in orded to explore its pathogenetic relationship to ENE and to PD.[6,7] Repin was found to be highly cytotoxic to both PC12 cells and mouse astrocytes in a dose-dependent manner with EC_{50} in PC12

cells and astrocytes being approximately 14 μM and 6.2 μM, respectively. Control cells showed well-defined nuclei with nuclear and cell membranes intact, while repin-exposed cells showed rupture of cell and nuclear membranes.

Marked depletion of cellular glutathione (GSH) is believed to be the main cause of repin cytotoxicity (Fig. 3.4). Repin rapidly reacts with GSH in a 1:1 ratio to afford a complex which lacks cytotoxicity.



glutathione (GSH)

Figure 3.4. Structure of glutathione (GSH).

Interestingly, when the GSH biosynthesis was inhibited in cells, this resulted in decreased cellular GSH level, but the cytotoxic effect differed considerably when compared to repin. This suggests that GSH depletion is not the sole mechanism underlying repin cytotoxicity. Current data suggests that oxidative stress plays a major role in repin toxicity with effects being accompanied by the rise in the level of reactive oxygen species (ROS) and damage to cellular, cytoplasmic, nuclear and mitochondrial membranes.[7]

Repin induced retrograde degeneration of dopaminergic neurons indicates that repin can influence striatal dopaminergic pathways and therefore play an important role in pathogenesis of the PD-like disorder in horses. It was also shown that repin causes apoptosis mediated by oxidative stress induced mitochondrial release of cytochrome c and activation of CASPASE 3.[8] Interestingly, pretreatment with reducing agents (*N*-acetyl-L-cysteine or reduced GSH) completely protected cells from repin induced

mitochondrial and dopaminergic toxicity, while the antioxidants, coenzyme-Q and ascorbic acid, completely blocked repin dopaminergic toxicity.[9]

Repin and a number of its close structural analogues were tested against replication of A549 (lung cancer) and MCF-7 (breast cancer) tumour cell lines (Fig. 3.5).[10]

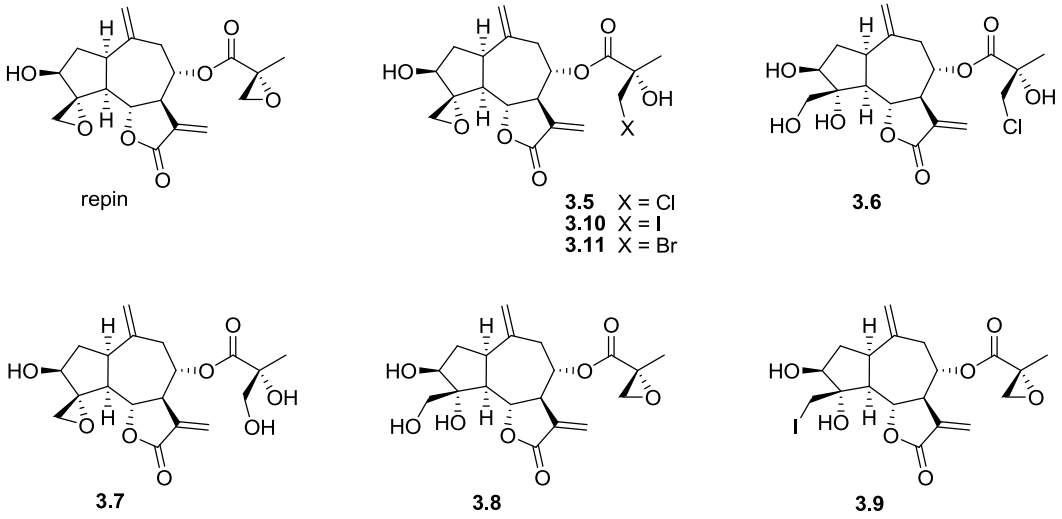


Figure 3.5. Repin and its natural and synthetis analogues.

Interestingly, compounds **3.6**-**3.8**, which contain a diol rather than chlorohydrin or epoxide on the 5-membered ring or the side chain, showed no activity against either cell line. Repin and chlorohyssopifolin C (**3.5**), which do contain these electrophilic moieties, showed good activity (Table 3.1). Repin was also demonstrated to be significantly potent against several other cell lines – 1A9 (ovarian cancer), KB (nasopharyngeal cancer), KB-VIN (KB drug-resistant variant), HCT-8 (ileocecal cancer). Substituting the epoxide on the 5-membered ring with halohydrin resulted in the loss of activity (compound **3.9**). Substituting the side chain epoxide for halohydrin results in compounds **3.10** and **3.11** that retain anti-tumour activity but are slightly less active than the parent diepoxide repin. Esterification of repin with the side chain of paclitaxel leads to increased potency in all tested cell lines except

KB-VIN.

Table 3.1. Anti-tumour activity of repin and its analogues compared to paclitaxel and mitomycin C.

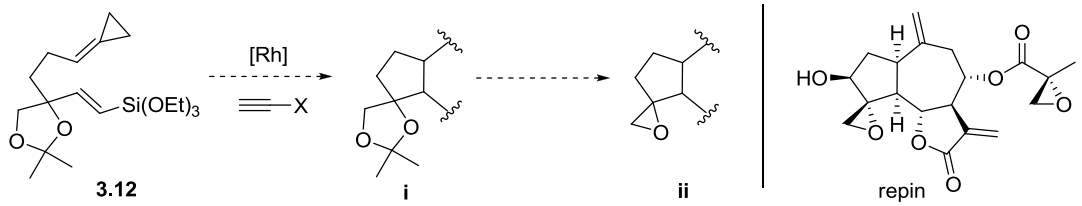
	IC_{50} (μM)/Cell Line					
Compound	A549	MCF-7	1A9	KB	KB-V	HCT-8
repin	2.5	1.1	0.3	1.4	0.8	0.8
3.5	9.3	1.5	0.8	2.0	1.5	1.6
3.6	>24.0	>24.0				
3.7	>26.3	>26.3				
3.8	>26.3	>26.3				
3.9	13.7		5.6	4.1	18.6	4.5
3.10	7.3		0.8	2.0	1.8	
3.11	4.3		1.1	1.1	6.3	1.3
paclitaxel			0.002	0.001		0.013
mitomycin C	0.3	1.5		0.6		0.6

3.3. Synthetic Studies Towards Repin

3.3.1. Limitations of the Carbocyclisation of Vinyl Silanes

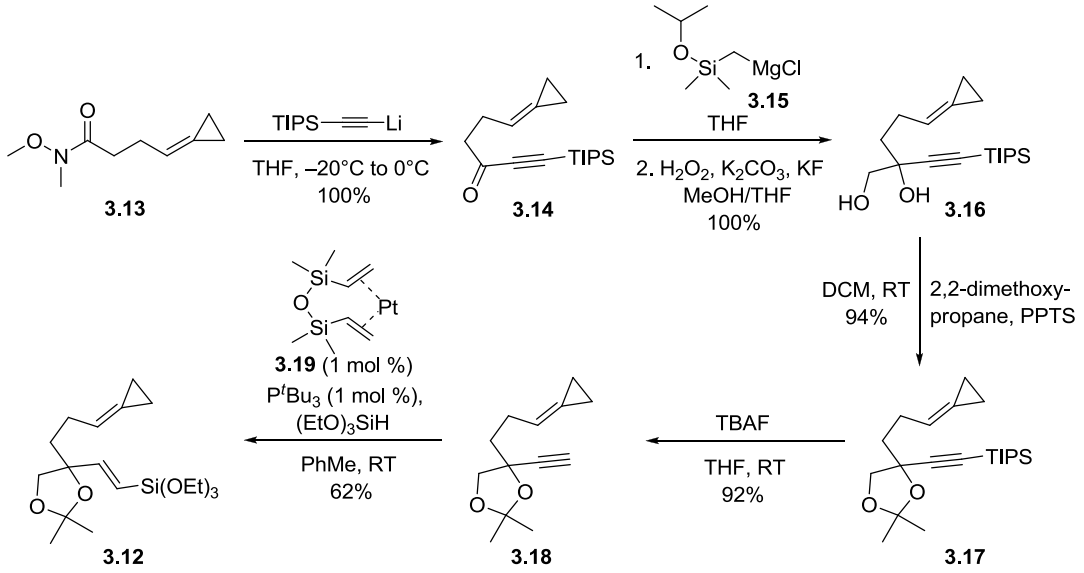
Due to its complex structure and intriguing biological activity, repin poses as an attractive target for total synthesis. In chapter 2 we described our solution to the introduction of the oxygen atom at the C6 position of the guaianolide skeleton. The key challenge was whether it would be possible to induce the desired relative stereochemistry in the cycloadduct by employing chiral vinyl silanes. At the outset of

our studies, we decided to prepare and test vinylsilane **3.12**, possessing α-stereogenic centre in the form of protected tertiary alcohol (Scheme 3.2). The choice of the diol motif **i** was not arbitrary since after deprotection such diol could undergo functional group interconversion to epoxide **ii**, that is present in repin (it was established earlier that the epoxide itself was not stable under the carbocyclisation conditions).



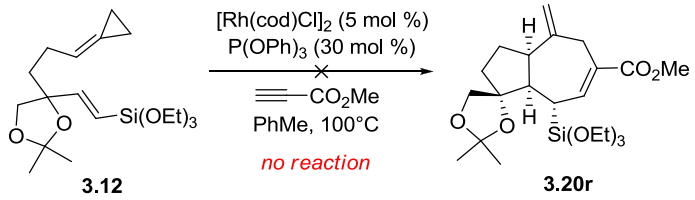
Scheme 3.2. Vinylsilane possessing α-stereogenic centre.

The synthesis of acetonide **3.12** commenced with the reaction of Weinreb amide[11] **3.13** and lithium triisopropylsilyl acetilyde, which afforded ynone **3.14** in good yield (Scheme 3.3). Treatment with Grignard reagent **3.15** and subsequent oxidation with hydrogen peroxide furnished diol **3.16** in excellent yield. The diol was protected as acetonide **3.17** and the silyl group was cleaved with TBAF. Resulting alkyne **3.18** was hydrosilylated using Karstedt's catalyst (**3.19**)[12] to afford desired *(E)*-vinyl silane **3.12** in good yield and with excellent regio- and stereoselectivity.



Scheme 3.3. Synthesis of acetonide **3.12**.

Unfortunately, when compound **3.12** was subjected to rhodium-catalysed [(3+2)+2] carbocyclisation conditions in the presence of methyl propiolate as an alkyne partner, the reaction failed to afford the desired bicycloheptadiene **3.20r** (eqn. 3.1). Acetonide **3.12** proved to be completely unreactive under standard reaction conditions.

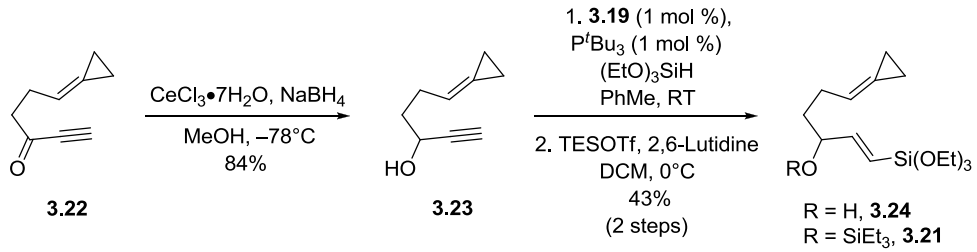


(3.1)

This unreactivity was rationalised due to the large steric encumbrance of the alkene. The additional substituents next to the double bond engage in nonbonding interactions with the metal. In combination with the bulky triethoxysilyl group, these interactions could prevent rhodium from carbometallating the olefin. Another reason for the lack of reactivity could be the absence of substitution in the tether. An unsubstituted CH_2 methylene unit can be expected to be far less efficient in preorganising the substrate for the cyclisation than $C(CO_2Me)_2$ linker, according to

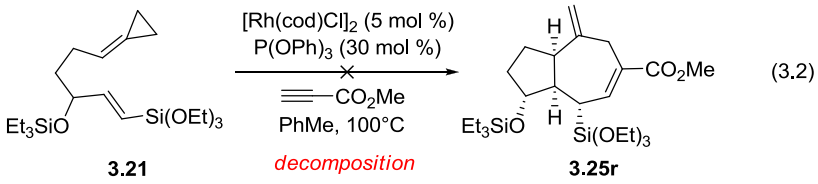
the Thorpe-Ingold effect.[13,14]

We hypothesised that a less hindered secondary alcohol could still act as a substrate in the reaction. Silyl protected secondary alcohol **3.21** was prepared from ynone **3.22** in 3 steps (Scheme 3.4). The Luche reduction[15] of **3.22** furnished propargylic alcohol **3.23**, which was then treated with triethoxysilane in a platinum-catalysed hydrosilylation reaction. The resulting *(E)*-vinylsilane **3.24** was protected as triethylsilyl ether **3.21** under standard conditions.



Scheme 3.4. Synthesis of secondary alcohol **3.21**.

To our dismay, when subjected to rhodium-catalysed [(3+2)+2] carbocyclisation conditions in the presence of methyl propiolate, vinylsilane **3.21** failed to afford the desired bicycloheptadiene **3.25r** (eqn. 3.2). In this case prolonged heating led to the decomposition of the starting material.



(3.2)

Despite the fact that we could not apply rhodium-catalysed [(3+2)+2] carbocyclisation reaction of vinylsilanes for the α-substituted substrates, we believe that this methodology could find its application in the target oriented synthesis for the preparation of simpler analogues of natural guaianolides for structure-activity

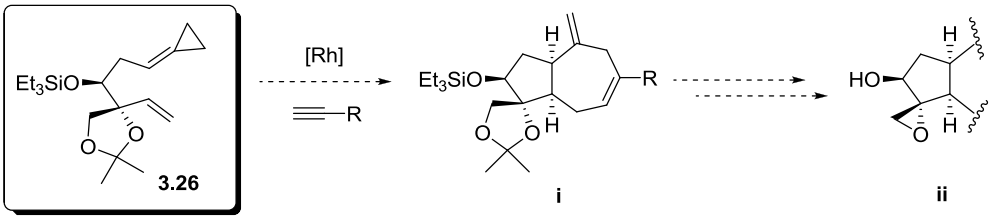
relationship studies.

3.3.2. Synthesis of the Carbocyclisation Precursor

3.3.2.1. Epoxidation/Epoxide Ring Opening Route

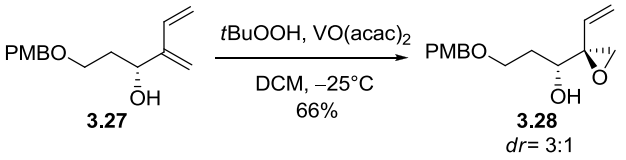
Since the rhodium-catalysed [(3+2)+2] carbocyclisation of vinyl silanes could not be applied to the synthesis of repin, we envisaged a different approach to this interesting synthetic target. While considering the possible ways of creating the 5,7-bicyclic scaffold of the molecule, we decided to employ the [(3+2)+2] carbocyclisation of a simpler olefin for the realization of this task. This reaction is much less sensitive to the steric hindrance around the double bond and would allow us to incorporate necessary substitution into the cyclisation precursor.

The challenge of introducing the C6 hydroxyl group into the molecule would be obviated by employing the highly functionalised cyclisation precursor **3.26**, which would reduce the amount of elaboration needed for the left-hand side of late stage intermediates (Scheme 3.5). ACP **3.26** would possess two stereocentres with the correct relative stereochemistry: a secondary alcohol protected as a silyl ether and a diol concealed in the form of acetonide. The diol moiety would act as a masked epoxide, which would be revealed later in the synthesis. However, there is an inherent risk using cyclisation precursor **3.26**, as there is little precedent in the literature on the stereochemical outcome of such a cycloaddition.



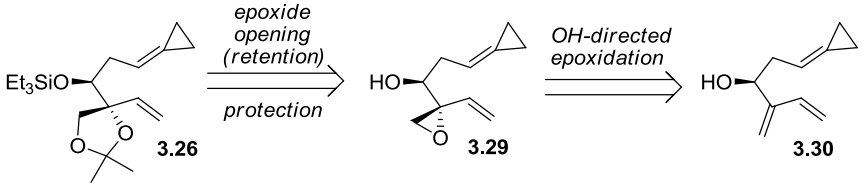
Scheme 3.5. Proposed carbocyclisation precursor – protected triol **3.26**.

The number of literature precedents describing stereoselective synthesis of protected triols such as **3.26** is very limited. Maier and Jogireddy used hydroxyl-directed epoxidation of the acyclic secondary alcohol **3.27** to furnish hydroxyepoxide **3.28** in a stereoselective manner, in their synthesis of luminacin D (eqn. 3.3).[16] In this case the pre-existing stereochemical information in **3.27** was transferred from the secondary alcohol to the newly formed stereogenic centre. The oxirane ring formed in this way could then theoretically be opened to a diol by means of nucleophilic attack by a suitable oxygen nucleophile.



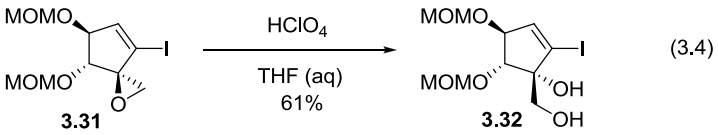
(3.3)

Epoxide ring opening by oxygen nucleophiles is a well established transformation that can take place under various conditions. However, in our case we would be limited in this choice by the need to effect the ring-opening of epoxide **3.29** with retention of the stereochemistry at the tertiary alcohol centre (Scheme 3.6).



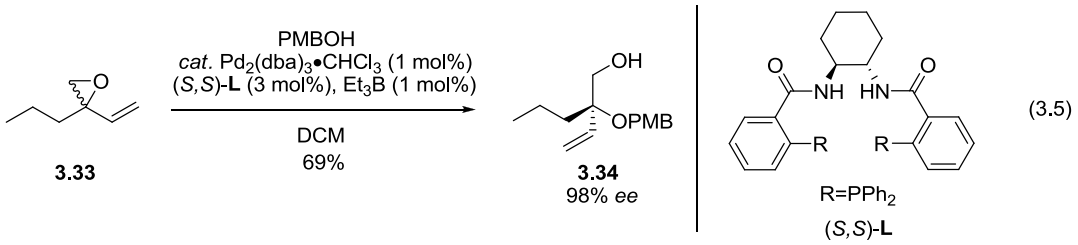
Scheme 3.6. Retrosynthetic scheme for the protected triol **3.26**.

Acidic conditions are often used to effect stereoselective epoxide ring-opening. This is illustrated by the conversion of **3.31** to **3.32** in the synthesis of kedarcidin chromophore ansamacrolide by Hirama *et al.* (eqn. 3.4).[17] However, the conditions lead to the inversion of the stereochemistry at the tertiary alcohol, and are therefore not suitable for our purpose.



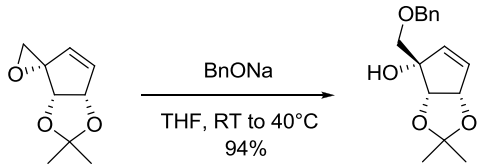
(3.4)

Palladium- and boron-co-catalysed asymmetric allylic alkylation, for the construction of chiral diols starting from racemic epoxides,[18] was successively used by Trost *et al.* in the synthesis of anti-HIV drug Tipranavir for the conversion of epoxide **3.33** to monoprotected diol **3.34** (eqn. 3.5).[19]



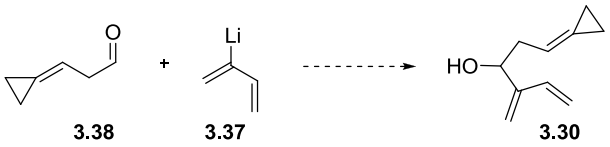
(3.5)

In our case, however, the pre-existing stereocentre could influence the stereochemical outcome of asymmetric transition metal-mediated transformations in either a matched or mismatched scenario. Therefore, we decided to opt for the epoxide ring opening under strongly basic conditions, which would theoretically afford the diol with the desired stereochemistry. Nokami *et al.* converted epoxide **3.35** to monoprotected diol **3.36**, with retention of the stereochemistry at the tertiary stereogenic centre, by treatment with sodium alkoxide (eqn. 3.6).[20]



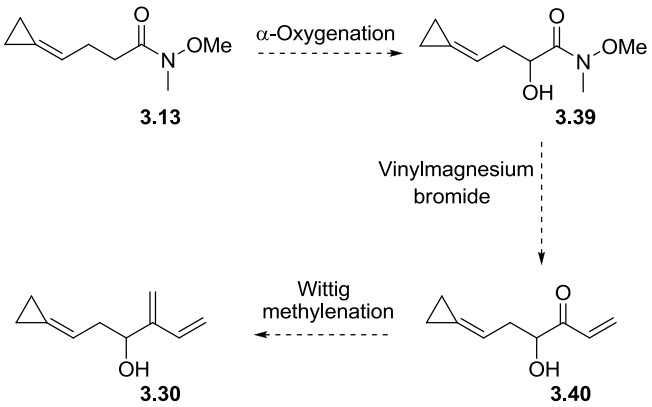
3.35 **3.36** (3.6)

We set out to employ Nokami's conditions for the synthesis of the triol **3.26**. However, the preliminary studies showed that the synthesis of the epoxidation precursor **3.30** was not trivial. Our initial plan to access alcohol **3.30** through an addition of the *in situ* generated organolithium **3.37**[21] to aldehyde **3.38** failed, due to the difficulties associated with the preparation of the aldehyde (eqn. 3.7).



3.38 **3.37** **3.30** (3.7)

As a consequence, it was elected to access **3.30** *via* a 3-step sequence, consisting of α-oxygenation of amide **3.13**, vinylmagnesium bromide addition to the product **3.39**, and methylenation of the enone **3.40** *via* Wittig olefination[22](Scheme 3.7).

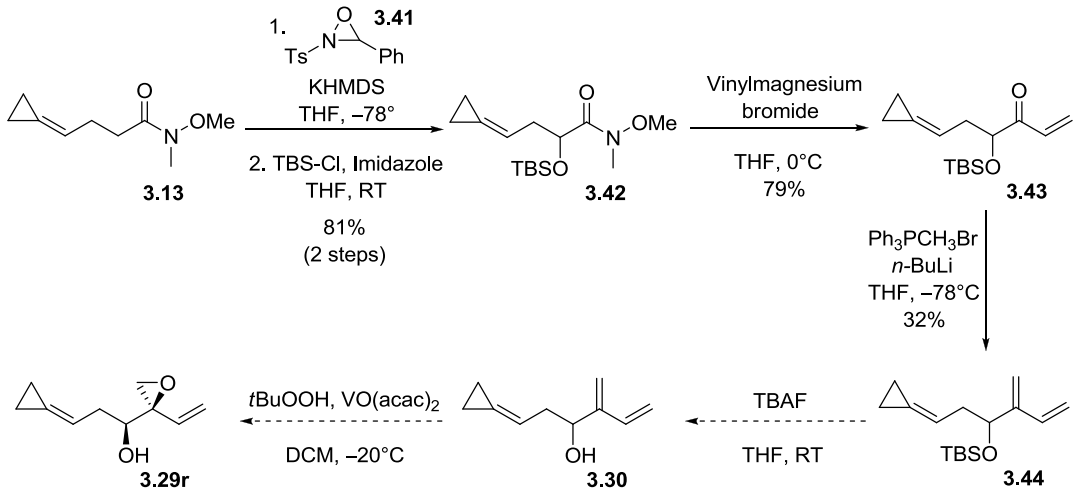


3.13 **3.39** **3.30** **3.40**

Scheme 3.7. Proposed synthetic route to **3.30** from easily accessible amide **3.13**.

After initial attempts we found out that it was necessary to employ a protecting group for the secondary alcohol generated in the α-oxygenation step. The synthesis

commenced with the α-oxygenation of ACP-containing amide **3.13** by Davis oxaziridine **3.41**[23], followed by silyl protection to give **3.42** (Scheme 3.8). Amide **3.42** was treated with vinylmagnesium bromide to furnish enone **3.43**, which was methylenated to afford diene **3.44** in low 32% yield.



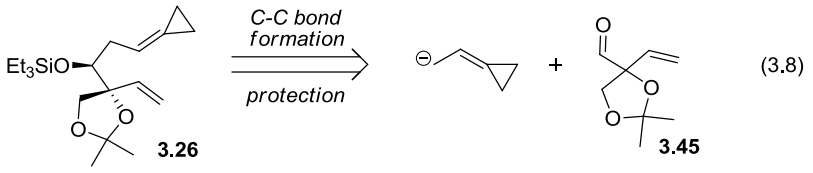
Scheme 3.8. Synthesis of the epoxidation precursor **3.30** starting from amide **3.13**.

The low yield of methylenation reaction, combined with the large number of steps, yielded a very inefficient route, even for preliminary studies. It was also questionable how reasonable it was to use an epoxide to create a diol, which would later be converted back to the same epoxide. Therefore, the epoxidation/epoxide ring opening strategy was abandoned at this stage.

3.3.2.2. Protected Glycerol Derivative Route

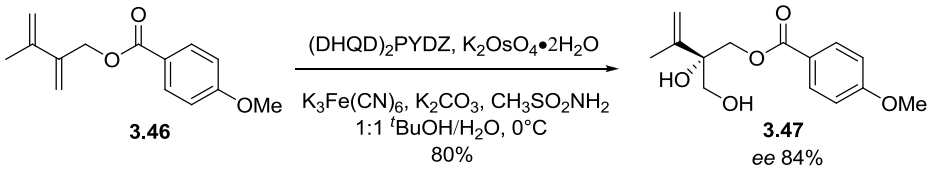
We stated above that the directed epoxidation strategy relies on the transfer of stereochemical information from the secondary alcohol to the newly formed tertiary alcohol centre. An alternative approach to this stereochemical motif would involve the initial generation of the tertiary alcohol with the desired stereochemistry, and transfer of this stereochemical information in the course of the formation of

secondary hydroxyl group (eqn. 3.8).



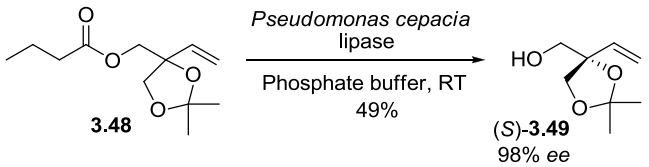
(3.8)

To realise this approach we would need to establish the desired stereochemistry at the tertiary alcohol centre first. It is known that asymmetric dihydroxylation of the proximal double bond of *p*-methoxybenozate ester of 2-hydroxymethyl-1,3-butadiene (**3.46**) can be selectively performed affording diol **3.47** in good yield with excellent regioselectivity (eqn. 3.9).[24]



(3.9)

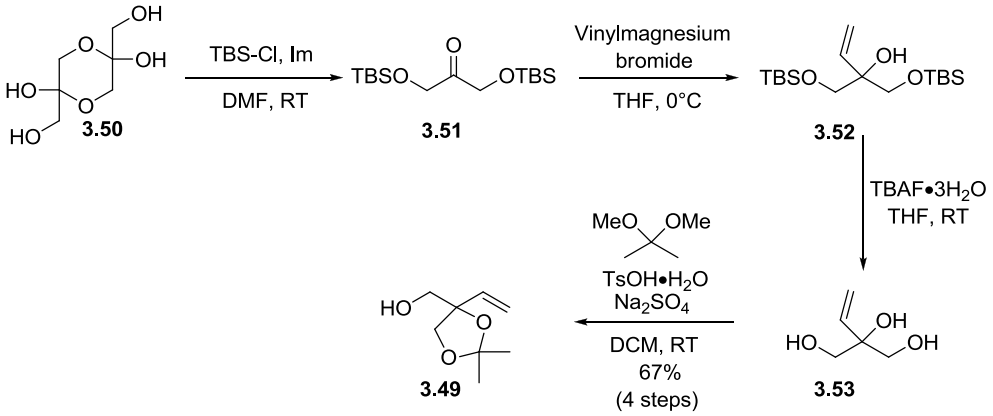
The enantiomeric excess, however, was rather low in this example – only 84%. Fortunately, known enzymatic kinetic resolution of ester **3.48**[25] generated alcohol (*S*)-**3.49** in near enantiopure form (eqn. 3.10). We elected to exploit this methodology in our synthesis of triol **3.26** with the hope that we would be able to furnish the secondary hydroxyl group in the correct relationship to the tertiary alcohol.



(3.10)

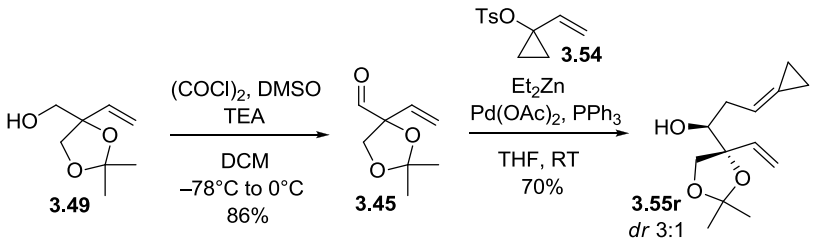
Racemic acetonide **3.49** was prepared in 4 steps according to the literature procedure[25] starting from 1,3-dihydroxyacetone dimer (**3.50**) (Scheme 3.9). The

dimer **3.50** was silyl protected to give **3.51**, which was then treated with vinylmagnesium bromide to afford the tertiary alcohol **3.52**. Deprotection of **3.52** was effected by TBAF•3H_2O in THF. Subsequent treatment of triol **3.53** with 2,2-dimethoxypropane under acid catalysed-conditions furnished acetonide **3.49** in 67% yield over 4 steps. We decided to continue our work in the racemic series and switch to enantiopure material only when we had the general synthetic route for repin established.



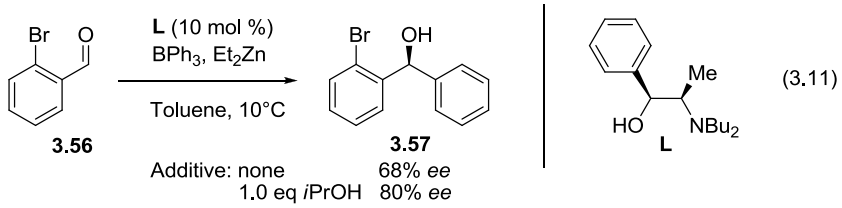
Scheme 3.9. Synthesis of racemic acetonide **3.49**.

Racemic **3.49** was subjected to Swern oxidation[26] conditions to give aldehyde **3.45** in 86% (Scheme 3.10). In the next step we employed organozinc ACP synthon addition to aldehyde developed by Salaün *et al*.[27] Utilizing a modified procedure used by Cordero *et al*.,[28] **3.45** was reacted with tosylate **3.54** to afford the **3.55r** in good yield and moderate stereoselectivity (70% yield and 3:1 dr).



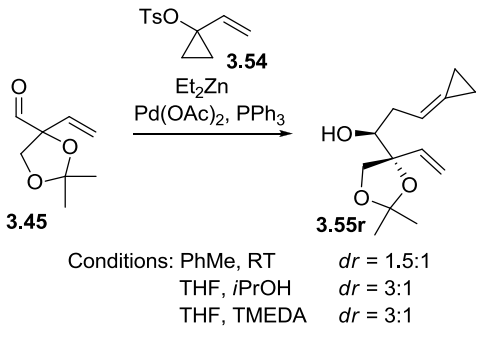
Scheme 3.10. Palladium-catalysed organozinc addition to aldehyde **3.45**.

Gratifyingly, this synthetic route allowed efficient access to **3.55r**, however, in only moderate diastereoselectivity. Dahmen *et al.* have shown that different solvents and additives can be used to influence the enantioselectivity in the reaction of *o*-bromobenzaldehyde (**3.56**) with phenylzinc (eqn. 3.11).[29]



(3.11)

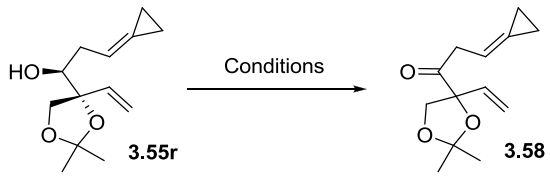
We were intrigued to assay whether additives and the dielectric nature of solvent used could improve the diastereocontrol of the organozinc addition. Unfortunately, switching the reaction solvent from THF to less coordinating toluene only diminished the diastereoselectivity to 1.5:1. TMEDA and *i*-PrOH additives failed to produce any improvement in diastereoselectivity when compared to the initial conditions (eqn. 3.12)



(3.12)

Another possible approach to improve the diastereomeric ratio would be to employ an oxidation/reduction protocol. A brief screening of oxidation methods showed Dess-Martin reagent[30] to be superior in effecting clean conversion of alcohol **3.55r** to β,γ-unsaturated ketone **3.58** (Table 3.2, entry 4).

Table 3.2. Oxidation of alcohol **3.55r** to β,γ-unsaturated ketone.



Entry[a]	Conditions	Yield
1	$(COCl)_2$, DMSO, then TEA, DCM, −78°C to RT	51% (partial isomerisation of the double bond)
2	TEMPO, $PhI(OAc)_2$, DCM, RT	no reaction
3	TPAP, NMO, MS 4Å, DCM, RT	68% (sluggish reaction; by-product formation)
4	*DMP, $NaHCO_3$, DCM, RT*	*90%*
5	PDC, MS 4Å, DCM, RT	43% (sluggish reaction; by-product formation)

[a]Selectivity for the desired product was determined by ^{1}H NMR analysis of crude reaction mixtures. Isolated yields are reported.

Other oxidants proved to be less efficient. The Swern conditions[26] caused partial migration of the double bond into conjugation with the ketone (entry 1). TPAP oxidation[31] was sluggish and failed to go to completion (entry 3). Interestingly, an apparent kinetic resolution appears to operate under these conditions, with the major diastereomer reacting faster than the minor diastereomer. This left the remaining starting material with an enriched ratio of the minor diastereomer (dr = 1:2.5 *vs*.

initial dr = 3:1).

Generally, the selectivity in reduction reactions of α-chiral α-oxygenated substrates can be predicted based on the Felkin-Ahn model or chelate controlled model in the case of a secondary alcohol.[32] Such a prediction, however, is much less reliable in case of tertiary alcohol derivatives with the groups R^2 and R^3 of similar size (Fig. 3.6).

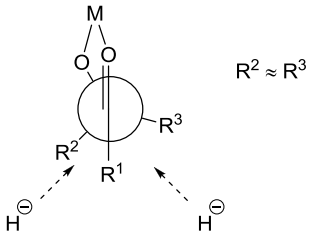
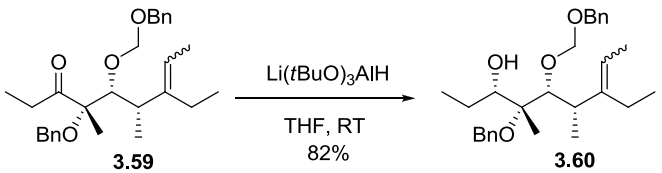


Figure 3.6. Chelate controlled model: difficulty predicting the direction of attack when $R^2 \approx R^3$.

Few literature data is available on the diastereoselective reduction of the ketones similar to **3.58**. The closest literature precedent was found in the studies performed by Heathcock *et al*. towards the synthesis of erythronolide A. The authors reported that when ketone **3.59** was treated with Li(O*t*Bu)$_3$AlH in THF, alcohol **3.60** was obtained as a single diastereomer (eqn. 3.13).[33]

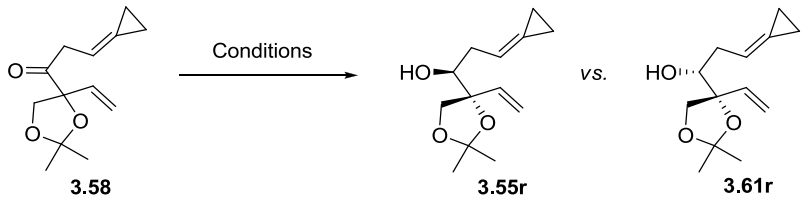


(3.13)

It is noteworthy to mention here that if the same mode of 1,2-stereoinduction would be seen in the reduction of our ketone **3.58**, this would result in the undesired diastereomer. Our attempts to accomplish the diastereoselective reduction of **3.58** are

summarised in Table 3.3.

Table 3.3. Diastereoselective reduction of ketone **3.58**.



Entry[a]	Conditions	Yield	*dr* (3.55r/3.61r)
1	$LiAlH_4$, THF, −78°C	83%	1:1.5
2	**$CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, −78°C**	**88%**	**9:1**
3	LiI, $LiAlH_4$, THF, −78°C	89%	2.7:1
4	DIBAL-H, DCM, −78°C	95%	4:1
5	$Zn(BH_4)_2$, DCM, 0°C	77%	1:1
6	$PhMe_2SiH$, cat. TBAF, THF, 0°C	80%	Migration of db, then reduction
7	**K-Selectride, THF, −78°C**	**74%**	**1:11**

[a]Diastereomeric ratios were determined by ^1H NMR analysis of crude reaction mixtures. Isolated yields are reported.

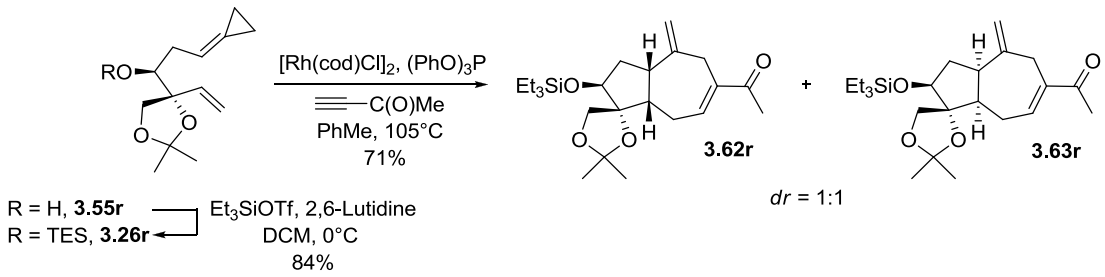
Luche reduction[15] gave the highest selectivity for the formation of diastereomer **3.55r** (Table 3.3, entry 2). For the opposite diastereomer **3.61r** – K-Selectride gave the highest selectivity (entry 7). The relative configuration of diastereomers **3.55r** and **3.61r** was tentatively assigned on the assumption that the sterically bulky non-coordinating K-Selectride would probably react in the same stereochemical manifold as Li(*t*BuO)$_3$AlH in the work of Heathcock (*vide supra*), thereby affording the undesired diastereomer **3.61r**. The stereochemistry of **3.55r** and **3.61r** was unambiguously determined at a later stage *via* X-ray crystallography of one of the

advanced intermediates in the synthesis, and corresponded to our initial assignment.

3.3.3. Rhodium-Catalysed [(3+2)+2] Carbocyclisation and Oxidation of the Cycloadduct

3.3.3.1. Cycloaddition with 3-Butyn-2-one

Diastereomer **3.55r** was then protected as triethylsilyl ether **3.26r** (Scheme 3.11). Gratifyingly, the minor diastereomer could be separated *via* chromatography on silica gel. With the pure **3.26r** in hand we were ready to try the crucial rhodium-catalysed [(3+2)+2] carbocyclisation. 3-Butyn-2-one was chosen as alkyne partner due to the good regioselectivities that were obtained in rhodium-catalysed cycloadditions with this π-component.[34] When ACP **3.26r** was treated with $[Rh(cod)Cl]_2$ modified with $P(OPh)_3$ in the presence of butyn-2-one, full conversion to bicyclic cycloadducts **3.62r** and **3.63r** was observed (71%). Unfortunately, no diastereocontrol was observed and reaction furnished **3.62r** and **3.63r** as a 1:1 mixture.



Scheme 3.11. Diastereomeric cycloadducts resulting from the carbocyclisation of **3.26r** with butyn-2-one.

Fortunately, the diastereomeric mixture was separable by chromatography on silica gel and relative configurations of both diastereomers could be assigned using

extensive 2D COSY and NOESY analysis. Crucial nOe signals between H_1 and H_4 were observed for diastereomer **3.63r**, indicating that both protons reside on the same face of the five-membered ring (Fig. 3.7). Diastereomer **3.63r** also showed strong nOe signals between H_6-H_8 and H_6-H_9, further confirming the suggested configuration. Moreover, the nOe signal between H_6-H_7 observed for the other diastereomer **3.62r** was also consistent with the expected structure. None of the compounds exhibited interactions between H_4-H_5 or H_4-H_6. The absence of nOe is not a proof, however it is indicative of our initial assignment of the stereochemistry of the alcohol **3.55r**.

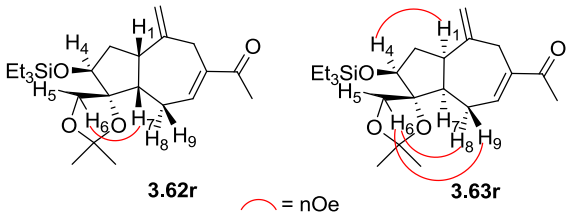


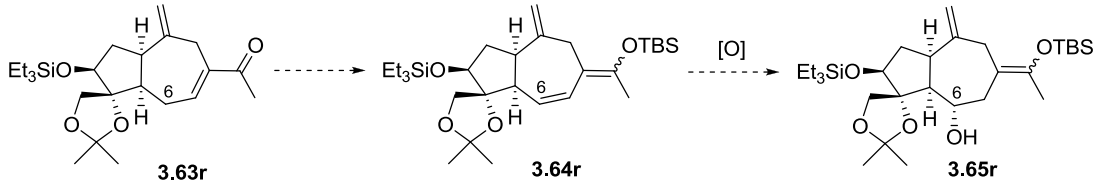
Figure 3.7. Stereochemical assignment of **3.62r** and **3.63r**.

3.3.3.2. Elaboration of the Cycloadduct

At this stage we were facing the challenge of introducing an oxygen functionality at the C6 position of **3.63r** and cleaving two extra carbon atoms at C8 (acetyl group) that were not present in the natural product (Fig. 3.8).

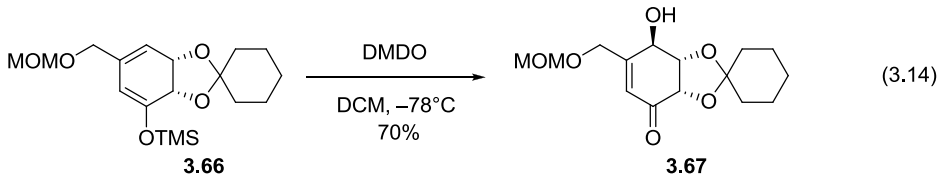
Figure 3.8. *Required modifications of the cycloadduct **3.63r**.*

We intended to effect C6 oxygenation *via* the formation of dienol silyl ether **3.64r** and regioselective oxygenation of its γ-position to furnish **3.65r** (Scheme 3.12).



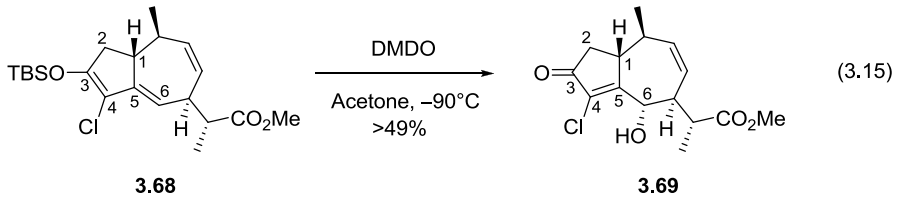
Scheme 3.12. Proposed route for introduction of C6 hydroxyl group.

Oxygenations of this type can be performed with excellent selectivities in many cases. For example, DMDO was used as an oxidant by Grierson *et al.* for the selective conversion of dienol silyl ether **3.66** to γ-hydroxylated product **3.67** in their studies towards the total synthesis of esperamicin-A1 (eqn. 3.14).[35]



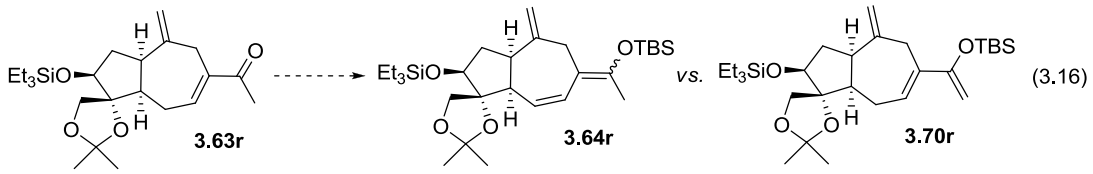
(3.14)

Similar conditions were employed by Deprés and Carret in their elegant synthesis of (±)-geigerin to effect C6 hydroxylation of silyl ether **3.68** (eqn. 3.15).[36]



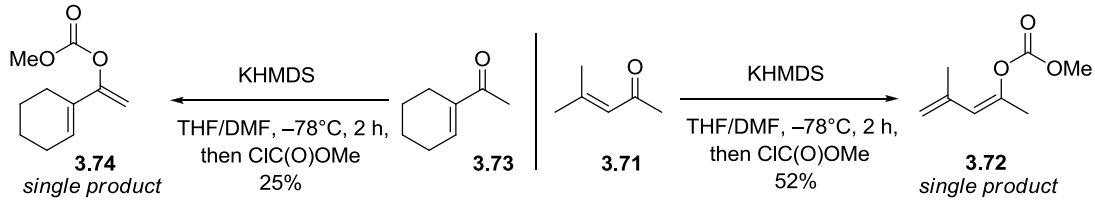
(3.15)

However, before we could utilize the envisaged oxidation, the dienol silyl ether **3.64r** had to be prepared in a regioselective manner. Two silyl enol ethers could be formed from **3.63r** - linearly conjugated **3.64r** and crossconjugated **3.70r** (eqn. 3.16).



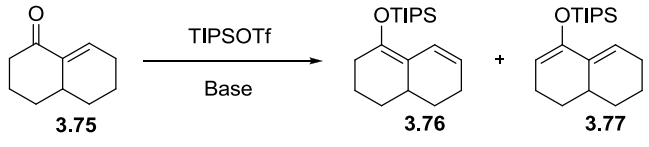
(3.16)

Generally, with judicious choice of reaction conditions it is possible to favour the formation of the desired regioisomer. This, however, depends strongly on the structure of the substrate. For instance, Kobayashi *et al*. showed that the acyclic enone **3.71** can be selectively converted to dienyl methyl carbonate **3.72** upon treatment with KHMDS in THF/DMF for several hours, followed by the addition of methyl chloroformate (Scheme 3.13). However, application of the same reaction conditions to the enone **3.73** resulted in the selective formation of the crossconjugated product **3.74**.[37]



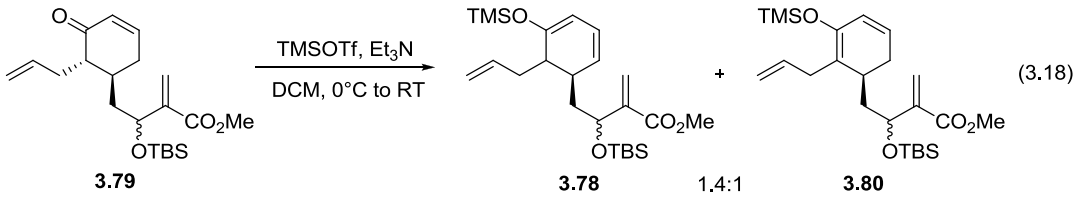
Scheme 3.13. Substrate dependant selectivity of enolisation.

Another such example can be found in the work of Maier and Varseev, who needed to convert enone **3.75** to linear silyl dienol ether **3.76** (eqn. 3.17). The authors discovered that only the crossconjugated product could be formed with high selectivity in this case. In the end, the best result for the linear product was achieved by treating **3.75** with TIPSOTf and DIPEA in DCM at −78°C, with silyl enol ethers **3.76** and **3.77** being formed in 68:32 ratio (eqn. 3.17).[38]

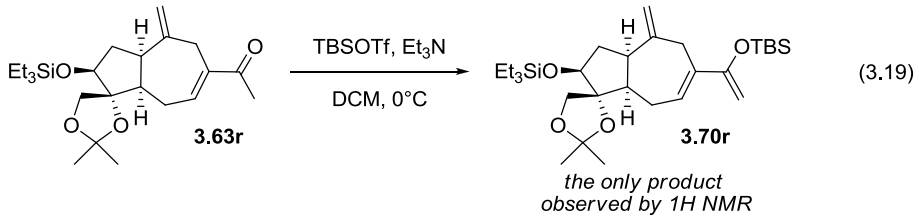


2,6-Lutidine, DCM, –20°C, 1 h: **3.76**/**3.77** = 0:100
KHMDS, THF/DMF, –78°C, 24 h: **3.76**/**3.77** = 50:50
DIPEA, DCM, –78°C, 24 h: **3.76**/**3.77** = 68:32

Rychnovsky and Sizemore showed that similar mild enolisation conditions can be used for preferential formation of the linear silyl dienol ether **3.78** from ketone **3.79**. Treatment of ketone **3.79** with TMSOTf and Et_3N in DCM at 0°C afforded a mixture of silyl enol ethers with a modest 1.4:1 selectivity for the formation of the linear product **3.78** (eqn. 3.18).[39]



These conditions were a good starting point for the preparation of silyl dienol ether **3.64r**. Unfortunately, when enone **3.63r** was subjected to TBSOTf and Et_3N in DCM at 0°C, only the cross-conjugated product **3.70r** was observed by the ^{1}H-NMR analysis of the crude reaction mixture (eqn. 3.19).

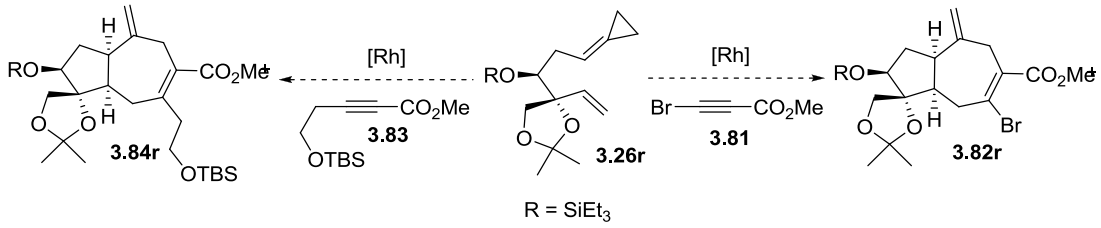


the only product observed by 1H NMR

3.3.3.3. Cycloaddition with Disubstituted Alkynes

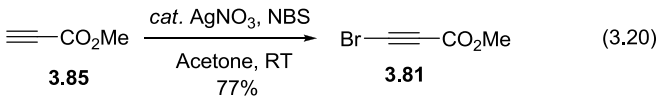
It was apparent from this result, that in order to obtain the linear silyl enol ether in this system, we needed to exclude the possibility of other enolisation. This could be achieved by employing a different type of alkyne in the rhodium-catalysed

carbocyclisation step. It was known from the work of Inglesby and Evans[34] that substituted methyl propiolate affords good regioselectivities in rhodium-catalysed [(3+2)+2] carbocyclisation with simple olefins. We chose methyl bromopropiolate (**3.81**) and hydroxyethyl substituted propiolate **3.83** as two test substrates (Scheme 3.14). The additional advantage of using these alkynes would be that the introduction of a bromide or a hydroxyethyl substituents could provide a good synthetic handle for the later formation of the lactone ring of repin.



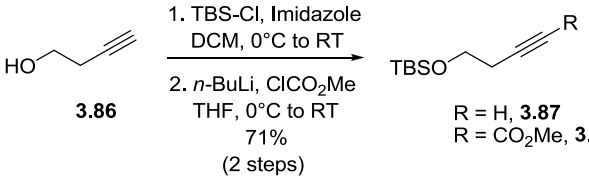
Scheme 3.14. Substituted methyl propiolates for [(3+2)+2] carbocyclisation.

Methyl bromopropiolate (**3.81**) was prepared in a straightforward manner in 77% yield by the bromination of methyl propiolate (**3.85**) in the presence of silver nitrate (eqn. 3.20).[40]



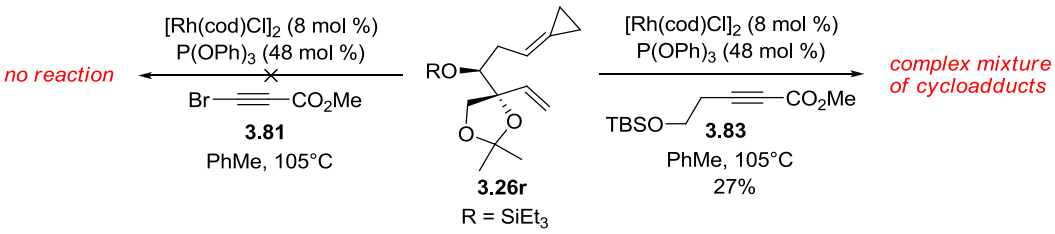
(3.20)

Hydroxyethyl substituted methyl propiolate **3.83** was prepared according to the procedure used by Ley *et al.*[41] The synthesis commenced with the monoprotection of commercially available 3-butyn-1-ol (**3.86**) as its TBS ether **3.87** (eqn. 3.21). Alkyne **3.87** was treated with *n*-BuLi, followed by methyl chloroformate, to afford the desired alkyne **3.83** in 75% yield over two steps.



(3.21)

When methyl bromopropiolate (**3.81**) and ACP **3.26r** were subjected to the rhodium-catalysed carbocyclisation conditions, no reaction was observed (Scheme 3.15). We believe that the steric bulk of the bromide substituent is responsible for the inhibition of the reaction. When subjected to the same reaction conditions, alkyne **3.83** afforded a complex inseparable mixture of cycloadducts in low 27% yield (Scheme 3.15). Because of the poor yield and inability to separate the isomers we did not undertake any further investigations of this reaction or its products.

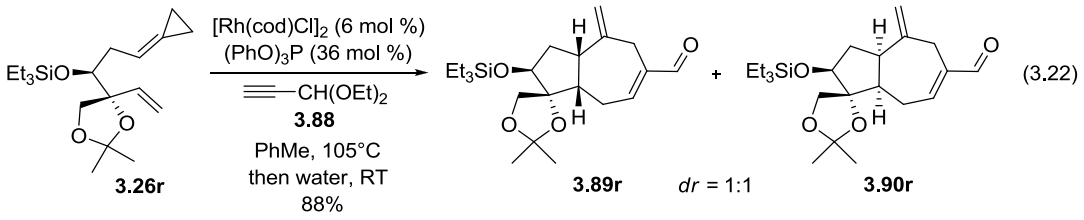


Scheme 3.15. Poor reactivity of disubstituted alkynes in the rhodium-catalysed [(3+3)+2] carbocyclisation with **3.26r**.

3.3.3.4. Cycloaddition with Propargyl Aldehyde Diethyl Acetal

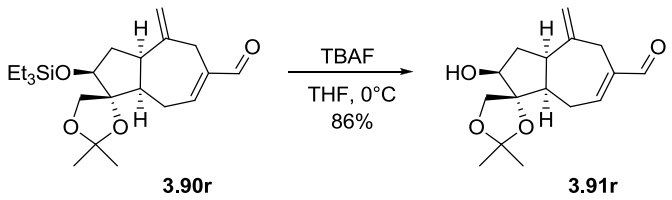
The lack of success in the reactions with substituted methyl propiolates made us search for the other potential alkyne reaction partners. We learned from our previous studies on the carbocyclisation of heteroatom substituted olefins, that propargyl aldehyde diethyl acetal (**3.88**) reacts with simple ACP-olefins with excellent regioselectivity. Moreover, its cycloadduct would also be a good substrate for silyl enol ether formation, due to the absence of another enolisable site. To our delight, when substrate **3.26r** was subjected to the standard rhodium-catalysed conditions in

the presence of acetal **3.88**, cycloadducts **3.89r** and **3.90r** were isolated in excellent yield of 88%. The reaction demonstrated the same lack of diastereocontrol affording a 1:1 mixture of diastereomers, but the high yield allowed for the preparation of large amounts of material (eqn. 3.22).



(3.22)

The diastereomers were separated by column chromatography on silica gel, and their relative stereochemistry was assigned based on the comparison of their ^{1}H-NMR spectra with the spectra of diastereomers **3.62r** and **3.63r** (*vide supra*, Scheme 3.11). Diastereomer **3.90r** was deprotected by treatment with TBAF to furnish alcohol **3.91r** in 86% yield (eqn. 3.23).



(3.23)

Single-crystal X-ray diffraction analysis of **3.91r** confirmed unambiguously the relative stereochemistry around the 5-membered ring to be as assigned previously (Figure 3.9).

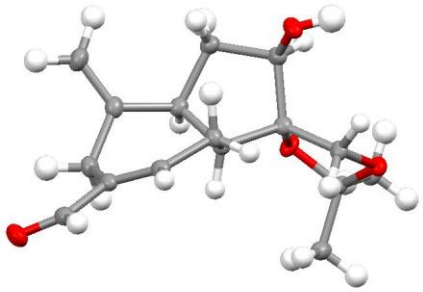
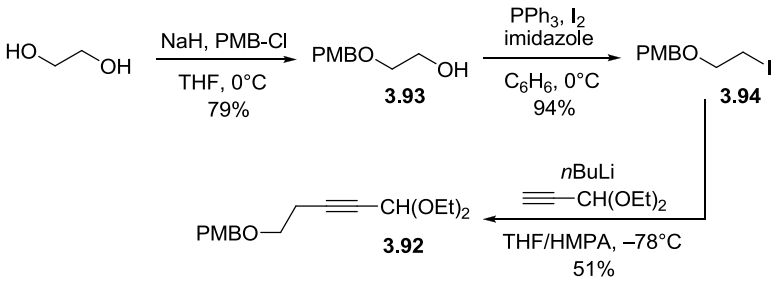


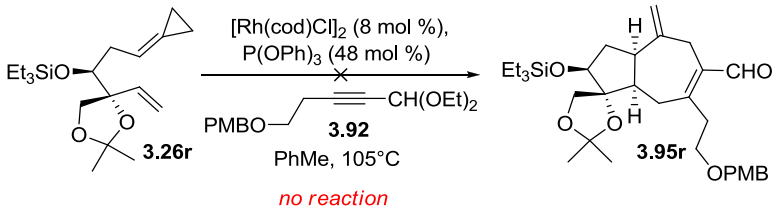
Figure 3.9. Crystal structure of alcohol **3.91r**.

Before proceeding with the silyl enol ether formation, we wanted to determine whether a substituted acetal would also be a viable alkyne partner in a carbocyclisation step. Substituted acetal **3.92** was prepared in 3 steps starting from ethyleneglycol, which was monoprotected as PMB ether **3.93**[42] and converted to iodide **3.94** by treatment with PPh_3/I_2[43] (Scheme 3.16). Iodide **3.94** was used to alkylate deprotonated acetal **3.88** to afford the target compound in 51% yield.



Scheme 3.16. Synthesis of substituted acetal **3.92**.

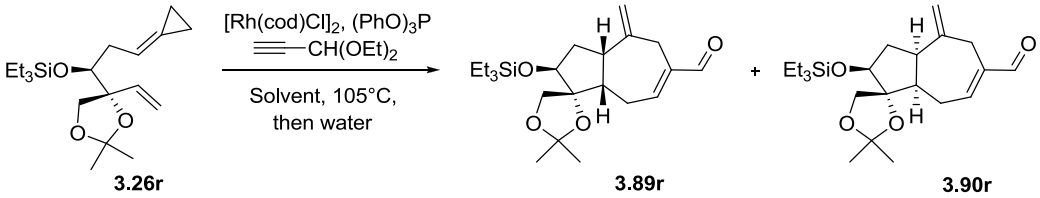
However, when the alkyne **3.92** and ACP **3.26r** were submitted to rhodium-catalysed carbocyclisation conditions, no product formation was observed (eqn. 3.24). As in the previous cases, disubstituted alkyne resulted in the deterioration of reactivity due to it's steric encumbrance.



(3.24)

Several attempts to improve the diastereoselectivity of the rhodium-catalysed carbocyclisation with the propargyl aldehyde diethyl acetal were undertaken. Solvent screening showed only minor deviations from the 1:1 diastereomeric ratio of the products for the solvents of different polarity and coordinating ability. Thus, THF and DCE (Table 3.4, entries 1 and 3) slightly favoured the desired diastereomer, while ethanol and chlorobenzene the undesired diastereomer (entries 2 and 6). Generally, the reactivity profile in all of the tested solvents was worse than in the standard solvent toluene. Most of the solvents assayed gave uncompleted reactions in the standard time and/or yielded a complex mixture of decomposition products.

Table 3.4. Sovent screening for the Rh-catalysed cycloaddition of **3.26r**.

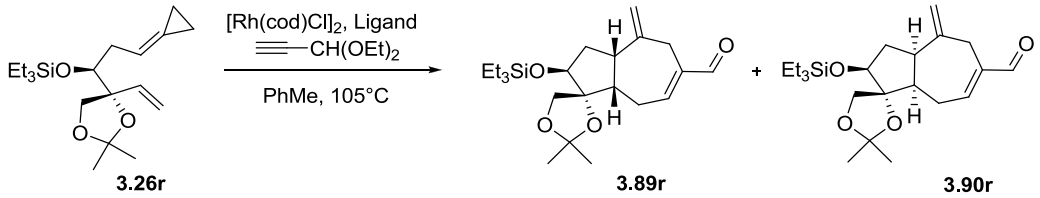


Entry[a]	Solvent	Yield[b]	Selectivity 3.89r/3.90r[c]
1	THF	62%	1:1.2
2	EtOH	53%	1.2:1
3	DCE	36%	1:1.2
4	Dioxane	57%	1:1.2
5	NMP	decomposition	decomposition
6	PhCl	59%	1.3:1
7	Heptane	reaction components insoluble	reaction components insoluble

[a]All reactions were carried on 0.12 mmol scale with 0.085 equiv $[Rh(cod)Cl]_2$, 0.51 equiv $P(OPh)_3$, and 3.0 equiv alkyne for 6-8 h. [b]Isolated yields. [c]Diastereomeric ratios were determined by ^1H NMR analysis of crude reaction mixtures.

Monophosphines are poor ligands for rhodium-catalysed [(3+2)+2] carbocyclisation, however bidentate phosphines can be successfully employed to obtain desired product in good yield.[34] Unfortunately, application of dppp as the ligand for rhodium in the reaction of **3.26r** did not result in the improvement of the selectivity (Table 3.5, entry 2). Phosphites other than $P(OPh)_3$ were also screened to assay the steric effect of the ligand on the diastereoselectivity. Neither sterically demanding tris(*o*-tolyl)phosphite, nor relatively unencumbered trimethylphosphite, produced any improvement in the diastereoselectivity when compared to triphenylphosphite (entries 3 and 4, respectively).

Table 3.5. Ligand screening for the Rh-catalysed cycloaddition of **3.26r**.



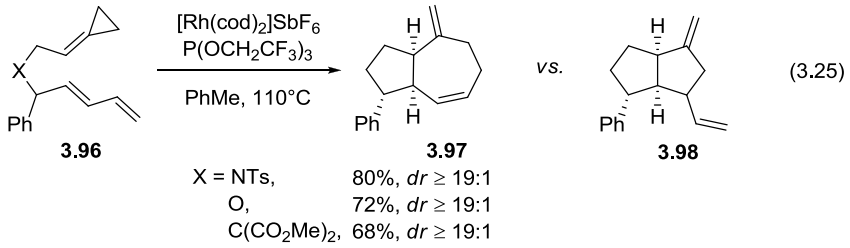
3.26r 3.89r 3.90r

Entry[a]	Ligand	Selectivity, 3.89/3.90[b]	Yield[c]
1	$P(OPh)_3$	1:1	88%
2	dppp	1:1	65%
3	tris(*o*-tolyl)phosphite	1:1	71%
4	$P(OMe)_3$	1:1	45%

[a]Reactions were carried on 0.15-0.25 mmol scale with 6 mol % of $[Rh(cod)Cl]_2$, 36 mol % of phosphite, and 300 mol % alkyne for 6-8 h. [b]Diastereomeric ratios were determined by ^1H NMR analysis of crude reaction mixtures. [c]Isolated yields.

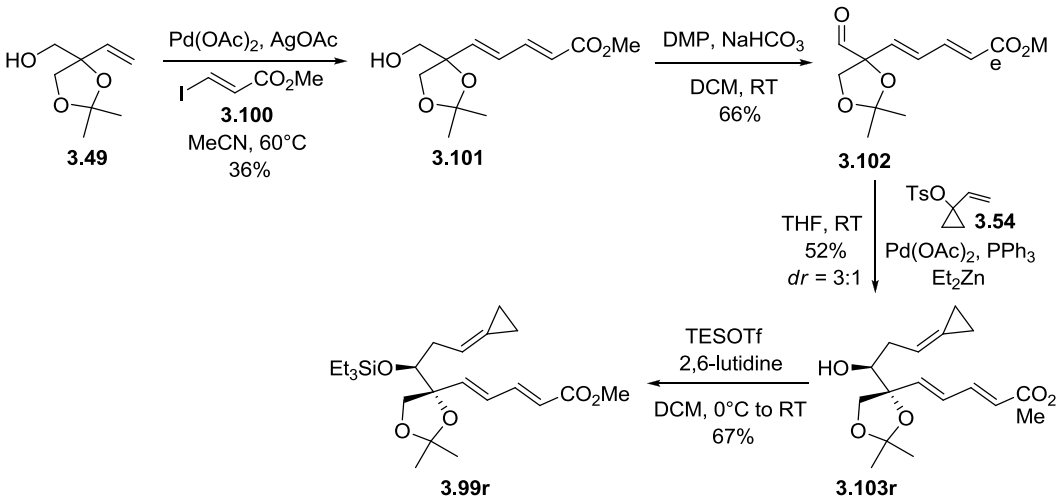
3.3.3.5. Investigation of the [(3+4)] Strategy

Unable to achieve stereocontrol in the rhodium-catalysed [(3+2)+2] carbocyclisation, we tried to circumvent this problem by employing another, yet unpublished, rhodium-catalysed reaction, developed in our group, for the creation of the desired bicyclic scaffold. Ojo and Evans demonstrated that cationic rhodium catalyst, modified with tris(2,2,2-trifluoroethyl)phosphite ligand, catalyses intramolecular [(3+4)] carbocyclisation of ACP-dienes **3.96** to furnish *cis*-fused 5,7-bicyclic cycloadducts **3.97** in good yields, in preference over 5,5-bicyclic products **3.98** (eqn. 3.25).[44] The critical feature which influenced our decision to implement this methodology was the high diastereoselectivity of the transformation in cases where the substrate bears a stereocentre α to the diene system.



(3.25)

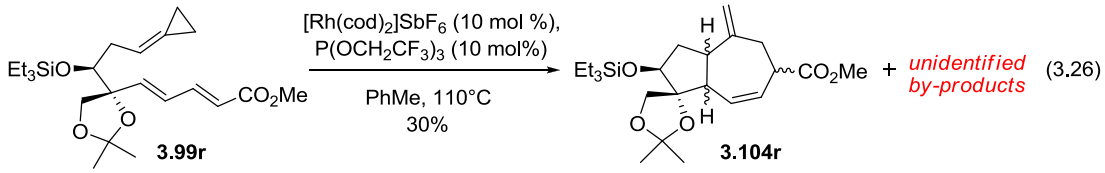
The synthesis of the precursor diene **3.99r** commenced from the known alcohol **3.49**, which was treated with (*E*)-methyl 3-iodoacrylate (**3.100**)[45] under cationic Heck coupling conditions used by Whiting *et al.*,[46] to afford diene **3.101** in modest 36% yield (Scheme 3.17). Dess-Martin oxidation[30] of **3.101** furnished aldehyde **3.102**, which was subjected to the conditions described previously for **3.45** (*vide supra*, Scheme 3.10) to afford ACP **3.103r** in 52% yield as a 3:1 mixture of diastereomers. Silyl protection of **3.103r** afforded silyl ether **3.99r** which was separable from the undesired diastereomer *via* chromatography on silica gel, and was isolated in 67% yield.



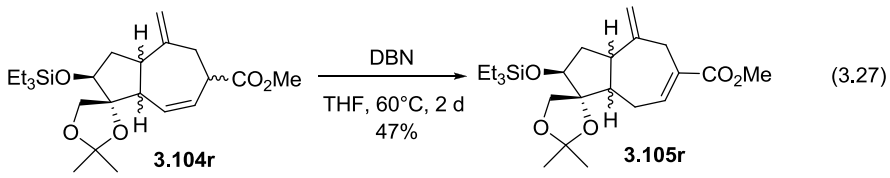
Scheme 3.17. Synthesis of ACP-diene **3.99r**.

When ACP-diene **3.99r** was subjected to the cationic $Rh(cod)_2SbF_6$ modified with tris(2,2,2-trifluoroethyl)phosphite, 5,7-bicycle **3.104r** was afforded in a low yield of

30%, together with complex mixture of by-products (eqn. 3.26).



Surprisingly, **3.104r** was formed as a single diastereomer, though at this stage we could not assign the relative configuration around the 5-membered ring. In order to simplify the assignment of the stereochemistry, we decided to isomerise the endocyclic double bond of **3.104r** into conjugation with the ester group. This was accomplished by treating **3.104r** with DBN at 60°C for 2 days, which resulted in the formation of isomerised product **3.105r** in 47% yield (eqn. 3.27).



The ^{1}H-NMR spectrum of **3.105r** was compared to the spectra of the cycloadducts obtained previously in a [(3+2)+2] carbocyclisation of precursor **3.26r** with different alkynes. Figure 3.10 shows ^{1}H-NMR spectra of diastereomeric cycloadduct pairs **3.62r**/**3.63r** and **3.89r**/**3.90r** from the reactions of ACP **3.26r** with 3-butyn-2-one and propargylaldehyde diethyl acetal, respectively. It can be seen that the appearance of the proton C3-**H** (appears between two doublets corresponding to C**H**$_2$O AB system) in the spectrum differs depending on whether it is *anti* or *syn* to the protons at the ring junction. The nature of the substituent on the electron-withdrawing group does not influence the conformation of the bicyclic system in a considerable manner. Therefore, we believe that the coupling pattern of the protons around the 5-

membered ring can be used as a guide for distinguishing the diastereomers.

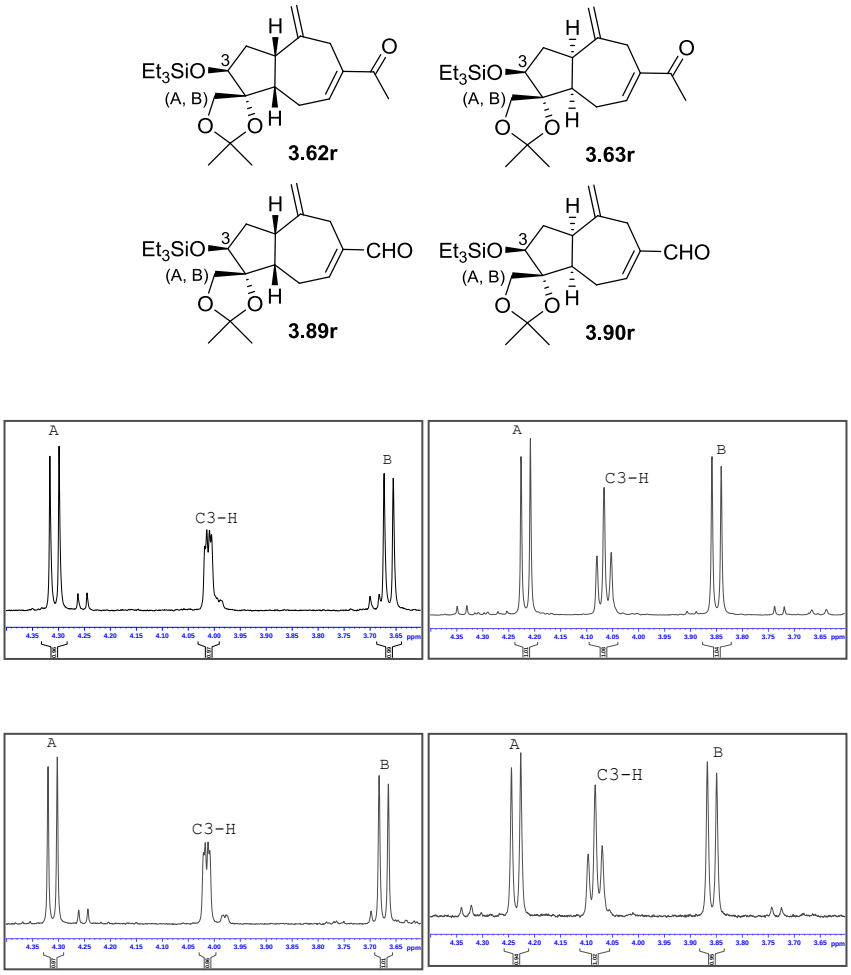


Figure 3.10. Distinctive ^{1}H NMR spectra fragments: Top left – **3.62r**, top right – **3.63r**, bottom left – **3.89r**, bottom right – **3.90r**.

The analysis of the corresponding ^{1}H-NMR fragment of the isomerised product **3.105r** shows that the coupling pattern and the chemical shifts correspond to the diastereomer in which the proton C3-**H** and the ring junction protons have an *anti* relationship (Fig. 3.11). Since this stereochemistry corresponds to the undesired diastereomer from the [(3+2)+2] carbocyclisation, [3+4] carbocyclisation reaction could not be applied to the current synthesis of repin and was not investigated further.

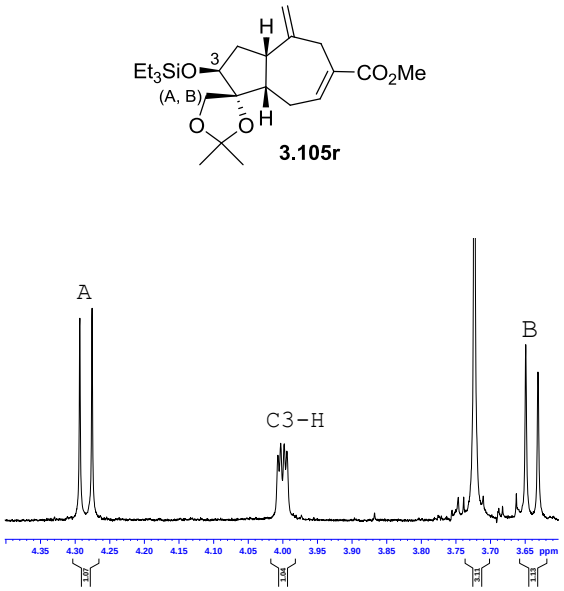
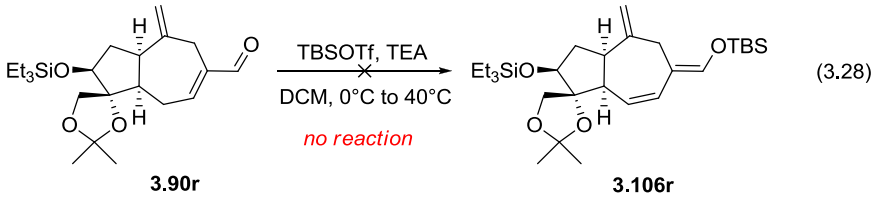


Figure 3.11. Stereochemical assignment of isomerised product **3.105r**.

At this point we decided to leave the optimisation of the carbocyclisation step for a later stage of investigations, and to proceed with the synthesis. Notwithstanding the lack of diastereoselectivity, the high efficiency of the [(3+2)+2] carbocyclisation reaction of ACP **3.26r** with propargyl aldehyde acetal allowed us to obtain sufficient amounts of the desired material for further studies. It is noteworthy to mention that the reaction was successfully conducted on 1.5 g scale without any decrease in yield or selectivity for *cis*-fused isomer.

3.3.3.6. Oxidation of the Aldehyde Cycloadduct

Our next task was the formation of the extended silyl enol ether and C6 oxygenation. Surprisingly, when aldehyde **3.90r** was subjected to soft enolisation conditions (TBSOTf, TEA, DCM, 0°C) no reaction took place (eqn. 3.28). Forcing the reaction by increasing the temperature to 40°C did not result in product formation either.



(3.28)

A possible explanation for the lack of reactivity of **3.90r** takes into account stereoelectronical requirements of the enolisation process. If we assume that the conformation of the 7-membered ring in **3.90r** is the same in solution as in the solid state, it could be that the steric hindrance around the proton H2 prevents deprotonation from taking place (Fig. 3.12). This is despite the fact that dihedral angle H1-C1-C2-H2 = 82.3° allows for good overlap of interacting orbitals (σ orbital of C2-H2 bond and LUMO of the conjugated aldehyde). The other, slightly less sterically hindered proton H3, has dihedral angle H1-C1-C2-H3 = 32.7°, and is, therefore, stereoelectronically less prone to deprotonation by weak amine base.[47]

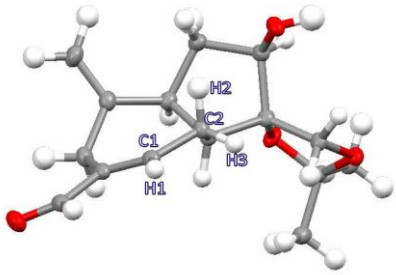
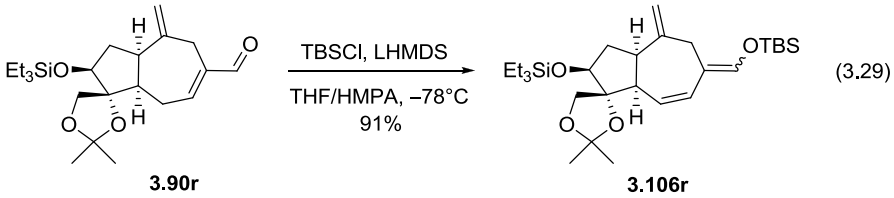


Figure 3.12. Stereoelectronic explanation of the lack of reactivity of **3.90r** towards enolisation by amine base: H1-C1-C2-H2 = 82.3°, H1-C1-C2-H3 = 32.7°

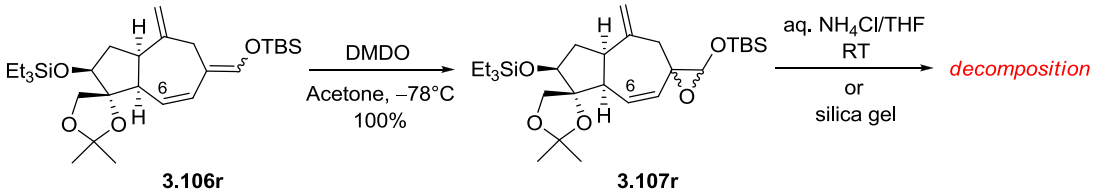
This problem was solved by employing more forcing reaction conditions, which included treatment of **3.90r** with LHMDS in the presence of TBS-Cl at −78°C. In this way the desired silyl dienol ether **3.106r** was obtained in excellent yield as a

single reaction product (eqn. 3.29).



3.90r 3.106r (3.29)

With the requisite **3.106r** in hand, we were ready to try the envisaged oxygenation of the C6 position to install the required hydroxyl functionality. Surprisingly, when silyl enol ether **3.106r** was subjected to DMDO in acetone at −78°C, the major oxidation products corresponded to the *α*- rather than expected *γ*-oxygenation pathway (Scheme 3.18). These results prompted us to investigate possible application of α-oxygenation in terms of our current synthesis. The epoxides **3.107r** formed in DMDO oxidation were found to be unstable and decomposed upon chromatography on silica gel. An attempt to treat the crude material with aq. NH_4Cl in THF, in order to release diastereomeric hydroxyaldehydes, resulted in a formation of complex mixture of products (Scheme 3.18).

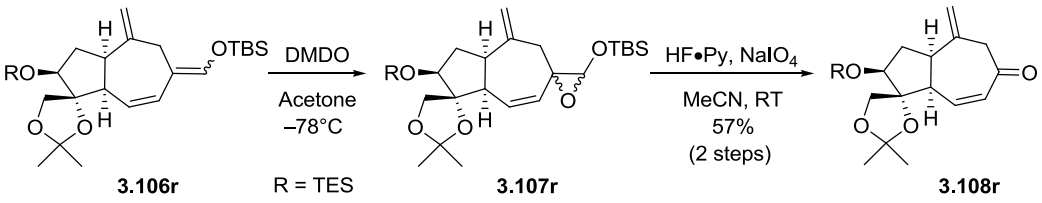


3.106r 3.107r

Scheme 3.18. Instability of the direct oxidation products of **3.106r**.

To circumvent the problems associated with the instability of the DMDO oxidation products, we employed a two-step one-pot procedure for the direct conversion of silyl enol ether **3.106r** to the ketone **3.108r** (Scheme 3.19). This involved treatment of **3.106r** with DMDO, subsequent removal of the volatiles, and subjection of the crude epoxides **3.107r** to the HF•Py complex and $NaIO_4$ in MeCN/water, according

to the procedure used previously by Razdan *et al.* in their synthetic work towards cannabinoids.[48] Following this procedure, we were able to convert **3.106r** into enone **3.108r** in 57% combined yield after the reprotection of some desilylated material. Successful implementation of the extended silyl enol ether formation/oxidation strategy allowed us to not only accomplish an important goal of extruding a carbon atom, which is not found in the natural product, but allowed us to introduce a keto group, which we could utilize as an important synthetic handle for the functionalisation of the 7-membered ring.



3.106r **3.107r** **3.108r**

Scheme 3.19. Oxidative cleavage of the exocyclic vinyl ether of **3.106r**.

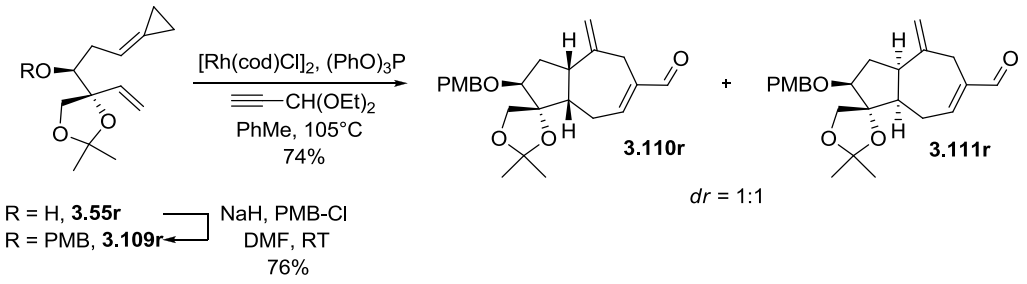
Other oxidation methods were tried in order to effect the oxygenation of **3.106r**, however all the procedures turned out to be inferior relative to the DMDO oxidation (Table 3.6). *m*CPBA showed the reactivity mode comparable to DMDO, but the reaction was slower and proceeded with by-product formation (entry 2). No reaction was observed with oxone, while dihydroxylation conditions suffered from the lack of selectivity and afforded complex inseparable mixtures of products (entries 3-5).

Table 3.6. Oxidation of extended silyl enol ether **3.106r**.

Entry[a]	Conditions	Yield[b]
1	DMDO, Acetone, −78°C	57%
2	*m*CPBA, DCM/10% Na_2CO_3, RT	41%
3	Oxone, $NaHCO_3$, THF/dioxane/water, RT	no reaction
4	0.1 eq OsO_4, 1.2 eq NMO, Acetone/water, RT	decomposition
5	$K_3[Fe(CN)_6]$, $K_2OsO_2(OH)_4$, DABCO, K_2CO_3, $CH_3SO_2NH_2$, *t*BuOH/Water, RT	decomposition

[a]All reactions were carried out with 0.009-0.039 mmol **3.106r**. [b]Isolated yields refer to the material obtained after treatment of crude oxidation mixtures with $NaIO_4$ and Py•HF.

In order to eliminate the necessity to reprotect the desilylated material, we prepared cyclisation precursor **3.109r**, in which alcohol at C3 was protected as a PMB ether, which would be stable in the presence of fluoride source. However, it turned out that the diastereomeric cycloadducts **3.110r** and **3.111r**, resulting from the carbocyclisation of **3.109r**, were inseparable on silica gel, which made us unable to proceed with the subsequent steps (Scheme 3.20).



Scheme 3.20. Rhodium-catalysed carbocyclisation of PMB-protected substrate **3.109r**.

3.3.4. Elaboration of Enone 3.108r: C6 Oxygenation

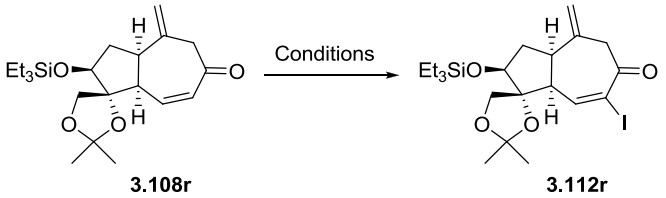
3.3.4.1. Michael Addition/Alkylation Route

With the enone **3.108r** in hand, we were facing the task of introducing oxygen functionality at the C6 position of the molecule and attaching a lactone side chain at C7 (Fig. 3.13).

Figure 3.13. Required modifications of the enone **3.108r**.

In order to functionalise the C7 position, we attempted to effect iodination of the enone double bond of **3.108r**. The resulting iodide **3.112r** could then potentially be employed as a substrate in a Pd-catalysed cross-coupling for the installation of the side chain. Brief screening of the reaction conditions, however, showed iodination to be a difficult transformation in this system (Table 3.7). Unreacted starting material was reisolated in all cases, except for the reaction with trimethylsilyl azide,[49] where decomposition was observed (entry 2).

Table 3.7. Screening of iodination conditions.

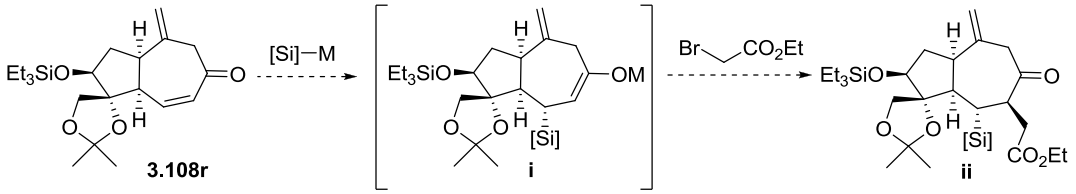


3.108r 3.112r

Entry[a]	Conditions	Observations
1	I_2, DCM/Pyridine 1:1, RT	no reaction
2	TMS-N_3, I_2, DCM, RT, 3 d	decomposition
3	I_2, DMAP, DCM, RT	no reaction

[a]All reactions were carried out with 0.013-0.026 mmol **3.108r**. TLC control.

Our next endeavour was to attempt the concept of applying a Michael addition/enolate alkylation sequence to enone **3.108r**, in order to introduce an oxygen functionality and the side chain simultaneously (Scheme 3.21). Intermolecular oxa-Michael additions are quite rare due to the reversibility of the process and the relatively poor nuceophilicity of alcohols.[50] Therefore, we decided to employ a silicon based group as a surrogate for oxygen in the Michael addition step.



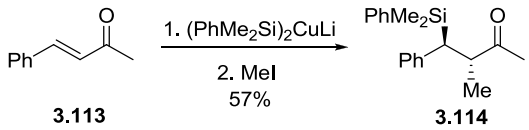
3.108r i ii

Scheme 3.21. Proposed sila-Michael addition/alkylation strategy.

We hypothesised that enone **3.108r** could be treated with a suitable silicon reagent to generate intermediate enolate **i**, which after quenching with an electrophile (e.g. ethyl bromoacetate) would afford the alkylated silane **ii** (Scheme 3.21). We anticipated that the initial addition step would occur from the less sterically hindered *convex* face of the molecule, whereas the approach of the electrophile would be governed by the

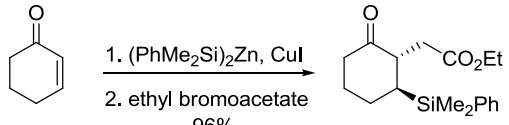
bulk of the newly introduced silyl group. Selective oxidation of the silyl group would later furnish the hydroxyl group at the correct position.

It is known that silyl cuprates undergo smooth addition to Michael acceptors, and that resulting enolates can be quenched by appropriate electrophiles. Fleming and Bernhard used this approach to convert enone **3.113** to alkylated silane **3.114** with 98:2 diastereoselectivity (eqn. 3.30).[51]



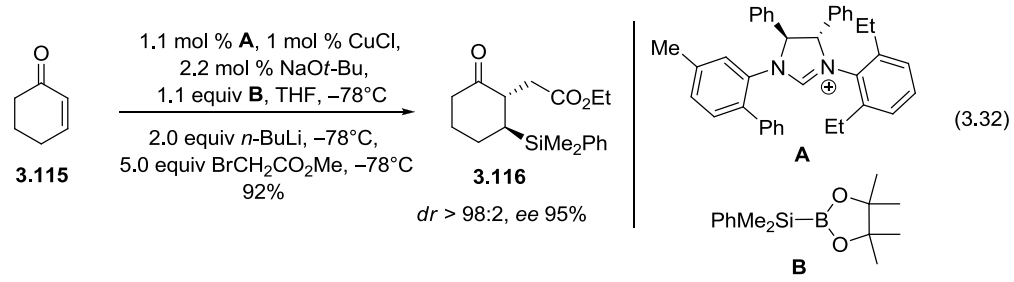
3.113 **3.114** (3.30)

Copper-catalysed silyl zincate addition can also be employed to accomplish this transformation. This method, originally developed by Oestreich[52], was used by Tietze *et al.* to convert 2-cyclohexenone (**3.115**) to disubstituted cyclohexanone **3.116** in excellent yield (eqn. 3.31).[53]

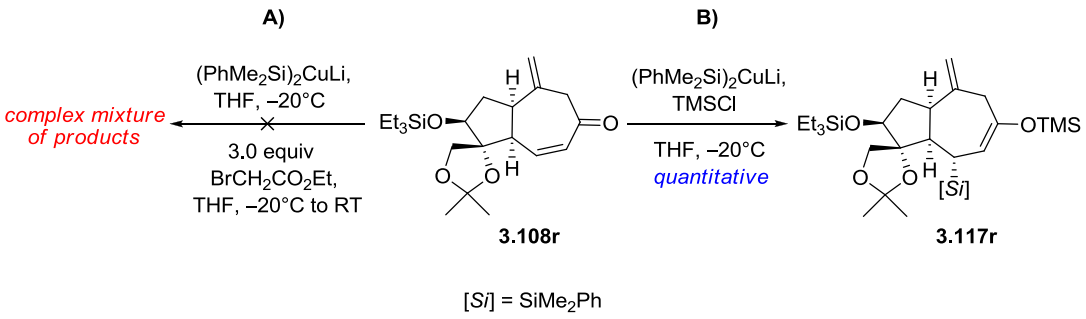


3.115 **3.116** (3.31)

The same transformation can be accomplished in enantioselective fashion by utilizing a catalytic methodology for the conjugate addition of a silyl-borate developed by Hoveyda *et al*. The reaction was catalysed by a chiral N-heterocyclic carbene and copper(I) chloride, which afforded **3.116** in an excellent yield and high enantioselectivity (eqn. 3.32).[54]



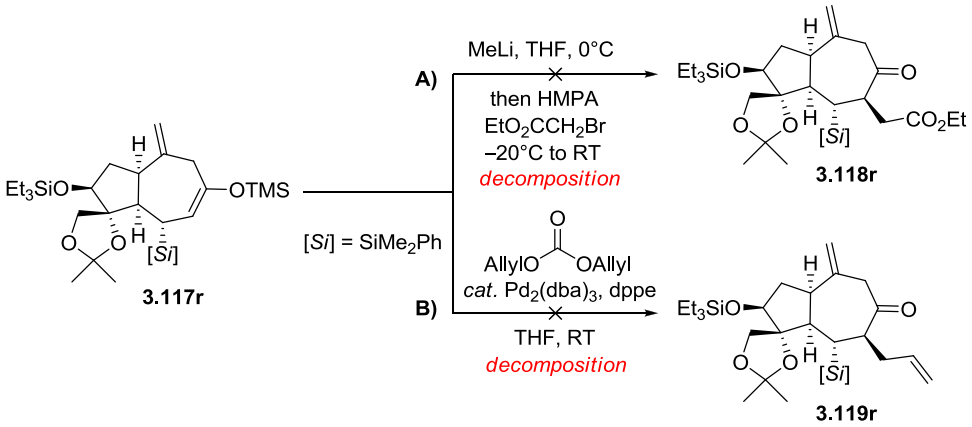
In this instance we decided to opt for the stoichiometric silyl cuprate addition as a method for introducing silyl substituent into our molecule. When enone **3.108r** was treated with $(PhMe_2Si)_2CuLi$[55] in THF at −20°C, followed by the addition of ethyl bromoacetate, a complex mixture of products was obtained (Scheme 3.22, A). Assuming that the basic nature of the intermediate enolate was responsible for the failure of the reaction, we conducted the Michael addition step in the presence of excess TMS-Cl, which is known to not only trap enolate as it forms, but also to speed up the overall reaction.[56] Under these reaction conditions, the silyl enol ether **3.117r** was formed in excellent yield as a single diastereomer (Scheme 3.22, B). We did not establish unambiguously the facial preference of the addition at this point, assuming that the attack from the less hindered face took place.



Scheme 3.22. Michael addition of silyl cuprate to **3.108r**.

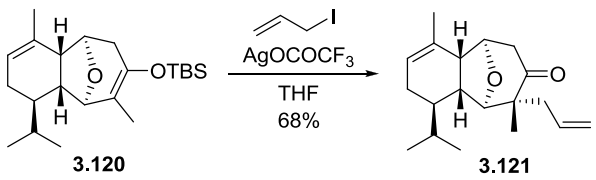
Unfortunately, the attempt to alkylate silyl enol ether **3.117r** by converting it to lithium enolate, and treating with ethyl bromoacetate, failed due to the extensive decomposition (Scheme 3.23, A). To avoid this, we decided to subject **3.117r** to mild

conditions of palladium-catalysed allylation of silyl enol ethers reported by Tsuji.[57] We believed that later we would be able to transform the allyl group into the requisite carboxylic acid residue *via* a series of oxidative transformations. However, when silyl enol ether **3.117r** was treated with diallyl carbonate in the presence of the $Pd_2(dba)_3$ modified with dppe, a complex mixture of products resulted (Scheme 3.23, B).



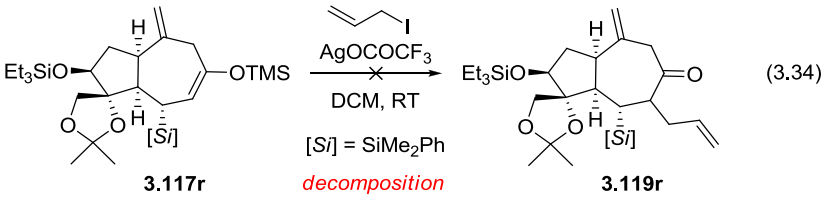
Scheme 3.23. Attempts to alkylate silyl enol ether **3.117r** via intermediate Li- or Pd-enolates.

Another mild method for the alkylation of silyl enol ethers was developed by Jefford *et al.*, and involved treatment of substrates with primary alkyliodides in the presence of silver trifluoroacetate.[58] This procedure was successfully employed by Molander *et al.* to convert **3.120** to allylated ketone **3.121** in 68% yield (eqn. 3.33).[59]



(3.33)

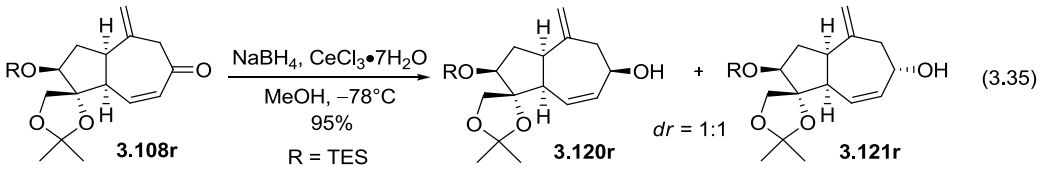
Unfortunately, when applied to silyl enol ether **3.117r**, these conditions only resulted in decomposition, similarly to the previously tried methods (eqn. 3.34).



3.3.4.2. Directed Epoxidation Route

In the light of these results, we were forced to review our strategy. We envisaged that the oxygen functionality could be conveniently introduced into the molecule *via* vanadium(V)-catalysed hydroxyl group-directed epoxidation of the double bond.[60] These reactions are known to proceed with good to excellent diastereoselectivities in cyclic systems.[61]

The ketone **3.108r** was reduced under Luche conditions[15] to afford a 1:1 mixture of diastereomers, that were separated by the chromatography on silica gel (eqn. 3.35).



The relative configurations of the diastereomeric alcohols could not be reliably assigned using 2D COSY and NOESY experiments and were unambiguously established at a later stage. Preliminary assignment of stereochemistry was carried out on the basis of the previously obtained crystal structure of aldehyde cycloadduct **3.91r** (*vide supra*, Fig. 3.9). The *exo*-methylene double bond of **3.91r** "protrudes" out of the plane of the 7-membered ring. Such conformation of **3.121r** would allow a possible nOe interaction between the protons H_{10}-H_{13} (Fig. 3.14). These distinctive nOe signals were indeed observed for one of the epimers, which was assigned the depicted structure **3.121r**.

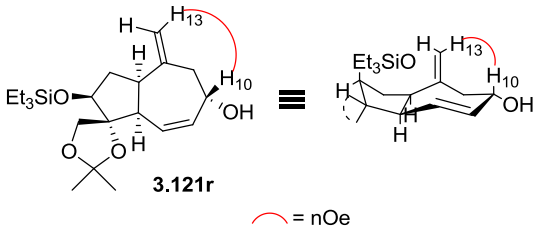
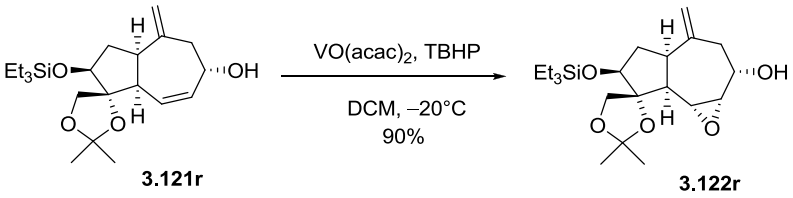


Figure 3.14. Stereochemical assignment of **3.121r**.

Following the stereochemical assignment, the hydroxyl group of the undesired epimer **3.120r** was inverted using a two step sequence, consisting of a Mitsunobu reaction[62] and hydrolysis (eqn. 3.36).

(3.36)

Gratifyingly, the envisaged hydroxyl group-directed epoxidation of **3.121r** proceeded without any issues affording the desired epoxyalcohol **3.122r** in an excellent 90% yield and as a single diastereomer (eqn. 3.37).



(3.37)

Interestingly, epimeric alcohol **3.120r** failed to undergo epoxidation when subjected to the identical reaction conditions. This fact supported our stereochemical assignment, since out of the two epimers, the one with the hydroxyl group residing on the more sterically hindered face of the molecule, was expected to undergo epoxidation more slowly.

The relative configuration of hydroxyepoxide **3.122r** was confirmed unambiguously *via* single-crystal X-ray diffraction analysis. Treatment of **3.122r** with *p*-nitrobenzoylchloride, followed by the TBAF effected desilylation, afforded crystalline derivative **3.123r**, the structure of which was in accordance with the NOESY data and the mechanism of the hydroxyl-group directed epoxidation (Fig. 3.15).

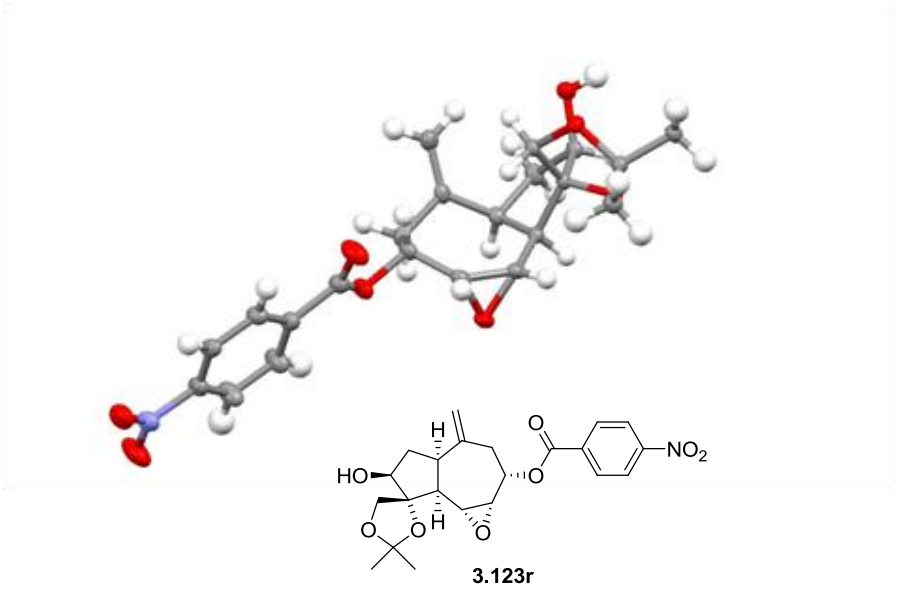
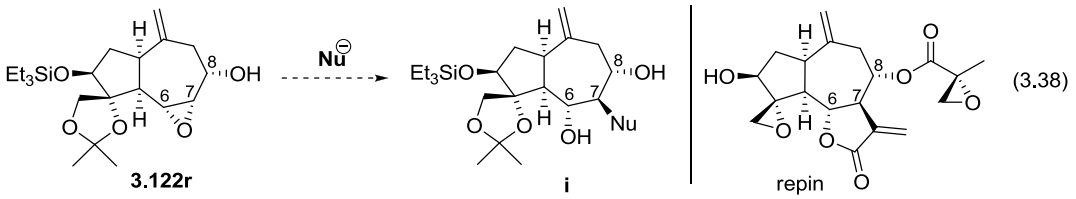


Figure 3.15. X-Ray structure of p-nitrobenzoate **3.123r**.

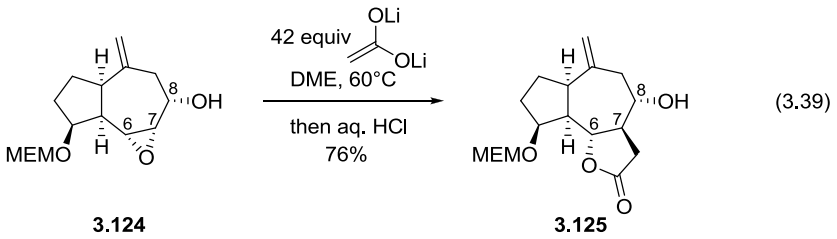
3.3.5. Studies Towards the Hydroxyepoxide Ring Opening

3.3.5.1. Intermolecular Epoxide Ring Opening

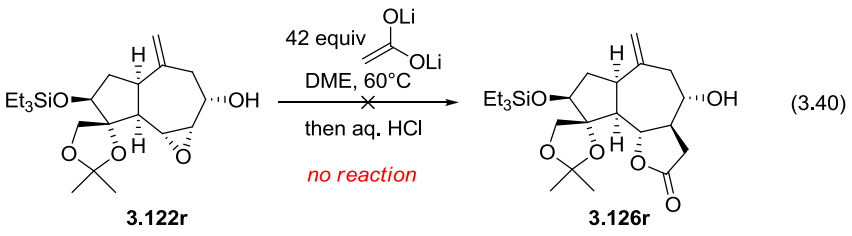
With hydroxy epoxide **3.122r** in hand, we were ready to face the next critical task in our synthesis, namely introduction of the lactone side chain. It was anticipated that this could be accomplished by the epoxide ring opening at C7 by an appropriate carbon based nucleophile (eqn. 3.38). Such an approach would also establish the required *anti* relationship between C6 hydroxyl group and the newly introduced side chain.



The closely related precedent was described by Rigby *et al.* in the eighties during the course of their studies towards the synthesis of C8 oxygenated guaianolides. The authors demonstrated that when hydroxyepoxide **3.124** was subjected to large excess of dilithioacetate in DME at 60°C, followed by the treatment with aqueous acid, lactone **3.125** could be isolated in 76% (eqn. 3.39).[63]



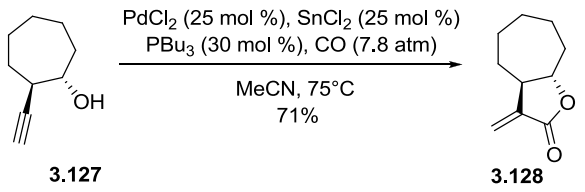
The authors did not observe formation of the products corresponding to the epoxide ring opening at C6 or lactonisation onto the C8 hydroxyl group. Considering the efficiency and selectivity of the above transformation, we were surprised to find out that when hydroxyepoxide **3.122r** was subjected to the above mentioned conditions, only the starting material was recovered, with none of the desired product being observed (eqn. 3.40).



Apparently, despite the structural similarities, the reactivity profile of our substrate **3.122r** was very different from that of the substrate used by Rigby *et al*. All attempts

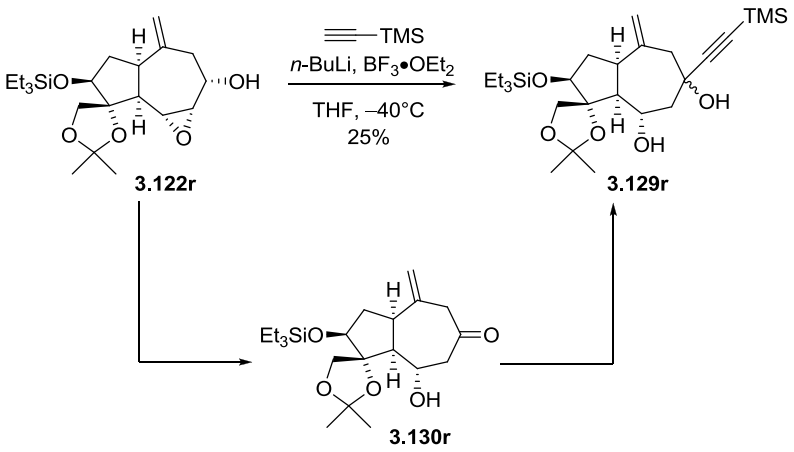
to drive the reaction forward by employing prolonged reaction times or an elevated temperature did not result in any improvement. This lack of reactivity can be explained by the sterically encumbered nature of the rear face of the epoxide, evidence of which can be seed from X-ray crystal structure of hydroxyepoxide **3.123r** (Fig. 3.15, *vide supra*). The methylene component of the acetonide sits above the rear face of the epoxide, therefore sterically inhibiting nucleophilic attack. The *exo*methylene double bond is also positioned in such a way that could obstruct an incoming nucleophile.

We hoped that changing the nature of the nucleophile could have a positive effect on the reactivity of **3.122r**. It is known that alkynyllithiums undergo S_N2 reactions with epoxides in the presence of BF_3•OEt_2.[64] Moreover, the resulting homopropargyl alcohols can be transformed into methylene lactone moiety in one step *via* a palladium-catalysed cyclocarbonylation under the conditions reported by Murray *et al*. as in the conversion of alkynol **3.127** to lactone **3.128** (eqn. 3.41).[65]



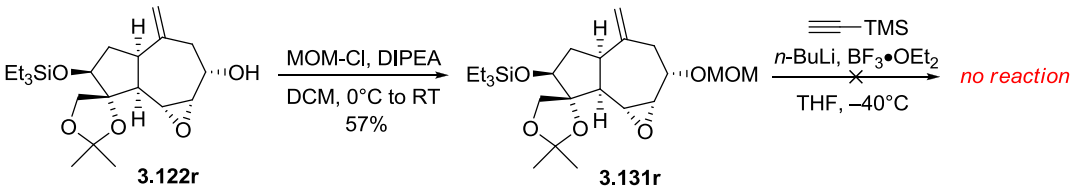
3.127 **3.128** (3.41)

Unfortunately, when **3.122r** was treated with lithium TMS-acetylide in the presence of BF_3•OEt_2, no desired product was formed. Unchanged starting material was reisolated, alongside a small amount of an unexpected product, which, based on 1H NMR analysis, was assigned the structure **3.129r**. Based on literature precedents,[66] we believe that **3.129r** could be formed *via* base and/or Lewis acid induced rearrangement of epoxialcohol **3.122r** to ketone **3.130r**, followed by the organolithium addition (Scheme 3.24).



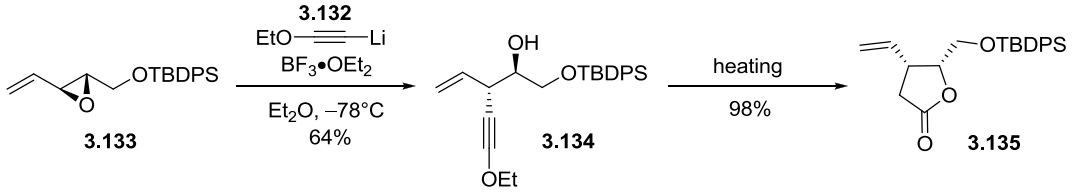
Scheme 3.24. Proposed route for the formation of product **3.129r**.

In order to prevent this side reaction, the hydroxyl group of **3.122r** was protected as a MOM ether (Scheme 3.25). Unfortunately, when **3.131r** was subjected to the above mentioned conditions, only the unreacted starting material could be recovered from the reaction mixture.



Scheme 3.25. Attempted ring opening of MOM-protected **3.131r**.

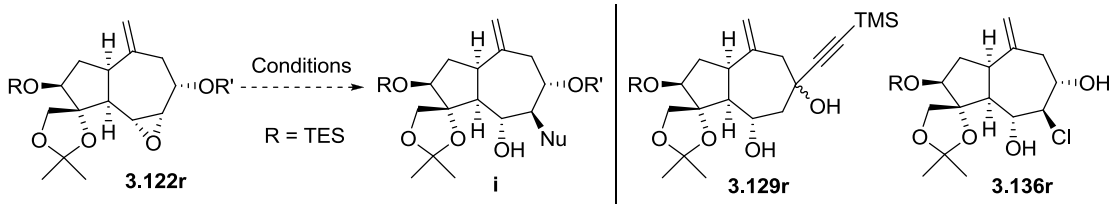
At this point we decided to change the nucleophile to lithium ethoxyacetylide (**3.132**), which was demonstrated by Somfai and Restorp to be a successful nucleophile for the epoxide opening of **3.133** in the presence of BF_3•OEt_2.[67] The authors claimed that the electron-donating group increases the reactivity of ethoxyacetylide when compared to TMS-acetylide. Conveniently, the resulting propargyl alcohol **3.134** can be transformed into γ-butyrolactone **3.135** simply by heating (Scheme 3.26).



Scheme 3.26. Lithium ethoxyacetylide epoxide ring opening and lactone formation.

However, when hydroxyepoxide **3.122r** was treated with lithium ethoxyacetylide (**3.132**), the reaction failed to afford the desired ring-opened product (Table 3.8, entry 5). As in the previous cases intact starting material was recovered. Different reaction temperatures and concentrations did not produce any change in reactivity. The same was true for the reaction of MOM-protected **3.131r** (Table 3.8, entry 10). At this point we felt it was necessary to screen a wider range of carbon based nucleophiles for the epoxide ring opening. Some of the nucleophiles tested were not relevant in terms of the synthesis, but we were primarily concerned with the identification of the reactive species that would furnish the ring-opened products at this stage.

Table 3.8. Reactions of **3.122r** with different carbon based nucleophiles.



Entry[a]	R`	Conditions	Product
1	H	Dilithioacetate, DME, 60°C	no reaction
2	-	Dilithioacetate, DME/HMPA, 60°C	no reaction
3	-	*t*-BuOAc, LDA, Et_2AlCl, THF, 0°C	**3.136r** (30%)
4	-	$Me_3SiC{\equiv}CH$, ^nBuLi, $BF_3{\cdot}OEt_2$, THF, −78°C to RT	**3.129r** (25%)
5	-	**3.132**, $BF_3{\cdot}OEt_2$, THF, −78°C to RT	no reaction
6	-	*i*-Propenylmagnesium bromide, CuI, Et_2O, −25°C	no reaction
7	-	MeLi, CuI, Et_2O, −50°C to RT	no reaction
8	-	KCN, $LiClO_4$, MeCN, 70°C	no reaction
9	MOM	**3.132**, Et_2AlCl, PhMe, −40°C to RT	no reaction
10	-	**3.132**, $BF_3{\cdot}OEt_2$, THF, −78°C to RT	no reaction
11	-	$Me_3SiC{\equiv}CH$, ^nBuLi, $BF_3{\cdot}OEt_2$, THF, −78°C to RT	no reaction

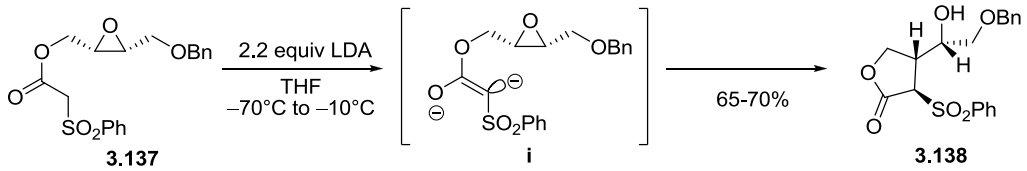
[a]All reactions were carried out with 0.006-0.015 mmol of **3.122r** or **3.131r** using large excess of nucleophile. Isolated yields are reported.

Grignard reagents are known to effect epoxide ring opening under copper-catalysed conditions.[68] In our case, however, hydroxyepoxide **3.122r** remained inert when subjected to *i*-propenylmagnesium bromide in the presence of CuI in Et_2O (Table 3.8, entry 6). The same absence of reactivity was observed when **3.122r** was treated with lithium dimethylcuprate and with potassium cyanide[69] (entries 7 and 8, respectively). Reaction of **3.122r** with lithium *tert*-butyl acetate enolate in the presence of Et_2AlCl failed to afford the desired product, but delivered the

chloroalcohol product **3.136r** in low yield (entry 3). The use of alkynylalanes[67] also did not lead to the formation of the desired product (entry 9).

3.3.5.2. Intramolecular Epoxide Ring Opening

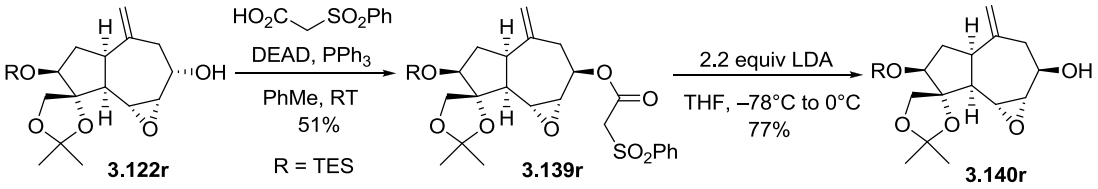
Disappointed by the inability to effect intermolecular epoxide ring opening with a variety of different nucleophiles, we decided to facilitate the reaction by conducting it in the intramolecular fashion. The single literature precedent that describes the formation of the five-membered ring *via* intramolecular epoxide ring opening with an ester enolate was disclosed by McCombie *et al*. in 1989.[70] The authors employed the sulfonylacetate **3.137**, which upon treatment with 2.2 equiv LDA afforded the sulfonyllactone **3.138** (Scheme 3.27). Interestingly, the monoanion of **3.137** is not stereoelectronically predisposed to cyclise, but, upon the addition of the second equivalent of base, α,α-dianion **i** is generated, which is able to undergo the reaction.



Scheme 3.27. Intramolecular epoxide ring opening by ester enolate.

What complicated the matter in our case was the fact that the hydroxyl group and the epoxide oxygen atom of **3.122r** are on the same face of the 7-membered ring. Such an arrangement would make it impossible for the tethered nucleophile to approach the oxirane ring at the angle required for the S_N2 attack, according to the Baldwin rules.[71] In order to circumvent this problem we decided to attach the sulfonylacetyl side chain *via* Mitsunobu reaction,[62] which would invert the stereochemistry at C8 and, therefore, afford the substrate more prone to intramolecular cyclisation (*anti*

relationship between tethered nucleophile and oxirane oxygen atom). The inversion reaction proceeded smoothly, but, when resulting ester **3.139r** was treated with two equivalents of LDA, no desired product was formed (Scheme 3.28). Instead, deacylated material **3.140r** was isolated. Deacylation process was described by McCombie *et al*. as a competing reaction in case of sterically challenging substrates.[70]



Scheme 3.28. Failure of the intramolecular epoxide ring opening.

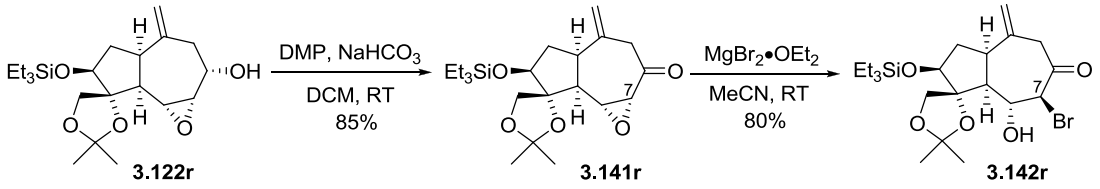
3.3.5.3. Epoxide Ring Opening with Halide Anions

It looked at this stage that we would have to review considerably our strategy for the functionalisation of the 7-membered ring. In the end we came up with an alternative strategy, which was inspired by the intriguing chloroalcohol product **3.136r** obtained earlier in the reaction of hydroxyepoxide **3.122r** with lithium *t*-butylacetate enolate/Et_2AlCl. We already mentioned that the ^1H NMR data and the HRMS of **3.136r** clearly indicated that oxirane ring was opened by a chloride anion. Halogen atoms are versatile functional groups, and we suggested that if we could effectively access halogenated ring-opened products, these might give us alternative possibility for the introduction of the side chain.

It is known that the presence of the carbonyl group α to a leaving group facilitates S_N2 substitution due to a favourable orbital overlap.[72] Therefore, we set out to oxidise the hydroxyl group of **3.122r** prior to attempting epoxide ring opening with a

halide anion. It must be noted that this type of activation could not be used with carbon based nucleophiles because of their tendency to undergo 1,2-addition to ketone, and their basic nature, which could cause isomerisation of the *exo*-methylene double bond.

The hydroxyl group of **3.122r** was oxidised using Dess-Martin reagent[30] in excellent yield (Scheme 3.29). Gratifyingly, when resulting epoxyketone **3.141r** was subjected to $MgBr_2 \bullet OEt_2$ in MeCN, according to the condition developed by Ha *et al.*,[73] bromohydrin **3.141r** was isolated in 80% yield (Scheme 3.29).

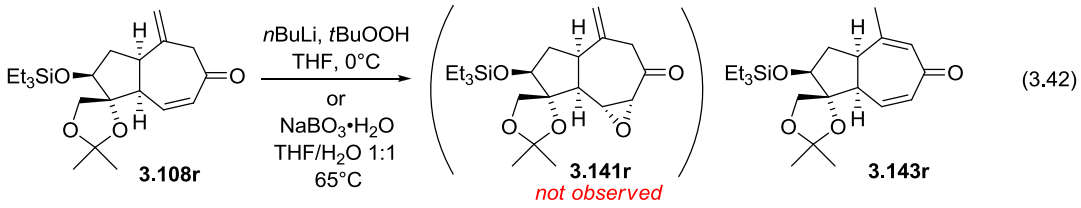


Scheme 3.29. Ketoepoxide ring opening with bromide anion.

The temperature and the reaction time were critical reaction parameters in this transformation. Initially, only one product is formed at room temperature. Prolonged reaction times and elevated temperatures lead to the appearance of a by-product, which we believe to be the epimeric bromide at C7. The first compound corresponds to the initial product of S_N2 epoxide ring opening by bromide anion, whereas the other epimer could be the result of a second S_N2 reaction of the bromoketone **3.142r** with the excess magnesium bromide, affording the double inversion product.

The fact that we used keto epoxide **3.141r** as a substrate in the epoxide ring opening reaction led us to examine whether we could furnish **3.141r** directly from the enone **3.108r** by means of nucleophilic epoxidation. When successful, this would eliminate two steps from our synthesis. However, it turned out that the high sensitivity of

enone **3.108r** towards basic conditions, made this route unavailable. Thus, when enone **3.108r** was treated with *t*-BuOOLi in THF,[74] the isomerisation of the *exo*methylene double bond into conjugation with the carbonyl was detected by ^{1}H-NMR of the crude reaction mixture (eqn. 3.42). The same undesired reaction pathway was observed when enone **3.108r** was treated with $NaBO_3 \bullet H_2O$ in THF/H_2O.[75] We believe that this outcome is a result of the combination of the high acidity of the protons α to the carbonyl group, and the hindered nature of C6, which slows down the rate of epoxidation, much the same way the iodination reaction was retarded in the earlier studies (*vide supra*).

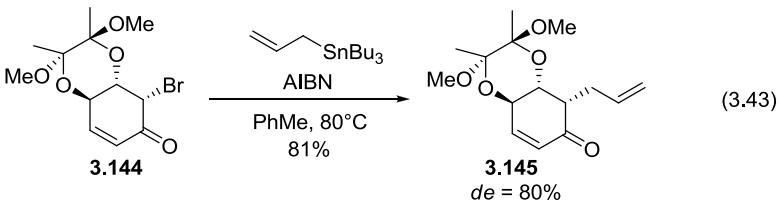


(3.42)

3.3.6. Installation of the Lactone Sidechain

3.3.6.1. Radical Allylation

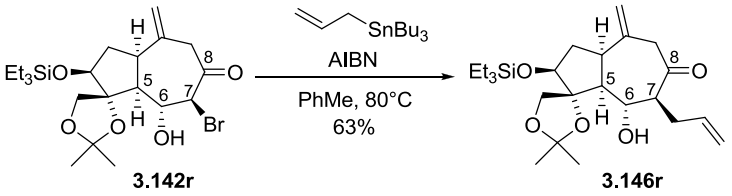
With the ring-opened product in hand, we were ready for the installation of the side chain. We envisaged that haloketone **3.142r** would be a suitable substrate for the functionalisation under radical conditions, for example allylation. This approach was employed before on many instances, for example for the allylation of ketobromide **3.144** by Schuster *et al*. in their synthesis of the B-*seco* limonoid scaffold (eqn. 3.43).[76]



(3.43)

It must be said that our decision to exploit radical chemistry was a direct result of our earlier studies. High propensity of enone **3.108r** to undergo isomerisation and decomposition in the presence of base made us look for the milder functionalisation conditions, and neutral radical based processes seemed like a promising alternative. The decision to attempt radical based functionalisation was also the reason why we were not concerned with the exact distribution of the diastereomeric bromides in the epoxide ring opening. The radical formed at C7 would be sp^2 hybridised due to the stabilisation by the keto group,[77] and the stereoselectivity of the allylation would be determined by other stereogenic centres present in the molecule.

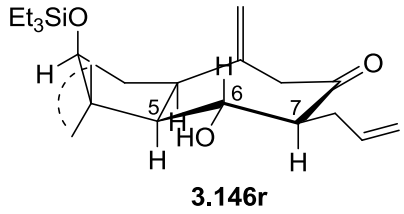
To our delight, when bromohydrin **3.142r** was treated with tributylallyltin in the presence of radical initiator AIBN, the allylated product **3.146r** was isolated in 63% yield as a single stereoisomer (eqn. 3.44).



(3.44)

The stereochemistry of the allylation product **3.146r** was assigned based on the ^{1}H NMR coupling constants. The C6-**H** appeared in a spectrum as an apparent triplet with both coupling constants superior to 9 Hz, which hinted at its *trans* relationship to both C5-**H** and C7-**H** (Fig. 3.16). Since the configuration at C6 should not have changed in the course of the reaction, the observed coupling constant meant that the reaction took place with retention of stereochemistry at C7. This was somehow surprising because it would mean that tributylallyltin approached the intermediate ketoradical from the more sterically hindered *concave* face. We propose that in this case it is the free hydroxyl group at C6, which is determining the direction of the

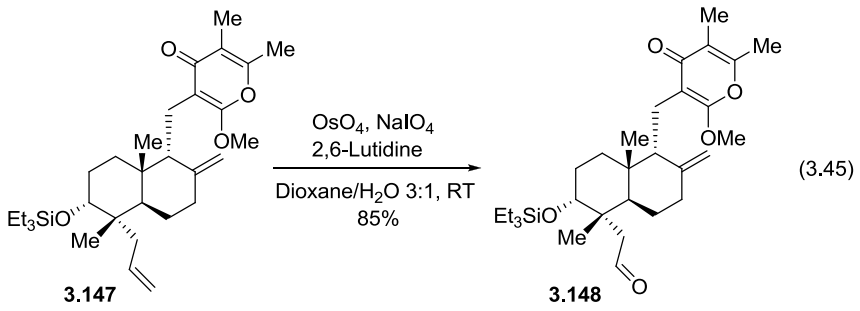
attack by shielding the radical on the convex face.



3.146r

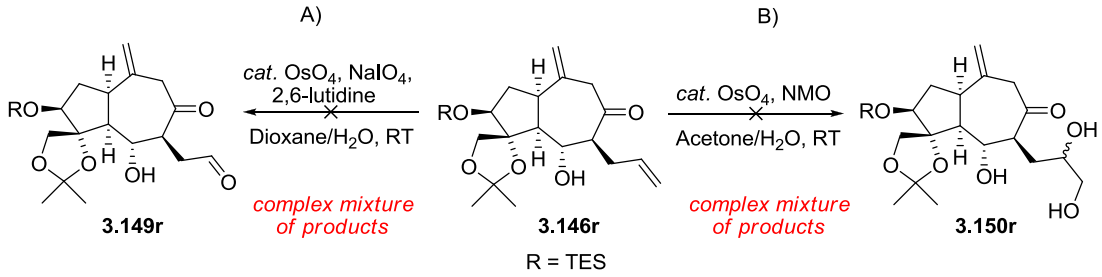
Figure 3.16. Anti, anti-relationship of proton C6-**H** to C5-**H** and C7-**H** in **3.146r**. Acetonide ring omitted for clarity.

At this stage we became concerned with the task of carrying out selective oxidation of the double bond of the allyl group in the presence of the *exo*methylene double bond. The most common approach to accomplish such a transformation involves initial dixydroxylation of the allyl group, followed by oxidative diol cleavage. In some cases both reactions can be conveniently performed in one pot, as in the conversion of **3.147** to aldehyde **3.148** by Katoh *et al*. in their synthesis of candelalides (eqn. 3.45).[78]



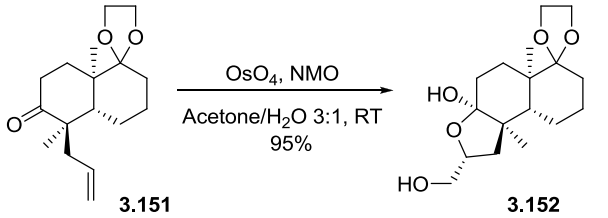
3.147 **3.148** (3.45)

Unfortunately, when the above mentioned reaction conditions were applied to our allylated product **3.146r**, a complex mixture of products resulted (Scheme 3.30, A). We attempted to conduct the transformation in a stepwise fashion by employing Upjohn conditions[79] for the dihydroxylation step, but the outcome was identical (Scheme 3.30, B).



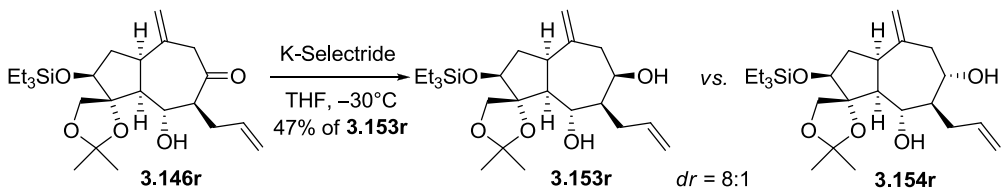
Scheme 3.30. Failed dihydroxylation/diol cleavage of **3.146r**.

It is known that a keto group in close proximity to the reacting double bond can influence the course of the reaction. For example, when Theodorakis *et al*. were trying to oxidatively cleave alkene **3.151**, they found out that a stable hemiacetal **3.152** was formed upon dihydroxylation, which considerably complicated the following cleavage step (eqn. 3.46).[80]



(3.46)

A similar scenario could be taking place in our system and causing the accumulation of highly polar intermediates. In order to exclude this as a possible reason for the failure of oxidative cleavage of **3.146r**, we decided to reduce the keto group of **3.146r** and protect the resulting hydroxyl group. We employed K-Selectride for the reduction of **3.146r**, since this reducing agent showed the best stereoselectivity (*dr* = 8:1), outperforming $NaBH_4$ reduction, Luche reduction,[15] and SmI_2 mediated reduction[81] (eqn. 3.47).



(3.47)

The relative configuration of major diastereomer **3.153r** was assigned using extensive 2D COSY and NOESY analysis. Critical nOe signals observed between H_8-H_1 and H_8-H_7 led us to believe that the newly formed hydroxyl group was *syn* to the allyl group (Fig. 3.17). This arrangement would correspond to the reducing agent approaching the carbonyl group from the less sterically hindered *convex* face *anti* to the α-allyl chain, which seemed highly likely for the bulky K-Selectride reagent.

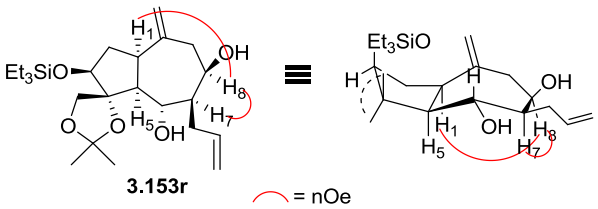
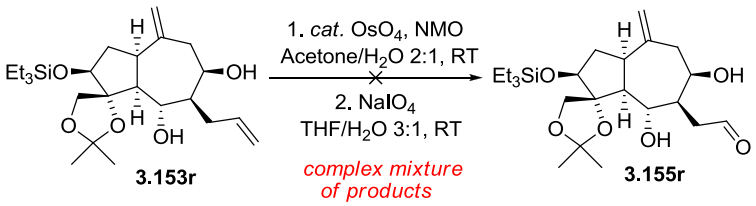


Figure 3.17. Stereochemical assignment of **3.153r**.

Unfortunately, we were not able to identify the reduction conditions that would furnish the C8 hydroxyl group with the desired configuration. We decided to proceed with **3.153r** hoping that at the later stage we would be able to invert the configuration of the secondary alcohol.

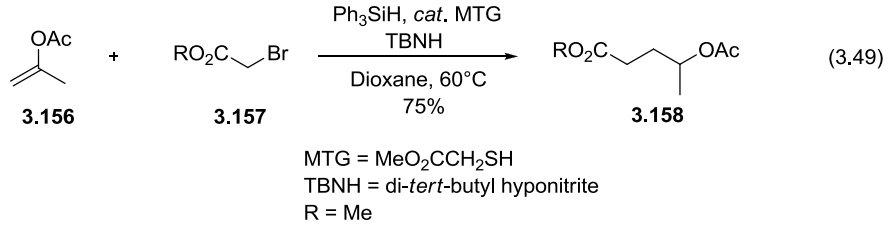
Alcohol **3.153r** was subjected to the standard dihydroxylation conditions but the outcome was identical to the previous attempts (eqn. 3.48). Instead of the desired aldehyde **3.155r**, the reaction afforded complex mixture of products.



(3.48)

3.3.6.2. Radical Alkylation/Lactonisation

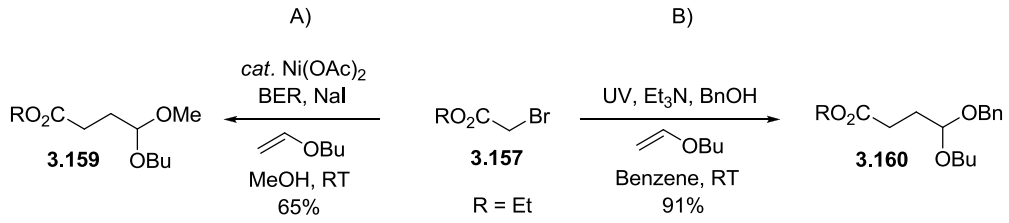
It was clear to us at this point that the selective oxidation of the allyl group would not be as straightforward as we initially planned. Moreover, even if we could accomplish the desired transformation, it would constitute a second carbon extrusion step in our synthesis, which was something we would rather avoid for the sake of step count and elegance. At this point we took a closer look at the nature of the radical formed by the abstraction of the bromine atom from **3.142r**. Radicals next to keto groups are stabilised by the orbital overlap between the SOMO of the radical and the LUMO of the carbonyl group.[82] This interaction lowers the energy of the orbital where the single electron is positioned and forms the so called electrophilic radical.[82] There are several synthetically relevant methodologies developed, that take advantage of this effect in order to enable radical reactions with electron-rich alkenes. For example, Roberts *et al*. developed a radical chain reductive alkylation of electron-rich olefin **3.156** with halocarbonyl compound **3.157** in the presence of a thiol catalyst (eqn. 3.49).[83]



(3.49)

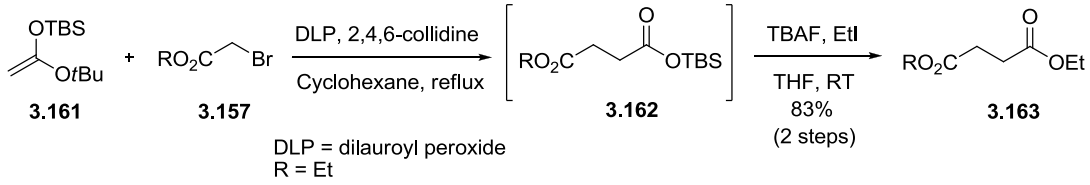
An interesting report on the reaction of halocarbonyl compound **3.157** with vinyl ethers was published by the Yoon group. The transformation takes place in the presence of $Ni(OAc)_2$ and "borohydride exchange resin" (BER), and affords acetal **3.159** as a product (Scheme 3.31, A).[84] Later, it was demonstrated by Curran and Ko that the same transformation can be carried out simply by irradiating the mixture of

reagents with a UV lamp in the presence of an amine base (Scheme 3.31, B).[85]



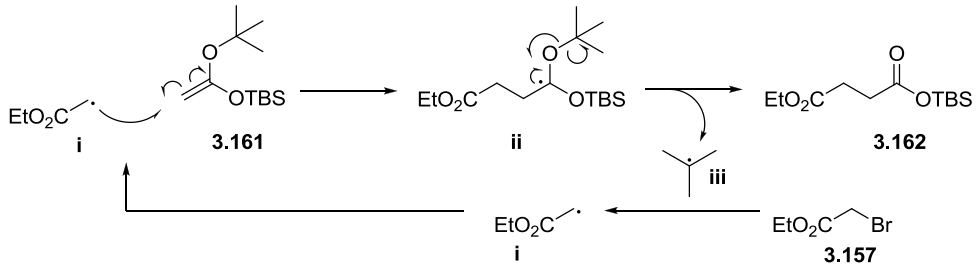
Scheme 3.31. Reactions of ethyl bromoacetate with butyl vinyl ether.

Application of one of the above mentioned conditions to our system would greatly simplify the following steps, since it would eliminate the necessity to differentiate between two similar double bonds. However, the paper that really caught our attention was a report from 2004 by Roberts *et al*., in which the authors demonstrated that a simple bromoester **3.157** could be reacted with silyl ketene acetal **3.161** in the presence of radical initiator to afford silyl ester **3.162**, which was then converted to alkyl ester **3.163** by treatment with TBAF and ethyliodide (Scheme 3.32).[86]



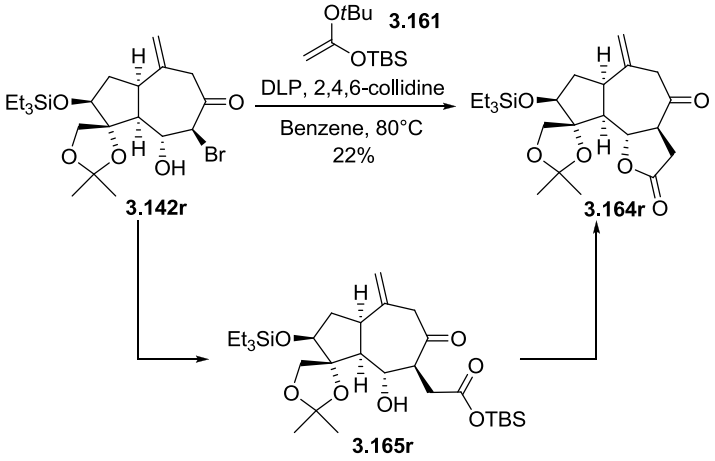
Scheme 3.32. Reaction of ethyl bromoacetate with silyl ketene acetal **3.161**.

The authors proposed the following mechanism for this transformation (Scheme 3.33). Once the electrophilic α-keto radical **i** is formed, it undergoes addition to the electron-rich silyl ketene acetal **3.161** to give radical species **ii**. This intermediate then undergoes β-scission to form a stable carbonyl group and generate a nucleophilic *t*-butyl radical **iii**, which abstracts bromide from the substrate and propagates the chain reaction.



Scheme 3.33. Proposed mechanism of the reaction of α-bromocarbonyl compounds with silyl ketene acetals.

When bromohydrin **3.142r** was treated with *O*-*tert*-butyl *O*-(*tert*-butyldimethylsilyl) ketene acetal **3.161** in the presence of Lauroyl peroxide (DLP) and 2,4,6-collidine in benzene at 80°C for 2 hours, the starting material was largely recovered together with a small amount of a new product (22%). This compound turned out to be lactone **3.164r**, formed from the intermediate silyl ester **3.165r**, which underwent lactonisation under reaction conditions (Scheme 3.34).



Scheme 3.34. Formation of the lactone **3.164r** from the haloketone **3.142r**.

Despite the low yield we were highly pleased with this result, since we not only installed the side chain with the right configuration but also obtained the desired lactone moiety in one step. It must be said that it is the first application of these

reaction conditions in the context of complex natural products synthesis, as well as the first application to bromohydrins for the direct lactone formation. Similarly to allylated product **3.146r**, the configuration of **3.164r** at C7 was assigned based on the coupling constants in ^{1}H-NMR.

It was determined that longer reaction times were needed for the formation of **3.164r** than reported in the original paper. The reason for this is not only the different reactivity of **3.142r** in the radical reaction, but also the time required for the intermediate silyl ester **3.165r** to cyclise to the lactone **3.164r**. If the reaction time is insufficient, the yield of the lactone is low and the intermediates complicate the isolation.

The fact that the starting material was largely recovered upon the first attempt, indicated that there might be some problems with the propagation step of the reaction - the abstraction of the bromine atom by *tert*-butyl radical. Roberts *et al*. showed that sometimes the use of silyl ketene acetal **3.166**, in which *tert*-butyl group is substituted for adamantyl residue, is beneficial for the yield (Fig. 3.18).[86]

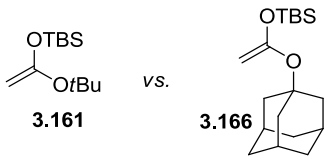
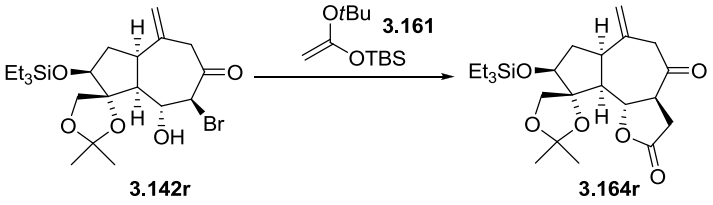


Figure 3.18. 1-Adamantyl residue in silyl ketene acetal.

The authors proposed two hypotheses for this improvement: 1) 1-adamantyl silyl ketene acetals are more stable to heterolytic cleavage than their *tert*-butyl counterparts, and 2) 1-adamantyl radical is more reactive (due to the geometry imposed by the cage structure) and might abstract bromine atom more efficiently. However, in our case we did not observe any considerable improvement in the

reaction profile with 1-adamantyl silyl ketene acetal **3.166**, with haloketone **3.142r** being recovered largely unchanged as before. Finally, it was found that an improvement in yield can be achieved by the portionwise addition of an increased amount of radical initiator (DLP) (Table 3.9, entry 2 *vs.* 1). The yield was further increased by employing a large excess of alkene (entry 3 *vs.* 2).

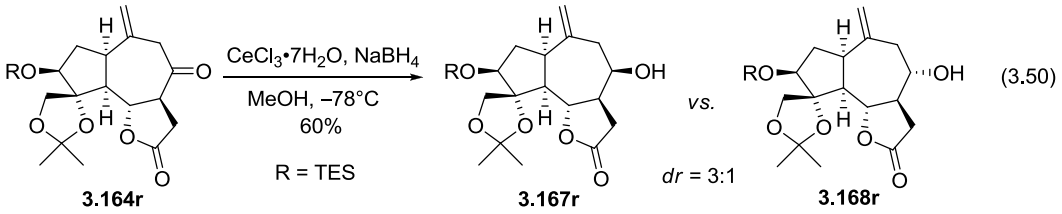
Table 3.9. The effect of the concentration of DLP and alkene on the reaction of bromohydrin **3.142r**.



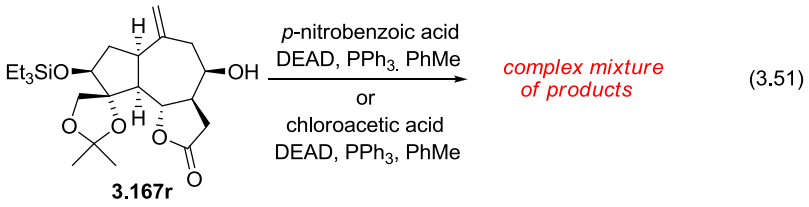
Entry[a]	Radical initiator, equiv	Alkene, equiv	Concentration, M	Yield[b]
1	DLP, 0.1	2.0	0.3	22%
2[c]	DLP, 0.4	2.0	0.3	34%
3[d]	DLP, 0.4	7.5	0.3	52%

[a]All reactions were carried at 80°C in benzene for 14-16 h. [b]Isolated yields. [c]Radical initiator added in 4 portions every 15 min. [d]Radical initiator added in 4 portions every 2 h.

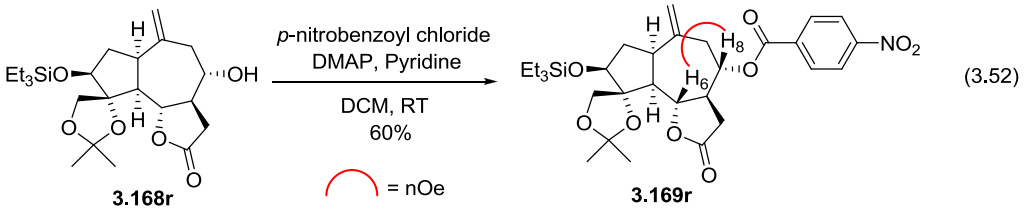
With the tricyclic lactone **3.164r** in hand, we were ready to reduce the keto group, and to establish the last out of the 7 stereocentres present in repin core. Unfortunately, we met the same difficulties as in the reduction of allylated ketone **3.146r** previously. When ketone **3.164r** was subjected to Luche reduction conditions, a mixture of epimeric alcohols **3.167r** and **3.168r** in a 3:1 ratio was isolated, favouring the undesired epimer **3.167r** (eqn. 3.50).



The diastereomeric mixture was separated by column chromatography on silica gel. In analogy to the reduction of the allylketone **3.146r**, the major epimer was assigned the structure **3.167r**, with the hydroxyl group residing on the *concave* face of the molecule. Unfortunately, after a series of experiments we realised that the stereochemistry of **3.167r** could not be effectively inverted using Mitsunobu reaction.[62] Several sets of conditions were examined[87,88] but the reactions afforded large amounts of by-products, most likely originating from competing elimination reactions (appearance of new olefinic signals in ^{1}H-NMR spectrum of the crude reaction mixtures was observed) (eqn. 3.51).



In order to obtain a material suitable for crystallisation, the minor epimer **3.168r** was converted into its *p*-nitrobenzoate **3.169r** by treatment with *p*-nitrobenzoyl chloride in DCM (eqn. 3.52).



Ester **3.169r** was analysed using 2D COSY and NOESY experiments, and single-

crystal X-ray diffraction. As expected a strong nOe signal between protons H_6-H_8 was observed. The crystal structure proved unambiguously that our initial assignment of the stereochemistry of the tricyclic lactone **3.164r** was correct and that intermediate **3.169r** possessed all the 7 stereocentres of the repin's core with the required relative configuration (Fig. 3.19).

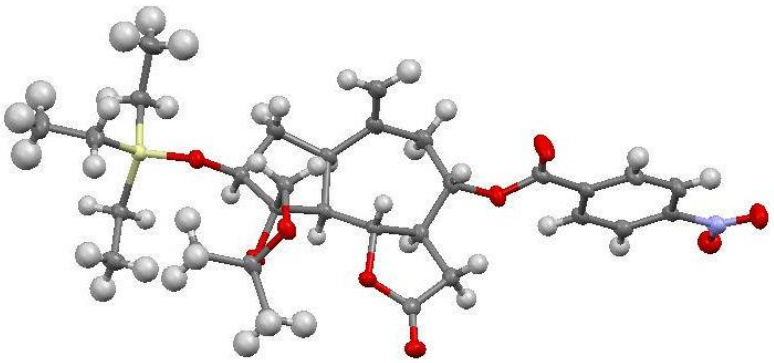
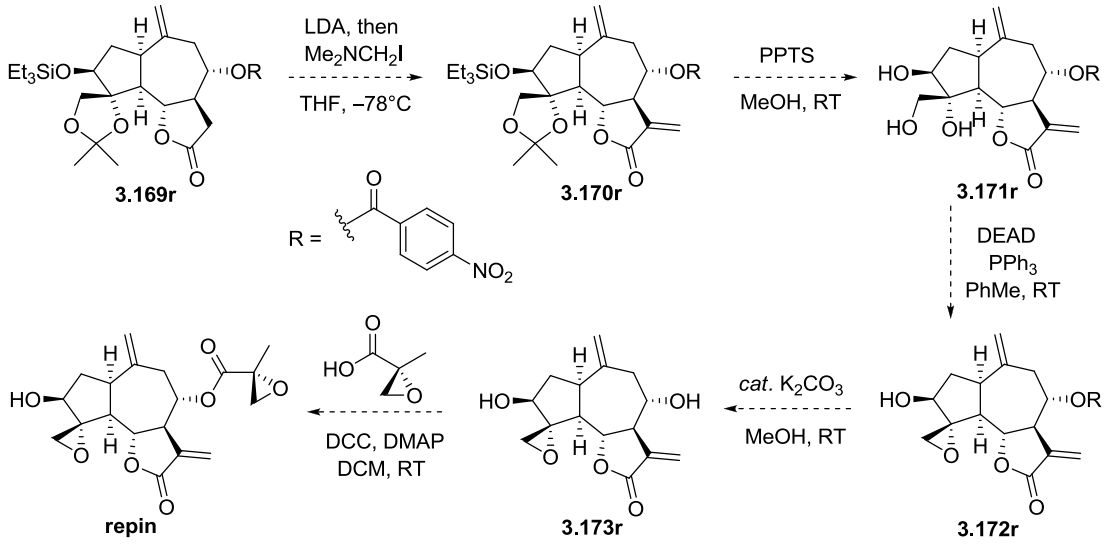


Figure 3.19. Crystal structure of p-nitrobenzoate **3.169r**.

We envisaged the following endgame for the completion of the synthesis: lactone exomethylene formation could be effected first using one of the available methods, for example treatment of enolate of **3.169r** with Eschenmoser's salt[89] (Scheme 3.35). Double cleavage of the silyl group and the acetonide of **3.170r** would then deliver triol **3.171r**. This triol would then be converted to the desired hydroxyepoxide **3.172r**, either in one step under Mitsunobu conditions,[90] or in two steps *via* tosylation/base induced cyclisation protocol.[91] Hydrolysis of the *p*-nitrobenzoate group would reveal a hydroxyl group in **3.173r**, which would be acylated with the side chain of repin to furnish the natural product. We believe that the acylation would be selective for the C8 hydroxyl group, since the other hydroxyl group at C3 is more sterically congested, and would be less available for the acylation.



Scheme 3.35. Synthesis of repin: envisaged endgame.

Current work is directed towards carrying out the envisaged transformations and finishing the first total synthesis of repin.

3.3.7. Conclusion

We have developed a synthesis of the tricyclic core of repin by utilizing rhodium-catalysed [(3+2)+2] carbocyclisation and radical alkylation/lactonisation as the key steps. We have demonstrated that rhodium-catalysed carbocyclisation can be successfully applied in complex systems to generate advanced intermediates *en route* to natural products. Our stereoselective approach to the lactone ring formation represents the first application of radical alkylation/lactonisation to bromohydrins for the direct lactone formation. Although our synthesis still suffers from poor selectivities of some transformations, we believe that once optimised, this novel route could provide a general entry into the family of guaianolide natural products.

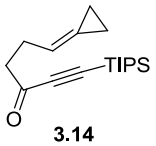
3.4. Experimental

3.4.1. General Information

Anhydrous MeCN was purchased from *Aldrich*. Et_3N, DIPEA and pyridine were distilled from CaH_2 under nitrogen and stored under 4Å MS.

Full assignment of signals in ^{1}H-NMR spectra is provided for key intermediates in order to point out crucial structural features. For other general information, see Chapter 2.

3.4.2. Experimental Procedures



3.14

6-Cyclopropylidene-1-(triisopropylsilyl)hex-1-yn-3-one (3.14)

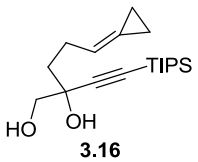
n-Butyllithium (4.62 mL of 2.5 M solution in hexanes, 11.6 mmol) was added to a solution of ethynyltriisopropylsilane (2.66 mL, 11.9 mmol) in THF (60 mL) at −30°C. After stirring for 5 min the mixture was warmed to 0°C and stirred for 10 more min. After recooling to −20°C, amide **3.13** (1.003 g, 5.93 mmol) was added as a solution in THF (3 mL, then washed 2x1 mL). The resulting mixture was stirred for 30 min at −20°C and for 2 h at 0°C. The reaction was quenched with the addition of 1M HCl solution and extracted with ether several times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting ketone **3.14** was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80-5.76 (m, 1H), 2.74 (t, *J*=7.3 Hz, 2H), 2.60-2.55 (m, 2H), 1.20-1.07 (m, 21H), 1.06-0.99 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 187.52 (e), 122.79 (e), 115.92 (o), 104.37 (e), 95.69 (e), 45.18 (e), 26.60 (e), 18.62 (o), 11.16 (o), 2.28 (e), 2.16 (e).

IR (neat) 2944 (s), 2146 (w), 1678 (s), 1462 (m), 1219 (w), 1054 (s), 882 (m), 679 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{18}H_{30}OSiNa$ 313.1964, found 313.1970.



3.16

5-Cyclopropylidene-2-((triisopropylsilyl)ethynyl)pentane-1,2-diol (3.16)

Magnesium turnings (0.668 g, 27.5 mmol) were placed in a flame-dried roundbottom flask. The flask was evacuated and refilled with argon. (Chloromethyl)(isopropoxy)dimethylsilane (4.67 mL, 25.9 mmol) was dissolved in THF (25 mL) and a portion of resulting solution (5 mL) was added to magnesium turnings with stirring at RT. To this mixture were added 4-5 drops of 1,2-dibromoethane and a slightly exotermic reaction started within several minutes whereupon the mixture turned grey. The remaining solution of silane was added to magnesium portionwise in the course of 15 min. After the end of addition the mixture was stirred at 60°C for 30 min and cooled to 0°C. A solution of ketone **3.14** (1.50 g, 5.16 mmol) in THF (3+2 mL) was added dropwise to the solution of Grignard reagent. The resulting mixture was stirred at 0°C for 1 h, quenched with precooled (0°C) sat. NH_4Cl solution, and extracted with EtOAc 3x20 mL. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* (bath temperature 21°C). The resulting oil was dissolved in THF/MeOH 1:1 (60 mL). $KHCO_3$ (0.775 g, 7.74 mmol), KF (0.900 g, 15.5 mmol) and 30 % H_2O_2 (3.0 mL) were added successively to the solution and the resulting mixture was stirred at RT for 2.5 h (TLC control). The reaction was quenched with sat. $Na_2S_2O_3$ solution, and after 10 min of stirring the mixture was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated *in*

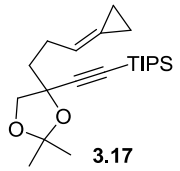
vacuo. Purification by flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:12 → 1:6 → 1:3) afforded **3.16** (1.665 g, 100%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85-5.80 (m, 1H), 3.68 (dd, *J*=11.0, 4.9 Hz, 1H), 3.53 (dd, *J*=11.0, 9.2 Hz, 1H), 2.56-2.42 (m, 2H), 2.51 (s, 1H), 1.93 (dd, *J*=9.1, 4.9 Hz, 1H), 1.86 (ddd, *J*=13.6, 10.2, 6.2 Hz, 1H), 1.80 (ddd, *J*=13.5, 10.4, 5.7 Hz, 1H), 1.09-1.06 (m, 21H), 1.04-1.03 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 122.22 (e), 117.64 (o), 108.18 (e), 86.95 (e), 72.62 (e), 70.11 (e), 37.37 (e), 27.13 (e), 18.75 (o), 11.22 (o), 2.38 (e), 2.05 (e).

IR (neat) 3364 (m), 2942 (s), 2865 (s), 2164 (w), 1462 (m), 1257 (m), 1049 (s), 996 (s), 882 (s), 809 (m), 677 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{19}H_{34}O_2SiNa$ 345.2226, found 345.2235.



3.17

((4-(3-Cyclopropylidenepropyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethynyl)triisopropylsilane (3.17)

PPTS (0.130 g, 0.520 mmol) was added to a solution of diol **3.16** (1.665 g, 5.160 mmol) and 2,2-dimethoxypropane (1.27 mL, 10.3 mmol) in DCM (50 mL) at RT. The resulting mixture was stirred for 36 h, quenched with Et_3N (2 mL), washed with sat. $NaHCO_3$ solution, and dried over Na_2SO_4. Purification by flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:80 → 1:40) afforded **3.17** (1.768 g, 94%) as a colourless oil.

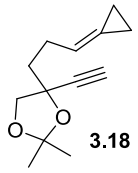
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81-5.76 (m, 1H), 4.14 (d, *J*=8.1 Hz, 1H), 3.85 (d, *J*=8.1 Hz, 1H), 2.50-2.33 (m, 2H), 1.94 (ddd, *J*=13.2, 11.3, 5.0 Hz, 1H), 1.83 (ddd, *J*=13.2, 11.5, 5.5 Hz, 1H), 1.52 (s, 3H), 1.40 (s, 3H), 1.09-1.06 (m, 21H), 1.03-1.02

(m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 121.95 (e), 117.39 (o), 110.70 (e), 109.21 (e), 85.49 (e), 77.48 (e), 75.30 (e), 39.83 (e), 27.59 (e), 27.12 (o), 26.07 (o), 18.75 (o), 11.31 (o), 2.29 (e), 2.02 (e).

IR (neat) 2942 (s), 2865 (s), 2166 (w), 1463 (m), 1369 (m), 1239 (m), 1064 (s), 882 (s), 828 (m), 677 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{22}H_{38}O_2SiNa$ 385.2539, found 385.2538.



4-(3-Cyclopropylidenepropyl)-4-ethynyl-2,2-dimethyl-1,3-dioxolane (3.18)

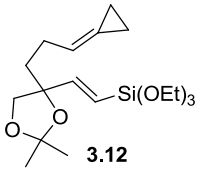
TBAF (1.0 M in THF, 5.54 mL, 5.54 mmol) was added to a solution of silane **3.17** (1.748 g, 4.820 mmol) in THF (50 mL) at 0°C. The reaction mixture was stirred at 0°C for 1 h and at RT for 1 h. After quenching with brine the mixture was extracted with Et_2O 3x20 ml. The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:80 → 1:40) afforded **3.18** (0.917 g, 92%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80-5.76 (m, 1H), 4.15 (d, *J*=8.3 Hz, 1H), 3.85 (d, *J*=8.3 Hz, 1H), 2.50 (s, 1H), 2.47-2.31 (m, 2H), 1.95 (ddd, *J*=13.2, 11.4, 5.1 Hz, 1H), 1.85 (ddd, *J*=13.2, 11.4, 5.6 Hz, 1H), 1.52 (s, 3H), 1.41 (s, 3H), 1.05-1.01 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 122.04 (e), 117.15 (o), 110.89 (e), 85.19 (e), 76.96 (e), 74.85 (e), 72.91 (e), 39.25 (e), 27.24 (e), 27.04 (o), 26.20 (o), 2.23 (e), 2.16 (e).

IR (neat) 3296 (w), 2982 (m), 2935 (w), 1453 (w), 1371 (m), 1210 (m), 1161 (m), 1063 (s), 861 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calculated for $C_{13}H_{19}O_2$ 207.1380, found 207.1386.



3.12

(E)-(2-(4-(3-Cyclopropylidenepropyl)-2,2-dimethyl-1,3-dioxolan-4-yl)vinyl)triethoxysilane (3.12)

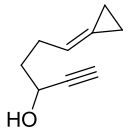
3.12 was prepared according to the general procedure A (Chapter 2) in 62% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (d, *J*=18.9 Hz, 1H), 5.77 (d, *J*=19.0 Hz, 1H), 5.76-5.73 (m, 1H), 3.88 (s, 2H), 3.82 (q, *J*=7.0 Hz, 6H), 2.31-2.23 (m, 1H), 2.20-2.12 (m, 1H), 1.83 (ddd, *J*=13.6, 11.3, 5.3 Hz, 1H), 1.76 (ddd, *J*=13.6, 11.5, 5.5 Hz, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.23 (t, *J*=7.0 Hz, 9H), 1.02-0.99 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.42 (o), 121.54 (e), 118.12 (o), 117.80 (o), 110.05 (e), 84.66 (e), 73.24 (e), 58.64 (e), 38.50 (e), 27.20 (o), 26.70 (e), 26.55 (o), 18.38 (o), 2.22 (e), 2.02 (e).

IR (neat) 2976 (m), 1618 (w), 1369 (w), 1076 (s), 958 (m), 778 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{19}H_{34}O_5SiNa$ 393.2073, found 393.2067.



3.23

6-Cyclopropylidenehex-1-yn-3-ol (3.23)

Cerium(III) chloride heptahydrate (3.30 g, 8.90 mmol) and sodium borohydride (0.440 g, 11.5 mmol) were added successively to a solution of ynone **3.22** (1.19 g, 8.90 mmol) in Methanol (60 mL) at −78°C. The reaction mixture was stirred for 20 min, diluted with Et_2O and quenched with sat. NH_4Cl solution. The dry ice/acetone bath was removed, the mixture was stirred for 20 min at RT and extracted with Et_2O 3x20 mL. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was taken in DCM/water 8:1 (36 mL), the layers were

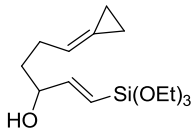
separated, and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:10 → 1:5 → 1:1) afforded **2.23** (1.02 g, 84%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80-5.76 (m, 1H), 4.41 (qd, *J*=6.5, 2.0 Hz, 1H), 2.48 (d, *J*=2.1 Hz, 1H), 2.40-2.35 (m, 2H), 1.93-1.85 (m, 2H), 1.82 (app d, *J*=5.7 Hz, 1H), 1.05-1.03 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 122.55 (e), 116.89 (o), 84.97 (e), 73.14 (e), 62.07 (o), 37.12 (e), 27.57 (e), 2.33 (e), 2.13 (e).

IR (neat) 3299 (m), 2980 (w), 1440 (w), 1334 (w), 1064 (s), 1016 (s), 930 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calculated for $C_9H_{13}O$ 137.0961, found 137.0960.



3.24

(E)-6-Cyclopropylidene-1-(triethoxysilyl)hex-1-en-3-ol (3.24)

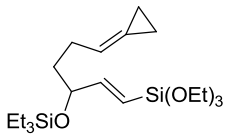
3.24 was prepared according to the general procedure A (Chapter 2) in 47% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (dd, *J*=19.0, 4.8 Hz, 1H), 5.80-5.76 (m, 1H), 5.66 (dd, *J*=18.9, 1.6 Hz, 1H), 4.19 (dtd, *J*=7.1, 5.2, 1.5 Hz, 1H), 3.83 (q, *J*=7.0 Hz, 6H), 2.32-2.27 (m, 2H), 1.77-1.64 (m, 2H), 1.24 (t, *J*=7.0 Hz, 9H), 1.04-1.02 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.83 (o), 122.14 (e), 118.03 (o), 117.58 (o), 73.78 (o), 58.70 (e), 36.27 (e), 27.93 (e), 18.38 (o), 2.36 (e), 2.08 (e).

IR (neat) 3408 (w), 2919 (w), 1390 (w), 1073 (s), 956 (m), 775 (m), 733 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{15}H_{28}O_4SiNa$ 323.1655, found 323.1651.



3.21

(E)-5-(3-Cyclopropylidenepropyl)-8,8-diethoxy-3,3-diethyl-4,9-dioxa-3,8-disilaundec-6-ene (3.21)

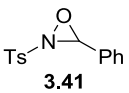
Chlorotriethylsilane (0.17 mL, 0.10 mmol) was added dropwise to the solution of alcohol **3.24** (0.200 g, 0.670 mmol) and imidazole (0.113 g, 1.66 mmol) in THF (7 mL) at 0°C. The resulting mixture was stirred at RT for 3 h, quenched with sat. $NaHCO_3$ and extracted with Et_2O 3x10 mL. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:20 → 1:10 → 1:5) afforded **3.21** (0.250 g, 91%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (dd, *J*=18.8, 5.2 Hz, 1H), 5.78-5.74 (m, 1H), 5.60 (dd, *J*=18.8, 1.4 Hz, 1H), 4.17 (qd, *J*=6.3, 1.4 Hz, 1H), 3.82 (q, *J*=7.0 Hz, 6H), 2.26-2.17 (m, 2H), 1.68-1.63 (m, 2H), 1.23 (t, *J*=7.0 Hz, 9H), 1.02-1.00 (m, 4H), 0.95 (t, *J*=8.0 Hz, 9H), 0.60 (q, *J*=8.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.56 (o), 121.44 (e), 118.01 (o), 117.55 (o), 74.64 (o), 58.58 (e), 37.43 (e), 27.66 (e), 18.39 (o), 7.01 (o), 5.09 (e), 2.25 (e), 2.09 (e).

IR (neat) 2973 (w), 1621 (w), 1167 (w), 1101 (s), 1076 (s), 958 (m), 778 (m), 742 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{21}H_{42}O_4Si_2Na$ 437.2519, found 437.2530.



3.41

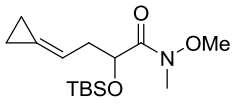
3-Phenyl-2-tosyl-1,2-oxaziridine (3.41)[92]

Oxaziridine **3.41** was prepared in 67% yield from (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide, according to the procedure used by García Ruano *et al.*

(2005).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94-7.92 (m, 2H), 7.49-7.39 (m, 7H), 5.45 (s, 1H), 2.50 (s, 3H).

IR (neat) 1390 (w), 1340 (m), 1238 (w), 1189 (s), 1088 (m), 775 (m), 688 (m) cm^{-1}.



3.42

2-(tert-Butyldimethylsilyloxy)-4-cyclopropylidene-N-methoxy-N-methylbutanamide (3.42)

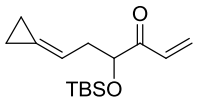
NaHMDS (14.5 ml 1 M in THF, 14.5 mmol) was added slowly to a solution of amide **3.13** (1.63 g, 9.60 mmol) in THF (100 ml) at −78°C. The resulting mixture was stirred for 15 min followed by the addition of oxaziridine **3.41** (3.05 g, 11.1 mmol). The reaction mixture was stirred at −78°C for 30 min, quenched with sat. NH_4Cl solution, and extracted with EtOAc (3x20 ml). Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Crude residue was dissolved in DCM (65 ml). To this solution imidazole (1.64 g, 24.1 mmol) and TBS-Cl (2.18 g, 14.5 mmol) were added successively at 0°C. The reaction mixture was stirred at RT for 2 h, quenched with sat. NH_4Cl solution and extracted with Et_2O (3x20 ml). Combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:20 → 1:10 → 1:5 → 1:2) afforded silyl ether **3.42** (2.35 g, 81%) as a colourless oil.

R_f = 0.20 (Et_2O/petroleum ether 1:5)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83-5.78 (m, 1H), 4.65-4.58 (m, 1H), 3.70 (s, 3H), 3.21 (bs, 3H), 2.62-2.50 (m, 2H), 1.09-0.98 (m, 4H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H).

IR (neat) 2929 (m), 2856 (m), 1679 (s), 1250 (m), 1134 (m), 1089 (m), 992 (m), 835 (s), 778 (s) cm^{-1}.

HRMS (CI, $[M+H]^+$) calculated for $C_{15}H_{29}O_3Si$ 300.1989, found 300.2001.



3.43

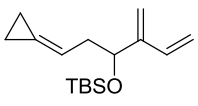
4-(tert-Butyldimethylsilyloxy)-6-cyclopropylidenehex-1-en-3-one (3.43)

Vinylmagnesium bromide (27.4 ml 1 M in THF, 27.4 mmol) was added slowly to a solution of amide **3.13** (2.35 g, 7.80 mmol) in THF (30 ml) at −78°C. The resulting mixture was slowly warmed to 0°C and stirred at this temperature for 2 h. The reaction mixture was quenched with sat. NH_4Cl solution and extracted with Et_2O (3x20 ml). Combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:40 → 1:20 → 1:10 → 1:2) afforded enone **3.43** (1.65 g, 79%) as a colourless oil.

$\mathbf{R_f}$ = 0.30 (Et_2O/petroleum ether 1:10)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (dd, *J*=17.6, 10.5 Hz, 1H), 6.36 (dd, *J*=17.5, 1.8 Hz, 1H), 5.77-5.72 (m, 1H), 5.73 (dd, *J*=10.7, 1.8 Hz, 1H), 4.24 (at, *J*=6.1 Hz, 1H), 2.54-2.50 (m, 2H), 1.08-0.95 (m, 4H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

HRMS (CI, $[M+H]^+$) calculated for $C_{15}H_{26}O_2Si$ 267.1775, found 267.1781.



3.44

tert-Butyl(1-cyclopropylidene-4-methylenehex-5-en-3-yloxy)-dimethylsilane (3.44)

n-BuLi (0.19 ml 2.5 M in hexanes, 0.5 mmol) was added slowly to a suspension of methyltriphenylphosphonium bromide (0.179 g, 0.500 mmol) (predried by evaporation with toluene) in THF (0.8 ml) at −78°C. The reaction mixture was

brought to 0°C, stirred for 30 min, and recooled to −78°C. A solution of enone **3.43** (0.053 g, 0.20 mmol) in THF (0.5 ml) was added. The reaction mixture was allowed to slowly warm up to RT and was stirred overnight. The mixture was quenched with sat. NH_4Cl solution and extracted with Et_2O. Combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:100 → 1:50) afforded diene **3.44** (0.017 g, 32%) as a colourless oil.

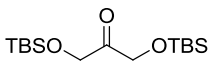
R_f = 0.40 (Et_2O/petroleum ether 1:50)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (dd, *J*=17.9, 11.2 Hz, 1H), 5.81-5.76 (m, 1H), 5.33 (d, *J*=17.9 Hz, 1H), 5.21 (s, 1H), 5.10 (d, *J*=1.7 Hz, 1H), 5.03 (d, *J*=11.2 Hz, 1H), 4.42 (dd, *J*=7.2, 4.3 Hz, 1H), 2.53-2.46 (m, 1H), 2.42-2.35 (m, 1H), 1.07-0.95 (m, 4H), 0.88 (s, 9H), 0.02 (s, 3H), −0.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.30 (e), 136.44 (o), 115.37 (o), 114.51 (e), 113.06 (e), 73.12 (o), 40.56 (e), 25.93 (o), 18.37 (e), 2.72 (e), 1.76 (e), −4.62 (o), −4.96 (o).

IR (neat) 2929 (w), 2856 (w), 1466 (w), 1252 (m), 1093 (m), 903 (m), 831 (s), 773 (s) cm^{-1}.

HRMS (CI, Ammonia, $[M+H]^+$) calculated for $C_{16}H_{29}OSi$ 265.1982, found 265.1990.



3.51

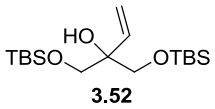
2,2,3,3,9,9,10,10-Octamethyl-4,8-dioxa-3,9-disilaundecan-6-one (3.51)[93]

TBS-Cl (32.6 g, 0.216 mol) was added in 4 portions to the solution of commercially available 1,3-dihydroxyacetone dimer (**3.50**) (10.0 g, 0.0560 mol) and imidazole (29.5 g, 0.433 mol) in DMF (80 ml) at 0°C. The reaction mixture was brought to RT, stirred for 4 h, and poured into water (600 ml). The mixture was extracted with Et_2O, and combined organic extracts were washed with water (2x50 ml), brine, dried over

Na_2SO_4, and concentrated *in vacuo*. The crude residue was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (s, 4H), 0.92 (s, 18H), 0.09 (s, 12H).

IR (neat) 2930 (w), 2858 (w), 1742 (w), 1253 (m), 1098 (m), 833 (s), 776 (s) cm^{-1}.



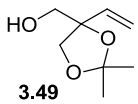
3.52

2,2,3,3,9,9,10,10-Octamethyl-6-vinyl-4,8-dioxa-3,9-disilaundecan-6-ol (3.52)[25]

A solution of ketone **3.51** (35.3 g, 0.111 mol) in THF (30 ml) was added slowly to vinylmagnesium bromide (220 ml 1 M in THF, 0.220 mol) in THF (350 ml) at 0°C. After the addition was finished, the ice/water bath was removed and the mixture stirred for additional 20 min. The reaction mixture was quenched with 1.5 M HCl (100 ml) and sat. NH_4Cl solution (50 ml), and extracted with Et_2O. Combined organic extracts were successively washed with sat. $NaHCO_3$ solution, water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue contained ~3:1 mixture of bissilane **3.52** and partially deprotected material, and was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (dd, *J*=17.5, 11.0 Hz, 1H), 5.41 (dd, *J*=17.5, 1.8 Hz, 1H), 5.18 (dd, *J*=11.0, 1.8 Hz, 1H), 3.58 (d, *J*=9.3 Hz, 2H), 3.48 (d, *J*=9.3 Hz, 2H), 0.89 (s, 18H), 0.05 (s, 12H).

IR (neat) 3566 (w), 2929 (w), 2858 (w), 1252 (m), 1076 (m), 833 (s), 774 (s) cm^{-1}.



3.49

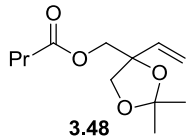
(2,2-Dimethyl-4-vinyl-1,3-dioxolan-4-yl)methanol (3.49)[25]

TBAF (240 ml 1 M in THF, 0.24 mol) was added to a solution of bissilane **3.52** (38.4 g, 0.111 mol) in THF (250 ml) at RT. Reaction mixture was stirred for 2 h, and the

volatiles were removed *in vacuo*. The residue was diluted with DCM and applied on a column (~1000 ml silica gel). Elution with DCM-MeOH 50:1 → 25:1 → 20:1 afforded a mixture of triol **3.53** with a tetrabutylammonium impurity in 1:1.5 ratio as a brown oil. This mixture was dissolved in DCM (280 ml) and 2,2-dimethoxypropane (135 ml), followed by the addition of Na_2SO_4 (15.7 g, 0.111 mol) and *p*-toluenesulfonic acid monohydrate (31.7 g, 0.167 mol). The resulting mixture was stirred for 20 h at RT (TLC control), quenched with sat. $NaHCO_3$ solution, and extracted with EtOAc. Combined organic extracts were washed successively with sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The heterogeneous residue was dissolved in EtOAc, washed with water (5 x 30 ml) and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:4 → 1:2) afforded acetonide **3.49** (11.7 g, 67% over 4 steps) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (dd, *J*=17.3, 10.9 Hz, 1H), 5.41 (dd, *J*=17.4, 1.3 Hz, 1H), 5.26 (dd, *J*=10.9, 1.2 Hz, 1H), 4.07 (d, *J*=8.5 Hz, 1H), 3.88 (d, *J*=8.5 Hz, 1H), 3.59 (dd, *J*=11.4, 5.7 Hz, 1H), 3.52 (dd, *J*=11.4, 7.5 Hz, 1H), 1.84 (dd, *J*=7.5, 5.7 Hz, 1H), 1.47 (s, 3H), 1.42 (s, 3H).

IR (neat) 3428 (w), 2987 (w), 1371 (m), 1212 (m), 1054 (s), 927 (m), 855 (m) cm^{-1}.



3.48

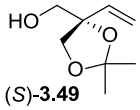
(2,2-dimethyl-4-vinyl-1,3-dioxolan-4-yl)methyl butyrate (3.48)[25]

Butyryl chloride (98 µl, 0.95 mmol) was added to a solution of alcohol **3.49** (0.100 g, 0.630 mmol) and Et_3N (0.26 ml, 1.9 mmol) in DCM (4 ml) at 0°C. The mixture was stirred at this temperature for 20 min, then slowly warmed to RT, and stirred overnight. The reaction mixture was quenched with water and extracted with DCM.

Combined organic extracts were washed with sat. $NaHCO_3$ solution, water, brine, dried over Na_2SO_4, and concentratred *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:10 → 1:5) afforded butyrate **3.48** (137 mg, 95%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (dd, *J*=17.3, 10.9 Hz, 1H), 5.44 (dd, *J*=17.3, 1.2 Hz, 1H), 5.23 (dd, *J*=10.9, 1.2 Hz, 1H), 4.12 (d, *J*=11.3 Hz, 1H), 4.06 (s, *J*=11.3 Hz, 1H), 4.04 (d, *J*=8.8 Hz, 1H), 3.85 (d, *J*=8.7 Hz, 1H), 2.32 (t, *J*=7.5 Hz, 2H), 1.66 (sextet, *J*=7.4 Hz, 2H), 1.46 (s, 3H), 1.41 (s, 3H), 0.95 (t, *J*=7.4 Hz, 3H).

IR (neat) 2966 (w), 1739 (s), 1371 (m), 1166 (s), 1059 (s), 987 (m), 929 (m), 857 (m) cm^{-1}.



(*S*)-**3.49**

(S)-(2,2-Dimethyl-4-vinyl-1,3-dioxolan-4-yl)methanol ((S)-3.49)[25]

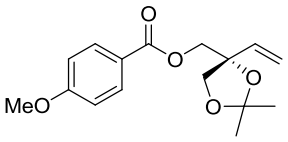
Pseudomonas cepacia lipase (37.8 U/mg, 7.1 mg) was added to a suspension of butyrate **3.48** (45.7 mg, 0.200 mmol) in phosphate buffer (2.6 ml, pH = 7). The resulting mixture was stirred vigorously at RT for 2h 20 min and extracted with EtOAc. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:5 → 1:2 → 1:1) afforded enantioenriched alcohol (*S*)-**3.49** (16.0 mg, 100%, based on 50% conversion) as a colourless oil. Enantiomeric excess of (*S*)-**3.49** (98% *ee*) was determined by HPLC analysis of the it's 4-methoxybenzoate derivative.

$[\alpha]_D^{20}$ –10.2 (c = 1.00, $CHCl_3$) Lit. $[\alpha]_D^{22}$ –11.9 (c = 1.00, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (dd, *J*=17.3, 10.9 Hz, 1H), 5.41 (dd, *J*=17.4, 1.3 Hz, 1H), 5.26 (dd, *J*=10.9, 1.2 Hz, 1H), 4.07 (d, *J*=8.5 Hz, 1H), 3.88 (d, *J*=8.5 Hz,

1H), 3.59 (dd, *J*=11.4, 5.7 Hz, 1H), 3.52 (dd, *J*=11.4, 7.5 Hz, 1H), 1.84 (dd, *J*=7.5, 5.7 Hz, 1H), 1.47 (s, 3H), 1.42 (s, 3H).

IR (neat) 3428 (w), 2987 (w), 1371 (m), 1212 (m), 1054 (s), 927 (m), 855 (m) cm^{-1}.



4-Methoxybenzoate of (*S*)-**3.49**

(*R*)-(2,2-Dimethyl-4-vinyl-1,3-dioxolan-4-yl)methyl 4-methoxybenzoate

4-Methoxybenzoyl chloride (36 mg, 0.21 mmol) and DMAP (1.3 mg. 0.010 mmol) were added to a solution of alcohol (*S*)-**3.49** (16.6 mg, 0.105 mmol) and Et_3N (37 µl, 0.26 mmol) in DCM (1.4 ml) at 0°C. The mixture was warmed to RT and stirred overnight. The reaction was quenched by the addition of water and the resulting mixture was extracted with Et_2O. Combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:8 → 1:4 → 1:2) afforded 4-methoxybenzoate of (*S*)-**3.49** (19.8 mg, 65%) as a colourless oil.

The enantiomeric excess of the 4-methoxybenzoate of (*S*)-**3.49** was determined by chiral HPLC analysis and was shown to be 98% *ee*. Chiralcel OJ-H column, IPA/Hex – 1:99, 1.5 ml/min, 25°C, 254 nm, t_r(major) = 8.8 min, t_r(minor) = 9.9 min.

$[\alpha]_D^{20}$ –11.5 (c = 0.79, $CHCl_3$)

$\mathbf{R_f}$ = 0.60 (Et_2O/petroleum ether 1:1)

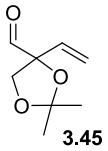
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02-7.99 (m, 2H), 6.94-6.91 (m, 2H), 6.01 (dd, *J*=17.3, 10.8 Hz, 1H), 5.50 (dd, *J*=17.3, 1.3 Hz, 1H), 5.27 (dd, *J*=10.9, 1.3 Hz, 1H), 4.32 (d, *J*=11.2 Hz, 1H), 4.27 (d, *J*=11.2 Hz, 1H), 4.17 (d, *J*=8.7 Hz, 1H), 3.92 (d, *J*=8.7 Hz, 1H), 3.86 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.96 (e), 163.53 (e), 137.59 (o), 131.75 (o), 122.30

(e), 115.94 (e), 113.70 (o), 110.56 (e), 82.03 (e), 70.85 (e), 66.87 (e), 55.44 (o), 26.99 (o), 26.14 (o).

IR (neat) 2987 (w), 1713 (s), 1606 (s), 1511 (m), 1371 (m), 1254 (s), 1166 9s), 1097 (s), 847 (m), 769 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calculated for $C_{16}H_{20}O_5$ 293.1389, found 293.1392.



3.45

2,2-Dimethyl-4-vinyl-1,3-dioxolane-4-carbaldehydemethoxybenzoate (3.45)

DMSO (5.4 ml, 76 mmol) was added to a solution of $(COCl)_2$ (3.65 ml, 41.7 mmol) in DCM (250 ml) at −78°C. The resulting mixture was stirred for 10 min before the addition of alcohol **3.49** (6.00 g, 37.9 mmol) in DCM (10 ml). Following the addition of alcohol the mixture was stirred for 10 min and Et_3N (26.4 ml, 190 mmol) was added slowly. The reaction mixture was warmed to −40°C (MeCN/dry ice bath), stirred for 20 min, and warmed to 0°C. After 10 min of stirring at this temperature, water was added, and phases were separated. Organic phase was washed successively with ice cold 0.1 M HCl solution, water, sat. $NaHCO_3$ solution, water, dried over Na_2SO_4 and concentrated *in vacuo* (bath T = 33°C, p = 150 mbar). Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:4 → 1:2) afforded aldehyde **3.45** (5.05 g, 85%) as a yellow oil.

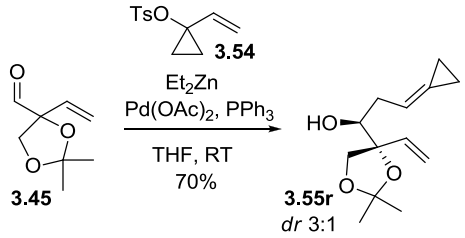
R_f = 0.5 (Et_2O/petroleum ether 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 5.83 (dd, *J*=17.3, 10.8 Hz, 1H), 5.49 (dd, *J*=17.3, 0.7 Hz, 1H), 5.34 (d, *J*=10.8 Hz, 1H), 4.44 (d, *J*=8.8 Hz, 1H), 3.79 (d, *J*=8.8 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.26 (o), 132.74 (o), 118.09 (e), 111.66 (e), 88.37 (e), 70.54 (e), 26.89 (o), 25.90 (o).

IR (neat) 3447 (w), 2989 (w), 1733 (m), 1372 (m), 1214 (m), 1160 (m), 1057 (s), 857 (m) cm^{-1}.

HRMS (CI, $[M+H]^+$) calculated for $C_8H_{12}O_3$ 157.0859, found 157.0860.



(S*)-3-Cyclopropylidene-1-((R*)-2,2-dimethyl-4-vinyl-1,3-dioxolan-4-yl)propan-1-ol (3.55r)

$Pd(OAc)_2$ (0.363 g. 1.62 mmol) and PPh_3 (1.017 g, 3.880 mmol) were dissolved in THF (320 ml) and the resulting mixture stirred for 15 min before the addition of 1-vinylcyclopropyl 4-methylbenzenesulfonate (**3.54**) (9.24 g, 38.8 mmol) in THF (10 ml) and aldehyde **3.45** (5.048 g, 32.30 mmol) in THF (10 ml). Following this the reaction flask was emerged into ice/water bath and diethylzinc (64.6 ml 1 M in hexanes, 64.6 mmol) was added. The ice/water bath was removed and the reaction mixture stirred for 2 h (TLC control) at RT, quenched with sat. NH_4Cl solution, and extracted with Et_2O. Combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:8 → 1:4 → 1:2) afforded alcohol **3.55r** (5.187 g, 72%, 3:1 diastereomeric mixture) as a yellow oil.

$\mathbf{R_f}$ = 0.35 (Et_2O/petroleum ether 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (dd, *J*=17.3, 10.9 Hz, 1H), 5.85-5.80 (m, 1H), 5.45 (dd, *J*=17.3, 1.6 Hz, 1H), 5.27 (dd, *J*=10.9, 1.7 Hz, 1H), 4.21 (d, *J*=8.6 Hz, 1H), 3.87 (d, *J*=8.6 Hz, 1H), 3.71 (dt, *J*=10.0, 2.9 Hz, 1H), 2.54-2.48 (m, 1H), 2.17-2.11 (m, 1H), 2.06 (d, *J*=3.1 Hz, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.12-1.02 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.68 (o), 124.81 (e), 115.95 (e), 114.64 (o), 110.06

(e), 85.76 (e), 74.42 (o), 70.20 (e), 34.12 (e), 27.01 (o), 26.50 (o), 2.83 (e), 2.07 (e).

IR (neat) 3473 (w), 2983 (m), 2876 (w), 1641 (w), 1371 (s), 1256 (s), 1213 (s), 1062 (s), 1003 (s), 929 (s), 862 (s) cm^{-1}.

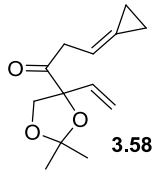
HRMS (CI, $[(M-OH)]^+$) calculated for $C_{13}H_{19}O_2$ 207.1380, found 207.1385.

Analytic data for the minor diastereomer **3.61r**:

(R*)-3-Cyclopropylidene-1-((R*)-2,2-dimethyl-4-vinyl-1,3-dioxolan-4-yl)propan-1-ol (3.61r)

R_f = 0.35 (Et_2O/petroleum ether 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (dd, *J*=17.3, 10.7 Hz, 1H), 5.85-5.80 (m, 1H), 5.43 (dd, *J*=17.3, 1.6 Hz, 1H), 5.28 (dd, *J*=10.7, 1.6 Hz, 1H), 4.10 (d, *J*=8.5 Hz, 1H), 3.88 (d, *J*=8.5 Hz, 1H), 3.67 (dt, *J*=9.0, 4.0 Hz, 1H), 2.42-2.35 (m, 1H), 2.35-2.33 (m, 1H), 2.12 (d, *J*=4.7 Hz, 1H), 1.47 (s, 3H), 1.42 (s, 3H), 1.12-1.00 (m, 4H).



3.58

3-Cyclopropylidene-1-(2,2-dimethyl-4-vinyl-1,3-dioxolan-4-yl)propan-1-one (3.58)

Dess-Martin periodinane (1.42 g, 3.34 mmol) was added to alcohol **3.55r** (0.500 g, 2.23 mmol) and $NaHCO_3$ (1.498 g, 17.83 mmol) in DCM (22 ml) at RT. The resulting mixture was stirred for 1 h (TLC control), quenched with sat. $NaHCO_3$ solution/sat. $Na_2S_2O_3$ solution (2:1), and extracted with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:8 → 1:4) afforded ketone **3.58** (0.448 g, 90%) as a colourless oil.

R_f = 0.60 (Et_2O/petroleum ether 1:2)

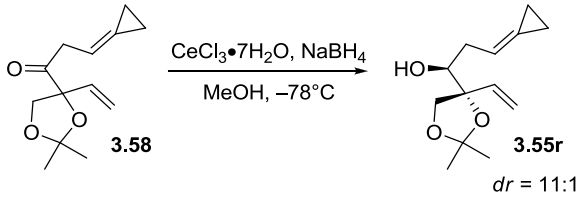
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dd, *J*=17.2, 10.7 Hz, 1H), 5.89-5.85 (m, 1H), 5.50 (dd, *J*=17.2, 1.1 Hz, 1H), 5.25 (dd, *J*=10.7, 1.1 Hz, 1H), 4.50 (d, *J*=8.8 Hz, 1H),

3.82 (d, *J*=8.7 Hz, 1H), 3.58 (ddquin, *J*=18.5, 6.8, 1.4 Hz, 1H), 3.50 (ddquin, *J*=18.5, 6.8, 1.4 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.13-1.08 (m, 2H), 1.01-0.97 (m, 2H).

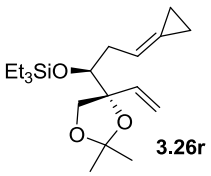
^{13}C NMR (125 MHz, $CDCl_3$) δ 209.85 (e), 136.05 (o), 126.18 (e), 116.33 (e), 111.43 (e), 110.25 (o), 89.89 (e), 71.56 (e), 40.45 (e), 26.47 (o), 25.95 (o), 3.07 (e), 1.80 (e).

IR (neat) 2986 (m), 1718 (s), 1373 (s), 1264 (m), 1215 (s), 1131 (m), 1061 (s), 1001 (s), 931 (s), 859 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{13}H_{18}O_3Na$ 245.1154, found 245.1145.



$CeCl_3$•$7H_2O$ (10.9 g, 29.2 mmol) and $NaBH_4$ (1.99 g, 52.6 mmol) were added to ketone **3.58** (3.25 g, 14.6 mmol) in MeOH (140 ml) at −78°C. After 20 min the reaction mixture was diluted with Et_2O, quenched with sat. NH_4Cl solution, and extracted with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Crude residue was dissolved in DCM, washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was used in the next step without further purification. Analytical sample of **3.55r** was obtained after purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:8 → 1:4 → 1:2 → 1:1).



((S*)-3-Cyclopropylidene-1-((R*)-2,2-dimethyl-4-vinyl-1,3-dioxolan-4-yl)propoxy)triethylsilane (3.26r)

TESOTf (0.60 ml, 2.7 mmol) was added to a solution of alcohol **3.55r** (0.400 g, 1.78

mmol) and 2,6-lutidine (0.62 ml, 5.4 mmol) in DCM (20 ml) at 0°C. The resulting mixture was stirred for 15 min, quenched with sat. $NaHCO_3$ solution, and extracted with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Two consecutive purifications by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:100) afforded silyl ether **3.26r** (0.507 g, 84%) as a colourless oil.

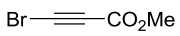
R_f = 0.60 (Et_2O/petroleum ether 1:40)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (dd, *J*=17.3, 10.9 Hz, 1H), 5.82-5.78 (m, 1H), 5.44 (dd, *J*=17.3, 2.1 Hz, 1H), 5.20 (dd, *J*=10.9, 2.1 Hz, 1H), 4.13 (d, *J*=8.6 Hz, 1H), 3.76 (dd, *J*=7.5, 3.8 Hz, 1H), 3.72 (d, *J*=8.6 Hz, 1H), 2.53-2.46 (m, 1H), 2.21-2.15 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.05-0.95 (m, 4H), 0.94 (t, *J*=7.9 Hz, 9H), 0.59 (q, *J*=8.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.21 (o), 123.11 (e), 116.11 (o), 114.89 (e), 109.99 (e), 86.28 (e), 76.73 (o), 72.31 (e), 35.70 (e), 27.35 (o), 26.39 (o), 7.09 (o), 5.46 (e), 2.63 (e), 1.87 (e).

IR (neat) 2955 (m), 2877 (m), 1458 (w), 1369 (m), 1213 (m), 1087 (s), 1003 (s), 926 (s), 866 (s), 725 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{19}H_{34}O_3NaSi$ 361.2175, found 361.2167.

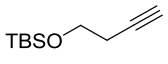


3.81

Methyl 3-bromopropiolate (3.81)[40]

3.81 was prepared in 77% yield from commercially available methyl propiolate, according to the procedure used by Ohwada *et al.* (2006).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H).



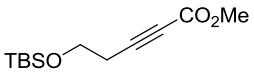
3.87

(But-3-ynyloxy)(tert-butyl)dimethylsilane (3.87)[41]

3.87 was prepared in 98% yield from commercially available 3-butyn-1-ol, according to the procedure used by Ley *et al.* (2010).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (t, *J*=7.2 Hz, 2H), 2.40 (td, *J*=7.2, 2.7 Hz, 2H), 1.96 (t, *J*=2.7 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H).

IR (neat) 3315 (w), 2930 (w), 2858 (w), 1472 (w), 1255 (m), 1101 (s), 834 (s), 774 (s) cm^{-1}.



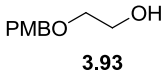
3.83

Methyl 5-(tert-butyldimethylsilyloxy)pent-2-ynoate (3.83)[41]

3.83 was prepared in 72% yield from **3.87**, according to the procedure used by Ley *et al.* (2010).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (t, *J*=7.0 Hz, 2H), 3.76 (s, 3H), 2.55 (t, *J*=6.9 Hz, 2H), 0.89 (s, 9H), 0.08 (s, 6H).

IR (neat) 2954 (w), 2857 (w), 2244 (w), 1716 (s), 1435 (w), 1248 (s), 1107 (s), 1074 (s), 835 (s) cm^{-1}.



3.93

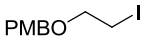
2-(4-Methoxybenzyloxy)ethanol (3.93)[42]

3.93 was prepared in 79% yield from commercially available ethyleneglycol, according to the procedure used by Waser *et al.* (2010).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 6.91-6.88 (m, 2H), 4.50 (s, 2H), 3.81 (s, 3H), 3.77-3.73 (m, 2H), 3.59-3.56 (m, 2H), 1.99 (t, *J*=6.2 Hz, 1H).

IR (neat) 3416 (br), 2933 (w), 2861 (w), 1611 (m), 1512 (s), 1245 (s), 1031 (s), 820

(m) cm^{-1}.



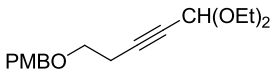
3.94

1-((2-Iodoethoxy)methyl)-4-methoxybenzene (3.94)[43]

3.94 was prepared in 94% yield from alcohol **3.93**, according to the procedure used by Brimble *et al.* (2009).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 6.91-6.87 (m, 2H), 4.51 (s, 2H), 3.81 (s, 3H), 3.71 (t, *J*=6.8 Hz, 2H), 3.26 (t, *J*=6.8 Hz, 2H).

IR (neat) 2834 (w), 1611 (m), 1511 (s), 1246 (s), 1172 (m), 1080 (m) 1033 (s), 820 (m) cm^{-1}.



3.92

1-((5,5-Diethoxypent-3-ynyloxy)methyl)-4-methoxybenzene (3.92)

n-BuLi (0.26 ml, 2.5 M in hexanes, 0.70 mmol) was added to 3,3-diethoxyprop-1-yne (86 µl, 0.60 mmol) in THF (6 ml) at −78°C, and the resulting mixture was stirred for 30 min before the addition of iodide **3.94** (0.175 g, 0.600 mmol) in HMPA (0.30 ml). The mixture was stirred at −78°C for 2 h and at −10°C for 2 h before being quenched with water and extracted with Et_2O. Combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:10 → 1:5 → 1:2) afforded alkyne **3.92** (0.090 g, 51%) as a colourless oil.

R_f = 0.20 (Et_2O/petroleum ether 1:10)

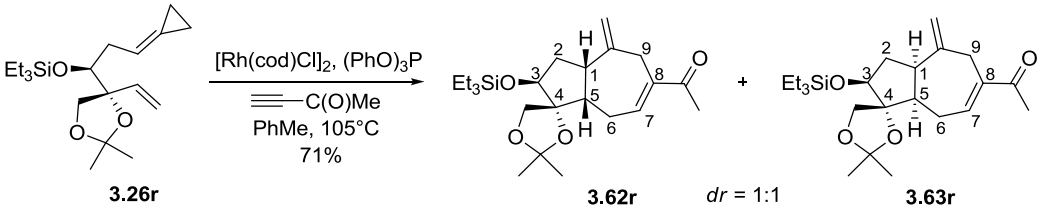
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 6.89-6.85 (m, 2H), 5.25 (t, *J*=1.6 Hz, 1H), 4.47 (s, 2H), 3.80 (s, 3H), 3.76-3.70 (m, 2H), 3.60-3.53 (m, 4H), 2.55 (td, *J*=7.2, 1.5 Hz, 2H), 1.22 (t, *J*=7.1 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.39 (e), 130.23 (e), 129.46 (o), 113.95 (o), 91.53

(o), 83.17 (e), 72.76 (e), 67.87 (e), 60.80 (e), 55.43 (o), 20.19 (e), 15.23 (o).

IR (neat) 2872 (w), 1721 (m), 1513 (m), 1246 (s), 1149 (m), 1083 (s), 1050 (s), 821 (m), 729 (m) cm^{-1}.

HRMS (CI, Ammonia, $[M+NH_4]^+$) calculated for $C_{17}H_{28}NO_4$ 310.2013, found 310.2015.



$P(OPh)_3$ (19 µl, 0.07 mmol) was added to the suspension of $[Rh(cod)Cl]_2$ (5.9 mg, 0.012 mmol) in PhMe (1 ml) and the resulting clear solution was stirred at 105°C for 5 min before the addition of ACP **3.26r** (0.068 g, 0.20 mmol) in PhMe (1 ml) and 3-butyn-2-one (47 µl, 0.60 mmol). After this the tube was sealed and the reaction mixture was stirred at 105°C for 5 h. The mixture was cooled to RT and applied directly on a column. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:16 → 1:8) afforded cycloadducts **3.62r** and **3.63r** in 1:1 ratio (0.058 g, 71% combined yield).

Analytical data for the undesired diastereomer:

1-((1R*,2S*,3aS*,8aS*)-2',2'-Dimethyl-4-methylene-2-(triethylsilyloxy)-3,3a,4,5,8,8a-hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6-yl)ethanone (3.62r)

R_f = 0.4 (Et_2O/petroleum ether 1:4)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (dd, *J*=8.6, 4.2 Hz, 1H, C7-**H**), 4.96 (s, 1H, =C**H_2**), 4.85 (s, 1H, =C**H_2**), 4.31 (d, *J*=8.8 Hz, 1H, C**H_2**O), 4.01 (dd, *J*=4.6, 2.0 Hz, 1H, C3-**H**), 3.66 (d, *J*=8.8 Hz, 1H, C**H_2**O), 3.32 (d, *J*=17.9 Hz, 1H, C9**H_2**), 3.02 (d, *J*=16.6 Hz, 1H, C9**H_2**), 3.02-2.97 (m, 1H, C1-**H**), 2.48-2.37 (m, 2H, C5-**H**, C6**H_2**),

2.29 (s, 3H, C(O)C**H$_3$**), 2.16-2.06 (m, 2H, C2**H$_2$**, C6**H$_2$**), 1.65 (ddd, *J*=13.1, 7.3, 1.9 Hz, 1H, C2**H$_2$**), 1.38 (s, 3H, C(C**H$_3$**)$_2$), 1.34 (s, 3H, C(C**H$_3$**)$_2$), 0.96 (t, *J*=7.9 Hz, 9H, SiCH$_2$C**H$_3$**), 0.61 (q, *J*=8.0 Hz, 6H, SiC**H$_2$**CH$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.50 (e), 146.20 (e), 142.78 (o), 140.84 (e), 112.11 (e), 109.77 (e), 92.19 (e), 76.57 (o), 68.20 (e), 46.25 (o), 44.22 (o), 38.15 (e), 35.49 (e), 27.30 (o), 26.46 (o), 25.61 (o), 24.26 (e), 6.96 (o), 5.02 (e).

IR (neat) 2953 (w), 2877 (w), 1666 (m), 1371 (m), 1238 (m), 1069 (s), 1007 (m), 887 (m), 726 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{23}H_{38}O_4SiNa$ 429.2437, found 429.2433.

Analytical data for the desired diastereomer:

1-((1R*,2S*,3aR*,8aR*)-2',2'-Dimethyl-4-methylene-2-(triethylsilyloxy)-3,3a,4,5,8,8a-hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6-yl)ethanone (3.63r)

R_f = 0.35 (Et_2O/petroleum ether 1:4)

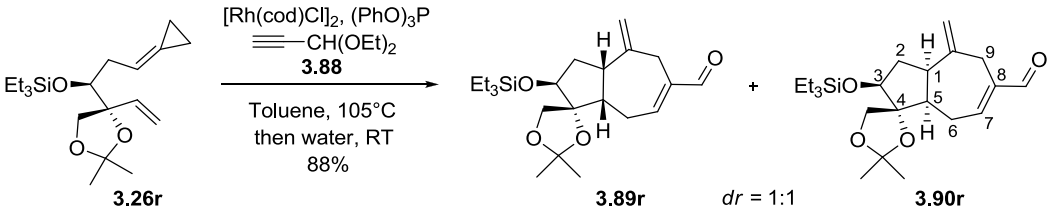
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, *J*=8.8, 4.4 Hz, 1H, C7-**H**), 4.96 (s, 1H, =C**H$_2$**), 4.79 (s, 1H, =C**H$_2$**), 4.22 (d, *J*=9.0 Hz, 1H, C**H$_2$**O), 4.07 (t, *J*=6.9 Hz, 1H, C3-**H**), 3.85 (d, *J*=8.9 Hz, 1H, C**H$_2$**O), 3.26 (d, *J*=16.9 Hz, 1H, C9**H$_2$**), 3.11 (d, *J*=16.8 Hz, 1H, C9**H$_2$**), 2.96 (q, *J*=9.1 Hz, 1H, C1-**H**), 2.58-2.50 (m, 1H, C6**H$_2$**), 2.30 (s, 3H, C(O)C**H$_3$**), 2.26-2.18 (m, 2H, C2**H$_2$**, C5-**H**), 2.08 (ddd, *J*=15.4, 8.8, 2.2 Hz, 1H, C6**H$_2$**), 1.64 (ddd, *J*=13.5, 10.4, 6.9 Hz, 1H, C2**H$_2$**), 1.39 (s, 6H, C(C**H$_3$**)$_2$), 0.97 (t, *J*=8.0 Hz, 9H, SiCH$_2$C**H$_3$**), 0.62 (q, *J*=8.0 Hz, 6H, SiC**H$_2$**CH$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.04 (e), 146.44 (e), 142.21 (o), 141.84 (e), 111.88 (e), 108.87 (e), 91.85 (e), 76.22 (o), 64.61 (e), 48.05 (o), 43.20 (o), 36.50 (e), 35.69 (e), 27.03 (o), 26.89 (o), 25.60 (o), 24.87 (e), 6.97 (o), 4.95 (e).

IR (neat) 2954 (w), 2877 (w), 1668 (s), 1373 (m), 1240 (s), 1136 (m), 1069 (s), 1007

(m), 860 (m), 727 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{23}H_{38}O_5SiNa$ 429.2437, found 429.2432.



$[Rh(cod)Cl]_2$ (0.139 g, 0.280 mmol) and $P(OPh)_3$ (0.44 ml, 1.7 mmol) were stirred in PhMe (50 ml) at 105°C for 5 min before the addition of ACP **3.26r** (1.594 g, 4.71 mmol) in PhMe (3 ml) and 3,3-diethoxyprop-1-yne (**3.88**) (2.03 ml, 14.1 mmol). The reaction mixture was stirred at 105°C for 6 h, additional portion of alkyne **3.88** (0.34 ml, 2.4 mmol) was added and the stirring continued for 1 h. Then water (1 ml) was added and the mixture was let to cool to RT. Additional amount of water (0.5 ml) was added and the mixture was stirred overnight. The solvent was largely removed *in vacuo* and the residue was applied directly on a column. Two consecutive purifications by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:20 → 1:10 → 1:5 and 1:10) afforded cycloadduct **3.90r** (0.818 g, 44%) as a yellow oil.

Analytical data for the undesired diastereomer:

(1R*,2S*,3aS*,8aS*)-2',2'-Dimethyl-4-methylene-2-(triethylsilyloxy)-3,3a,4,5,8,8a-hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6-carbaldehyde (3.89r)

R_f = 0.30 (Et_2O/petroleum ether 1:5)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (s, 1H), 6.80-6.77 (m, 1H), 4.99 (s, 1H), 4.90 (s, 1H), 4.31 (d, *J*=8.9 Hz, 1H), 4.02 (dd, *J*=4.6, 1.9 Hz, 1H), 3.67 (d, *J*=8.9 Hz, 1H), 3.27 (d, *J*=17.8 Hz, 1H), 3.02 (app. q, *J*=9.3 Hz, 1H), 2.94 (d, *J*=17.8 Hz, 1H), 2.54-2.43 (m, 2H), 2.77 (dd, *J*=13.8, 8.3 Hz, 1H), 2.11 (ddd, *J*=13.2, 10.7, 4.5 Hz, 1H), 1.68 (ddd, *J*=13.2, 7.4, 2.0 Hz, 1H), 1.38 (s, 3H), 1.34 (s, 3H), 0.96 (t, *J*=8.0 Hz, 9H),

0.61 (q, *J*=8.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 194.73 (o), 153.75 (o), 145.38 (e), 142.27 (e), 112.66 (e), 109.89 (e), 92.18 (e), 76.75 (o), 68.16 (e), 46.30 (o), 44.29 (o), 36.35 (e), 35.60 (e), 27.29 (o), 26.45 (o), 24.99 (e), 6.95 (o), 5.02 (e).

IR (neat) 2954 (m), 2876 (m), 1686 (s), 1645 (m), 1369 (m), 1236 (m), 1146 (m), 1072 (s), 1004 (m), 884 (m), 725 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{22}H_{36}O_4NaSi$ 415.2281, found 415.2269.

Analytical data for the desired diastereomer:

(1R*,2S*,3aR*,8aR*)-2',2'-Dimethyl-4-methylene-2-(triethylsilyloxy)-3,3a,4,5,8,8a-hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6-carbaldehyde (3.90r)

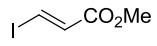
R_f = 0.25 (Et_2O/petroleum ether 1:5)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H, C**H**O), 6.73 (dd, *J*=8.5, 3.7 Hz, 1H, C7-**H**), 4.97 (s, 1H, =C**H$_2$**), 4.82 (s, 1H, =C**H$_2$**), 4.23 (d, *J*=9.0 Hz, 1H, C**H$_2$**O), 4.08 (t, *J*=6.7 Hz, 1H, C3-**H**), 3.86 (d, *J*=9.0 Hz, 1H, C**H$_2$**O), 3.26 (d, *J*=17.1 Hz, 1H, C9**H$_2$**), 3.01-2.96 (m, 1H, C1-**H**), 2.98 (d, *J*=18.0 Hz, 1H, C9**H$_2$**), 2.58 (app. t, *J*=14.9 Hz, 1H, C6**H$_2$**), 2.33-2.20 (m, 3H, C2**H$_2$**, C5-**H**, C6**H$_2$**), 1.65 (ddd, *J*=13.5, 10.4, 6.9 Hz, 1H, C2**H$_2$**), 1.40 (s, 3H, C(C**H$_3$**)$_2$), 1.39 (s, 3H, C(C**H$_3$**)$_2$), 0.97 (t, *J*=8.0 Hz, 9H, $SiCH_2C$**H$_3$**), 0.62 (q, *J*=8.0 Hz, 6H, SiC**H$_2$**CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 194.22 (o), 153.03 (o), 146.04 (e), 143.17 (e), 112.33 (e), 108.99 (e), 91.86 (e), 76.33 (o), 64.70 (e), 48.36 (o), 43.30 (o), 36.44 (e), 34.53 (e), 27.04 (o), 26.92 (o), 25.71 (e), 6.96 (o), 4.68 (e).

IR (neat) 2954 (m), 2876 (m), 1687 (s), 1644 (m), 1457 (w), 1369 (m), 1209 (m), 1135 (m), 1062 (s), 1006 (m), 861 (m), 745 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{22}H_{36}O_4NaSi$ 415.2281, found 415.2272.

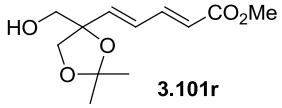


3.100

(E)-Methyl 3-iodoacrylate (3.100)[45]

3.100 was prepared in 86% yield from commercially available methyl propiolate, according to the procedure used by Goldring *et al.* (2009).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J*=14.9 Hz, 1H), 6.88 (d, *J*=14.9 Hz, 1H), 3.75 (s, 3H).



3.101r

(2E,4E)-Methyl 5-(4-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)penta-2,4-dienoate (3.101r)

AgOAc was handled in the darkness. The reaction was carried out with fumehood lights switched off.

$Pd(OAc)_2$ (17.0 mg, 0.0760 mmol) and AgOAc (0.430 g, 2.58 mmol) were suspended in MeCN (5 ml) and the mixture was degassed by one freeze-pump-thaw cycle. To this mixture was added alcohol **3.49** (0.240 g, 1.52 mmol) and (*E*)-methyl 3-iodoacrylate (**3.100**) (0.431 g, 2.03 mmol) in MeCN (5 ml). The mixture was degassed by two freeze-pump-thaw cycles, brought to 60°C and stirred for 11 h. The mixture was cooled to RT, filtered through a plug of Celite® (washed with Et_2O) and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:2 → 1:1) afforded diene **3.101r** (0.133 g, 36%) as a yellow oil.

R_f = 0.15 (Et_2O/petroleum ether 1:2)

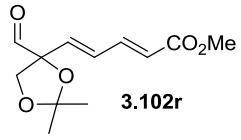
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (ddd, *J*=15.4, 11.2, 0.8 Hz, 1H), 6.51 (ddd, *J*=15.4, 11.1, 0.7 Hz, 1H), 6.14 (dt, *J*=15.4, 0.8 Hz, 1H), 5.93 (dt, *J*=15.4, 0.8 Hz, 1H), 4.10 (d, *J*=8.6 Hz, 1H), 3.88 (d, *J*=8.6 Hz, 1H), 3.75 (s, 3H), 3.62 (d, *J*=11.5 Hz,

1H), 3.55 (d, *J*=11.3 Hz, 1H), 1.85 (br s, 1H), 1.48 (s, 3H), 1.42 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.36 (e), 143.66 (o), 141.88 (o), 128.77 (o), 122.09 (o), 110.76 (e), 83.66 (e), 70.34 (e), 66.12 (e), 51.78 (o), 27.10 (o), 26.32 (o).

IR (neat) 3481 (w), 2989 (w), 1718 (s), 1646 (m), 1436 (w), 1254 (s), 1148 (s), 1058 (s), 1003 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{12}H_{18}O_5Na$ 265.1052, found 265.1046.



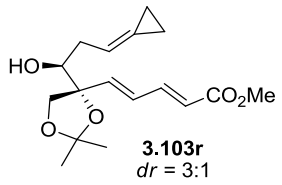
(2E,4E)-Methyl 5-(4-formyl-2,2-dimethyl-1,3-dioxolan-4-yl)penta-2,4-dienoate (3.102r)

Dess-Martin periodinane (0.347 g, 0.820 mmol) was added to alcohol **3.101r** (0.132 g, 0.550 mmol) and $NaHCO_3$ (0.320 g, 3.81 mmol) in DCM (5.5 ml) at RT. The reaction mixture was stirred for 2 h, quenched with sat. $NaHCO_3$ solution/sat. $Na_2S_2O_3$ solution (2:1), and extracted with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:1) afforded aldehyde **3.102r** (0.087 g, 66%) as a colourless oil.

R_f = 0.4 (Et_2O/petroleum ether 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (d, *J*=1.0 Hz, 1H), 7.28-7.23 (m, 1H), 6.56 (ddd, *J*=15.3, 11.2, 0.7 Hz, 1H), 6.04 (d, *J*=15.4 Hz, 1H), 5.97 (d, *J*=15.4 Hz, 1H), 4.46 (d, *J*=8.8 Hz, 1H), 3.83 (dd, *J*=8.9, 1.1 Hz, 1H), 3.76 (s, 3H), 1.50 (s, 3H), 1.47 (s, 3H).

IR (neat) 2989 (w), 1721 (s), 1645 (w), 1330 (w), 1240 (m), 1147 (m), 1059 (m), 1003 (m) cm^{-1}.



(2E,4E)-Methyl 5-((R*)-4-((S*)-3-cyclopropylidene-1-hydroxypropyl)-2,2-dimethyl-1,3-dioxolan-4-yl)penta-2,4-dienoate (3.103r)

$Pd(OAc)_2$ (8.0 mg, 0.036 mmol) and PPh_3 (23.0 mg, 0.0860 mmol) were dissolved in THF (3.6 ml). The flask was evacuated and backfilled with Ar. The mixture was stirred for 15 min before the addition of 1-vinylcyclopropyl tosylate (**3.54**) (0.102 g, 0.430 mmol) and aldehyde **3.102r** (0.086 g, 0.36 mmol). The reaction flask was placed in ice/water bath and Et_2Zn (0.72 ml 1.0 M in hexanes, 0.72 mmol) was added. Ice/water bath was removed and the reaction mixture was stirred at RT for 3 h. The reaction was quenched with sat. NH_4Cl solution and extracted with Et_2O. Combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:8 → 1:4) afforded a 3:1 mixture of ACP-diene **3.103r** and undesired diastereomer (0.058 g, 52%) as a yellow oil.

Only the data for the major diastereomer is reported.

R_f = 0.3 (Et_2O/petroleum ether 1:2)

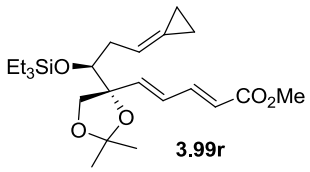
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (ddd, *J*=15.4, 11.2, 0.6 Hz, 1H), 6.55 (ddd, *J*=15.4, 11.2, 0.7 Hz, 1H), 6.28 (dt, *J*=15.3, 0.8 Hz, 1H), 5.93 (dt, *J*=15.4, 0.7 Hz, 1H), 5.81-5.77 (m, 1H), 4.27 (d, *J*=8.7 Hz, 1H), 3.86 (d, *J*=8.7 Hz, 1H), 3.76 (s, 3H), 3.76-3.75 (m, 1H), 2.53-2.48 (m, 1H), 2.14-2.06 (m, 1H), 2.02 (br s, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.13-1.02 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.55 (e), 144.08 (o), 141.78 (o), 128.58 (o), 125.53 (e), 121.49 (o), 114.26 (o), 110.49 (e), 85.32 (e), 74.64 (o), 70.88 (e), 51.79 (o),

34.46 (e), 27.06 (o), 26.42 (o), 2.98 (e), 2.23 (e).

IR (neat) 3434 (w), 2929 (m), 1720 (s), 1644 (m), 1371 (m), 1257 (s), 1145 (s), 1064 (s), 1004 (s), 825 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{17}H_{24}O_5Na$ 331.1521, found 331.1524.



3.99r

(2E,4E)-Methyl 5-((R*)-4-((S*)-3-cyclopropylidene-1-(triethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)penta-2,4-dienoate (3.99r)

TESOTf (74 µl, 0.33 mmol) was added to a solution of alcohol **3.103r** (0.067 g, 0.22 mmol) and 2,6-lutidine (76 µl, 0.65 mmol) in DCM (2 ml) at 0°C. The reaction mixture was brought to RT, stirred for 15 min, quenched with sat. $NaHCO_3$ and extracted with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:20) afforded silyl protected **3.99r** (0.062 g, 67%) as a colourless oil.

R_f = 0.2 (Et_2O/petroleum ether 1:20)

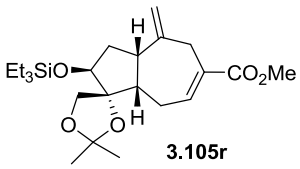
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J*=15.4, 11.2 Hz, 1H), 6.53 (dd, *J*=15.3, 11.2 Hz, 1H), 6.37 (d, *J*=15.4 Hz, 1H), 5.89 (d, *J*=15.4 Hz, 1H), 5.79-5.75 (m, 1H), 4.16 (d, *J*=8.7 Hz, 1H), 3.79 (dd, *J*=7.2, 4.1 Hz, 1H), 3.75 (s, 3H), 3.73 (d, *J*=8.8 Hz, 1H), 2.51-2.44 (m, 1H), 2.17 (dt, *J*=14.9, 7.8 Hz, 1H), 1.42 (s, 3H), 1.41 (s, 3H), 1.05-0.92 (m, 4H), 0.95 (t, *J*=7.9 Hz, 9H), 0.60 (q, *J*=8.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.70 (e), 144.63 (o), 142.36 (o), 127.73 (o), 123.56 (e), 120.69 (o), 115.69 (o), 110.46 (e), 86.08 (e), 76.83 (o), 72.33 (e), 51.68 (o), 35.85 (e), 27.29 (o), 26.31 (o), 7.07 (o), 5.47 (e), 2.68 (e), 1.90 (e).

IR (neat) 2953 (m), 2876 (m), 1721 (s), 1644 (m), 1370 (m), 1215 (m), 1107 (s),

1002 (s), 726 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{23}H_{38}O_5SiNa$ 445.2386, found 445.2377.



3.105r

(1R*,2S*,3aS*,8aS*)-Methyl 2',2'-dimethyl-4-methylene-2-(triethylsilyloxy)-3,3a,4,5,8,8a-hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6-carboxylate (3.105r)

$Rh(cod)_2SbF_6$ (12.0 mg, 0.0210 mmol) and tris(2,2,2-trifluoroethyl)phosphite (5 µl, 0.02 mmol) were stirred for 10 min at 110°C in PhMe (0.8 ml). ACP-diene **3.99r** (30.1 mg, 0.0710 mmol) in PhMe (1 ml) was added *via* syringe pump in a course of 2.5 h. After the end of addition the mixture was stirred at 110°C for 20 h, cooled to RT, and applied directly on a column. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:20 → 1:10 → 1:5) afforded [3+4] cycloadduct **3.104r** (9.2 mg, 30%), which was dissolved in THF (0.7 ml). To this solution was added DBN (18 µl, 0.15 mmol) and the resulting mixture was stirred at 57°C for 2 days. The reaction mixture was acidified with 0.1 M HCl and extracted with Et_2O. Combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:10 → 1:5) afforded isomerised product **3.105r** (4.2 mg, 47%) as a colourless oil.

R_f = 0.25 (Et_2O/petroleum ether 1:5)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (ddt, *J*=8.6, 4.6, 1.9 Hz, 1H), 5.00 (s, 1H), 4.87 (s, 1H), 4.28 (d, *J*=8.9 Hz, 1H), 4.00 (dd, *J*=4.6, 2.1 Hz, 1H), 3.72 (s, 3H), 3.64 (d, *J*=8.9 Hz, 1H), 3.35 (dt, *J*=17.9, 1.8 Hz, 1H), 3.07 (d, *J*=18.0 Hz, 1H), 3.00 (app. q, *J*=10.0 Hz, 1H), 2.46 (ddd, *J*=12.3, 10.1, 2.5 Hz, 1H), 2.38-2.31 (m, 1H), 2.14-2.03

(m, 2H), 1.65 (ddd, *J*=13.2, 7.2, 2.1 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H), 0.96 (t, *J*=7.9 Hz, 9H), 0.60 (q, *J*=8.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.32 (e), 145.86 (e), 141.38 (o), 131.02 (e), 112.26 (e), 109.79 (e), 92.21 (e), 76.59 (o), 68.07 (e), 51.91 (o), 46.28 (o), 44.06 (o), 39.82 (e), 35.51 (e), 27.37 (o), 26.41 (o), 23.84 (e), 6.96 (o), 5.04 (e).

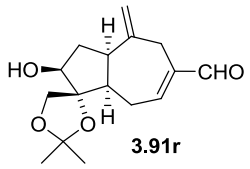
IR (neat) 2953 (m), 2876 (m), 1714 (s), 1434 (m), 1369 (m), 1237 (s), 1067 (s), 1005 (m), 893 (m), 743 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{23}H_{38}O_5SiNa$ 445.2386, found 445.2375.

Analytical data for the intermediate [3+4] product **3.104r**:

R_f = 0.30 (Et_2O/petroleum ether 1:5)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddd, *J*=10.8, 5.5, 2.3 Hz, 1H), 5.80 (ddd, *J*=10.8, 4.2, 1.7 Hz, 1H), 4.84 (s, 1H), 4.81 (d, *J*=1.1 Hz, 1H), 4.27 (d, *J*=8.9 Hz, 1H), 4.00 (d, *J*=4.0 Hz, 1H), 3.72 (s, 3H), 3.67 (d, *J*=8.9 Hz, 1H), 3.39-3.33 (m, 1H), 3.05 (dm, *J*=10.9 Hz, 1H), 2.97 (td, *J*=10.5, 7.5 Hz, 1H), 2.63 (dd, *J*=13.7, 6.3 Hz, 1H), 2.55 (dd, *J*=13.6, 11.7 Hz, 1H), 2.06 (ddd, *J*=13.3, 10.2, 4.1 Hz, 1H), 1.65 (ddd, *J*=13.2, 7.3, 1.0 Hz, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 0.97 (t, *J*=8.0 Hz, 9H), 0.62 (q, *J*=8.0 Hz, 6H).



3.91r

(1R*,2S*,3aR*,8aR*)-2-Hydroxy-2',2'-dimethyl-4-methylene-3,3a,4,5,8,8a-hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6-carbaldehyde (3.91r)

TBAF•$3H_2O$ (0.024 g, 0.076 mmol) was added to a solution of aldehyde **3.90r** (0.025 g, 0.064 mmol) in THF (0.60 ml) at RT. The reaction mixture was stirred for 10 min, quenched with sat. NH_4Cl solution, and extracted with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by

flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:4 → 1:2 → 1:1) afforded alcohol **3.91r** (0.009 g, 53%) as a colourless oil.

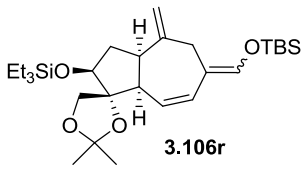
R_f = 0.15 (Et_2O/petroleum ether 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 6.75 (ddt, *J*=8.5, 4.1, 1.4 Hz, 1H), 5.01 (s, 1H), 4.86 (s, 1H), 4.23 (d, *J*=9.2 Hz, 1H), 4.16 (td, *J*=7.7, 2.4 Hz, 1H), 3.87 (d, *J*=9.2 Hz, 1H), 3.26 (d, *J*=17.5 Hz, 1H), 3.00 (d, *J*=17.9 Hz, 1H), 2.97 (q, *J*=9.3 Hz, 1H), 2.59-2.51 (m, 1H), 2.42 (ddd, *J*=12.6, 9.5, 2.5 Hz, 1H), 2.34-2.24 (m, 2H), 2.00 (d, *J*=3.5 Hz, 1H), 1.69 (ddd, *J*=13.6, 10.4, 8.3 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 194.22 (o), 152.35 (o), 145.52 (e), 143.05 (e), 112.56 (e), 108.81 (e), 91.14 (e), 76.38 (o), 64.42 (e), 47.84 (o), 42.20 (o), 35.14 (e), 34.70 (e), 27.05 (o), 26.88 (o), 25.22 (e).

IR (neat) 3461 (w), 2917 (w), 1681 (m), 1642 (w), 1265 (m), 1057 (m), 733 (s), 702 (m) cm^{-1}.

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



3.106r

tert-Butyl-((1R*,2S*,3aR*,8aR*)-2',2'-dimethyl-4-methylene-2-(triethylsilyloxy)-3,3a,4,5-tetrahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6(8aH)-ylidene)methoxy)dimethylsilane (3.106r)

LHMDS (8.3 ml 1.0 M in THF, 8.3 mmol) was added to a flask containing THF (35 ml) and cooled to −78°C. To this solution were added HMPA (6 ml) and TBS-Cl (8.3 ml 1.0 M in THF, 8.3 mmol). Finally, a solution of aldehyde **3.90r** (0.818 g, 2.08 mmol) in THF (3 ml) was added dropwise, and the resulting mixture was stirred at −78°C for 30 min. The reaction mixture was quenched with sat. $NaHCO_3$ and extracted with Et_2O. Combined organic extracts were washed with brine, dried over

Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:80 → 1:40) afforded silyl enol ether **3.106r** (1.024 g, 97%) as a colourless oil.

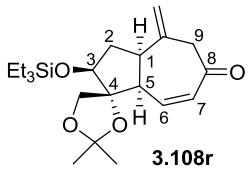
R_f = 0.4 (Et_2O/petroleum ether 1:40)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (s, 1H), 5.85 (dd, *J*=12.0, 2.2 Hz, 1H), 5.25 (dd, *J*=12.0, 4.8 Hz, 1H), 4.82 (s, 1H), 4.72 (t, *J*=1.7 Hz, 1H), 4.27 (d, *J*=8.5 Hz, 1H), 4.13 (t, *J*=7.5 Hz, 1H), 3.88 (d, *J*=8.5 Hz, 1H), 3.35 (d, *J*=14.4 Hz, 1H), 3.14 (app. q, *J*=9.0 Hz, 1H), 3.06-3.01 (m, 1H), 2.92 (dd, *J*=14.4, 1.5 Hz, 1H), 2.24 (dt, *J*=13.1, 7.6 Hz, 1H), 1.53-1.49 (m, 1H), 1.40 (s, 3H), 1.40 (s, 3H), 0.97 (t, *J*=8.0 Hz, 9H), 0.94 (s, 9H), 0.61 (q, *J*=7.9 Hz, 6H), 0.16 (s, 3H), 0.15 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.85 (e), 139.97 (o), 128.96 (o), 122.79 (o), 121.84 (e), 111.09 (e), 108.93 (e), 92.38 (e), 77.17 (o), 65.47 (e), 48.53 (o), 45.48 (o), 37.99 (e), 33.12 (e), 26.98 (o), 26.93 (o), 25.76 (o), 18.36 (e), 6.98 (o), 5.05 (e), −5.13 (o), −5.15 (o).

IR (neat) 2955 (w), 1638 (w), 1368 (w), 1252 (m), 1175 (m), 1060 (m), 1005 (w), 835 (s), 781 (m), 742 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{28}H_{50}O_4NaSi_2$ 529.3145, found 529.3151.



3.108r

(1R*,2S*,3aR*,8aR*)-2',2'-Dimethyl-4-methylene-2-(triethylsilyloxy)-3,3a,4,5-tetrahydro-2H-spiro[azulene-1,4'-[1,3]dioxolan]-6(8aH)-one (3.108r)

DMDO (0.1 M in acetone) was prepared according to the procedure used by Adam *et al.* (1991)[94]

DMDO (40.2 ml 0.1 M in acetone, 4.02 mmol) was added slowly to a solution of silyl enol ether **3.106r** (2.040 g, 4.020 mmol) in acetone (40 ml) at −78°. The

resulting mixture was stirred for 15 min and warmed to RT. Volatiles were removed *in vacuo* and the residue dissolved in MeCN/H_2O 4:1 (40 ml). To this solution $NaIO_4$ (1.718 g, 8.030 mmol) and HF•Pyridine complex (0.29 ml, 3.2 mmol) were added and the resulting mixture was stirred at RT for 2 h. Reaction mixture was diluted with H_2O and extracted with hexanes/Et_2O (2:1). Combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:8 → 1:4 → 1:2, then EtOAc/petroleum ether 2:1 → 1:1) afforded enone **3.108r** (0.665 g, 46%) and desilylated material (0.231 g, R_f = 0.05 (Et_2O/petroleum ether 1:2)), which was dissolved in DMF (9 ml) and treated with imidazole (0.137 g, 2.01 mmol) and TES-Cl (0.190 ml, 1.14 mmol) at 0°C. After being stirred at 0°C for 15 min and at RT for 3 h, the reaction mixture was quenched with H_2O and extracted with Et_2O. Combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:8 → 1:4 → 1:2) afforded enone **3.108r** (0.208 g, 63%), which was combined with the material obtained directly after oxidative cleavage to give 0.873 g of **3.108r** (57% combined yield from silyl enol ether **3.106r**) as a colourless oil.

R_f = 0.5 (Et_2O/petroleum ether 1:2)

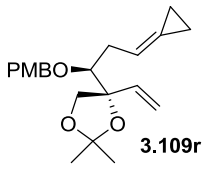
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (dd, *J*=12.2, 4.2 Hz, 1H, C6-**H**), 5.95 (dt, *J*=12.2, 2.1 Hz, 1H, C7-**H**), 5.02 (s, 1H, =C**H_2**), 4.89 (d, *J*=1.4 Hz, 1H, =C**H_2**), 4.38 (d, *J*=9.1 Hz, 1H, C**H_2**O), 4.16 (t, *J*=6.0 Hz, 1H, C3-**H**), 3.95 (d, *J*=9.1 Hz, 1H, C**H_2**O), 3.35 (d, *J*=15.2 Hz, 1H, C9**H_2**), 3.27 (app. q, *J*=9.2 Hz, 1H, C1-**H**), 3.22 (d, *J*=15.2 Hz, 1H, C9**H_2**), 3.06 (dt, *J*=7.8 Hz, 3.7 Hz, 1H, C5-**H**), 2.43 (ddd, *J*=13.6, 8.4, 7.0 Hz, 1H, C2**H_2**), 1.49 (ddd, *J*=13.8, 10.2, 5.3 Hz, 1H, C2**H_2**), 1.42 (s, 3H,

C(C**H$_3$**)$_2$), 1.41 (s, 3H, C(C**H$_3$**)$_2$), 0.96 (t, *J*=8.0 Hz, 9H, SiCH$_2$C**H$_3$**), 0.61 (q, *J*=7.9 H, 6H, SiC**H$_2$**CH$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.00 (e), 144.26 (o), 142.50 (e), 131.62 (o), 114.84 (e), 109.82 (e), 91.79 (e), 77.53 (o), 65.95 (e), 52.32 (e), 50.50 (o), 44.54 (o), 38.25 (e), 26.94 (o), 26.91 (o), 6.90 (o), 4.98 (e).

IR (neat) 2955 (m), 2877 (m), 1672 (s), 1370 (m), 1231 (m), 1213 (m), 1090 (s), 1058 (s), 1006 (s), 857 (m), 745 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{21}H_{34}O_4NaSi$ 401.2124, found 401.2131.



3.109r

(R*)-4-((S*)-3-Cyclopropylidene-1-(4-methoxybenzyloxy)propyl)-2,2-dimethyl-4-vinyl-1,3-dioxolane (3.109r)

Alcohol **3.55r** (0.200 g, 0.890 mmol) in DMF (2 ml) was added to NaH (0.0430 g 60% wt, 1.07 mmol) in DMF (4 ml) at 0°C. The resulting mixture was warmed to RT and stirred for 4 h. The reaction mixture was quenched with H_2O and extracted with Et_2O. Combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:80 → 1:40 → 1:20) afforded protected alcohol **3.109r** (0.234 g, 76%) as a colourless oil.

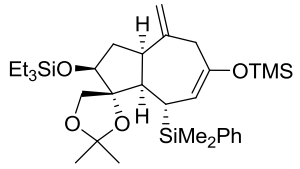
R_f = 0.5 (Et_2O/petroleum ether 1:10)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.20 (m, 2H), 6.88-6.84 (m, 2H), 6.04 (dd, *J*=17.3, 10.9 Hz, 1H), 5.90-5.85 (m, 1H), 5.46 (dd, *J*=17.2, 2.0 Hz, 1H), 5.20 (dd, *J*=10.8, 2.0 Hz, 1H), 4.60 (d, *J*=11.0 Hz, 1H), 4.51 (d, *J*=11.0 Hz, 1H), 4.12 (d, *J*=8.6 Hz, 1H), 3.80 (s, 3H), 3.78 (d, *J*=8.6 Hz, 1H), 3.53 (dd, *J*=8.0, 3.5 Hz, 1H), 2.58-2.51 (m, 1H), 2.34-2.26 (m, 1H), 1.43 (s, 3H), 1.41 (s, 3H), 1.07-0.96 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.23 (e), 137.82 (o), 131.02 (e), 129.29 (o), 123.17 (e), 115.89 (o), 115.09 (e), 113.82 (o), 110.06 (e), 85.95 (e), 82.90 (o), 73.53 (e), 71.86 (e), 55.41 (o), 33.61 (e), 27.15 (o), 26.50 (o), 2.74 (e), 1.93 (e).

IR (neat) 2983 (w), 2873 (w), 1612 (m), 1514 (s), 1370 (m), 1248 (s), 1082 (s), 1003 (m), 929 (m), 823 (m) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{221}H_{28}O_4Na$ 367.1885, found 367.1897.



3.117r

((1R*,2S*,3aR*,8S*,8aR*)-8-(Dimethyl(phenyl)silyl)-2',2'-dimethyl-4-methylene-2-(triethylsilyloxy)-3,3a,4,5,8,8a-hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6-yloxy)trimethylsilane (3.117r)

A 0.57 M solution of $PhMe_2SiLi$ in THF was prepared from commercially available $PhMe_2SiCl$, according to the procedure used by Fleming *et al.* (1998).[55]

$PhMe_2SiLi$ (0.19 ml 0.57 M in THF, 0.10 mmol) was added to CuCN (5.2 mg, 0.058 mmol) in THF (0.3 ml) at 0°C. The dark green mixture was cooled to −20°C and stirred for 15 min before the addition of a solution of enone **3.108r** (20.1 mg, 0.0520 mmol) and TMS-Cl (20 µl, 0.16 mmol) in THF (0.2 ml). The reaction mixture was stirred at −20°C for 40 min, diluted with pentane (2 ml), and washed successively with ice cold sat. $NaHCO_3/H_2O$ (1:1) solution, water and brine. Organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (Et_3N pretreated silica gel, eluting with diethyl ether/petroleum ether, 1:100 → 1:50) afforded silyl ether **3.117r** (31.2 mg, 100%) as a colourless oil.

R_f = 0.4 (Et_2O/petroleum ether 1:50)

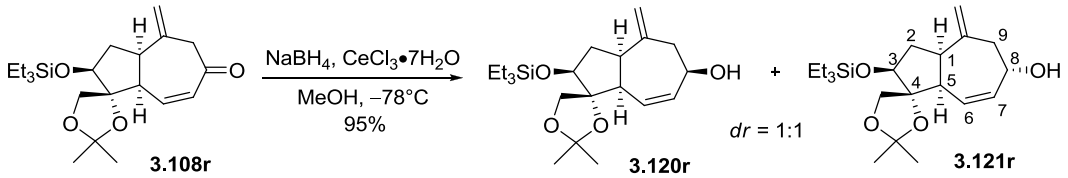
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65-7.61 (m, 2H), 7.26-7.18 (m, 3H), 5.16 (dd,

J=8.7, 1.0 Hz, 1H), 4.71 (s, 1H), 4.69 (d, *J*=8.4 Hz, 1H), 4.68 (s, 1H), 4.48 (d, *J*=8.4 Hz, 1H), 4.14 (dd, *J*=10.6, 6.6 Hz, 1H), 3.20 (d, *J*=17.6 Hz, 1H), 2.91 (d, *J*=17.6 Hz, 1H), 2.87 (td, *J*=11.0, 8.1 Hz, 1H), 2.65 (d, *J*=11.8 Hz, 1H), 2.51 (d, *J*=8.6 Hz, 1H), 1.84 (dt, *J*=12.7, 7.1 Hz, 1H), 1.62-1.55 (m, 1H), 1.52 (s, 3H), 1.50 (s, 3H), 1.01 (t, *J*=8.0 Hz, 9H), 0.63-0.57 (m, 6H), 0.43 (s, 3H), 0.42 (s, 3H), 0.15 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 184.88 (e), 146.76 (e), 145.31 (e), 134.00 (o), 129.01 (o), 127.87 (o), 116.11 (e), 108.72 (o), 107.79 (e), 93.26 (e), 76.39 (o), 64.20 (e), 48.28 (o), 42.49 (o), 41.40 (e), 38.00 (e), 27.60 (o), 26.54 (o), 23.67 (o), 7.04 (o), 5.16 (e), 0.66 (o), −2.08 (o), −2.18.

IR (neat) 2955 (m), 2877 (w), 1664 (w), 1368 (w), 1250 (m), 1151 (s), 1053 (m), 895 (m), 839 (s), 730 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{32}H_{54}O_4NaSi_3$ 609.3228, found 609.3226.



$CeCl_3$•$7H_2O$ (1.724 g, 4.630 mmol) and $NaBH_4$ (0.315 g, 8.33 mmol) were added to enone **3.108r** (0.876 g, 2.31 mmol) in MeOH (45 ml) at −78°C. After 20 min the reaction mixture was diluted with Et_2O, quenched with sat. NH_4Cl solution, and extracted with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Crude residue was dissolved in DCM, washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:2 → 1:1) afforded alcohols **3.120r** and **3.121r**, epimeric at C8, in 1:1 ratio (0.842 g, 95% combined yield).

Analytical data for the undesired epimer **3.120r**:

(1R*,2S*,3aR*,6R*,8aR*)-2',2'-Dimethyl-4-methylene-2-(triethylsilyloxy)-3,3a,4,5,6,8a-hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolan]-6-ol (3.120r)

R_f = 0.25 (Et_2O/petroleum ether 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (dt, *J*=11.8, 2.9 Hz, 1H), 5.47 (ddd, *J*=11.9, 3.7, 1.8 Hz, 1H), 4.91 (s, 1H), 4.83 (s, 1H), 4.44-4.38 (m, 1H), 4.31 (d, *J*=8.7 Hz, 1H), 4.10 (t, *J*=7.0 Hz, 1H), 3.88 (d, *J*=8.7 Hz, 1H), 3.05 (app. q, *J*=9.4 Hz, 1H), 2.86 (dq, *J*=9.0, 2.8 Hz, 1H), 2.71 (dd, *J*=13.3, 4.7 Hz, 1H), 2.41 (dd, *J*=13.3, 6.1 Hz, 1H), 2.23 (dt, *J*=13.2, 7.5 Hz, 1H), 1.85 (d, *J*=8.9 Hz, 1H), 1.48 (ddd, *J*=13.9, 11.1, 7.4 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 0.96 (t, *J*=8.0 Hz, 9H), 0.61 (q, *J*=8.1 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 146.16 (e), 133.04 (o), 126.70 (o), 112.81 (e), 109.25 (e), 91.67 (e), 68.94 (o), 65.70 (e), 48.28 (o), 44.86 (o), 42.71 (e), 37.33 (e), 26.96 (o), 26.93 (o), 6.95 (o), 5.00 (e).

IR (neat) 3410 (w), 2955 (m), 2877 (m), 1642 (w), 1457 (w), 1369 (m), 1213 (m), 1123 (m), 1058 (s), 1005 (s), 863 (m), 728 (s) cm^{-1}.

HRMS (CI (Ammonia), $[M+H]^+$) calculated for $C_{21}H_{33}O_4Si$ 377.2143, found 377.2155.

Analytical data for the desired epimer **3.121r**:

(1R*,2S*,3aR*,6S*,8aR*)-2',2'-Dimethyl-4-methylene-2-(triethylsilyloxy)-3,3a,4,5,6,8a-hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolan]-6-ol (3.121r)

R_f = 0.2 (Et_2O/petroleum ether 1:2)

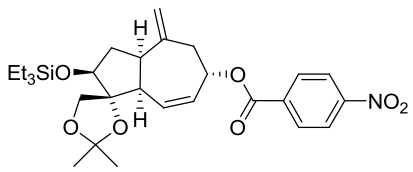
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (dddd, *J*=12.3, 3.9, 2.6, 1.2 Hz, 1H, C7-**H**), 5.57 (ddd, *J*=12.4, 4.1, 1.2 Hz, 1H, C6-**H**), 4.90 (s, 1H, =C**H$_2$**), 4.83 (s, 1H, =C**H$_2$**), 4.26 (d, *J*=8.5 Hz, 1H, C**H$_2$**O), 4.21-4.15 (m, 1H, C8-**H**), 4.12 (t, *J*=7.5 Hz, 1H, C3-**H**), 3.78 (d, *J*=8.5 Hz, 1H, C**H$_2$**O), 3.05 (app. q, *J*=9.3 Hz, 1H, C1-**H**), 2.98-2.94 (m, 1H, C5-**H**), 2.71 (dd, *J*=12.4, 5.4 Hz, 1H, C9**H$_2$**), 2.32 (dd, *J*=12.4, 9.0 Hz, 1H, C9**H$_2$**),

2.20 (dt, *J*=13.1, 7.5 Hz, 1H, C2**H$_2$**), 1.66 (d, *J*=7.5 Hz, 1H, **OH**), 1.45-1.34 (m, 1H, C2**H$_2$**), 1.40 (s, 3H, C(C**H$_3$**)$_2$), 1.40 (s, 3H, C(C**H$_3$**)$_2$), 0.96 (t, *J*=7.9 Hz, 9H, SiCH$_2$C**H$_3$**), 0.61 (q, *J*=8.2 Hz, 6H, SiC**H$_2$**CH$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.69 (e), 131.53 (o), 128.00 (o), 112.66 (e), 109.10 (e), 91.81 (e), 76.47 (o), 70.40 (o), 65.34 (e), 48.01 (o), 43.38 (o), 42.59 (e), 37.45 (e), 26.96 (o), 26.85 (o), 6.96 (o), 5.01 (e).

IR (neat) 3344 (w), 2954 (m), 2877 (m), 1641 (w), 1369 (m), 1212 (m), 1059 (s), 1010 (s), 861 (s), 802 (m), 728 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{21}H_{36}O_4NaSi$ 403.2281, found 403.2284.



4-Nitrobenzoate of **3.121r**

(1R*,2S*,3aR*,6S*,8aR*)-2',2'-Dimethyl-4-methylene-2-(triethylsilyloxy)-3,3a,4,5,6,8a-hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6-yl 4-nitrobenzoate

DEAD (0.51 ml, 3.2 mmol) was added to a solution of alcohol **3.120r** (0.421 g, 1.11 mmol), PPh_3 (0.841 g, 3.21 mmol) and 4-nitrobenzoic acid (0.444 g, 2.65 mmol) in PhMe (20 ml) at 0°C. The mixture was allowed to warm to RT and stirred overnight. Solvent was partially removed *in vacuo* and the concentrated solution was applied on a column. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:40 → 1:20 → 1:10) afforded 4-nitrobenzoate of **3.121r** (0.476 g, 81%) as a colourless oil.

R$_f$ = 0.5 (Et_2O/petroleum ether 1:5)

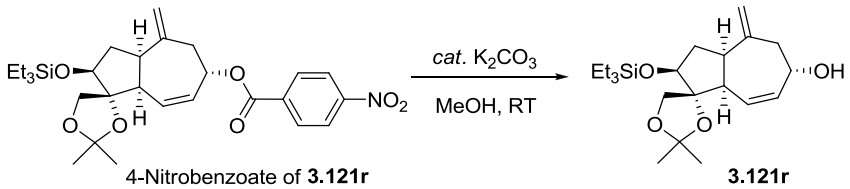
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30-8.27 (m, 2H), 8.23-8.20 (m, 2H), 5.79 (dd, *J*=12.3, 3.2 Hz, 1H), 5.73 (dddd, *J*=12.3, 3.9, 2.4, 1.0 Hz, 1H), 5.54-5.49 (m, 1H),

5.05 (s, 1H), 4.92 (s, 1H), 4.29 (d, *J*=8.7 Hz, 1H), 4.15 (t, *J*=7.2 Hz, 1H), 3.84 (d, *J*=8.7 Hz, 1H), 3.13 (app. q, *J*=9.4 Hz, 1H), 3.05-3.01 (m, 1H), 2.88 (dd, *J*=12.6, 5.9 Hz, 1H), 2.57 (dd, *J*=12.6, 9.4 Hz, 1H), 2.28 (dt, *J*=13.3, 7.9 Hz, 1H), 1.50-1.44 (m, 1H), 1.42 (s, 3H), 1.41 (s, 3H), 0.97 (t, *J*=8.0 Hz, 1H), 0.62 (q, *J*=7.9 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.16 (e), 150.69 (e), 144.61 (e), 136.06 (e), 131.42 (o), 130.91 (o), 126.81 (o), 123.86 (o), 113.67 (e), 109.27 (e), 91.64 (e), 76.64 (o), 73.97 (o), 65.49 (e), 48.08 (o), 43.18 (o), 39.57 (e), 37.18 (e), 27.02 (o), 26.83 (o), 6.95 (o), 5.02 (e).

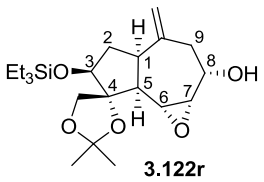
IR (neat) 2955 (w), 1721 (s), 1528 (s), 1339 (m), 1266 (s), 1099 (s), 1059 (m), 946 (m), 857 (m), 718 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{28}H_{39}NO_7SiNa$ 552.2394, found 552.2413.



4-Nitrobenzoate of **3.121r** **3.121r**

K_2CO_3 (0.025 g, 0.18 mmol) was added to 4-nitrobenzoate of **3.121r** (0.476 g, 0.900 mmol) in MeOH (10 ml) at RT. The reaction mixture was stirred for 2 h, diluted with Et_2O, quenched with sat. NH_4Cl solution, and extracted with Et_2O. Combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:4 → 1:2 → 1:1) afforded alcohol **3.121r** (0.253 g, 74%) as a colourless oil.



3.122r

(1aS*,2S*,4aR*,4'R*,6S*,7aS*,7bR*)-2',2'-Dimethyl-4-methylene-6-(triethylsilyloxy)octahydro-1aH-spiro[azuleno[4,5-b]oxirene-7,4'-[1,3]dioxolan]-2-ol (3.122r)

$VO(acac)_2$ (0.037 g, 0.14 mmol) was added to alcohol **3.121r** (0.670 g, 1.76 mmol) in DCM (35 ml) at RT. After 5 min the mixture was cooled to −25°C and stirred at this temperature for 15 min before the addition of ^{t}BuOOH (0.51 ml 5.5 M in nonane, 2.8 mmol). Resulting deep violet solution was stirred at −25°C overnight whereupon the colour changes to brown and TLC shows full consumption of the starting material. The mixture was allowed to warm to RT, stirred for 20 min, quenched with sat. Na_2SO_3 solution and extracted with Et_2O. Combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:4 → 1:2 → 1:1) afforded epoxyalcohol **3.122r** (0.634 g, 91%) as a colourless oil.

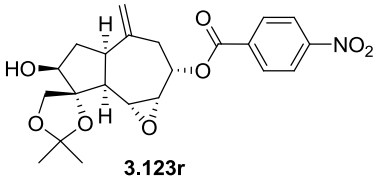
R_f = 0.35 (Et_2O/petroleum ether 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (s, 1H, =C**H_2**), 4.87 (s, 1H, =C**H_2**), 4.34 (d, *J*=9.0 Hz, 1H, C**H_2**O), 4.20-4.15 (m, 2H, C3-**H**, C8-**H**), 3.96 (d, *J*=9.0 Hz, 1H, C**H_2**O), 3.28 (app. t, *J*=4.4 Hz, 1H, C6-**H**), 3.24 (app. t, *J*=4.1 Hz, 1H, C7-**H**), 2.95 (app. q, *J*=8.9 Hz, 1H, C1-**H**), 2.58 (dd, *J*=13.4, 5.2 Hz, 1H, C9**H_2**), 2.53 (dd, *J*=8.8, 4.3 Hz, 1H, C5-**H**), 2.30-2.21 (m, 2H, C9**H_2**, C2**H_2**), 2.03 (d, *J*=6.2 Hz, 1H, O**H**), 1.52-1.49 (m, 1H, C2**H_2**), 1.43 (s, 3H, C(C**H_3**)$_2$), 1.40 (s, 3H, C(C**H_3**)$_2$), 0.97 (t, *J*=7.9 Hz, 9H, $SiCH_2C$**H_3**), 0.62 (q, *J*=7.9 Hz, 6H, SiC**H_2**CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.27 (e), 113.31 (e), 109.27 (e), 91.00 (e), 77.00 (o), 68.52 (o), 65.53 (e), 57.55 (o), 55.98 (o), 48.91 (o), 42.12 (o), 40.78 (e), 37.11 (e), 26.87 (o), 26.75 (o), 6.94 (o), 4.98 (e).

IR (neat) 3429 (w), 2954 (m), 2876 (m), 1639 (w), 1457 (m), 1396 (m), 1211 (m), 1052 (s), 1016 (s), 895 (m), 728 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{21}H_{36}O_5NaSi$ 419.2230, found 419.2218.



3.123r

(1aS*,2S*,4aR*,4'R*,6S*,7aS*,7bR*)-6-Hydroxy-2',2'-dimethyl-4-methyleneoctahydro-1aH-spiro[azuleno[4,5-b]oxirene-7,4'-[1,3]dioxolane]-2-yl 4-nitrobenzoate (3.123r)

4-Nitrobenzoyl chloride (10.3 mg, 0.0550 mmol) and DMAP (0.7 mg, 0.006 mmol) were added to a solution of epoxyalcohol **3.122r** (11.2 mg, 0.0280 mmol) and Et_3N (14 µl, 0.10 mmol) in DCM (0.3 ml) at RT. The reaction mixture was stirred overnight, quenched with H_2O and extracted with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:10 → 1:5 → 1:2) afforded 4-nitrobenzoate of **3.122r** (15.0 mg, 99%) as a colourless oil. This material was dissolved in THF (0.5 ml) and cooled to 0°C before the addition of TBAF (41 µl, 0.040 mmol). The resulting mixture was stirred for 1 h at RT, quenched with sat. NH_4Cl and extracted with Et_2O. Combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:4 → 1:2 → 1:1) afforded deprotected alcohol **3.123r** (8.5 mg, 72%) as a colourless oil.

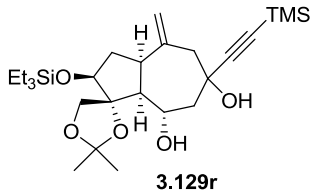
R_f = 0.2 (Et_2O/petroleum ether 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32-8.25 (m, 4H), 5.44 (ddd, *J*=11.1, 4.7, 1.8 Hz, 1H), 5.21 (s, 1H), 5.19 (s, 1H), 4.35 (d, *J*=9.2 Hz, 1H), 4.30 (dd, *J*=9.5, 4.9 Hz, 1H), 3.7 (d, *J*=9.2 Hz, 1H), 3.43 (dt, *J*=4.4, 1.8 Hz, 1H), 3.32 (dd, *J*=4.3, 3.7 Hz, 1H), 3.05 (dd, *J*=7.9, 3.7 Hz, 1H), 2.86-2.80 (m, 1H), 2.62 (dd, *J*=12.2, 4.6 Hz, 1H), 2.44-2.35 (m, 2H), 1.75 (dt, *J*=14.8, 4.8 Hz, 1H), 1.45 (s, 3H), 1.38 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.15 (e), 150.87 (e), 143.59 (e), 135.47 (e), 131.10 (o), 123.75 (o), 116.41 (e), 108.15 (e), 90.51 (e), 78.06 (o), 75.04 (o), 65.15 (e), 57.48 (o), 54.83 (o), 48.28 (o), 42.63 (o), 37.39 (e), 34.88 (e), 27.24 (o), 26.23 (o).

IR (neat) 3423 (w), 2983 (w), 2927 (w), 1722 (m), 1527 (m), 1348 (w), 1273 (s), 1101 (s), 908 (m), 721 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{22}H_{25}NO_8Na$ 454.1478, found 454.1475.



3.129r

(1R*,2S*,3aR*,8S*,8aS*)-2',2'-Dimethyl-4-methylene-2-(triethylsilyloxy)-6-((trimethylsilyl)ethynyl)octahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6,8-diol (3.129r)

n-BuLi (0.100 ml 2.5 M in THF, 0.250 mmol) was added to trimethylsilylacetylene (35 µl, 0.25 mmol) in THF (0.25 ml) at −78°C. The resulting mixture was stirred for 15 min before the addition of the solution of hydroxyepoxide **3.122r** (10.0 mg, 0.0250 mmol) in THF (0.2 ml) and BF_3•OEt_2 (38 µl, 0.30 mmol). After being stirred for 1 h at −78°C the reaction mixture was warmed to −30°C and stirred for additional 1 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution and extracted with Et_2O. Combined organic extracts were washed with brine, dried over Na_2SO_4

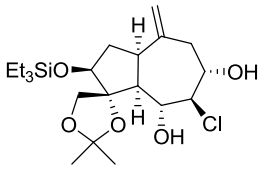
and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:4) afforded tertiary alcohol **3.129r** (3.2 mg, 25%) as a colourless oil.

R_f = 0.3 (EtOAc/petroleum ether 1:4)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.92 (s, 1H), 4.23 (d, *J*=9.1 Hz, 1H), 4.09 (dd, *J*=8.3, 7.4 Hz, 1H), 4.00 (d, *J*=9.1 Hz, 1H), 3.94 (t, *J*=10.0 Hz, 1H), 3.09 (d, *J*=1.9 Hz, 1H), 2.85 (q, *J*=9.4 Hz, 1H), 2.66 (dd, *J*=12.2, 2.2 Hz, 1H), 2.28-2.22 (m, 2H), 2.19-2.09 (m, 3H), 2.02 (dd, *J*=13.0, 10.3 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 0.98 (t, *J*=8.0 Hz, 9H), 0.63 (q, *J*=8.0 Hz, 6H), 0.17 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.66 (e), 115.70 (e), 108.53 (e), 107.80 (e), 91.55 (e), 90.80 (e), 75.07 (o), 69.68 (e), 67.02 (o), 64.16 (e), 53.89 (o), 52.70 (e), 51.18 (e), 39.75 (o), 35.35 (e), 26.70 (o), 26.42 (o), 6.94 (o), 5.02 (e), 0.04 (o).

HRMS (ESI, $[M+Na]^+$) calculated for $C_{26}H_{46}O_5NaSi_2$ 517.2782, found 517.2784.



3.136r

(1R*,2S*,3aR*,6S*,7R*,8R*,8aS*)-7-Chloro-2',2'-dimethyl-4-methylene-2-(triethylsilyloxy)octahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6,8-diol (3.136r)

n-BuLi (44 µl 2.5 M in THF, 0.11 mmol) was added to *i*-Pr_2NH (16 µl, 0.11 mmol) in THF (0.15 ml) at −78°C. The resulting mixture was briefly warmed to 0°C and cooled back to −78°C. ^{t}BuOAc (14 µl, 0.11 mmol) was added and the mixture stirred for 30 min before being warmed to −40°C. Et_2AlCl (0.110 ml 1.0 M in hexanes, 0.110 mmol) was added, and the mixture was stirred for 15 min before the addition of the solution of hydroxyepoxide **3.122r** (3.1 mg, 0.0080 mmol) in THF (0.15 ml). The reaction mixture was stirred 45 min at −40°C and overnight at RT. The reaction

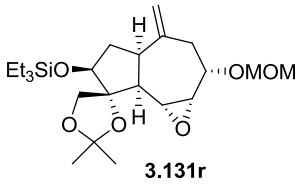
mixture was quenched with sat. NH_4Cl solution and extracted with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:8 → 1:4 → 1:2) afforded chloride **3.136r** (1.0 mg, 30%) as a colourless oil.

R_f = 0.40 (EtOAc/petroleum ether 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.83 (s, 1H), 4.57 (d, *J*=6.4 Hz, 1H), 4.39 (d, *J*=9.9 Hz, 1H), 4.28 (dd, *J*=10.9, 6.5 Hz, 1H), 4.18 (d, *J*=9.9 Hz, 1H), 4.16-4.10 (m, 2H), 3.16 (d, *J*=10.0 Hz, 1H), 2.84-2.76 (m, 1H), 2.62 (br s, 1H), 2.47-2.37 (m, 2H), 2.09 (dt, *J*=11.9, 5.9 Hz, 1H), 1.97 (br s, 1H), 1.84 (dt, *J*=13.0, 11.4 Hz, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 0.98 (t, *J*=8.0 Hz, 9H), 0.63 (q, *J*=8.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.26 (e), 112.92 (e), 107.97 (e), 92.68 (e), 77.23 (o), 73.78 (o), 71.82 (o), 65.62 (e), 59.42 (o), 45.84 (o), 42.34 (o), 29.28 (e), 38.14 (e), 27.48 (o), 26.59 (o), 6.98 (o), 5.05 (e).

MS (ESI, $[M+Na]^+$) calculated for $C_{21}H_{37}O_5SiCl(35)$ 455.2, found 455.2; calculated for $C_{21}H_{37}O_5SiCl(37)$ 457.2, found 457.2.



3.131r

Triethyl((1aS*,2S*,4aR*,4'R*,6S*,7aS*,7bR*)-2-(methoxymethoxy)-2',2'-dimethyl-4-methyleneoctahydro-1aH-spiro[azuleno[4,5-b]oxirene-7,4'-[1,3]dioxolane]-6-yloxy)silane (3.131r)

MOM-Cl (21 µl, 0.28 mmol) was added to a solution of hydroxyepoxide **3.122r** (22.0 mg, 0.0550 mmol) and DIPEA (68 µl, 0.39 mmol) in DCM (0.6 ml) at 0°C. The mixture was stirred at RT overnight, quenched with brine and extracted with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*.

Purification by flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:8 → 1:4 → 1:2) afforded MOM ether **3.131r** (13.6 mg, 57%) as a colourless oil.

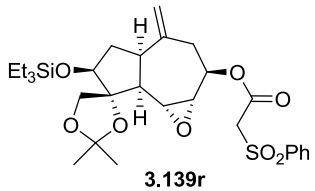
R_f = 0.70 (Et_2O/petroleum ether 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.91 (s, 1H), 4.78 (d, *J*=7.1 Hz, 1H), 4.77 (d, *J*=7.1 Hz, 1H), 4.32 (d, *J*=9.1 Hz, 1H), 4.21 (dd, *J*=8.1, 5.2 Hz, 1H), 4.03 (ddd, *J*=10.7, 5.1, 2.9 Hz, 1H), 3.89 (d, *J*=9.1 Hz, 1H), 3.43 (s, 3H), 3.28-3.25 (m, 1H), 3.21 (t, *J*=4.2 Hz, 1H), 2.87 (app. q, *J*=8.1 Hz, 1H), 2.68 (dd, *J*=8.0, 3.9 Hz, 1H), 2.51 (dd, *J*=12.5, 5.1 Hz, 1H), 2.33 (dt, *J*=14.1, 8.4 Hz, 1H), 2.20 (app. t, *J*=11.6 Hz, 1H), 1.52 (ddd, *J*=13.9, 7.6, 5.5 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 0.97 (t, *J*=7.9 Hz, 9H), 0.62 (q, *J*=7.9 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.41 (e), 113.95 (e), 108.88 (e), 95.77 (e), 91.14 (e), 77.65 (o), 76.29 (o), 65.54 (e), 57.50 (o), 55.72 (o), 55.24 (o), 49.38 (o), 42.97 (o), 38.02 (e), 37.32 (e), 26.78 (o), 26.65 (o), 6.96 (o), 5.00 (e).

IR (neat) 2954 (w), 2878 (w), 1370 (w), 1212 (w), 1148 (m), 1097 (m), 1033 (s), 893 (m), 727 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{23}H_{40}O_6NaSi$ 463.2492, found 463.2496.



3.139r

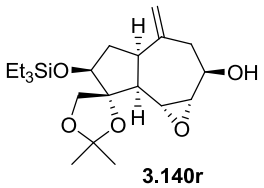
(1aS*,2R*,4aR*,4'R*,6S*,7aS*,7bR*)-2',2'-Dimethyl-4-methylene-6-(triethylsilyloxy)octahydro-1aH-spiro[azuleno[4,5-b]oxirene-7,4'-[1,3]dioxolane]-2-yl 2-(phenylsulfonyl)acetate (3.139r)

DEAD (6 µl, 0.04 mmol) was added to a solution of hydroxyepoxide **3.122r** (5.4 mg, 0.014 mmol), PPh_3 (10.4 mg, 0.0390 mmol) and 2-(phenylsulfonyl)acetic acid (6.5

mg, 0.033 mmol) in PhMe (0.27 ml) at 0°C. The mixture was stirred at RT overnight and applied directly on a column. Purification by flash chromatography (silica gel, eluting with Et_2O/petroleum ether, 1:40 → 1:20 → 1:10) afforded ester **3.139r** (4.0 mg, 51%) as a colourless oil.

R_f = 0.50 (Et_2O/petroleum ether 1:10)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.95 (m, 2H), 7.72-7.68 (m, 1H), 7.62-7.58 (m, 2H), 4.97 (s, 1H), 4.92 (s, 1H), 4.79 (dt, *J*=10.0, 6.9 Hz, 1H), 4.34 (d, *J*=9.1 Hz, 1H), 4.19 (d, *J*=14.0 Hz, 1H), 4.14 (d, *J*=14.0 Hz, 1H), 4.07 (t, *J*=6.0 Hz, 1H), 4.00 (d, *J*=9.1 Hz, 1H), 3.16 (dd, *J*=6.3, 5.0 Hz, 1H), 2.99 (dd, *J*=6.8, 5.0 Hz, 1H), 2.86 (q, *J*=9.1 Hz, 1H), 2.73 (dd, *J*=14.3, 6.9 Hz, 1H), 2.39 (dd, *J*=14.3, 10.0 Hz, 1H), 2.17-2.10 (m, 2H), 1.68 (ddd, *J*=13.9, 8.3, 5.8 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 0.97 (t, *J*=7.9 Hz, 9H), 0.62 (q, *J*=7.9 Hz, 6H).



3.140r

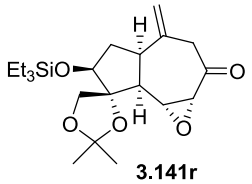
(1aS,2R,4aR,4'R,6S,7aS,7bR)-2',2'-Dimethyl-4-methylene-6-(triethylsilyloxy)octahydro-1aH-spiro[azuleno[4,5-b]oxirene-7,4'-[1,3]dioxolan]-2-ol (3.140r)

Ester **3.139r** (4.0 mg, 0.0070 mmol) in THF (0.1 ml) was added to LDA (0.17 ml 0.48 M in THF, 0.080 mmol) at −78°C and the resulting mixture was gradually warmed to 0°C (3 h), and quenched with sat. NH_4Cl solution. The mixture was extracted with Et_2O and combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford deacylated **3.140r** (2.1 mg, 77%) as a colourless oil.

R_f = 0.35 (EtOAc/petroleum ether 1:3)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.91 (d, *J*=1.1 Hz, 1H), 4.35 (d, *J*=9.1

Hz, 1H), 4.09 (t, *J*=6.4 Hz, 1H), 4.00 (d, *J*=9.1 Hz, 1H), 3.88 (dt, *J*=9.6, 6.2 Hz, 1H), 3.14 (app. t, *J*=5.3 Hz, 1H), 3.00 (dd, *J*=6.0, 5.0 Hz, 1H), 2.84 (q, *J*=9.1 Hz, 1H), 2.64 (dd, *J*=14.2, 6.0 Hz, 1H), 2.47 (dd, *J*=14.2, 9.6 Hz, 1H), 2.19 (dd, *J*=9.7, 5.6 Hz, 1H), 2.15 (ddd, *J*=14.3, 8.0, 5.5 Hz, 1H), 1.65 (ddd, *J*=13.7,8.9, 6.4 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 0.97 (t, *J*=7.9 Hz, 9H), 0.63 (q, *J*=8.0 Hz, 6H).



3.141r

(1aR*,4aR*,4'R*,6S*,7aS*,7bR*)-2',2'-Dimethyl-4-methylene-6-(triethylsilyloxy)hexahydro-1aH-spiro[azuleno[4,5-b]oxirene-7,4'-[1,3]dioxolan]-2(3H)-one (3.141r)

Dess-Martin periodinane (0.969 g, 2.28 mmol) was added to hydroxyepoxide **3.122r** (0.604 g, 1.52 mmol) and $NaHCO_3$ (0.640 g, 7.61 mmol) in DCM (15 ml) at RT. The resulting mixture was stirred for 1 h (TLC control), quenched with sat. $NaHCO_3$ solution/sat. $Na_2S_2O_3$ solution (2:1), and extracted with Et_2O. Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:8 → 1:4) afforded epoxiketone **3.141r** (0.508 g, 85%) as a colourless oil.

R_f = 0.70 (Et_2O/petroleum ether 1:2)

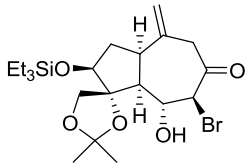
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (s, 1H), 5.02 (s, 1H), 4.27 (d, *J*=9.3 Hz, 1H), 4.15 (dd, *J*=7.3, 4.2 Hz, 1H), 3.85 (d, *J*=9.3 Hz, 1H), 3.43 (d, *J*=4.7 Hz, 1H), 3.40-3.35 (m, 2H), 3.23 (d, *J*=15.6Hz, 1H), 3.05 (app. q, *J*=8.4 Hz, 1H), 2.73 (dd, *J*=8.1, 3.8 Hz, 1H), 2.28 (ddd, *J*= 14.3, 9.1, 7.4, 1H), 1.53 (ddd, *J*=14.2, 7.9, 4.1 Hz, 1H), 1.38 (s, 6H), 0.96 (t, *J*=8.0 Hz, 9H), 0.62 (q, *J*=8.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 204.87 (e), 139.96 (e), 116.28 (e), 109.09 (e), 91.24

(e), 77.14 (o), 65.21 (e), 59.66 (o), 56.17 (o), 50.18 (o), 48.61 (e), 43.41 (o), 37.03 (e), 26.85 (o), 26.65 (o), 6.95 (o), 4.84 (e).

IR (neat) 2954 (m), 2877 (m), 1705 (s), 1458 (w), 1370 (m), 1242 (m), 1055 (s), 1007 (m), 862 (s), 729 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{21}H_{34}O_5NaSi$ 417.2073, found 417.2067.



3.142r

(1R*,2S*,3aR*,7S*,8R*,8aS*)-7-bromo-8-hydroxy-2',2'-dimethyl-4-methylene-2-(triethylsilyloxy)hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolan]-6(7H)-one (3.142r)

$MgBr_2$•OEt_2 (0.089 g, 0.35 mmol) was suspended in MeCN (1.5 ml) at RT. To this solution was added epoxiketone **3.141r** (0.055 g, 0.14 mmol) in MeCN (1.5 ml), and the resulting mixture was stirred at RT for 2 h. Then additional $MgBr_2$•OEt_2 (0.036 g, 0.14 mmol) was added and the mixture stirred at RT for 1.5 h and at 50°C for 30 min. After the mixture was cooled to RT, brine was added, and the resulting mixture was extracted with EtOAc. Combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:8 → 1:4 → 1:2) afforded bromohydrin **3.142r** (0.053 g, 80%) as a colourless oil.

$\mathbf{R_f}$ = 0.65 (Et_2O/petroleum ether 1:2)

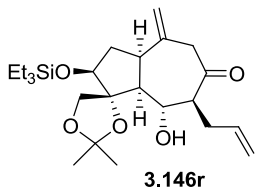
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (s, 1H), 5.10 (s, 1H), 4.31 (ddd, *J*=11.2, 8.5, 2.6 Hz, 1H), 4.29 (d, *J*=9.6 Hz, 1H), 4.19 (dd, *J*=8.5, 1.5 Hz, 1H), 4.05 (t, *J*=6.9 Hz, 1H), 4.02 (d, *J*=9.6 Hz, 1H), 3.94 (d, *J*=16.7 Hz, 1H), 3.36 (d, *J*=2.8 Hz, 1H), 3.15 (dm, *J*=16.0 Hz, 1H), 2.90 (q, *J*=9.2 Hz, 1H), 2.16 (dd, *J*=10.9, 9.5 Hz, 1H), 2.12 (ddd,

J=13.7, 8.6, 6.6 Hz, 1H), 1.59 (ddd, *J*=13.7, 10.0, 7.5 Hz, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 0.98 (t, *J*=8.0 Hz, 9H), 0.64 (q, *J*=7.9 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.12 (e), 140.08 (e), 115.80 (e), 108.90 (e), 91.59 (e), 75.01 (o), 72.60 (o), 64.49 (e), 59.53 (o), 51.49 (o), 47.58 (e), 40.38 (o), 34.86 (e), 26.89 (o), 26.00 (o), 6.88 (o), 4.94 (e).

IR (neat) 3457 (w), 2955 (m), 2877 (m), 1710 (s), 1357 (m), 1214 (s), 1128 (m), 1047 (s), 1005 (s), 857 (m), 728 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{21}H_{35}O_5SiNaBr(79)$ 497.1335, found 497.1354; calculated for $C_{21}H_{35}O_5SiNaBr(81)$ 499.1314, found 499.1331.



3.146r

(1R*,2S*,3aR*,7S*,8R*,8aS*)-7-Allyl-8-hydroxy-2',2'-dimethyl-4-methylene-2-(triethylsilyloxy)hexahydro-2H-spiro[azulene-1,4'-[1,3]dioxolan]-6(7H)-one (3.146r)

Toluene was degased by bubbling Ar for 30 min.

Allyltributylstannane (0.12 ml, 0.40 mmol) and AIBN (0.13 ml 0.20 M in PhMe, 0.026 mmol) were added to bromohydrin **3.142r** (63.0 mg, 0.132 mmol) in PhMe (0.6 ml) at RT. The mixture was brought to 85°C and stirred for 6 h. Another portion of AIBN (66 µl 0.20 M in PhMe, 0.013 mmol) was added and the mixture was stirred at 85°C for 12 h, cooled to RT, and applied directly on a column. Purification by flash chromatography (silica gel, eluting with diethyl ether/petroleum ether, 1:4) afforded allylated product **3.146r** (36.3 mg, 63%) as a colourless oil.

R_f = 0.30 (Et_2O/petroleum ether 1:4)

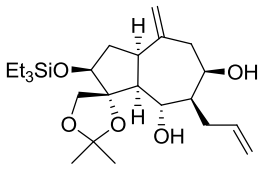
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dddd, *J*=17.0, 10.1, 8.0, 6.3 Hz, 1H), 5.06-4.98

(m, 4H), 4.26 (d, *J*=9.7 Hz, 1H), 4.07 (d, *J*=9.7 Hz, 1H), 4.05 (t, *J*=6.6 Hz, 1H), 3.90 (td, *J*=9.8, 2.6 Hz, 1H), 3.32 (d, *J*=16.7 Hz, 1H), 3.13 (d, *J*=16.6 Hz, 1H), 2.98 (q, *J*=8.6 Hz, 1H), 2.79 (d, *J*=3.1 Hz, 1H), 2.68-2.55 (m, 2H), 2.38 (dt, *J*=13.8, 8.2 Hz, 1H), 2.27-2.18 (m, 2H), 1.68-1.61 (m, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 0.98 (t, *J*=7.9 Hz, 9H), 0.64 (q, *J*=7.9 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.68 (e), 141.74 (e), 135.38 (o), 116.99 (e), 114.63 (e), 108.26 (e), 92.00 (e), 75.70 (o), 69.35 (o), 65.14 (e), 62.16 (o), 53.38 (o), 51.35 (e), 42.24 (o), 35.41 (e), 34.82 (e), 27.28 (o), 26.19 (o), 6.87 (o), 4.91 (e).

IR (neat) 3470 (w), 2955 (m), 1703 (m), 1640 (m), 1370 (m), 1213 (s), 1049 (s), 1005 (s), 898 (s), 744 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{24}H_{40}O_5SiNa$ 459.2543, found 459.2544.



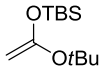
3.153r

(1R*,2S*,3aR*,6R*,7R*,8S*,8aS*)-7-Allyl-2',2'-dimethyl-4-methylene-2-(triethylsilyloxy)octahydro-2H-spiro[azulene-1,4'-[1,3]dioxolane]-6,8-diol (3.153r)

A solution of allylated ketone **3.146r** (3.0 mg, 0.0069 mmol) in THF (0.1 ml) was added to K-Selectride (27 µl 1.0 M in THF, 0.027 mmol) in THF (0.1 ml) at −78°C. The mixture was warmed to −30°C, stirred for 30 min, and quenched with H_2O/EtOH 1:2 (0.05 ml). The resulting mixture was warmed to RT and treated with 3.0 M NaOH (0.1 ml) and 30% H_2O_2 (0.05 ml). After 1 h of stirring, the mixture was extracted with EtOAc. Combined organic extracts were washed with sat. $Na_2S_2O_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:4 → 1:2) afforded diol **3.153r** (1.4 mg, 47%) as a colourless oil.

R_f = 0.30 (Et_2O/petroleum ether 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (dddd, *J*=17.0, 10.1, 8.5, 6.2 Hz, 1H), 5.13 (d, *J*=17.0 Hz, 1H), 5.03 (d, *J*=10.1 Hz, 1H), 4.94 (s, 1H), 4.89 (s, 1H), 4.27 (d, *J*=9.7 Hz, 1H), 4.09 (d, *J*=9.7 Hz, 1H), 4.04 (t, *J*=5.8 Hz, 1H), 4.02-3.98 (m, 1H), 3.44 (td, *J*=9.5, 3.3 Hz, 1H), 2.99 (q, *J*=8.7 Hz, 1H), 2.85 (d, *J*=3.5 Hz, 1H), 2.61-2.57 (m, 2H), 2.54 (dd, *J*=13.5, 6.6 Hz, 1H), 2.41-2.33 (m, 2H), 2.27-2.18 (m, 2H), 1.79 (br s, 1H), 1.74-1.67 (m, 1H), 1.58-1.51 (m, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 0.98 (t, *J*=8.0 Hz, 9H), 0.65 (q, *J*=7.9 Hz, 6H).



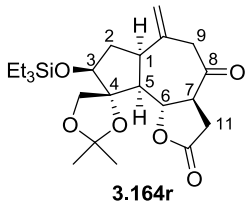
3.161

(1-tert-Butoxyvinyloxy)(tert-butyl)dimethylsilane (3.161)[95]

3.161 was prepared in 100% yield from commercially available *t*-BuOAc, according to the procedure used by Danishefsky *et al.* (1981).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.47 (d, *J*=1.4 Hz, 1H), 3.45 (d, *J*=1.3 Hz, 1H), 1.35 (s, 9H), 0.93 (s, 9H), 0.19 (s, 6H).

IR (neat) 2931 (w), 2859 (w), 1648 (s), 1248 (s), 1156 (s), 987 (s), 852 (s), 781 (s) cm^{-1}.



3.164r

(3aS*,4'R*,6aR*,8S*,9aS*,9bR*)-2',2'-Dimethyl-6-methylene-8-(triethylsilyloxy)octahydro-2H-spiro[azuleno[4,5-b]furan-9,4'-[1,3]dioxolane]-2,4(5H)-dione (3.164r)

Benzene was degased by bubbling Ar for 30 min.

Lauroyl peroxide (0.10 ml 0.20 M in benzene, 0.020 mmol) was added to a solution

of silyl enol ether **3.161** (0.232 g, 1.01 mmol), 2,4,6-collidine (5 µl, 0.04 mmol) and bromohydrin **3.142r** (0.096 g, 0.20 mmol) in benzene (0.2 ml) at RT. The resulting mixture was brought to 80°C. Same amount of lauroyl peroxide (0.10 ml 0.20 M in benzene, 0.020 mmol) was added after 2 h, 4 h, and 6 h (0.08 mmol in total). Additional portion of silyl enol ether **3.161** (0.116 g, 0.500 mmol) was added after 5 h. After total stirring time of 24 h, the reaction mixture was cooled to RT and applied directly on a column. Purification by flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:8 → 1:4 → 1:2) afforded lactone **3.164r** (0.046 g, 52%) as a colourless oil.

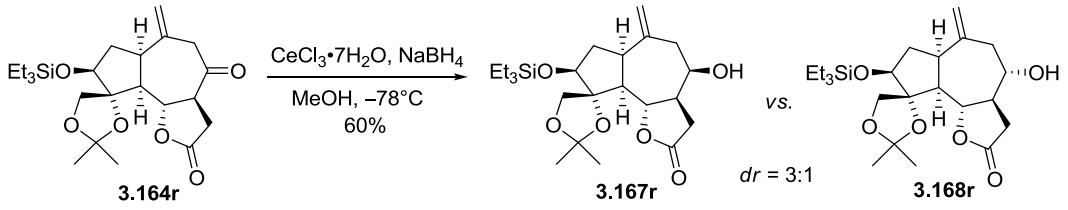
R_f = 0.20 (Et_2O/petroleum ether 1:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29 (d, *J*=1.5 Hz, 1H, =C**H_2**), 5.01 (s, 1H, =C**H_2**), 4.79 (t, *J*=10.7 Hz, 1H, C6-**H**), 4.27 (d, *J*=9.9 Hz, 1H, C**H_2**O), 4.20 (d, *J*=9.9 Hz, 1H, C**H_2**O), 4.06 (dt, *J*=6.6, 1.6 Hz, 1H, C3-**H**), 3.57 (td, *J*=10.0, 7.7 Hz, 1H, C1-**H**), 3.50 (td, *J*=11.0, 9.1 Hz, 1H, C7-**H**), 3.26 (dd, *J*=17.9, 0.9 Hz, 1H, C9**H_2**), 3.20 (d, *J*=17.8 Hz, 1H, C9**H_2**), 2.97 (dd, *J*=18.2, 11.4 Hz, 1H, C11**H_2**), 2.47 (dd, *J*=18.3, 9.1 Hz, 1H, C11**H_2**), 2.49-2.42 (m, 1H, C2**H_2**), 2.39 (ddd, *J*=10.8, 7.5, 0.9 Hz, 1H, C5-**H**), 1.51 (ddd, *J*=14.5, 9.7, 1.8 Hz, 1H, C2**H_2**), 1.43 (s, 3H, C(C**H_3**)$_2$), 1.35 (s, 3H, C(C**H_3**)$_2$), 0.94 (t, *J*=8.0 Hz, 9H, $SiCH_2C$**H_3**), 0.63-0.58 (m, 6H, SiC**H_2**CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 203.95 (e), 174.41 (e), 140.90 (e), 120.17 (e), 108.89 (e), 92.52 (e), 78.37 (o), 77.0 (o), 65.70 (e), 57.97 (o), 51.93 (o), 46.66 (e), 46.42 (o), 38.28 (e), 29.01 (e), 27.86 (o), 26.28 (o), 6.89 (o), 4.82 (e).

IR (neat) 2955 (m), 2877 (m), 1788 (s), 1718 (s), 1458 (w), 1369 (m), 1212 (s), 1062 (s), 1007 (s), 861 (m), 743 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{23}H_{36}O_6SiNa$ 459.2179, found 459.2188.



$CeCl_3•7H_2O$ (0.138 g, 0.370 mmol) and $NaBH_4$ (25.1 mg, 0.668 mmol) were added to a solution of ketone **3.164r** (0.081 g, 0.19 mmol) in MeOH (3.7 ml) at −78°C. The reaction mixture was stirred for 20 min, diluted with Et_2O, and quenched with sat. NH_4Cl solution. The mixture was extracted with Et_2O. Combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:4 → 1:2 → 1:1) afforded diastereomeric alcohols **3.167r** and **3.168r** in a 3.5:1 ratio (0.049 g, 60% combined yield) as a colourless oil.

Analytical data for the undesired epimer:

(3aR*,4R*,4'R*,6aR*,8S*,9aS*,9bS*)-4-Hydroxy-2',2'-dimethyl-6-methylene-8-(triethylsilyloxy)decahydro-2H-spiro[azuleno[4,5-b]furan-9,4'-[1,3]dioxolan]-2-one (3.167r)

R_f = 0.45 (EtOAc/petroleum ether 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (s, 1H), 4.93 (s, 1H), 4.59 (t, *J*=10.2 Hz, 1H), 4.28 (d, *J*=9.8 Hz, 1H), 4.09 (d, *J*=9.8 Hz, 1H), 4.04 (dd, *J*=6.0, 4.4 Hz, 1H), 3.98-3.95 (m, 1H), 3.15 (q, *J*=9.0 Hz, 1H), 2.90-2.82 (m, 1H), 2.51-2.32 (m, 5H), 2.23 (app. t, *J*=10.0 Hz, 1H), 1.56 (ddd, *J*=14.1, 8.0, 4.1 Hz, 1H), 1.41 (s, 3H), 1.41 (s, 3H), 0.97 (t, *J*=7.9 Hz, 9H), 0.65-0.60 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.08 (e), 143.68 (e), 116.43 (e), 108.73 (e), 92.06 (e), 77.81 (o), 75.78 (o), 65.15 (o), 65.11 (e), 54.00 (o), 47.98 (o), 43.72 (o), 42.62 (e), 37.41 (e), 31.03 (e), 27.73 (o), 26.10 (o), 6.93 (o), 4.96 (e).

IR (neat) 3461 (w), 2953 (w), 2877 (w), 1777 (m), 1747 (m), 1208 (s), 1062 (s),

1004 (s), 899 (s), 727 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{23}H_{38}O_6SiNa$ 461.2335, found 461.2322.

Analytical data for the desired epimer:

(3aR*,4S*,4'R*,6aR*,8S*,9aS*,9bS*)-4-Hydroxy-2',2'-dimethyl-6-methylene-8-(triethylsilyloxy)decahydro-2H-spiro[azuleno[4,5-b]furan-9,4'-[1,3]dioxolan]-2-one (3.168r)

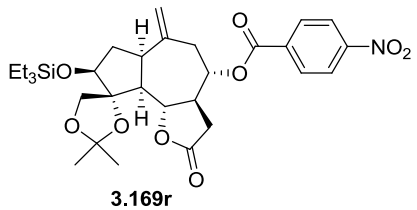
R_f = 0.40 (EtOAc/petroleum ether 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.96 (s, 1H), 4.49 (t, *J*=10.3 Hz, 1H), 4.24 (d, *J*=9.8 Hz, 1H), 4.09 (d, *J*=9.8 Hz, 1H), 4.04 (dd, *J*=6.4, 4.0 Hz, 1H), 3.67 (dt, *J*=9.5, 5.3 Hz, 1H), 3.19 (app. q, *J*=9.2 Hz, 1H), 2.81 (dd, *J*=17.6, 8.7 Hz, 1H), 2.70 (dd, *J*=13.4, 5.2 Hz, 1H), 2.40 (dd, *J*=17.6, 11.6 Hz, 1H), 2.19 (dd, *J*=13.4, 5.5 Hz, 1H), 1.50 (ddd, *J*=14.3, 7.6, 4.1 Hz, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 0.97 (t, *J*=7.9 Hz, 9H), 0.65-0.60 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.54 (e), 143.57 (e), 116.09 (e), 108.81 (e), 92.06 (e), 79.41 (o), 75.89 (o), 74.28 (o), 65.00 (e), 54.68 (o), 49.33 (o), 44.02 (o), 43.06 (e), 37.52 (e), 34.93 (e), 27.71 (o), 26.09 (o), 6.95 (o), 4.94 (e).

IR (neat) 3448 (w), 2953 (w), 2877 (m), 1776 (s), 2336 (s), 1149 (s), 1062 (s), 1009 (s), 862 (s), 728 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{23}H_{38}O_6SiNa$ 461.2335, found 461.2327.



3.169r

(3aR*,4S*,4'R*,6aR*,8S*,9aS*,9bS*)-2',2'-Dimethyl-6-methylene-2-oxo-8-(triethylsilyloxy)decahydro-2H-spiro[azuleno[4,5-b]furan-9,4'-[1,3]dioxolane]-4-yl 4-nitrobenzoate (3.169r)

A solution of alcohol **3.168r** (11.8 mg, 0.0270 mmol) and pyridine (8 µl, 0.1 mmol) in DCM (0.27 ml) was added to a vial containing 4-nitrobenzoyl chloride (10.0 mg, 0.0540 mmol) at 5°C, followed by the addition of DMAP (13 µl 0.40 M in DCM, 0.0054 mmol). The resulting mixture was stirred at RT for 3.5 h, quenched with sat. NH_4Cl solution, and extracted with Et_2O. Combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, eluting with EtOAc/petroleum ether, 1:5, then Et_2O/petroleum ether 1:2) afforded 4-nitrobenzoate **3.169r** (9.4 mg, 60%) as a white solid.

R_f = 0.45 (EtOAc/petroleum ether 1:4)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33-8.30 (m, 2H), 8.21-8.17 (m, 2H), 5.16 (s, 1H), 5.13 (dt, *J*=9.9, 5.2 Hz, 1H), 5.02 (s, 1H), 4.66 (dd, *J*=10.5, 9.6 Hz, 1H), 4.28 (d, *J*=9.8 Hz, 1H), 4.14 (d, *J*=9.8 Hz, 1H), 4.06 (dd, *J*=6.0, 3.2 Hz, 1H), 3.29 (app. q, *J*=9.0 Hz, 1H), 2.82 (dd, *J*=14.0, 4.9 Hz, 1H), 2.73-2.66 (m, 2H), 2.51-2.32 (m, 4H), 1.54 (ddd, *J*=14.4, 7.7, 3.3 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 0.99 (t, *J*=7.9 Hz, 9H), 0.65 (q, *J*=7.9 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.42 (e), 164.01 (e), 150.97 (e), 142.56 (e), 135.24 (e), 130.89 (o), 123.88 (o), 117.47 (e), 108.84 (e), 92.22 (e), 79.17 (o), 77.06 (o), 76.02 (o), 65.21 (e), 55.05 (o), 46.43 (o), 44.52 (o), 38.77 (e), 37.70 (e), 34.56 (e), 27.77 (o), 26.12 (o), 6.97 (o), 4.95 (e).

IR (neat) 2954 (w), 2877 (w), 1781 (s), 1722 (s), 1528 (s), 1269 (s), 1062 (s), 1008 (s), 861 (s), 719 (s) cm^{-1}.

HRMS (ESI, $[M+Na]^+$) calculated for $C_{30}H_{41}NO_9SiNa$ 610.2448, found 610.2449.

3.5. References

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Supporting Information: X-Ray Crystallographic Reports

Chapter 2: Structure report for 2.23

Data recorded by Dr. John Bacsa.

Crystal and Refinement Data	
$C_{27}H_{26}O_5$	
M = 430.48	
colourless needle	
0.50 × 0.21 × 0.11 mm^3	
triclinic, space group *P*-1 (No. 2)	
a = 8.3014(15) Å	
b = 11.049(2) Å	
c = 12.814(2) Å	
α = 112.709(2)°	
β = 93.086(2)°	
γ = 95.074(2)°	
V = 1075.0(3) $Å^3$	
Z = 2	
D_c = 1.330 g/cm^3	
T = 100(2)K	
8878 reflections collected, 4617 unique	
R_{int} = 0.0306	
Final *GooF* = 1.018	
R1 = 0.0515	
wR2 = 0.1320	
393 parameters, 0 restraints	
μ = 0.091 mm^{-1}	

Chapter 2: Structure report for 2.42g

Data recorded by Dr. Craig Robertson.

Crystal and Refinement Data

Bond precision: C-C = 0.0040 Å,

Wavelength = 0.71073

Cell: a = 9.1507(6), b = 31.657(2), c = 10.5468(7)

$\alpha = 90$, $\beta = 104.169(2)$, $\gamma = 90$

Temperature: 296 K

Reported Data

Volume = 2962.3(3)

Space group = P 1 21/n 1

Hall group = −P 2yn

Molecular formula = $C_{26}H_{43}NO_5SSi_2$

Mw = 537.86

Density = 1.206 g/cm^3

Z = 4

Mu = 0.224 mm^{-1}

F000 = 1160.0

h, k, l (max) = 11, 39, 13

N_{ref} = 6133

T_{min}/T_{max} = 0.515/0.745

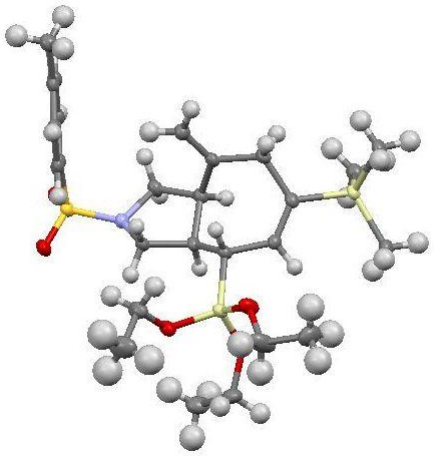
Correction method = Empirical

Data completeness = 0.994

Theta (max) = 26.530

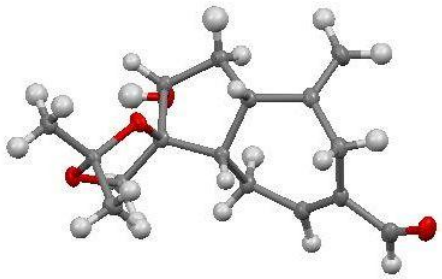
R = 0.0540(5085); wR2 = 0.1257(6133)

S = 1.099; Npar = 331



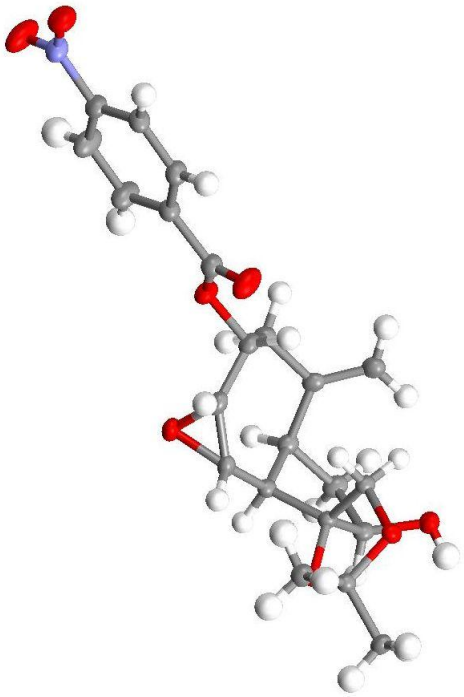
Chapter 3: Structure report for 3.91r

Data recorded by Dr. Craig Robertson.

Crystal and Refinement Data Bond precision: C-C = 0.0019 Å, Wavelength = 0.71073 Cell: a = 7.9275(19), b = 8.424(2), c = 11.416(3) $\alpha = 86.257(6)$, $\beta = 76.799(7)$, $\gamma = 77.110(6)$ Temperature: 296 K ***Reported Data*** Volume = 723.4(3) Space group = P −1 Hall group = −P 1 Molecular formula = $C_{16}H_{22}O_4$ Mw = 278.34 Density = 1.278 g/cm^3 Z = 2 Mu = 0.091 mm^{-1} F000 = 300.0 h, k, l (max) = 9, 10, 14 N_{ref} = 2948 T_{min}/T_{max} = 0.684/0.745 Correction method = Empirical Data completeness = 0.988 Theta (max) = 26.450 R = 0.0392(2663); wR2 = 0.1388(2948) S = 1.159; Npar = 269	

Chapter 3: Structure report for 3.123r

Data recorded by Dr. Craig Robertson.

Crystal and Refinement Data	
Bond precision: C-C = 0.0019 Å, Wavelength = 0.71073 Cell: a = 9.6909(6), b = 11.6079(8), c = 19.0566(14) $\alpha = 76.860(2)$, $\beta = 81.741(2)$, $\gamma = 87.293(2)$ Temperature: 100 K ***Reported Data*** Volume = 2065.7(2) Space group = P −1 Hall group = −P 1 Molecular formula = $C_{22}H_{25}NO_8$ Mw = 431.43 Density = 1.387 g/cm^3 Z = 4 Mu = 0.106 mm^{-1} F000 = 912.0 h, k, l (max) = 12, 14, 23 N_{ref} = 8527 T_{min}/T_{max} = 0.973/1.000 Correction method = Empirical Data completeness = 0.989 Theta (max) = 26.570 R = 0.0386(7731); wR2 = 0.1005(8527) S = 1.029; Npar = 584	

Chapter 3: Structure report for 3.169r

Data recorded by Dr. Craig Robertson.

Crystal and Refinement Data

Bond precision: C-C = 0.0029 Å, Wavelength = 0.71073

Cell: a = 9.1481(4), b = 17.5404(8), c = 19.8298(9)

$\alpha = 73.559(2)$, $\beta = 82.565(2)$, $\gamma = 87.653(2)$

Temperature: 100 K

Reported Data

Volume = 3026.1(2)

Space group = P −1

Hall group = −P 1

Molecular formula = $C_{30}H_{41}NO_9Si$

Mw = 587.73

Density = 1.290 g/cm^3

Z = 4

Mu = 0.131 mm^{-1}

F000 = 1256.0

h, k, l (max) = 11, 21, 24

N_{ref} = 12541

T_{min}/T_{max} = 0.475/0.745

Correction method = Empirical

Data completeness = 0.994

Theta (max) = 26.550

R = 0.0494(9287); wR2 = 0.1349(12541)

S = 1.029; Npar = 765