New Synthetic Applications of the Diels-Alder Reaction

A thesis submitted for the degree of
Doctor of Philosophy of The Australian National University

by

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Declaration

I declare that the material presented in this thesis represents the result of original work carried out by the author and has not been submitted for any other degree. This thesis is less than 100, 000 words in length.

Natalie A. Miller

3 November, 2006

Acknowledgements

Firstly, I would like to acknowledge my supervisor, Associate Professor Michael Sherburn. Thanks Mick for providing your advice and encouragement over the last few years. I may not have seemed so happy about the move from Sydney to Canberra to do my PhD under your supervision, but it is a decision I definitely don't regret.

To the Sherburn Group members, both past and present, thank you all for your help and friendship. In particular I would like to thank Emma Pearson, Laurence Kwan and *Team 213* (Alan Payne and Nick Kanizaj) for making the PhD experience more enjoyable.

Thanks must go to Prof. Michael Paddon-Row, for calculating the transition structures in this thesis. Thanks to Dr Tony Willis, Dr Alison Edwards and Dr Peter Turner for single crystal X-ray analyses. Thanks also to Chris Blake for assistance with NMR and Michael Carland, Tony Herlt and other technical staff at the Research School of Chemistry.

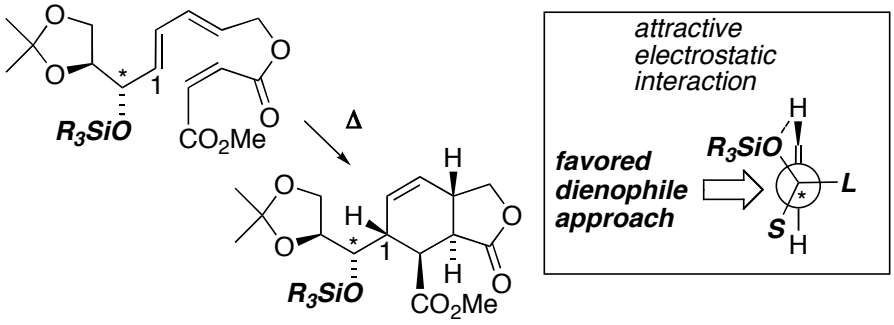
I would also like to thank my parents for their support, especially since I moved to Canberra. As I have finally finished being a student, it is almost time to get a real job!

Abstract

Some 78 years after its discovery the Diels-Alder reaction is still one of the most useful and powerful transformations in synthetic organic chemistry. Nevertheless, there are many unexplored possibilities and aspects of the Diels-Alder reaction that are poorly understood. This thesis explores the development of new, efficient and stereocontrolled synthetic strategies using the Diels-Alder reaction as a key element. In order to gain a deeper understanding of the stereochemical outcome of both the intermolecular and intramolecular Diels-Alder reactions detailed synthetic and computational investigations have been carried out.

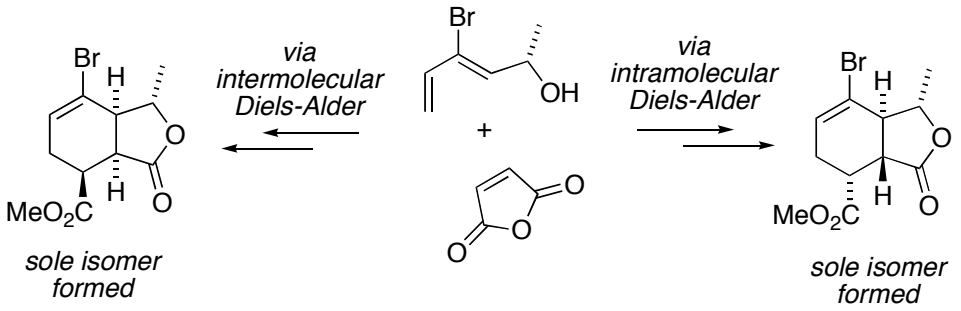
There are five chapters of results and discussion in this thesis, each of them dealing with aspects of the Diels-Alder reaction. New methods of controlling the stereochemical outcome of the Diels-Alder reaction are presented in chapters two and three. The development and application of powerful cascade Diels-Alder strategies for natural product synthesis are explored in chapters four, five and six.

The stereochemical outcome of the intramolecular Diels–Alder reaction of ester-linked 1,3,8-nonatrienes has been controlled by substituents about a stereogenic centre attached to C1 (Scheme 1). The scope and limitations of this approach have been investigated, with variation in substrate structure about the allylic stereocentre and the dienophile. Silyloxy groups are much superior to hydroxy, alkoxy and ester groups in their stereocontrolling ability. Computational modelling carried out by Prof. Michael Paddon-Row is used to explain the experimental results.



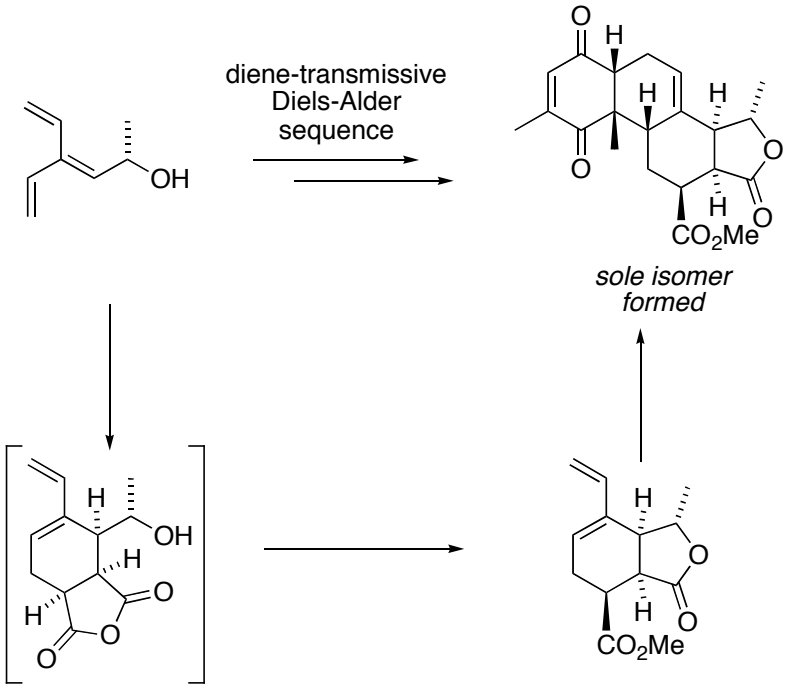
Scheme 1

Moderately stereoselective cycloaddition reactions have been rendered *completely* stereoselective simply by the replacement of a hydrogen in the precursor by a bromine (Scheme 2). Taken together with the ability to select for either *cis* or *trans*-bicyclic lactone acids from simple dienols and maleic anhydride, operationally simple stereocontrolled approaches to enantiomerically pure bicyclic building blocks with complimentary stereochemistries are now in hand.



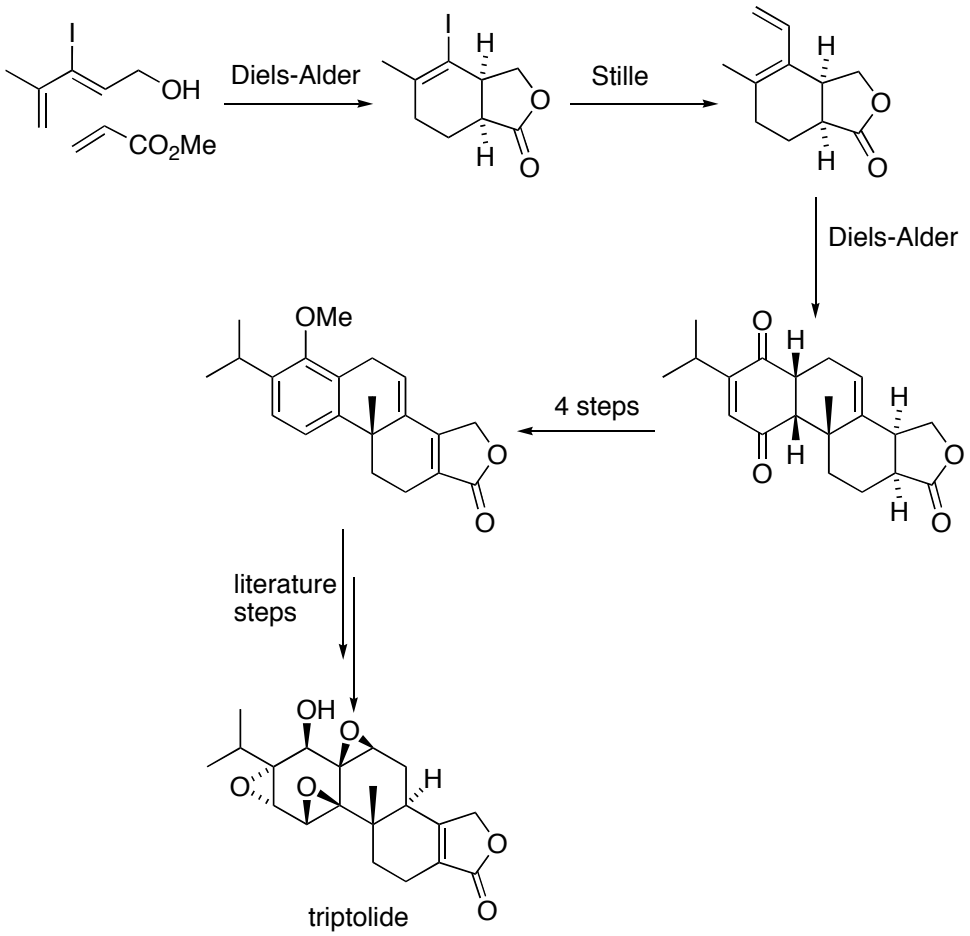
Scheme 2

Dendralenes are acyclic cross-conjugated oligo-alkenes with much synthetic potential. They are particularly attractive precursors for Diels-Alder reactions, since they function as multi-dienes, thereby allowing rapid access to polycyclic frameworks. A short and general synthetic route to substituted dendralenes has been developed. The cycloaddition chemistry of chiral [3]dendralenes is controlled, allowing the assembly of tetracyclic systems common to numerous biologically interesting terpenoid natural products (Scheme 3).



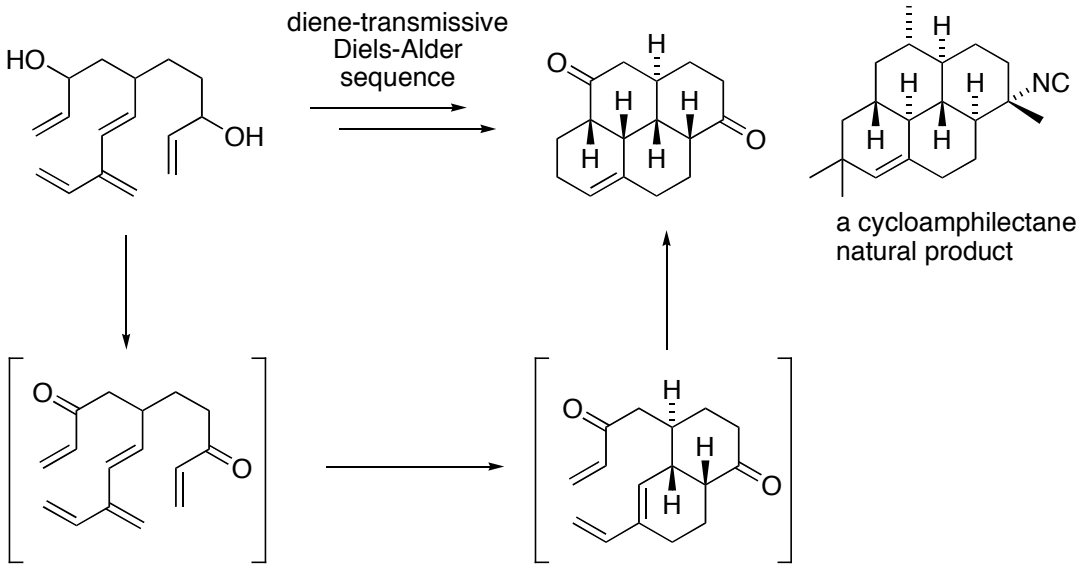
Scheme 3

The new methods developed have been applied to the synthesis of natural products. A concise formal total synthesis of triptolide, a biologically active natural product, was completed (Scheme 4). A sequence involving two intermolecular Diels-Alder reactions was used to form the tetracyclic core.



Scheme 4

Finally, an intramolecular/intramolecular diene-transmissive Diels-Alder sequence has been used to synthesise fused tetracyclic frameworks, such as those found in cycloamphilectane natural products (Scheme 5).



Scheme 5

Abbreviations

χρ	chiral group
Ac	acetyl
AIBN	2,2'-azo-*bis*-isobutyronitrile
BHT	2,6-di-*tert*-butyl-4-methylphenol
BMS	borane methyl sulfide complex
Bn	benzyl
c	concentration (g/L)
COSY	correlated spectroscopy
δ	chemical shift (in parts per million)
d	day/s or doublet/s
DA	Diels-Alder
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
d.e.	diastereomeric excess
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DIBALH	diisobutylaluminium hydride
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
EI	electron impact
equiv	molar equivalents
Et	ethyl
ETDA	ester tethered Diels-Alder
EWG	electron withdrawing group
eV	electron Volts
h	hour/s
HMPA	Hexamethylphosphoramide
HMQC	heteronuclear multiple quantum correlation
HOMO	highest occupied molecular orbital

HSQC	heteronuclear single quantum correlation
Hz	hertz
IMDA	intramolecular Diels-Alder
^{i}Pr	isopropyl
IR	infrared
lk	like (facial selectivity)
LUMO	lowest unoccupied molecular orbital
μ	micro
m	milli
M	molar concentration
MA	maleic anhydride
Me	methyl
MHz	megahertz
min	minute
MOM	methoxymethyl
m.p.	melting point
Ms	mesyl
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
Ph	phenyl
$PhCH_3$	toluene
PhH	benzene
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
rt	room temperature
s	singlet
t	time or triplet
T	temperature
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
TfO	trifluoromethanesulfonate

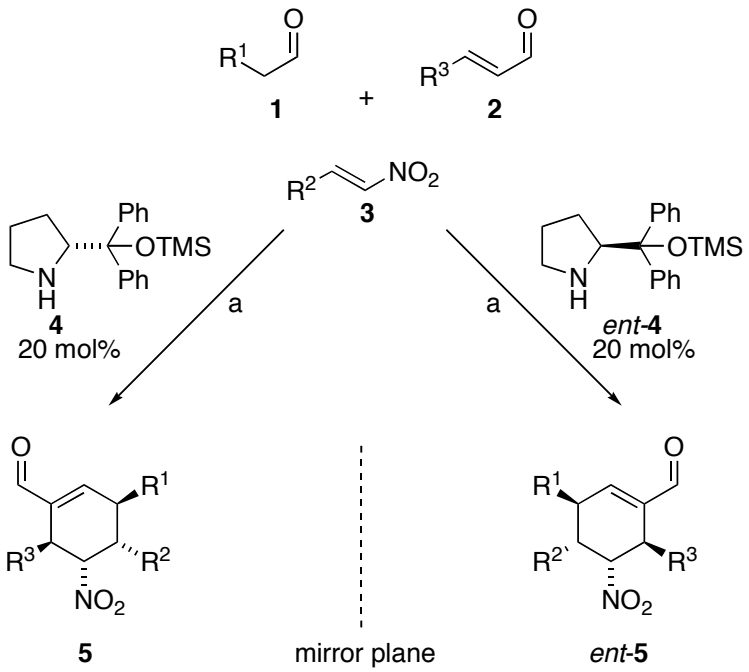
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
tlc	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
TS	transition structure
ul	unlike (facial selectivity)

Table of Contents

1 Introduction

There is much demand for efficient and practical syntheses of complex organic molecules. It is for this reason that cascade sequences are increasingly being applied to the total synthesis of natural products and other target molecules.[1,2] Cascade or domino sequences are defined as two or more reactions carried out in one-pot in which subsequent reactions only occur as a result of functionality that is formed in the previous step.[3] Cascade sequences are attractive to organic chemists as they often result in a dramatic increase in molecular complexity, with several new bonds and stereocentres being formed at once.

While the value of cascade sequences has long been known there is a continuing interest in developing new and more impressive cascade events. One recent example is the organocatalysed Michael/Michael/aldol condensation sequence in which four new stereocentres were generated in a single step with a high level of diastereoselectivity and complete enantioselectivity (Scheme 1.1).[4]



Scheme 1.1 *Reagents and conditions:* (a) Toluene, 0 °C, RT, 25-58%.

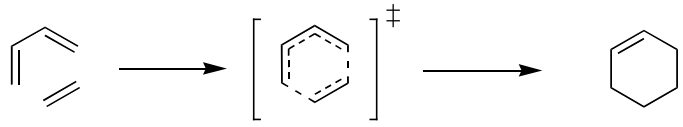
As with conventional synthesis the reactions incorporated into a cascade sequence should be versatile, high yielding and selective. Thus both the intermolecular and intramolecular Diels-Alder reactions are ideally suited for use in cascade sequences.

1.1 The Intermolecular Diels-Alder Reaction

1.1.1 Introduction

Since the first report of the Diels-Alder reaction in 1928[5] it has become one of the most useful and powerful transformations in organic synthesis.[2,6-10]

The Diels-Alder reaction involves the concerted [4+2] cycloaddition of a conjugated diene to a dienophile to form a six membered ring containing a double bond (Scheme 1.2). The thermodynamic driving force of the reaction is the formation of two σ-bonds at the expense of two π-bonds. The reaction often proceeds under mild conditions to give up to four new stereocentres, allowing the rapid assembly of structurally complex molecules.



Scheme 1.2 The Diels-Alder reaction

1.1.2 The Diene and Dienophile.

For a Diels-Alder reaction to occur the diene must be able to adopt the s-*cis* conformation (Figure 1.1). The preferred conformation of 1,3-butadiene is the s-*trans* form, where the steric hindrance between the 'inside' hydrogens is reduced. The more populated the s-*cis* conformation is in the ground state, the more reactive the diene will be, thus a bis-*exo*-methylene diene will be more reactive than a semicylic or acyclic diene. Examples of dienes capable of undergoing the Diels-Alder reaction are illustrated in Figure 1.2.

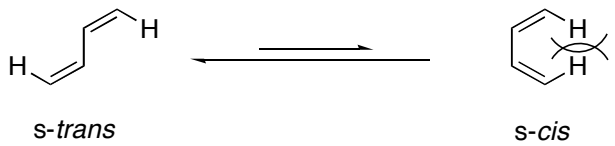


Figure 1.1 The preferred conformation of 1,3-butadiene

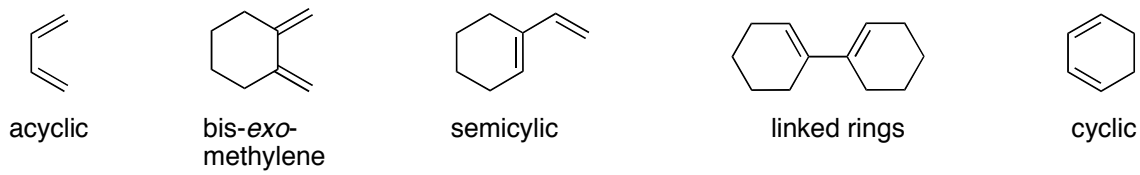
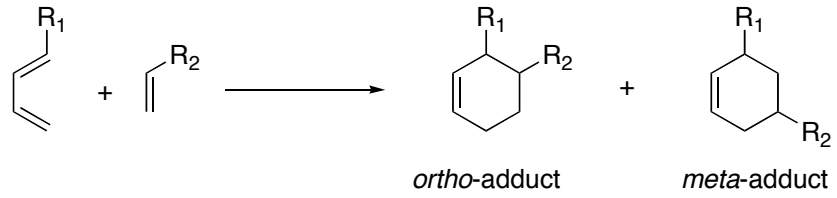


Figure 1.2 Dienes capable of undergoing the Diels-Alder reaction

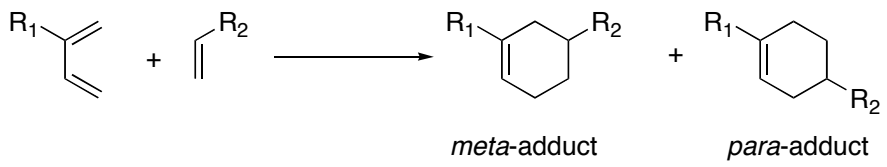
The dienophile may be acyclic, cyclic or alkynic. An electron-withdrawing group (EWG) is usually attached to the dienophile, reducing the amount of energy required for the Diels-Alder reaction to occur.[11] Examples of EWGs used include aldehydes, esters and ketones.

1.1.3 Regioselectivity

If both diene and dienophile are unsymmetrically substituted, two regioisomeric products may be formed by a Diels-Alder reaction. If the diene is substituted at a terminal position, *ortho*- and *meta*-adducts are produced (Scheme 1.3). If the diene bears a substituent at an internal position, *meta*- and *para*-adducts may be formed (Scheme 1.4). For electronic reasons the *ortho*- and *para*-adducts are usually favoured.[11,12]



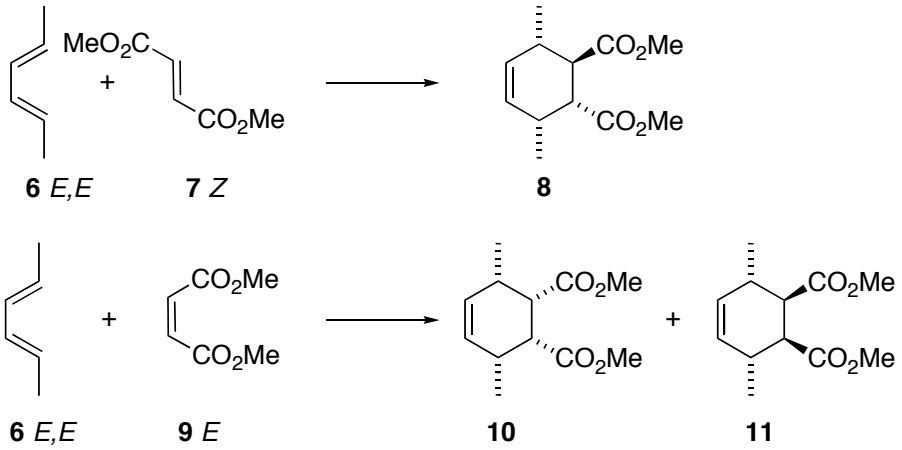
Scheme 1.3 Diels-Alder reaction of a terminally substituted diene



Scheme 1.4 Diels-Alder reaction of an internally substituted diene

1.1.4 Cis-stereospecificity

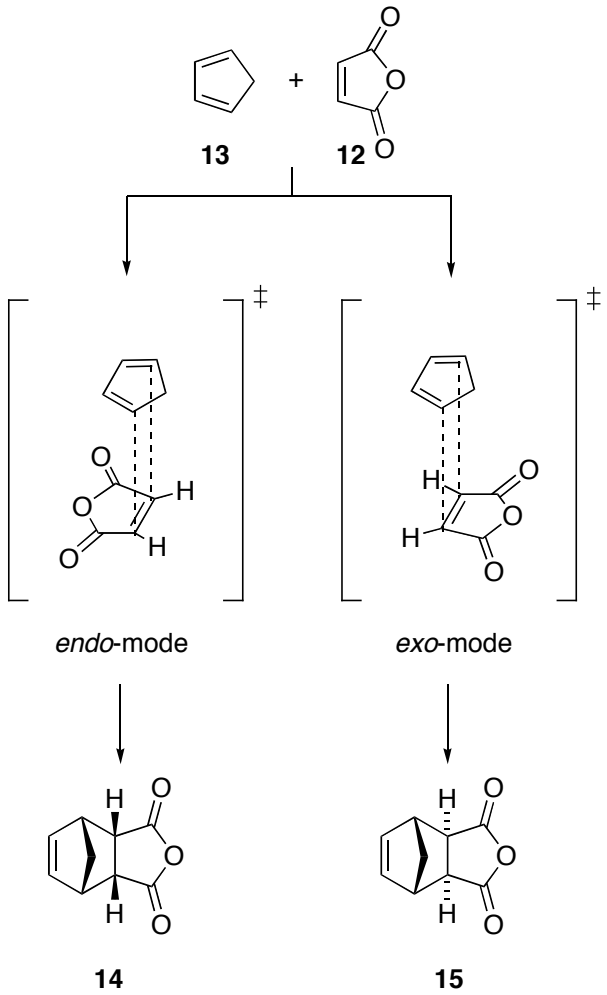
Concerted Diels-Alder reactions are *suprafacial* with respect to both reactants, which means that both σ-bonds are formed on the same π-face of the diene and dienophile. As a result, the relative stereochemistries of both the diene and dienophile are conserved (Scheme 1.5).



Scheme 1.5 *Cis*-stereospecificity in Diels-Alder reactions

1.1.5 Endo/exo-*stereoselectivity*

The *endo*/*exo* cycloaddition modes of the Diels-Alder reaction are defined by the orientation of the dienophile with respect to the diene. The *endo*-mode is the transition state spatial arrangement in which the larger dienophile substituents are closer to C2 and C3 of the diene (Scheme 1.6). The *exo*-mode is the arrangement where the dienophile substituents lie away from the diene.



Scheme 1.6 *endo*- and *exo*-cycloaddition modes of the Diels-Alder reaction between maleic anhydride and cyclopentadiene

The *endo/exo* selectivity of the intermolecular Diels-Alder reaction can, in general, be explained by the Alder *endo* rule.[13] According to this rule the *endo*-transition state is favoured because of maximum orbital overlap between the diene and the unsaturated substituents of the dienophile.[14] The stabilizing overlap between the lobes of the atomic orbitals that do not participate in the formation of σ bonds are known as secondary orbital interactions (SOI) (Figure 1.3).[15] However, the existence of this orbital overlap has not been unequivocally proven and there are many exceptions to the rule.[16]

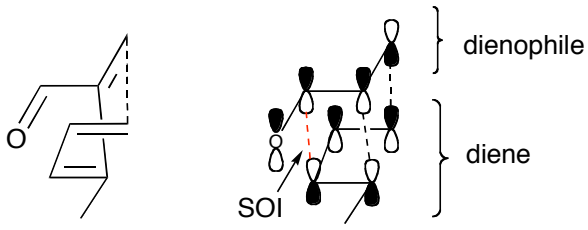
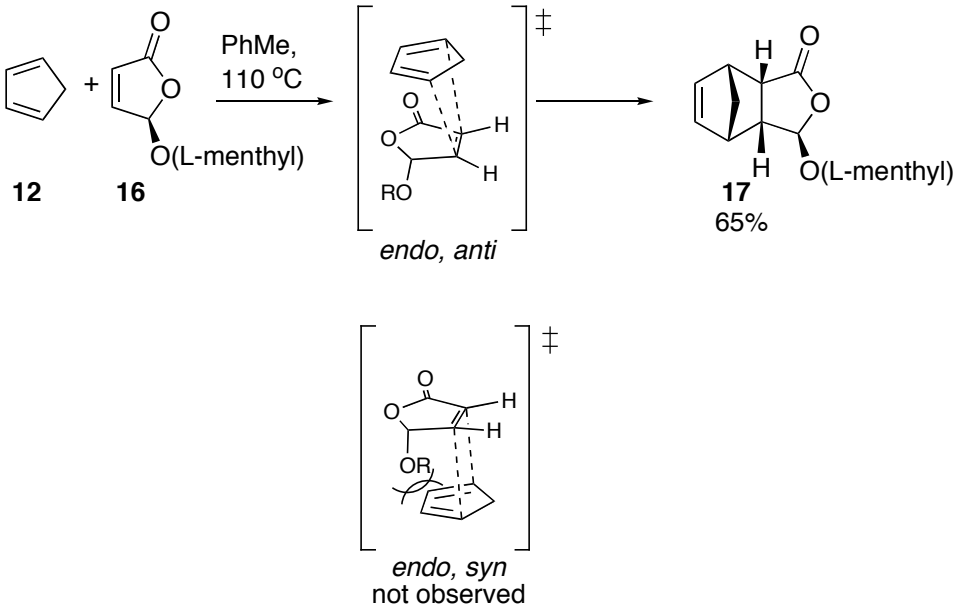


Figure 1.3 An example of secondary orbital interactions between acrolein and penta-1,3-diene.

1.1.6 π-Diastereofacial Selectivity

If the diene or dienophile is unsymmetrically substituted, different stereoisomers may be formed as a result of cycloadditions involving different combinations of the diene and dienophile π-faces. Generally, the cycloaddition mode that minimises steric hinderance between the diene and dienophile will be favoured (Scheme 1.7).[17]

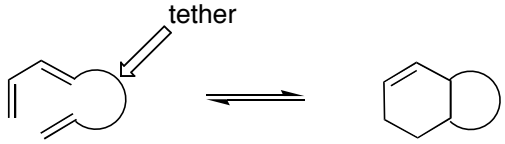


Scheme 1.7 π-Diastereofacial selectivity in the Diels-Alder reaction between cyclopentadiene and a chiral maleic anhydride analogue.

1.2 The Intramolecular Diels-Alder Reaction

1.2.1 Introduction

The intramolecular Diels-Alder (IMDA) reaction differs from the intermolecular Diels-Alder reaction in that a tether links the diene and dienophile, thereby producing two rings in one step (Scheme 1.8).



Scheme 1.8 The intramolecular Diels-Alder reaction

The first IMDA reaction was reported in 1953,[18] but it was not until the 1960s that more detailed reports were made.[19-21] The IMDA reaction often has entropic, regiochemical and stereochemical advantages over the intermolecular Diels-Alder reaction, but the reaction outcome is usually less predictable. Despite this, the IMDA reaction has been featured in the total synthesis of many natural products.[1,2,8,22-25]

1.2.2 The Tether and Regioselectivity

The nature of the tether in the IMDA reaction precursor will influence both the regio- and stereochemistry of the product. Tethers are often made up entirely of carbon atoms, including unsaturated carbons that are part of carbonyl, olefinic or aromatic groups. A number of other functional groups have been incorporated into the tether, such as amines, amides, esters and ethers.

There are two general ways in which the diene and dienophile may be connected by the tether (Figure 1.4). Reactions where the tether is attached to the terminal carbon of the diene are referred to as Type 1 (**a** and **b**, Figure 1.4). The diene may be *E*- (**a**) or *Z*-substituted (**b**). Type 2 reactions occur when the tether is attached to the internal carbon of the diene (**c**, Figure 1.4).

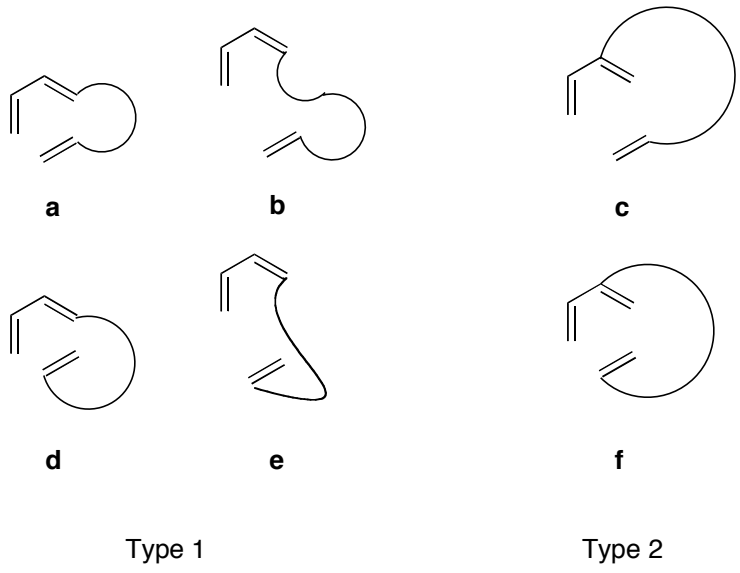


Figure 1.4 Tether connections for IMDA reactions

The length of the tether will influence the regiochemical outcome of the IMDA reaction. For each tether connection in **a**, **b** and **c**, the dienophile may approach the diene with the opposite regioselectivity, as shown in **d**, **e** and **f** respectively (Figure 1.4). Until recently it was thought that no reaction would occur if the tether contained less than three atoms due to strain in the transition state.[26] In 2005, however, Houk reported examples of IMDA reactions with just one atom in the tether.[27] For Type 1 IMDA reactions, the most common tether length is three to five atoms, there are a number of examples of longer tethers.[27-30]

This study will deal mainly with *E*-dienes connected to a dienophile through a three-atom ester tether (Figure 1.5). The ester tether is easily prepared it also allows complete regiochemical control as all precursors cyclise *via* arrangement **a**, not **d** (Figure 1.4).

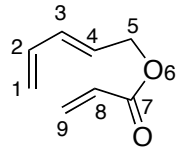


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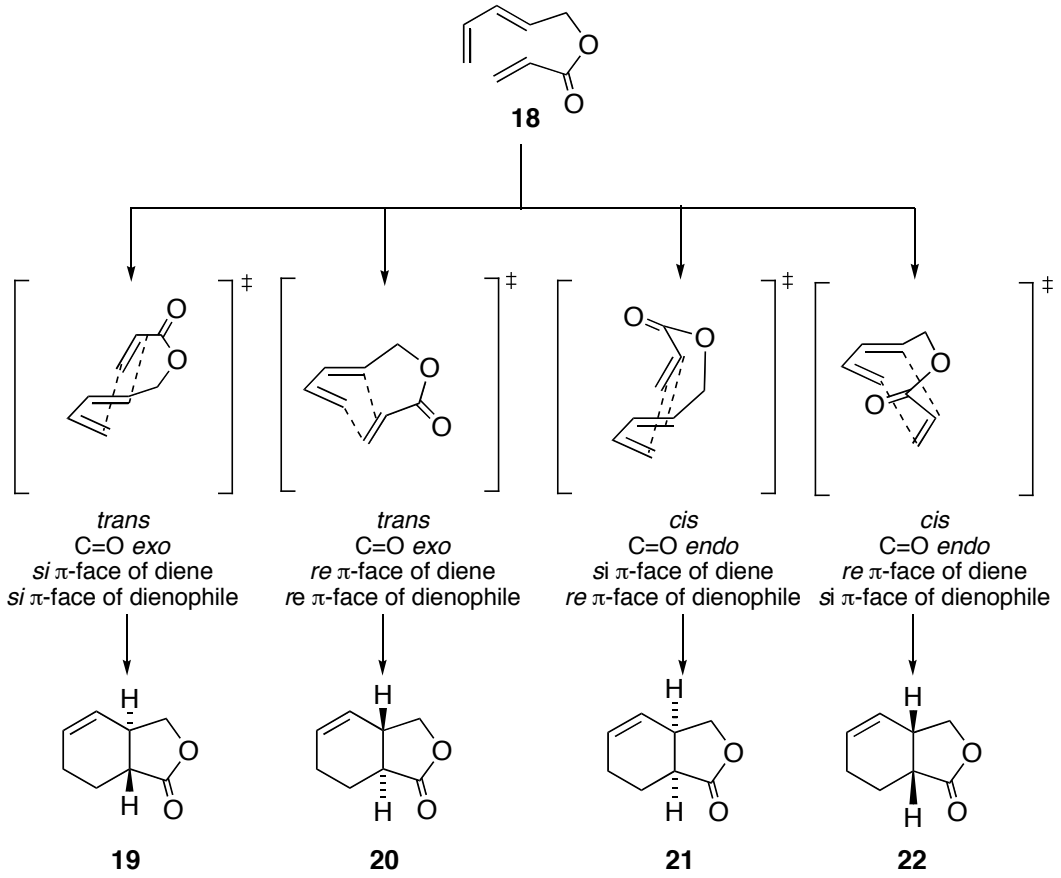
Figure 1.5 *E*-diene system with a three-atom ester tether (1,3,8-nonatriene)

1.2.3 Endo/exo-*Stereoselectivity*

The *endo/exo* cyclisation modes of the ester tethered IMDA reaction are defined by the orientation of the tether carbonyl group with respect to the diene. If the carbonyl group is proximal to the diene the reaction proceeds via the *endo*-transition state, resulting in the formation of the *cis*-fused cycloadducts. If the carbonyl group is distant from the diene the reaction proceeds via the *exo*-transition state and *trans*-fused cycloadducts are formed. The terms *endo* and *exo* will not be used to describe transition states and products as they are ambiguous terms when describing some dienophile patterns, such as *E*-1,2-disubstituted dienophiles. The terms *cis* and *trans* will be used in their place.

As the diene and dienophile moieties in IMDA precursors are generally unsymmetrically substituted, there are two distinct π-faces of both diene and dienophile. Thus, two *trans*-mode cyclisations are possible, with the dienophile *si* π-face reacting with the *si* π-face of the diene, or the dienophile *re* π-face reacting with the *re* π-face of the diene. For the *cis*-mode of addition the dienophile may approach such that its *si* π-

face reacts with the *re* π-face of the diene or so its *re* π-face reacts with the *si* π-face of the diene (Scheme 1.9). With an achiral precursor such as **18**, in the absence of any external chiral influence, the racemate of any *cis* or *trans* adducts would be obtained.



Scheme 1.9 The four possible cyclisation modes for an ester-tethered IMDA reaction

1.2.4 π-Diastereofacial Selectivity

Any IMDA precursor can naturally be divided into three components: the diene, tether and dienophile. Reported methods for obtaining π-diastereofacial selectivity from IMDA reactions involve the placement of suitable substituents on the tether,[31-39] attaching an auxiliary to the dienophile terminus[40-42] and through enantioselective cycloaddition of achiral trienes with chiral Lewis acids,[43-50] or organocatalysts.[6,10] Methods for controlling the π-diastereofacial outcome of IMDA reactions involving substituents on the diene have remained fairly unexplored.

1.3 Mechanism and Theoretical Aspects of the Diels-Alder Reaction

The mechanism of the Diels-Alder reaction may be concerted with partial formation of the two new σ–bonds at the transition state. The transition state of a concerted mechanism may be synchronous, with both bonds forming to the same extent, or asynchronous, with one bond forming advanced of the other. The other possibility is a non-concerted, stepwise mechanism through an intermediate with a single σ–bond formed between the diene and dienophile followed by formation of the second bond. The stepwise mechanism may be of a zwitterionic or diradical nature (Figure 1.6).

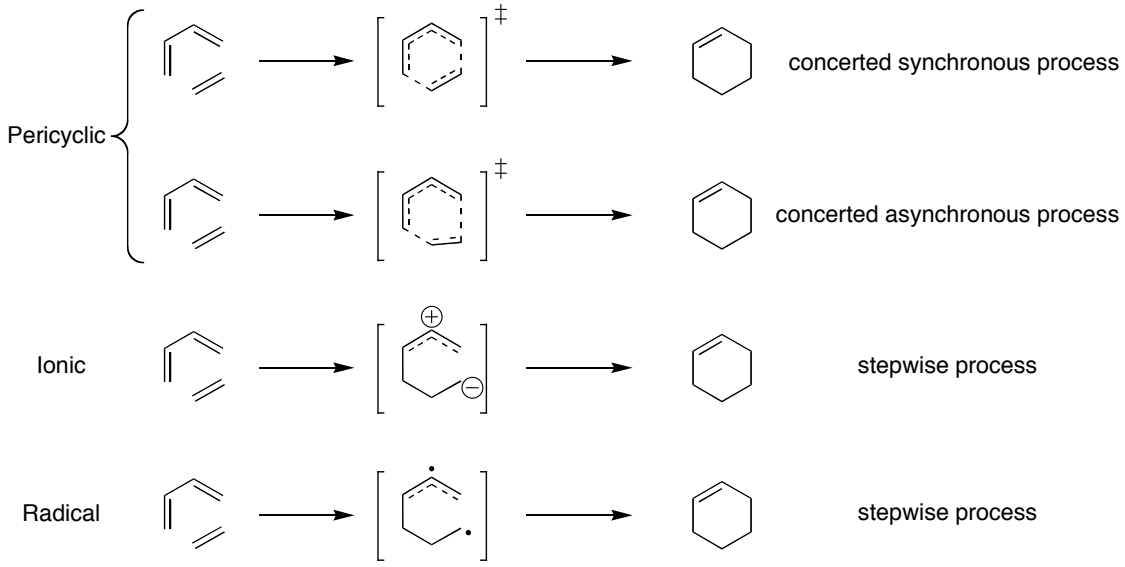


Figure 1.6 Possible mechanisms of the Diels-Alder reaction

The mechanism most widely accepted for a Diels-Alder reaction between a symmetrical diene and symmetrical dienophile is a concerted synchronous process.[51,52] If either the diene or dienophile is unsymmetrical, the Diels-Alder reaction is thought to proceed via a concerted asynchronous process.[51,52] This asynchronicity is due to advanced bond formation between the reactant termini with the largest MO coefficients (Figure 1.7).[53-56]

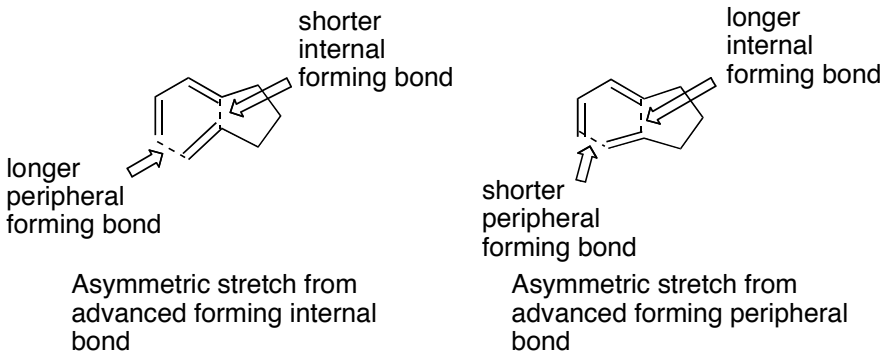
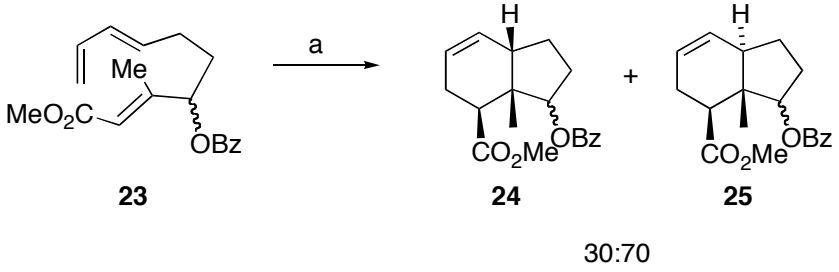


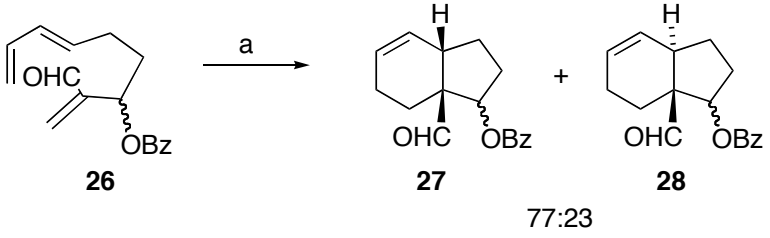
Figure 1.7 Asynchronicity in Diels-Alder reactions

Several groups have proposed models based on asynchronicity to explain the *cis/trans* selectivities of the Diels-Alder reaction.[53-57] White[56] and Roush[54] both proposed that during IMDA reactions of C9 EWG-substituted 1,3,8-nonatrienes (see Figure 1.5), formation of the internal bond is advanced of the peripheral bond in the transition state. This would lead to a pseudo-5-membered transition state. The major product would have a *trans*-ring fusion because the *trans*-1,2-disubstituted 5-membered ring suffers less steric strain than the *cis*-fused isomer (Scheme 1.10).[54]



Scheme 1.10 *Reagents and conditions:* (a) PhMe, BSA, 240 ^{o}C, 11 h, 87%

It was also proposed that 1,3,8-nonatrienes carrying a C8 EWG substituent would preferentially cyclise *via* a pseudo-9-membered transition state, where the formation of the peripheral bond was advanced. This would lead to the major product possessing a *cis*-ring fusion (Scheme 1.11), since a skewed *cis*-fused transition state will minimise non-bonding interactions between the diene and dienophile.[54]

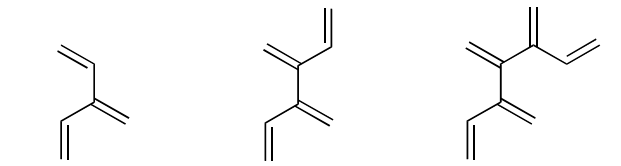


Scheme 1.11 *Reagents and conditions:* (a) CCl_4, BHT, 150 ^{o}C, 18 h, 87%

Whilst a detailed review of computational aspects of the Diels-Alder reaction is out of the scope of this thesis, some key findings are presented below. Paddon-Row and Sherburn recently reported models based on combined synthetic-computational studies.[58] It was found that for C9 substituted 1,3,8-nonatrienes (see Figure 1.5), the IMDA reaction *cis/trans* selectivity is strongly dependant on the dienophile *E/Z* configuration. C1 substituents, however, have no effect on the *cis*/*trans* selectivity. In all cases the forming internal bond in the transition state was advanced of the forming peripheral bond, irrespective of C9/C1 substitution. Despite this, some IMDA reactions of C9 substituted 1,3,8-nonatrienes are *cis*-selective while others are *trans*-selective. The origin of this selectivity is not precisely known, but it is suspected to be a result of secondary orbital interactions, steric and electrostatic effects.[15]

1.4 Dendralenes and Diene-Transmissive Diels-Alder Sequences

Dendralenes are acyclic cross-conjugated oligo-alkenes with much synthetic potential (Figure 1.8).[59-62] The parent [3]dendralene was first synthesised in 1955[63-65] but it was not until 2000 that a general route to this class of compounds was developed.[60,66]



29 [3]dendralene | **30** [4]dendralene | **31** [5]dendralene

Figure 1.8 The parent dendralenes

Diene-transmissive Diels-Alder (DTDA) sequences involve the addition of a dienophile to a dendralene, forming a new diene unit that may participate in a second Diels-Alder reaction with a different dienophile (Figure 1.9). DTDA sequences were reported along with the first syntheses of the dendralenes.[63-65,67]

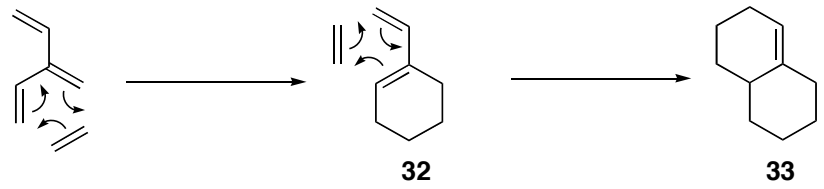


Figure 1.9 A diene-transmissive Diels-Alder reaction

The parent (unsubstituted) [3]dendralene contains two equivalent diene units. If the [3]dendralene bears a substituent at any one of the four possible positions, the two diene units are no longer equivalent (Figure 1.10).

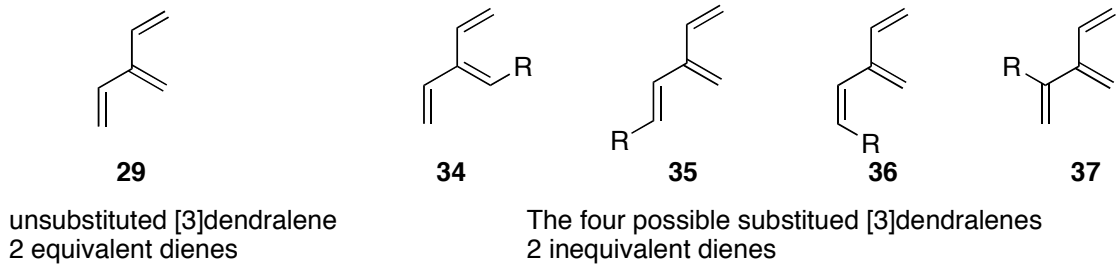


Figure 1.10 Mono-substituted [3]dendralenes

In addition to regiochemistry associated with diene/dienophile orientation, *endo*/*exo* selectivity and π-diastereofacial selectivity, site selectivity of the dienophile addition between the two diene units must also be considered for DTDA sequences of substituted dendralenes.

1.5 Aims

We aim to explore the development of new, efficient and stereocontrolled synthetic strategies using the Diels-Alder reaction as a key element.

The first aim of this project is to gain a better understanding of stereochemical outcome of both the intermolecular and intramolecular Diels-Alder reactions through combined experimental and computational studies. These results will then be applied to the synthesis of biologically active natural products.

There have been many reports describing methods to control the π-diastereofacial selectivity of IMDA reactions (see section *1.2.3*). The possibility of controlling the π-diastereofacial selectivity of IMDA reactions by placing a stereogenic centre allylic to the diene but remote to the tether has remained unexplored. This method of π-diastereofacial control will be investigated in chapter two (Figure 1.11). Computational modelling carried out by Prof. Michael Paddon-Row will be used to explain the experimental results.

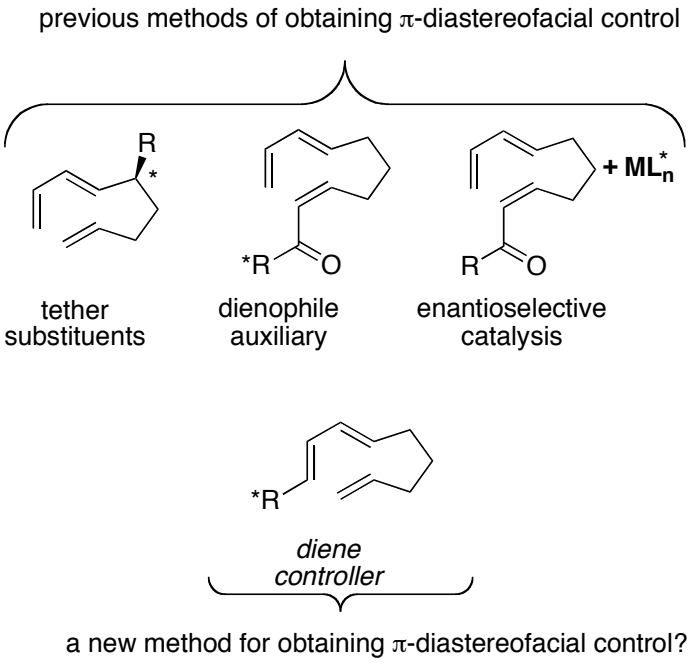
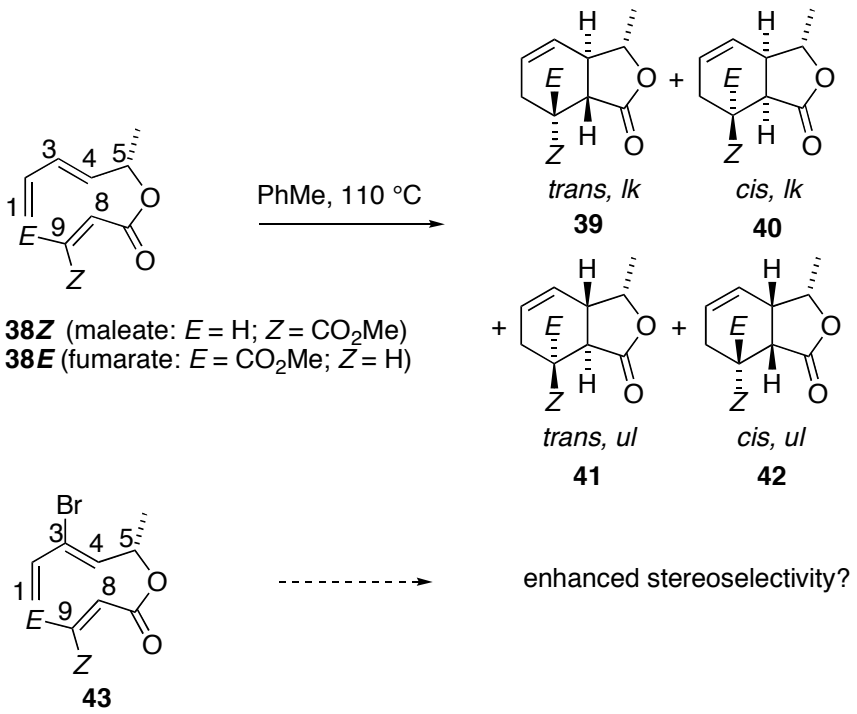


Figure 1.11 Obtaining π-diastereofacial selectivity in IMDA reactions

The Diels–Alder reaction is by no means fully optimised since it commonly delivers more than one stereoisomeric product and, furthermore, methods to effect a switch in stereoselectivity are rare. It has previously been shown that IMDA precursors **38*Z*** and **38*E*** cyclise to give mixtures of all four possible cycloadducts. Chapter three will explore the use of a removable bromine substituent to enhance the stereoselectivity of both inter- and intramolecular Diels-Alder reactions (Scheme 1.12).

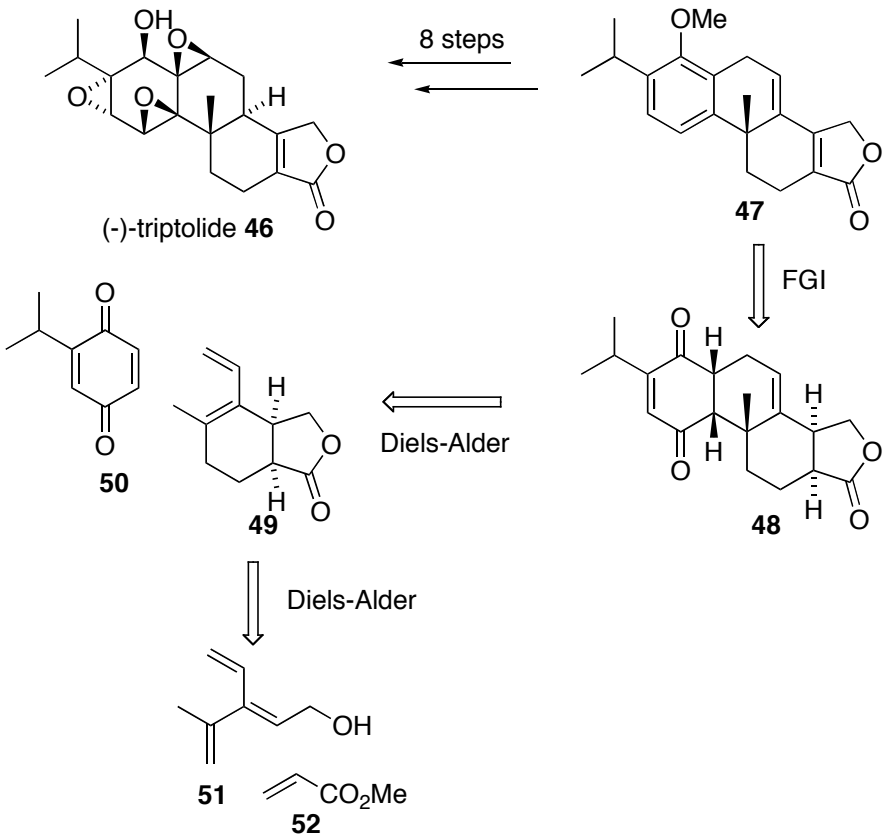


Scheme 1.12 Enhanced stereoselectivity through the use of a removable bromine substituent?

Dendralenes are acyclic cross-conjugated oligo-alkenes with much synthetic potential. They are particularly attractive precursors for Diels-Alder reactions, since they function as multi-dienes, thereby allowing rapid access to polycyclic frameworks. We aim to develop a short and general synthetic route to substituted dendralenes. It will be demonstrated that DTDA sequences can be used for the rapid assembly of enantiomerically pure polycyclic compounds (Scheme 1.13).

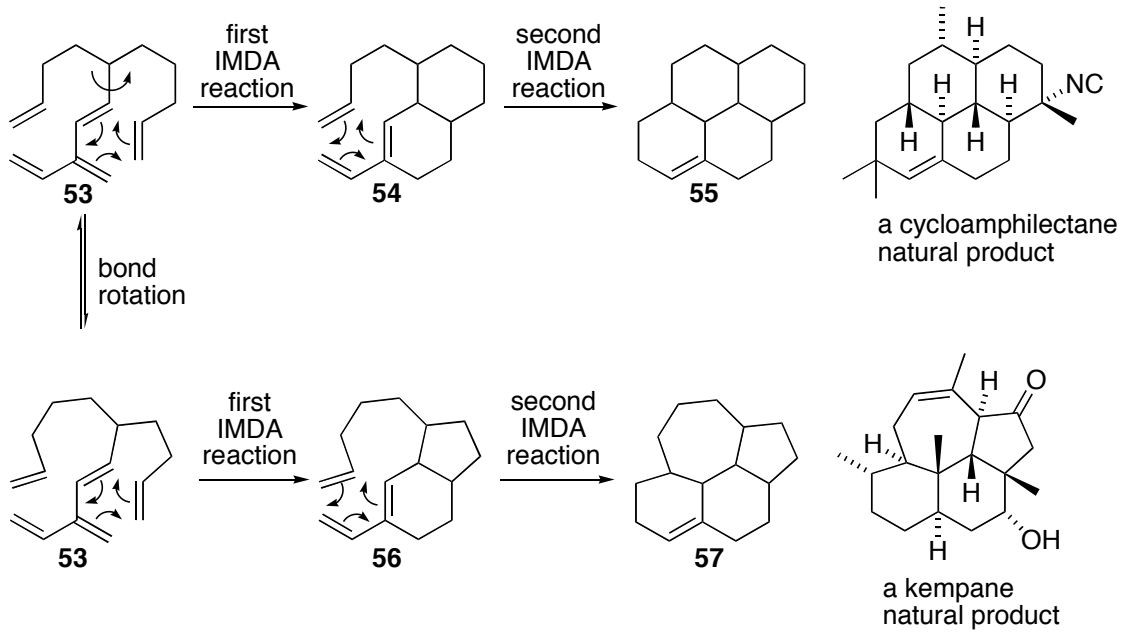
Scheme 1.13 A diene-transmissive Diels-Alder sequence to give fused tetracycles

The new methods developed in earlier chapters will be applied to the synthesis of natural products. A formal total synthesis of triptolide, a biologically active natural product, will be undertaken (Scheme 1.14). A sequence involving two intermolecular Diels-Alder reactions will be used to form the tetracyclic core.



Scheme 1.14 Retrosynthetic analysis of triptolide

Having shown that *internally*-substituted dendralenes are useful for the rapid construction of steroid like frameworks, we aim to demonstrate that a *terminally*-substituted dendralene may be used for the construction of cycloamphilectane or kempane carbon skeletons, depending on the regioselectivity of the IMDA additions (Scheme 1.15).



Scheme 1.15 Diene-transmissive Diels-Alder pathways to different tetracycles.

2 Allylic Stereocontrol of the Intramolecular Diels-Alder Reaction

2.1 Introduction

Despite the popularity of the IMDA reaction in synthesis, accurate predictions of the stereochemical outcome of the reaction are rare. As the diene and dienophile moieties in IMDA precursors are generally unsymmetrically substituted there are two distinct π-faces of both diene and dienophile. This leads to four stereoisomeric products (see Scheme 1.9). In order to accurately predict the stereochemical outcome of an IMDA reaction, the origin of π-diastereofacial selectivity must be elucidated. π-Diastereofacial selectivity may be governed by steric or electronic interactions between the diene and dienophile or by conformational effects in the tether.

Reported methods for achieving π-diastereofacial selectivity during IMDA reactions involve the placement of suitable substituents on the tether,[31-35,37-39] attaching an auxiliary to the dienophile terminus[40-42] and through enantioselective cycloaddition of achiral trienes with chiral Lewis acids[43,44,46-50] or organocatalysts.[6,10] The possibility of controlling the stereochemical outcome of IMDA reactions by placing a stereogenic centre allylic to the diene but remote from the tether has remained unexplored (Figure 2.1).

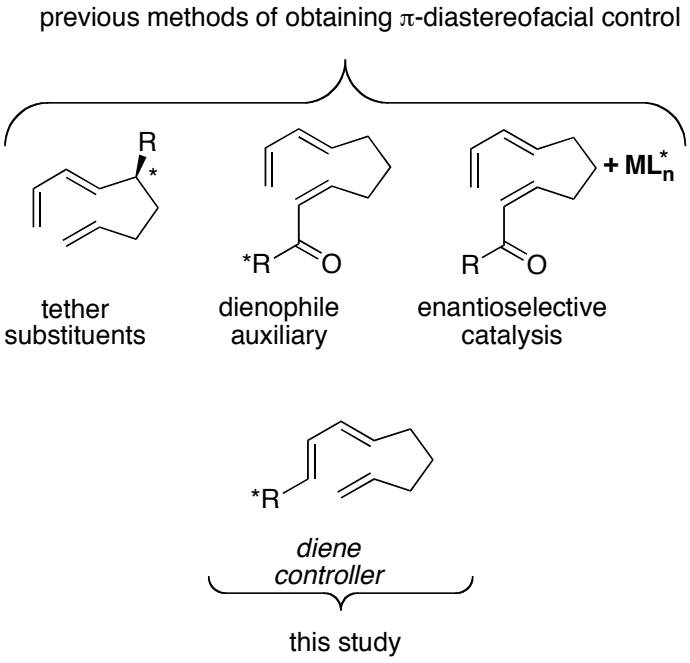


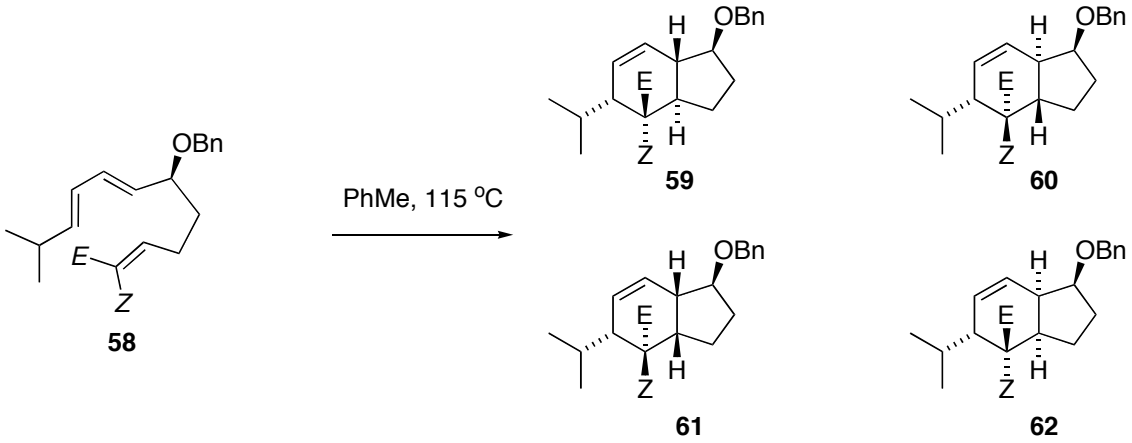
Figure 2.1 Obtaining π-diastereofacial selectivity in IMDA reactions

2.2 Reported Methods of π-Diastereofacial Control

2.2.1 Tether Substituents

There are many reported methods for the stereochemical control of an IMDA reaction through the use of a substituent on the tether. For example, the total synthesis of (±)-dendrobine involved the cyclisation of an IMDA precursor bearing a stereocentre allylic to the diene as the key step.[68,69] In an earlier study of related IMDA reactions, Roush reported the cyclisation of trienes **58a/b** to give the *trans* adducts **59** and **60** in preference to the *cis* adducts **61** and **62** (Table 2.1).[37] The preference for *trans*-fused products was thought to be due to the conformational preference of the tether and the π-diastereofacial selectivities were a result of ^{1,3}A-strain between the vinylic hydrogen at C3 and the substituent at C5. This example highlights the interdependence of *endo*/*exo* selectivity and π-diastereofacial selectivity.

Table 2.1

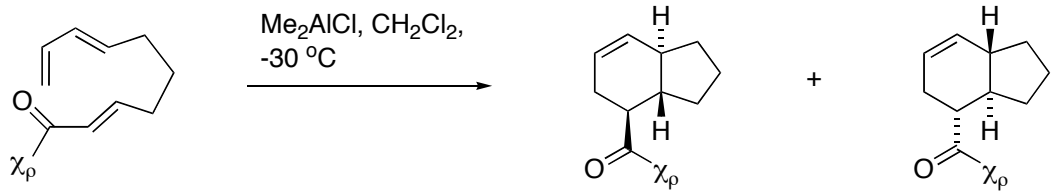


Triene substrate **58**	E/Z	Reaction time (h)	Isolated yield (%)	Adduct ratio[c,d,e] **59:60:61:62**
a	H/CO_2Me	110	64	53:30:13:4
b	CO_2Me/H	44	92	29:37:0:34

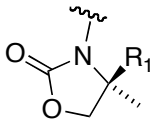
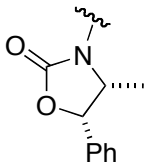
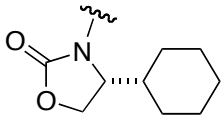
2.2.2 Chiral Auxiliaries at the Dienophile Terminus

The use of chiral auxiliaries attached to the dienophile terminus to control the π-diastereofacial selectivity of IMDA reactions was first reported in 1982 by Roush.[42] Evans obtained much higher yields and selectivities in 1984 through the use of chiral triene-N-acyloxazolidones (Table 2.2).[40]

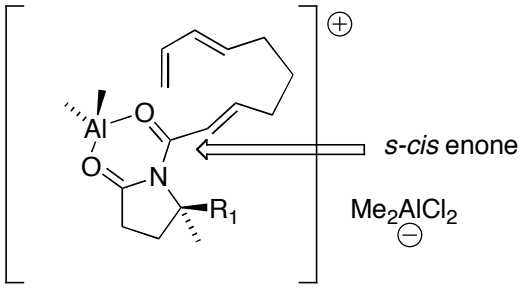
Table 2.2



63 **64** **65**

Chiral Auxiliary		Triene **63**	Ratio (**64:65**)	Isolated Yield of major isomer (%)
	R_1 = *i*Pr	a	83:17	60
	R_1 = CH_2Ph	b	95:5	73
		c	15:85	70
		d	3:97	65

The high levels of π-diastereofacial selectivity observed in these reactions are thought to be due to the in situ formation of the *s-cis* bidentate chelated dienophile **66**. Lewis Acids accelerate Diels-Alder reactions by lowering the LUMO of the dienophile, making it closer in energy to the HOMO of the diene.

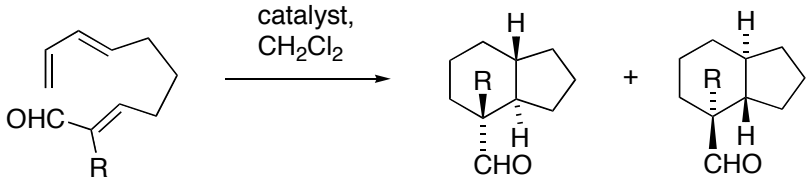


66

2.2.3 Enantioselective Catalysis

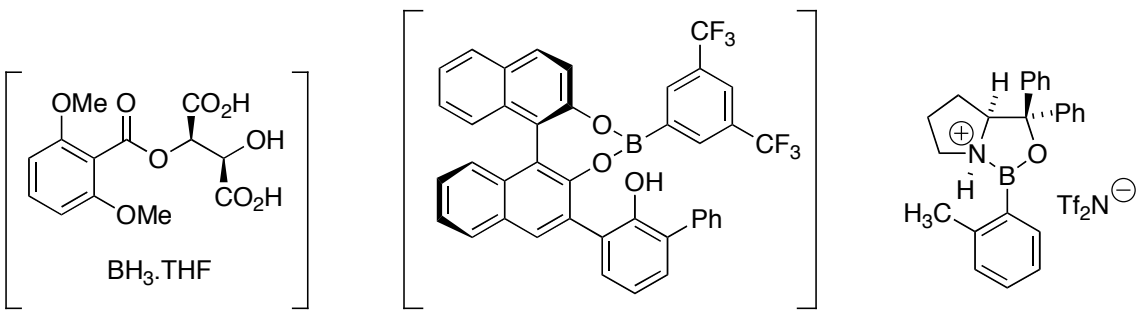
Enantioselective catalysis of the IMDA reaction may be used to obtain enantiomerically pure cycloadducts from achiral, acyclic substrates. The boron catalysts **A** and **B** have been used by Yamamoto to successfully control the enantioselectivity of IMDA reactions of achiral trienes **67a/b** (Table 2.3 entry 1-3).[45,47,50] More recently Corey reported the use of the N-protonated oxazaborolidine catalyst **C** in the IMDA reactions of trienes **67b/c** to give excellent yields and enantioselectivities (Table 2.3, entry 4-5).[43]

Table 2.3



67 **68** **69**

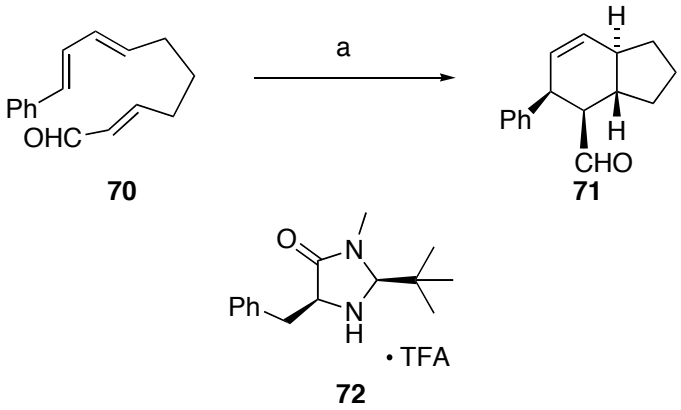
Entry	Triene **67**	R	Catalyst	Temp (^oC)	Ratio **68:69**	Yield (%)
1	a	H	A	- 40	4:96	84
2	a	H	B	- 40	90:10	95
3	b	Me	A	- 20	27:73	74
4	b	Me	C	- 78	95:5	93
5	c	Br	C	- 78	97:3	-



A B C

MacMillan recently reported the use an organocatalyst to control the enantioselectivity of IMDA reactions. IMDA reaction of **70** in the presence of imidazolidinone catalyst **72** resulted in the formation of **71** with >20:1 *endo/exo* selectivity and 93% ee (Scheme

2.1). The catalyst lowers the LUMO of the dienophile via the reversible formation of an iminuim ion.

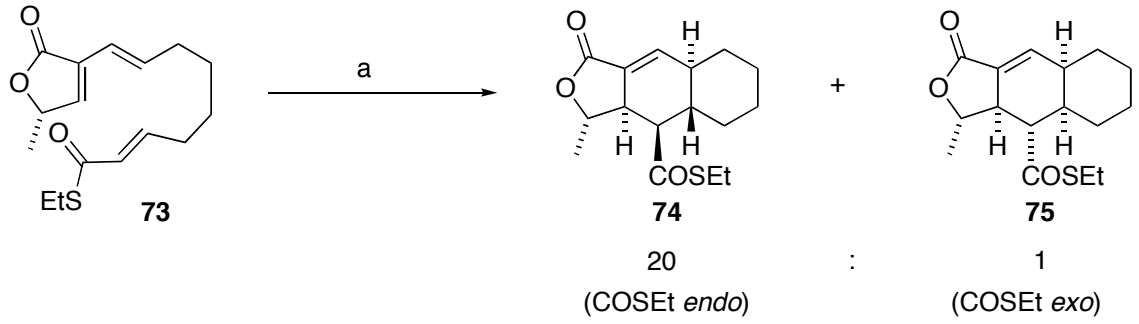


Scheme 2.1 *Reagents and conditions:* (a) 20 mol% **72**, CH_3CN (2% H_2O), -20 ^oC, 20 h, 84%, 93% *ee*.

2.2.4 Diene Auxiliaries

Previous reports of IMDA reactions of substrates with diene auxiliaries employ either conformationally restricted semicylic dienes[70-73] or are complicated by the presence of additional tether substituents and dienophile auxiliaries.[74-76]

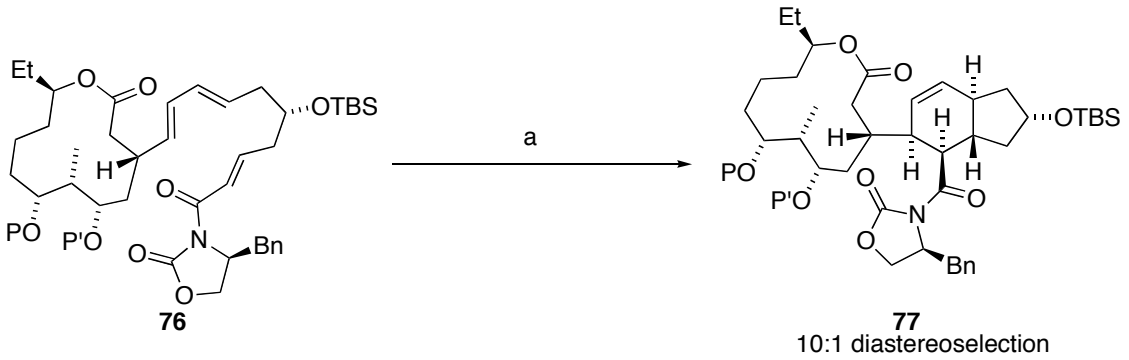
In his total synthesis of (+)-himbacine Hart employed the IMDA reaction of a precursor bearing a stereocentre allylic to the diene terminus (Scheme 2.2).[71] In this example the diene is semicylic and the stereogenic centre is located in the lactone ring, allylic to the diene. Dienophile approach is favoured from the top face, away from the methyl substituent.



Scheme 2.2 *Reagents and conditions*: (a) SiO_2-EtAlCl, PhMe, 40 ^oC, 96 h, 75%

The total synthesis of (+)-lepicidin A involved the IMDA reaction of **76** (Scheme 2.3).[76] In addition to the stereocentre allylic to the terminus of the diene, this precursor has

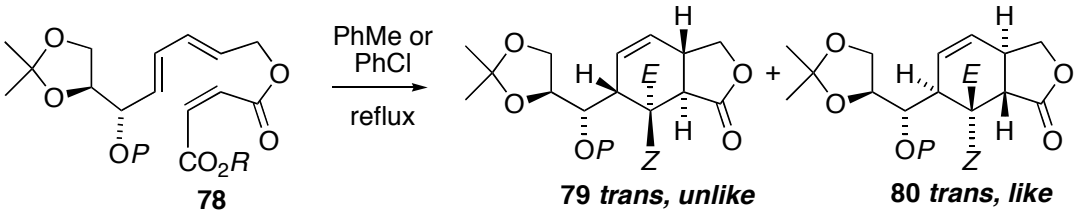
several other stereocentres that could influence the stereochemical outcome of the IMDA reaction.



Scheme 2.3 *Reagents and conditions:* (a) Me_2AlCl, CH_2Cl_2, 0 °C to rt, 71%.

An initial study into the effect of placing a stereogenic centre allylic to the diene but remote from the tether in an IMDA precursor carried out by Sherburn and Lilly demonstrated that high levels of stereoselectivity could be obtained.[77] It was reported that the ester-linked 1,3,8-nonatriene **78** cyclised under thermal conditions to give a mixture of the two *exo*-cycloadducts in good yields (Table 2.4). The reasons for the stereochemical outcome of the IMDA reactions were not known.

Table 2.4



Triene substrate **78**	P/E/Z	Solvent/ Reaction time[a] (h)	Isolated yield[b] (%)	Adduct ratio[c] **79:80**
a	H/H/CO_2Me	PhMe/5	86	66:34
b	TMS/H/CO_2Me	PhMe/12	67	82:12
c	TBS/H/CO_2Me	PhMe/15	80	91:9
d	TIPS/H/CO_2Me	PhMe/18	68	96:4

[a] Time required for >95% conversion, as judged by ^{1}H NMR. [b] Combined isolated yield for the two adducts after chromatography. [c] Determined from ^{1}H NMR spectra of crude reaction mixtures.

The Seebach–Prelog descriptors *like* and *unlike* are used to describe the cycloadducts arising from IMDA reactions of this type.[78] The term *like* describes a cycloadduct resulting from the approach of the dienophile to the *re* face of the diene with an allylic stereocentre of *R* configuration. The term *unlike* refers to *si/R* and *re/S* combinations. For consistent use of this convention, the priorities of the groups about the allylic stereocenter are assigned such that the sp^2 carbon has a higher priority than the sp^3 carbon.[79,80]

2.3 Aims

The scope and limitations of the allylic stereocontrol method for IMDA reactions will be explored. IMDA reactions of ester-linked 1,3,8-nonatriene **78** will be carried out, along with cycloaddition reactions of three additional groups of substrates; namely, triene esters **81**, **82** and **83** (Figure 2.2). Series **81**, diastereomeric with **78**, will be prepared to investigate the dependence of stereoselectivity upon the relative configurations at the allylic and homoallylic stereocentres. Chiral trienes **82** and **83** would uncouple the effects of the allylic and homoallylic stereocentres, allowing a more general assessment of the applicability of this approach. To shed light upon stereoselectivities, these reactions will be examined computationally by Prof. Michael Paddon-Row (UNSW), using the hybrid B3LYP functional together with the 6-31G(d) basis set. It is generally accepted that B3LYP/6-31G(d) models give reliable geometries of transition structures (TSs) and activation energies for pericyclic reactions.[58,81-86]

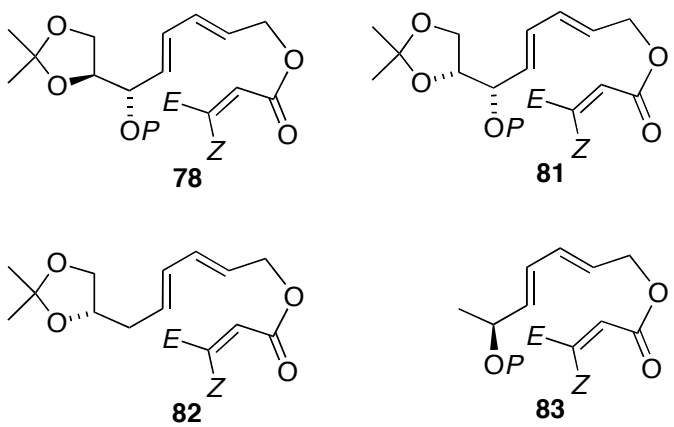


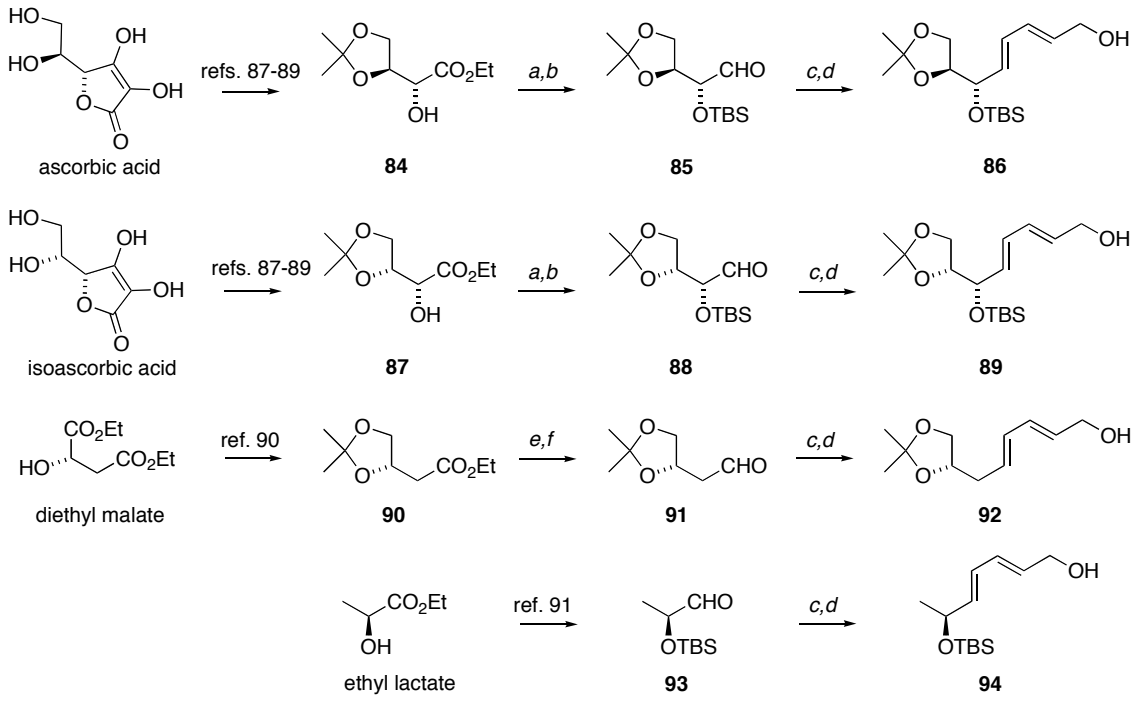
Figure 2.2 Chiral trienes under investigation. The effect of the groups *P*, *E*, and *Z* upon IMDA stereoselectivity will be examined.

2.4 Experimental Results

2.4.1 Synthesis of the Chiral Dienols

Chiral dienols **86**, **89**, **92** and **94** were prepared from the inexpensive and readily available chiral precursors L-ascorbic acid, D-isoascorbic acid, L-malic acid and L-lactic acid respectively, as shown in Scheme 2.3. The syntheses of these dienols follow the same general pathway, involving the chain extension of a chiral ester into the corresponding conjugated diene.

Thus, ascorbic and isoascorbic acids were smoothly converted into monoacetonides[87] before oxidative cleavage with potassium carbonate and hydrogen peroxide in water. The resulting potassium carboxylates were treated with ethyl iodide to give α-hydroxy esters **84** and **87**.[88,89] Regioselective reduction of diethyl malate with borane-dimethyl sulfide complex, followed by treatment of the resulting diol with 2,2-dimethoxypropane[90] produced acetonide **90** in 70% yield after distillation. Silylation of the α-hydroxy esters followed by reduction with DIBALH at low temperature produced aldehydes **85**, **88** and **93**[91] cleanly. Chain extensions were carried out by Horner–Wadsworth–Emmons reaction with phosphonate **95** to selectively give the *E,E*-dienes (J = 15.4-15.1 Hz).[92] The diene esters were reduced cleanly to the dienols with DIBALH. In the malate series, a two step reduction-oxidation[93] sequence was necessary for conversion of ester **90** into aldehyde **91**. Wadsworth–Horner–Emmons reaction between aldehyde **91** and the lithium salt of phosphonate **95**[92] gave the *E,E*-dienoate ester in a disappointing yield. DIBALH reduction gave dienol **92** in 93% yield as a colourless oil.



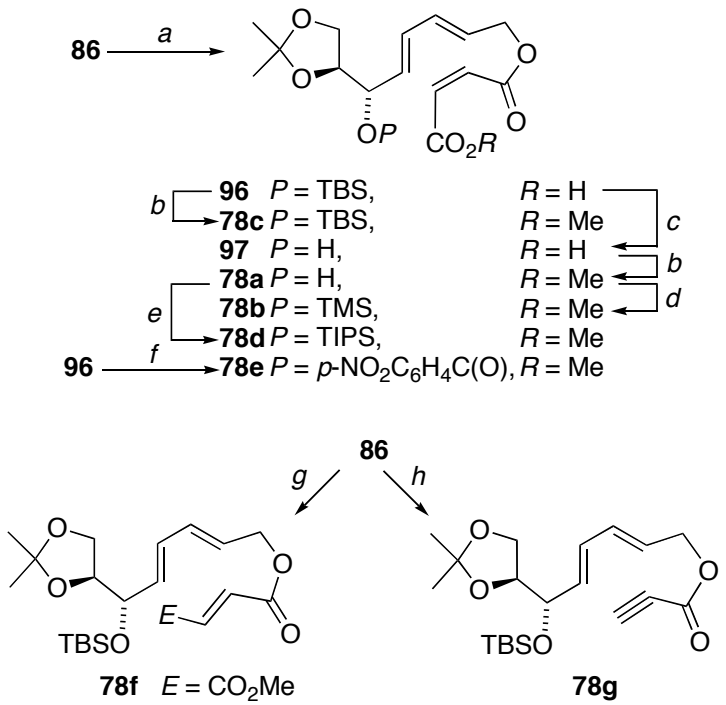
Scheme 2.4 *Reagents and conditions*: (*a*) TBSCl, imidazole, DMF, rt, ascorbate 68%; isoascorbate 91%. (*b*) DIBALH, CH_2Cl_2, –100 °C to –78 °C, ascorbate 86%; isoascorbate 58%. (*c*) $LiN(Si(CH_3)_3)_2$, $(CH_3O)_2P(=O)CH_2CH=CHCO_2Me$ (**95**), THF, –78 °C, ascorbate 49%; isoascorbate 70%; malate 21%; lactate 42%. (*d*) DIBALH, Et_2O, 0 °C, isoascorbate 80%; lactate 88%; ascorbate 74%; malate 93%. (e) $LiAlH_4$, THF, 0 °C, 92%; (f) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, 100%.

2.4.2 Triene Synthesis and IMDA Reactions

2.4.2.1 The ascorbate series

Ascorbic acid-derived dienol **86** was converted into precursors for IMDA reaction differing in both the stereocentre oxygen substituent *P* and the nature of the dienophile. Seven triene derivatives were prepared (Scheme 2.5, **78a–g**).

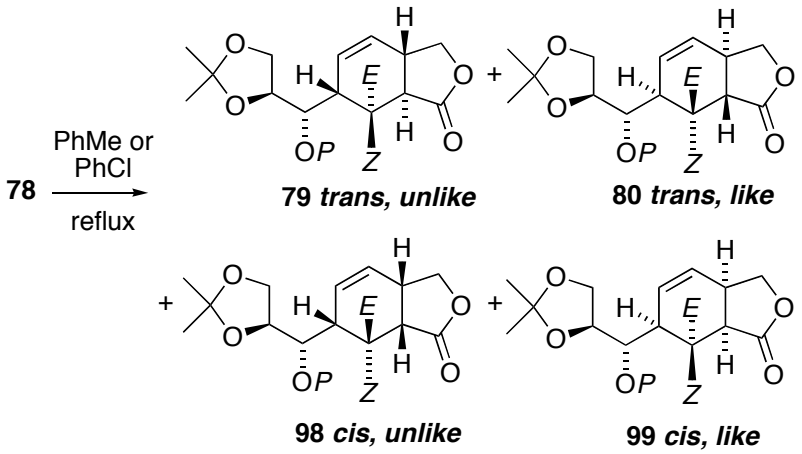
Reaction of dienol **86** with maleic anhydride furnished a near quantitative yield of carboxylic acid **96**, which was treated with diazomethane to give diester **78c**. Desilylation of diester **78c** gave an unacceptably low yield (26%) of secondary alcohol **78a**. A much better result (85% yield) was, however, obtained by deprotection of acid **96**. The resulting hydroxy acid **97** was converted to methyl ester **78a**, which was used to prepare trimethylsilyl derivative **78b** and triisopropylsilyl derivative **78d** by exposure to the appropriate trialkylsilyl triflate. Reaction of alcohol **78a** with *para*-nitrobenzoyl chloride gave ester **78e**. Fumarate ester **78f** and propynoate ester **78g** were prepared by Steglich esterification of dienol **86** with the requisite carboxylic acid.



Scheme 2.5 *Reagents and conditions*: (*a*) maleic anhydride, Et_3N, DMAP, CH_2Cl_2, rt, 99%. (*b*) CH_2N_2, Et_2O, **96** → **78c**, 74%; **97** → **78a**, 80%. (*c*) *n*-Bu_4NF, THF, rt, 85%. (*d*) TMSOTf, Et_3N, DMAP, CH_2Cl_2, rt, 51%. (*e*) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 91%. (*f*) *p*-$NO_2C_6H_4COCl$, pyridine, DMAP, 25 °C, 82%; (*g*) *(E)*-$HO_2CCH{=}CHCO_2Me$, DCC, DMAP, Et_2O, rt, 96%. (*h*) $HO_2CC{\equiv}CH$, DCC, DMAP, Et_2O, rt, 65%.

Precursors **78a**–**e** underwent IMDA reactions at high dilution in boiling toluene producing mixtures of the four possible cycloadducts (Table 2.5). In all five cases, two of the four adducts were formed in significantly larger amounts than the other two.

Table 2.5 IMDA reactions of ascorbic acid-derived trienes **78a–f.**



Triene substrate **78**	P/E/Z	Solvent/ Reaction time[a] (h)	Isolated yield[b] (%)	Adduct ratio[c,d,e] **79:80:98:99**
a	H/H/CO_2Me	PhMe/5	86	56:32:8:4
b	TMS/H/CO_2Me	PhMe/12	67	80:14:4:2
c	TBS/H/CO_2Me	PhMe/15	80	86:9:4:1
d	TIPS/H/CO_2Me	PhMe/18	68	92:7:1:0
e	PNB/H/CO_2Me	PhMe/12	95	49:39:6:6
f	TBS/CO_2Me/H	PhCl/53	62	12:3:82:3

[a] Time required for >95% conversion, as judged by ^{1}H NMR. [b] Combined isolated yield for the four adducts after chromatography. [c] Determined from ^{1}H NMR spectra and HPLC analyses of crude reaction mixtures. Differences +/– 3%. [d] Kinetic product ratios are reported: control experiments confirmed that all cycloadducts were stable to the reaction conditions. [e] The two minor adducts were not fully characterized.

The stereochemistry of each the two major cycloadducts from the three silyl ether substrates **78b–d** were elucidated using 2D NMR experiments.* Finally, the identities of cycloadducts **79e** and **80e** were confirmed by esterification of the alcohols **79a** and **80a** with *para*-nitrobenzoyl chloride in the usual manner. Insufficient quantities of the two minor cycloadducts were obtained from these experiments for full characterization.

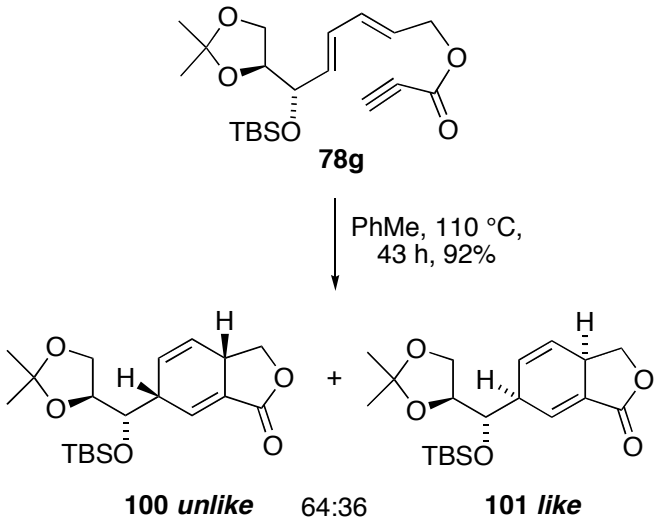
The stereoselectivities observed for maleate derivatives **78a–e** (Table 1) are intriguing in that the level of π-diastereofacial selectivity varies considerably with group *P*. The

* These 2D NMR experiments were carried out and analysed by M. Lilly

alcohol substrate **78a** exhibits only modest *unlike*[78-80] π-diastereofacial preference between the two *trans*-cycloadducts but this improves considerably after the installation of common silyl protecting groups.[94] A progressive improvement in *unlike* selectivity is observed as the size of the silyl group is increased (*cf.* **78b** → **78c** → **78d**). The TIPS derivative **78d**, the most sterically demanding protecting group examined, instigates a remarkably high level of stereocontrol. Conversely – and unexpectedly – the *para*-nitrobenzoate derivative **78e** exhibits the lowest π-diastereofacial selectivity of the five substrates.

As expected, the fumarate precursor **78f** was significantly less reactive than the corresponding maleate **78c**.[56] The same isolated yields and stereochemical outcomes were obtained when **78f** was heated in toluene and chlorobenzene, although the former required prolonged reaction times for complete conversion. Fumarate **78f** underwent cycloaddition with virtually complete *unlike*-selectivity and high *cis*-selectivity, the latter feature being in stark contrast to previous findings with pentadienyl fumarates, which generally furnish mildly *trans*-selective IMDA reactions.[56,58,84,86,95-104]

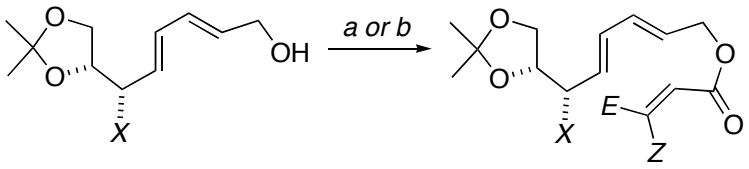
The last precursor derived from ascorbic acid, the alkynic dienophile **78g**, underwent a smooth IMDA reaction at 110 °C (Scheme 2.6).[56] Lacking questions of *cis/trans*-stereoselectivity, this substrate perhaps best exemplifies the *unlike* π-diastereofacial preference found in this series. The IMDA reaction of the corresponding 2-butynoate ester was thwarted by aromatisation of the cycloadducts under the reaction conditions.



Scheme 2.6 IMDA reaction of ascorbic acid-derived alkynoate **78g**.

2.4.2.2 Isoascorbate and malate series.

To determine if the outcomes of these reactions were dependent upon the *relative* stereochemistry of this starting material or if the allylic stereocentre is necessary for stereoselectivity the IMDA reactions of two more series of substrates were performed. The isoascorbic acid-derived dienol **89** was converted into maleate and fumarate derivatives **81a** and **81b** in the same manner as described previously (Scheme 2.7) while the malic acid-derived dienol **92** was transformed into corresponding trienes **82x** and **82y**.



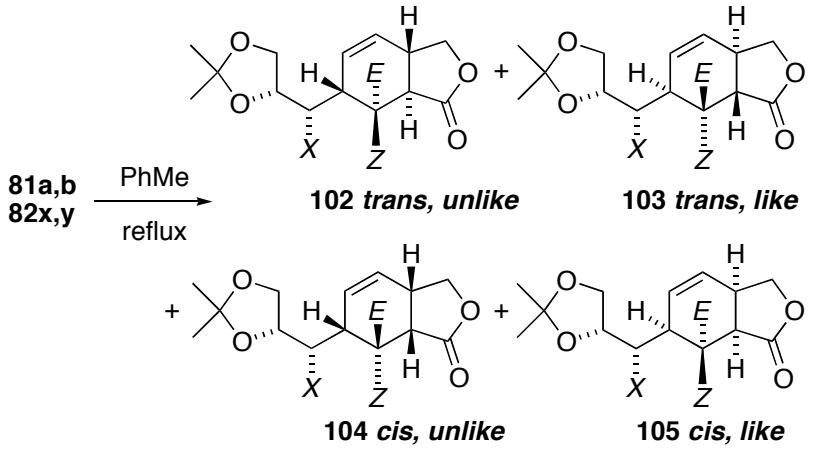
89 *X* = OTBS
92 *X* = H

81a *X* = OTBS *E* = H *Z* = CO_2Me
81b *X* = OTBS *E* = CO_2Me, *Z* = H
82x *X* = H *E* = H *Z* = CO_2Me
82y *X* = H *E* = CO_2Me *Z* = H

Scheme 2.7 *Reagents and conditions*: (*a*) maleic anhydride, Et_3N, DMAP, CH_2Cl_2, rt, then CH_2N_2, Et_2O, 0 °C, **89** → **81a**, 74%; **92** → **82x**, 56%. (*b*) *(E)*-$HO_2CCH{=}CHCO_2Me$, DCC, DMAP, Et_2O, rt, **89** → **81b**, 78%; **92**→ **82y**, 74%.

The isoascorbic acid-derived precursors underwent IMDA reactions with approximately the same ease as the ascorbic acid series, whereas the malic acid derived precursors cyclized somewhat more rapidly (Table 2.6).

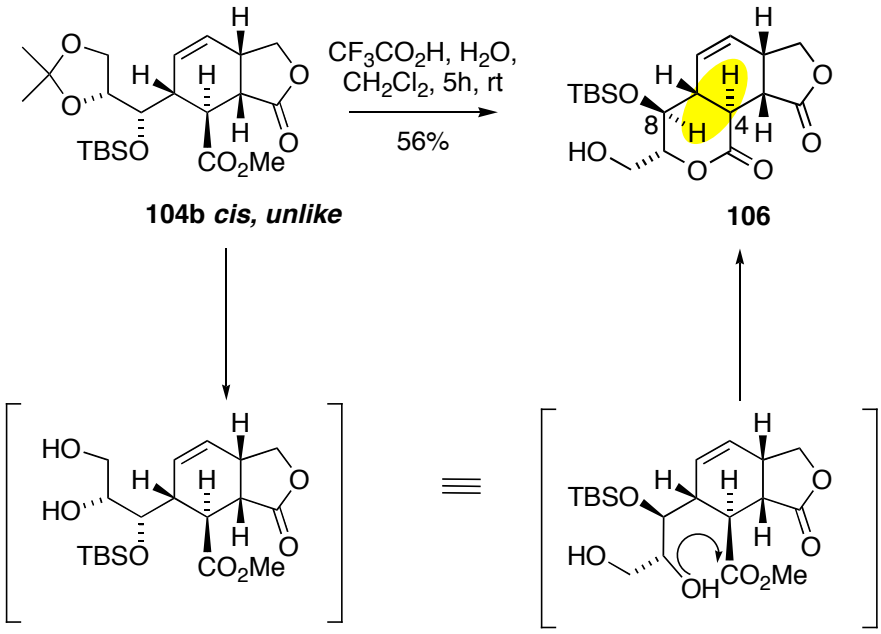
Table 2.6 IMDA reactions of isoascorbic acid and malic acid derived precursors **81a,b** and **82x,y**.



Triene substrate	X/E/Z	Solvent/ Reaction time[a] (h)	Isolated yield[b] (%)	Adduct ratio[c,d,e] **102:103:104:105**
81a	OTBS/H/CO_2Me	PhMe/9.5	86	78:16:4:2
81b	OTBS/CO_2Me/H	PhCl/72	89	9:6:66:19
82x	H/H/CO_2Me	PhMe/3.5	89	41:39:11:9
82y	H/CO_2Me/H	PhCl/43	89	32:33:18:17

[a] Time required for >95% conversion, as judged by ^{1}H NMR. [b] Combined isolated yield for the four adducts after chromatography. [c] Determined from ^{1}H NMR spectra and HPLC analyses of crude reaction mixtures. [d] Kinetic product ratios are reported: control experiments confirmed that all cycloadducts were stable to the reaction conditions. [e] The stereochemical identities of the two minor adducts were not elucidated.

Product stereochemistries in the isoascorbate series were determined through NMR experiments and comparison to the data for the other series. The stereochemical identity of the major product from fumarate precursor **81b** was established by selective acetal deprotection/lactonization to **106** (Scheme 2.8). It was thought that exposure of **104b** to triflouroacetic acid would result in removal of the silyl protecting group. However ^{1}H NMR revealed that the silyl group was still present but the acetal protecting group had instead been selectively removed. The stereochemistry of the bis-lactone **106** was determined through 2D NMR experiments. A NOESY cross peak between H-4 and H-8 (highlighted in yellow) is an indicator of the product stereochemistry (Figure 2.3).



Scheme 2.8 Acetonide deprotection/lactonization of **104b.**

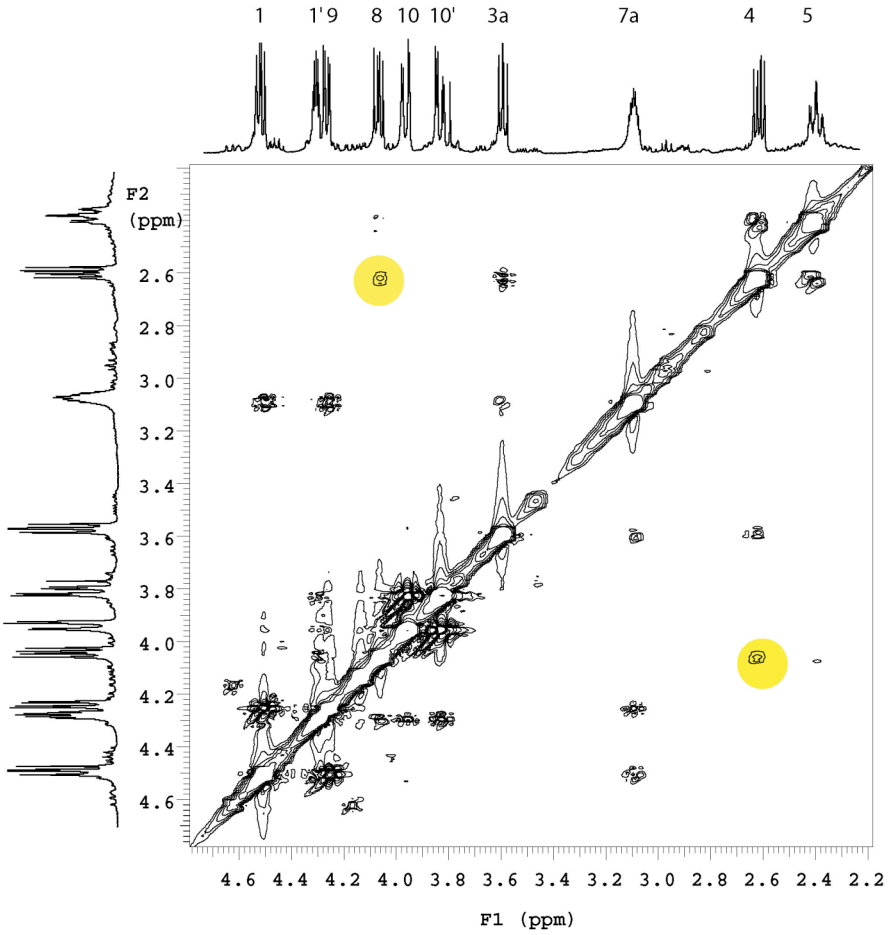


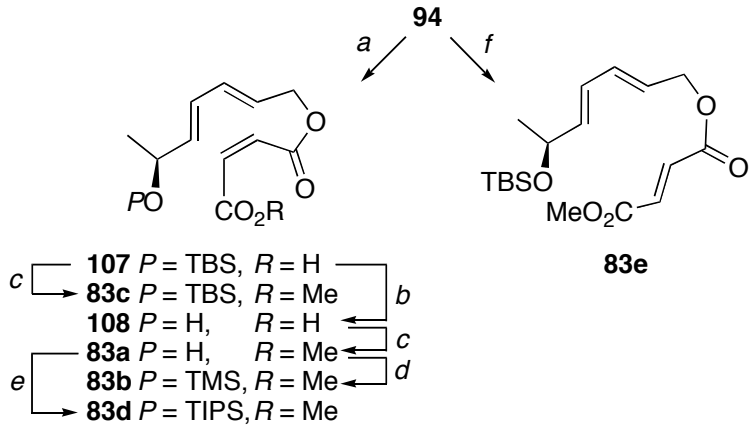
Figure 2.3 NOESY spectrum for **106**.

In the malic acid products, the ring junction stereochemistry was clearly evident from NMR coupling constants. The ring junction geometry of cycloadducts **102x, 103x, 102y** and **103y** was evident from the large *trans*-diaxial coupling constants (^3J = 14.2-13.6 Hz) between the ring junction hydrogens.

The major diastereomer obtained from intramolecular cycloadditions of isoascorbic acid-derived substrates **81a** and **81b** (Table 2.6) correlates with those obtained in the ascorbic acid series **78c** and **78f** (Table 2.5). Thus, a *Z*-dienophile precursor (i.e. **81a** or **78c**) gives the *trans, unlike* adduct whereas the *E*-dienophile precursor (i.e. **81b** or **78f**) gives the *cis, unlike* adduct. The adduct ratios are similar but not identical, indicating a contribution to the overall stereochemical outcome by the configuration at the homoallylic site. No π-diastereofacial selectivity was witnessed in cyclisation of either maleate **82x** or fumarate **82y**, however, indicating that a lone homoallylic stereocentre is insufficient to invoke stereoselection. It is noteworthy that the *E*-dienophile precursor **82x** undergoes a *trans*-selective IMDA reaction, a result which is consistent with previous findings[56,58,84,86,95-104] but in contrast to those of the other three fumarate precursors in the present study.

2.4.2.3 Lactate series

In the research described so far, it has been demonstrated that stereogenic elements at the diene terminus can induce high levels of stereoselectivity upon IMDA reactions. Ascorbate and isoascorbate-derived systems **78** and **81** are complicated by the presence of two stereocentres and an acetal functional group. To determine if precursors lacking these structural features would also give rise to stereoselective IMDA reactions and, furthermore, to minimize the assumptions made in the computational modelling of this reaction, we elected to carry out a synthetic study on dienol **94**. Thus, lactic acid-derived dienol **94** was converted into the four maleate esters **83a–d**, and the fumarate ester **83e** using similar procedures to those described previously (Scheme 2.9).

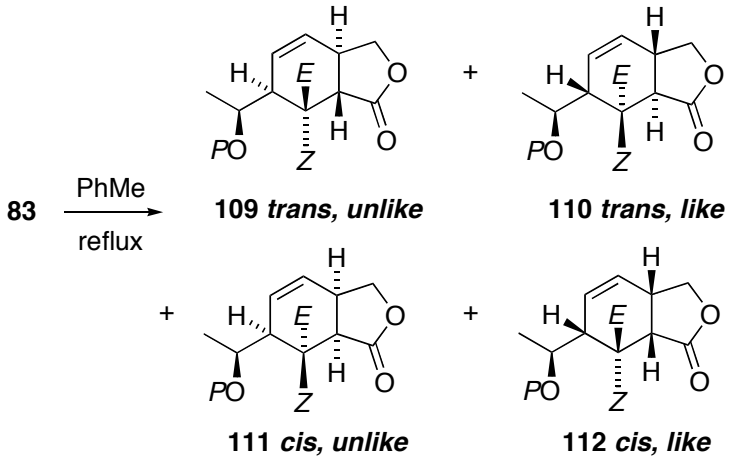


Scheme 2.9 *Reagents and conditions*: (*a*) maleic anhydride, Et_3N, DMAP, CH_2Cl_2, rt, 75%. (*b*) *n*-Bu_4NF, THF, rt, 44%. (*c*) CH_2N_2, Et_2O, 0 °C, **107 → 83c**; 87%, **107–83a**, 44%. (*d*) TMSOTf, Et_3N, DMAP, CH_2Cl_2, rt, 88%. (*e*) TIPSOTf, Et_3N, CH_2Cl_2, rt, 78%. (*f*) *(E)*-$HO_2CCH{=}CHCO_2Me$, DCC, DMAP, Et_2O, rt, 89%.

The five triene precursors underwent IMDA reactions in refluxing toluene (Table 2.7) over slightly shorter reaction times than those of the corresponding ascorbic and isoascorbic acid-derived precursors (Table 2.5 and Table 2.6). Furthermore, mixtures of the four possible cycloadducts were produced in all cases.

The four cycloadducts obtained from IMDA reaction of the maleate TBS ether **83c** were separated by HPLC. The ring junction geometry of cycloadducts **109c** and **110c** was evident from the large *trans*-diaxial coupling constants (^3J = 13.5 Hz) between the ring junction hydrogens. On the basis of 2D NMR experiments it was possible only to elucidate the relative stereochemistry at the four new stereocentres; the lack of conformational preference about the C1'–C5 bond precluded the correlation of new with existing stereochemistry in this set of cycloadducts. Thus, whereas the *endo/exo*-stereoselectivity of these IMDA reactions could be ascertained readily, the π-diastereofacial selectivity was more elusive.

Table 2.7 IMDA reactions of lactic acid derived trienes **83a–e**



Triene substrate **83**	P/E/Z	Solvent/ Reaction time[a] (h)	Isolated yield[b] (%)	Adduct ratio[c,d] **109:110:111:112**
a	H/H/CO_2Me	PhMe/4.5	88	41:36:5:18[e]
b	TMS/H/CO_2Me	PhMe/6.5	83	56:30:6:8
c	TBS/H/CO_2Me	PhMe/7.25	96	61:27:5:7
d	TIPS/H/CO_2Me	PhMe/8.25	85	63:26:5:6
e	TBS/CO_2Me/H	PhCl/43	73	8:28:40:24

[a] Time required for >95% conversion, as judged by ^{1}H NMR. [b] Combined isolated yield for the four adducts after chromatography. [c] Determined from ^{1}H NMR spectra and HPLC analyses of crude reaction mixtures. Differences +/– 3%. [d] Kinetic product ratios are reported: control experiments confirmed that all cycloadducts were stable to the reaction conditions. [e] Tricyclic *bis*-lactones **113** and **114** were isolated instead of *cis*-adducts **111a** and **112a** in this series. See main text for an explanation.

The identities of the four sets of products from each of the reactions of **83a**, **83b** and **83d** were correlated with the four derived from **83c** by interconversions. Thus, crude reaction mixtures obtained by heating **83b** and **83c** were treated with trifluoroacetic acid. NMR and GC analyses of these reaction mixtures linked the TMS and TBS cycloadducts with those derived from the alcohol precursor **83a**. Attempts to deprotect TIPS-protected cycloadducts were unsuccessful, so two trans-alcohols **109a** and **110a** were converted to TIPS ethers **109d** and **110d**, respectively. Cis-adducts **111a** and **112a** in this series rapidly form tricyclic bis-lactones **113** and **114** respectively (Figure 2.4) under the reaction conditions. Crystal structures were obtained of compounds **110a**, **113**, **114** (Figure 2.4). Treatment of compound **110e** with trifluoroacetic acid generated the alcohol which spontaneously lactonized to bislactone **115**. Similar treatment of **111e** with TFA gave alcohol **116**. The structures of **115** and **116** were also confirmed by single crystal X-ray analyses (Figure 2.4).

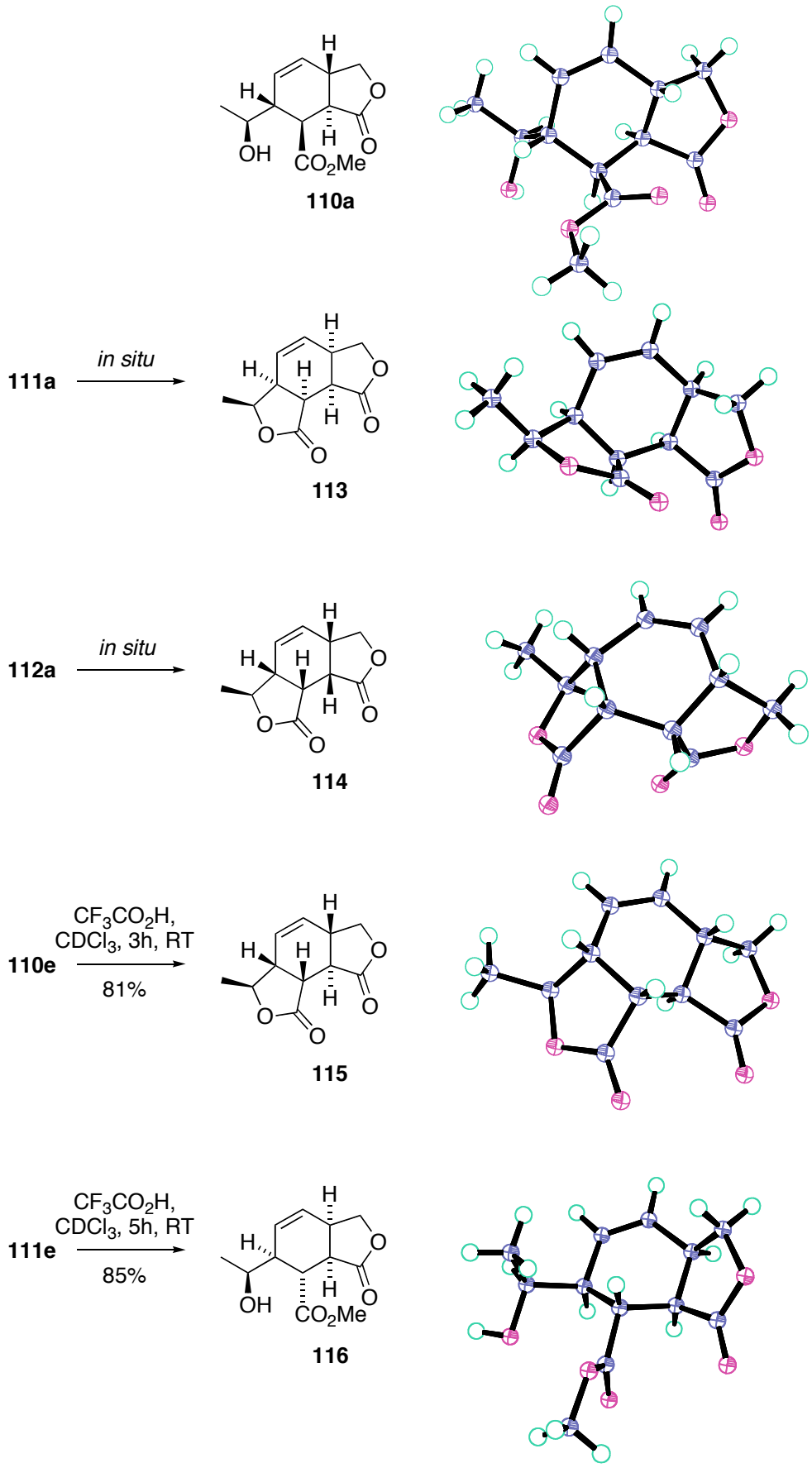


Figure 2.4 Thermal ellipsoid diagrams of **110a**, **113**, **114**, **115** and **116**. Ellipsoids show 30% probability levels.

The main features of the lactate series can be summarized as follows. The *Z*-dienophile precursors **83a–d**, once again, undergo strongly *trans*-selective IMDA reactions. The alcohol substrate **83a** exhibits a very small π-diastereofacial selectivity during cycloaddition. The corresponding silyl ethers undergo more stereoselective IMDA reactions, with higher levels of π-diastereofacial selectivity being obtained with larger silyl groups. Nevertheless, the highest level of π-facial selectivity delivered by a lactate-derived precursor (**83d**, *unlike:like* = 68:32) is considerably lower than that witnessed in the ascorbate series (**78d**, *unlike:like* = 93:7). The *E*-dienophile precursor **83e** undergoes a reaction with considerably lower stereoselectivity than the corresponding ascorbate and isoascorbate trienes, **78f** and **81b** respectively. Once again, however, the *cis,unlike* diastereomer is the major adduct.

2.5 Discussion

Whilst the stereoselectivity of IMDA reactions of precursors **78, 81, 82** and **83** varies considerably, the following generalizations can be made: (1) Maleate esters of dienols **86**, **89**, **92** and **94** undergo *trans*-selective IMDA reactions, whereas the corresponding fumarate esters are generally *cis*-selective. The exception is fumarate **82y**, which undergoes a *trans*-selective IMDA reaction. These selectivities are more pronounced the larger the substituents attached to the allylic stereocentre; (2) Chiral allylic alcohols (**78a** and **83a**) give poor to moderate levels of π-diastereofacial selectivity in IMDA reactions. Silyl ether derivatives of these allylic alcohol precursors give moderate to high levels of π-facial stereoselectivity, with an increase in the size of the silyl protecting group leading to an increase in stereoselection. An allylic benzoyloxy derivative gave essentially no π-facial discrimination in these reactions; (3) An increase in the size of the alkyl group leads to an increase in π-facial stereoselectivity (compare results of substrates **78** and **81** with those of **83**); (4) The two diastereomeric dienols **86** and **89** gave similar but non-identical stereoisomer ratios, a result which demonstrates that the allylic stereocentre controls the outcome of these reactions to a large extent; (5) An allylic stereocentre appears to be necessary for π-facial stereoselectivity, since substrates carrying an allylic methylene and homoallylic stereocentre (**82x**,**y**) gave no stereocontrol.

These experimental results clearly demonstrate that the presence of an allylic stereocentre can indeed give rise to high levels of stereoselectivity in IMDA reactions. Inspection of molecular models and literature searches gave no clear reasons for the observed experimental stereoselectivities. The C* substituents would be expected to adopt an approximately staggered arrangement with respect to the developing C1–C9 bond,[105,106] with allylic alkyl, silyloxy, and hydrogen substituents distributed among the *inside* (*in*), *anti* (*an*), and *outside* (*ou*) positions in TSs, as depicted by **117** (Figure 2.5). The facial selectivity is determined by the positional preferences of the C* substituents for the *in*, *an* and *ou* sites in the TS. What are these preferences? This question was answered by model computational studies.

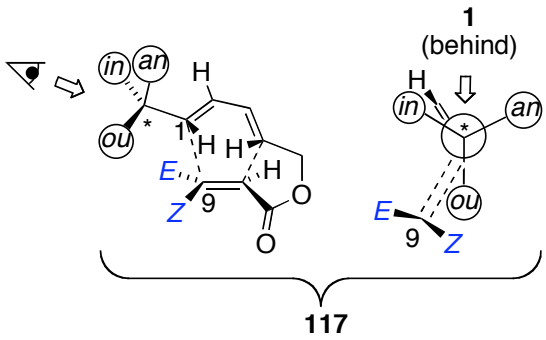


Figure 2.5 A representation of one of the *trans*-TSs. The Newman projection formula on the right depicts a view along the C*–C1 bond of the structure on the left.

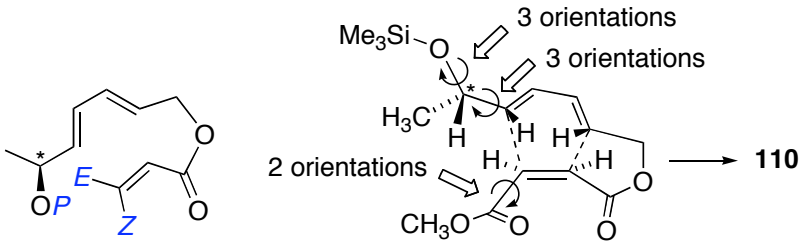
2.6 Computational Results and Discussion[Ψ]

2.6.1 Computational Modelling

B3LYP/6-31G(d) density functional theory calculations were conducted on maleate and fumarate IMDA precursors **83b**, **83f** and **83g** (Figure 2.5). The computational modelling of these reactions is complicated by the large number of possible reactive orientations of each precursor. Thus, in addition to the three conformations about the C*–C1 bond, three conformations about the allylic C*–O bond and s-*cis*/s-*trans* orientations of the C9–CO_2CH_3 bond are feasible (Figure 2.5). In principle, therefore, a total of 72 diastereomeric TSs can be envisioned *for each IMDA precursor*, with 18 diastereomeric TSs leading to each of the four cycloadducts, **109**, **110**, **111** and **112.** It was impractical to calculate all 72 TSs at this level of theory for each IMDA precursor

[Ψ] Calculations were carried out by Prof. Michael Paddon-Row (UNSW) and the results were interpreted by Assoc. Prof. Michael Sherburn and Prof. Michael Paddon-Row.

and, consequently, relaxed potential energy scans were carried out on model TSs to locate the lowest energy conformation about the allylic C*–O bond. IMDA TSs for **83f** in which the ester adopts the s-*cis* conformation were found to be slightly (2.5 – 6.0 kJ mol^{-1}) lower in energy than the corresponding s-*trans* TSs. In all other respects, the two sets of TSs, one with s-*cis* and the other with s-*trans* ester conformations showed very similar trends, particularly with respect to facial selectivity; hence discussion here will be limited to the s-*cis* TSs.



83b: *P* = $OSiMe_3$, *E* = H, *Z* = CO_2Me **83b**: ***trans, like*** TSs
83f: *P* = $OSiH_3$, *E* = H, *Z* = CO_2Me
83g: *P* = $OSiH_3$, *E* = CO_2Me, *Z* = H

Figure 2.6 Structures of the three precursors under scrutiny by DFT and the 18 possible diastereomeric TSs for the *trans, like* IMDA cycloaddition mode of 83b.

These considerations led to a more manageable three TSs leading to each of the four diastereomeric adducts. These three TSs, corresponding to three low energy conformations about the C*–C1 bond; cf. Figure 2.4, were located for each of the four cycloaddition modes (*cis/trans*; *like/unlike* combinations) and their relative energies (including zero-point energies) were used to construct a predicted Boltzmann distribution of stereoisomeric cycloadducts. The structures and relative energies of 12 diastereomeric TSs for the IMDA reaction of C*–OSiH_3 *Z*-dienophile precursor **83f** are depicted in Figure 2.6.

For both C*–OSiH_3 triene **83f** and C*–OSiMe_3 triene **83b**, theory correctly predicts the major – minor product sequence: the predicted Boltzmann populations of IMDA adducts from the reaction of **83b** at 383K in the gas phase (**109b**:**110b**:**111b**:**112b** = 81.9:15.3:1.2:1.6) compares favourably with the experimentally determined ratio in refluxing toluene (Table 3, entry 2; **109b**:**110b**:**111b**:**112b** = 56:30:6:8). Considering the complexity and multiplicity of TSs examined and the omission of solvent effects in the calculations – which are expected to be small, considering the low polarity of the toluene and chlorobenzene solvents used in the experiments – the close correlation between theory and experiment is remarkable, providing compelling evidence in support of the reliability of our theoretical model.

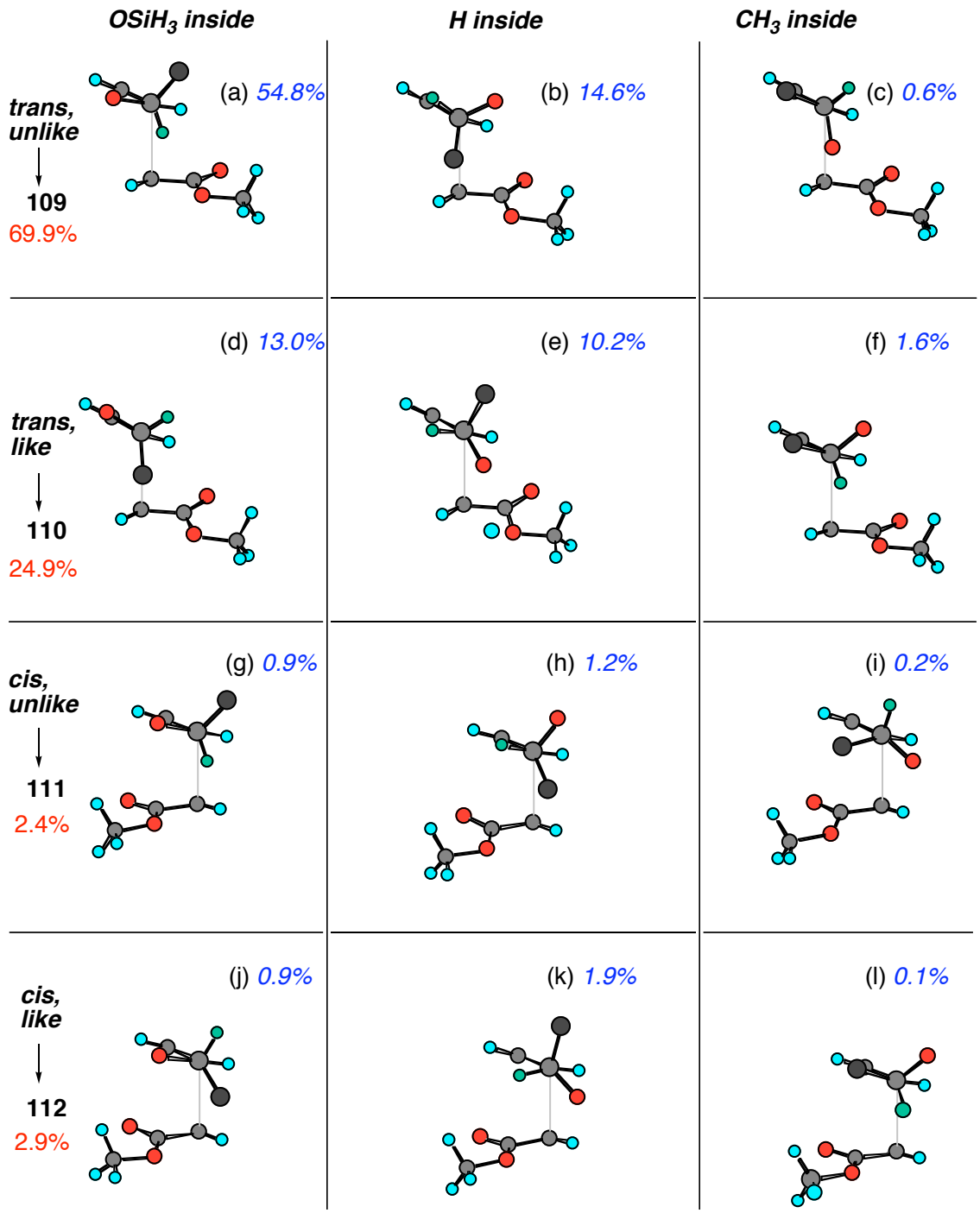


Figure 2.7 TSs and calculated Boltzmann populations (blue for individual TSs, red is the total for each diastereomeric adduct) at 383K for the IMDA reaction of **83f**. The twelve TSs are viewed down the C1–C* axis and the developing C1–C9 bond is depicted as a vertical grey line. C*–H is coloured green, C*–CH_3 is coloured black and some atoms are omitted for clarity. Structures (a)–(c) lead to the *trans, unlike* adduct **109f**; (d)–(f) lead to *trans, like* adduct **110f**; (g)–(i) lead to *cis, unlike* adduct **111f**; and (j)–(l) lead to the *cis, like* adduct **112f**. Structures on the left have the –$OSiMe_3$ group *inside*, those in the centre column have the –H *inside*, and those on the right have the –CH_3 *inside*. To facilitate comparisons between TSs, dienophile approach from below is depicted throughout, hence the configuration at the allylic stereocentre is inverted in the *unlike* TSs.

For the *E*-dienophile series, the predicted IMDA adduct ratio from the reaction of $OSiH_3$ substrate **83g** is **109**:**110**:**111**:**112** = 25:20:50:5 at 405K in the gas phase. Experimentally, in refluxing chlorobenzene solution (405K), the ratio of products *for the –OTBS substrate* ***83e*** is 8:28:40:24. Thus, theory correctly predicts: (1) a less stereoselective IMDA reaction for a fumarate ester than the corresponding maleate ester; (2) the identity of the major product, the *cis, unlike* diastereoisomer, (3) the *cis/trans*-selectivity of the reaction and (4) in a qualitative manner, the π-diastereofacial selectivity within the *cis*-adduct manifold. There is a discrepancy between theory and experiment, however, in the π-diastereofacial selectivity of the *trans*-adducts (expt: *unlike*:*like* = 22:78; theory *unlike*:*like* = 57:43) Nevertheless, once again, overall there is a very good correlation between experiment and theory, which demonstrates the validity of the computational model. Extensive CPU times were necessary to carry out these calculations and it was not feasible to carry out a similar computational analysis on TBS fumarate precursor **83e**.

2.6.2 TS Geometries and Relative Energies.

For all three trienes examined computationally, the lowest energy IMDA TSs have *unlike* stereochemistry and exhibit a conformation in which the C*–silyloxy group adopts the *inside* position, the C*–methyl group is in the *anti* position, and the C9-CO_2Me group adopts the *exo* orientation (*cf.* Figure 2.5). The preferences of the methyl and silyloxy groups for the *anti* and the *inside* positions, respectively, in the lowest energy TSs are a consequence of their respective innate tendencies to adopt these positions in both the transition state and the ground state, irrespective of the presence of the other substituent.

For all TSs located, the forming *internal* (C4–C8) bond is considerably shorter than the developing *peripheral* (C1–C9) bond, giving rise to significant bond-forming asynchronicity (see Figure 1.7). This is exemplified in Figure 2.8 with the most stable TSs for each of the three series of precursors, **83f**, **83b** and **83g**. The two 9-*Z*-CO_2Me TSs, ***trans, unlike*-83fTS-(a)** and ***trans, unlike*-83bTS-(a)** have large bond-forming asynchronicities of 0.75 and 0.77 Å, respectively, whereas the 9-*E*-CO_2Me TS ***cis, unlike*-83gTS-(g)** exhibits slightly lower levels of bond-forming asynchronicity of 0.56 Å. Similar bond-forming asynchronicities and trends are found in the other TSs.

These geometric features are consistent with findings on related systems.[58,84,86] Inspection of the profiles of the 36 IMDA TSs located for trienes **83b, 83f** and **83g** reveals that the allylic substituents show little staggering about the forming *peripheral* bond (r_2) that is normally characteristic of additions to allylic systems.[105,106]Indeed, the C1–C* conformations in these TSs are essentially the same as those for isolated allylic ethers, with one substituent eclipsing the double bond.[107,108] This is hardly a surprising finding, given the highly extended length of the developing *peripheral* bond.[58,84,86]

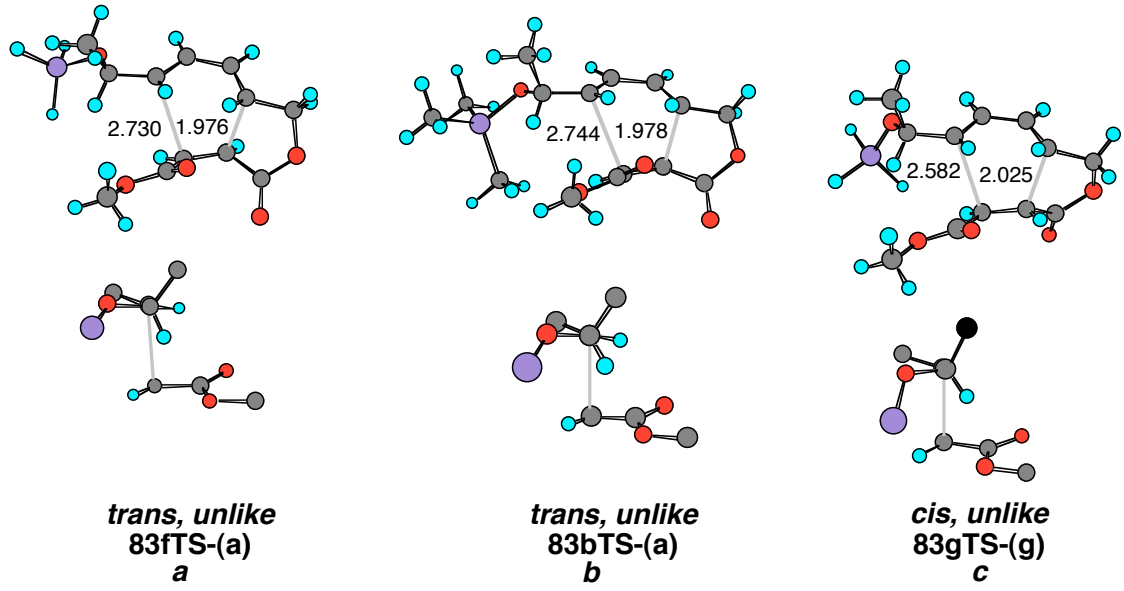


Figure 2.8 Most stable TSs for each of the three series of precursors. ***a***: ***trans, unlike*-83fTS-(a)** (Figure 5a); ***b***: ***trans, unlike83*-(a)** (see Figure S1a[28]); ***c***: ***cis, unlike*-83gTS-(g)** (see Figure S2g[28]). Upper: front views (forming bond lengths in Å). Lower: Newman projections down the O–C* bond. Most H atoms and C3 – C8 have been omitted for clarity.

Our model for the favoured TS for IMDA reactions, in which the silyloxy group adopts the *inside* position and the alkyl group the *anti* position, is reminiscent of that proposed for *intermolecular* 1,3-dipolar cycloadditions of nitrile oxides to chiral allylic ethers.[106,109]

2.6.3 Origin of unlike *π-Diastereofacial Selectivities.*

The considerably lower π-facial selectivities observed experimentally in IMDA reactions of alcohol substrates **78a** and **83a** and the *p*-nitrobenzoate ester **78e** vs. the corresponding silyl ethers (Tables 2.5 and 2.7) may be explained by an attractive electrostatic interaction between the oxygen atom and the hydrogen atom at C2.

Calculations show that the charge on oxygen is significantly higher for silyl alkyl ethers than for alcohols, dialkyl ethers or *p*-nitrobenzoate esters, which supports an electrostatic argument. Further evidence for the effect being electrostatic in nature was obtained by examining the preferred conformations of allylic alcohol derivatives. Increased stabilization of the –OR *inside* conformation in IMDA reactions should lead to even higher levels of facial stereocontrol than those witnessed in Tables 2.5-2.7. This might be achieved using the alkoxide anion group ($-O^-$). Attempts to examine the IMDA reactions of metal alkoxides derived from alcohol **83a** were thwarted by the instability of the ester groups in the presence of the alkoxide.

2.6.4 Magnitude of π-Diastereofacial Selectivities.

Theory predicts an IMDA reaction for the maleate $SiMe_3$ substrate which is considerably more π-diastereofacially selective than that of the SiH_3 substrate [*unlike:like* = 5.9:1 ($SiMe_3$); 2.8:1 (SiH_3)]. This result is in qualitative agreement with the experimental findings, which demonstrate that the larger the silyl protecting group, the higher the π-diastereofacial selectivity.

2.6.5 Anomalous Fumarate cis *Stereoselectivities.*

In the maleate series, for both SiH_3 (Figure 2.6) and $SiMe_3$ substrates, TSs leading to the *trans*-fused bicyclic products are considerably more stable than those leading to the *cis*-fused adducts. These results are consistent with the experimental findings, and are in agreement with computational and synthetic investigations of smaller achiral pentadienyl maleate substrates.[84]

In the case of fumarate systems, TSs leading to *trans*- and *cis*-fused adducts are generally quite similar in energy, with a slight *trans* IMDA selectivity generally witnessed in the laboratory with small achiral substrates. In stark contrast, substrates **78f**, **81b** and **83e** undergo IMDA reactions with anomalously high (up to 85:15) *cis*-selectivities. The origin of this unprecedented preference for the *cis*-cycloadduct can be traced, once again, to preferred inside location of the C*–$OSiR_3$ substituent (Figure 2.8). In the fumarate *trans*-TSs, the *E*-CO_2Me group must reside directly beneath the *inside* silyloxy group, which necessitates a destabilizing *gauche* conformation between the SiH_3 and C*–CH_3 groups about the C*–O bond (highlighted in the dashed box in

Figure 2.8). In the corresponding *cis*-TS, the *E*-CO_2Me group is located in the *exo*-position, hence the *inside* silyl group is free to adopt a lower energy conformation about the C*–O bond in which it avoids the C*–methyl group [note the positioning of the SiH_3 group in the *endo* region in ***cis, unlike*-TS-(g)**]. The destabilization of ***trans, unlike*-83gTS-(a)**, relative to ***cis, unlike*-83gTS-(g)**, will be amplified by the presence of larger silyl groups, which will result in a higher selectivity for the *cis* fused adduct.

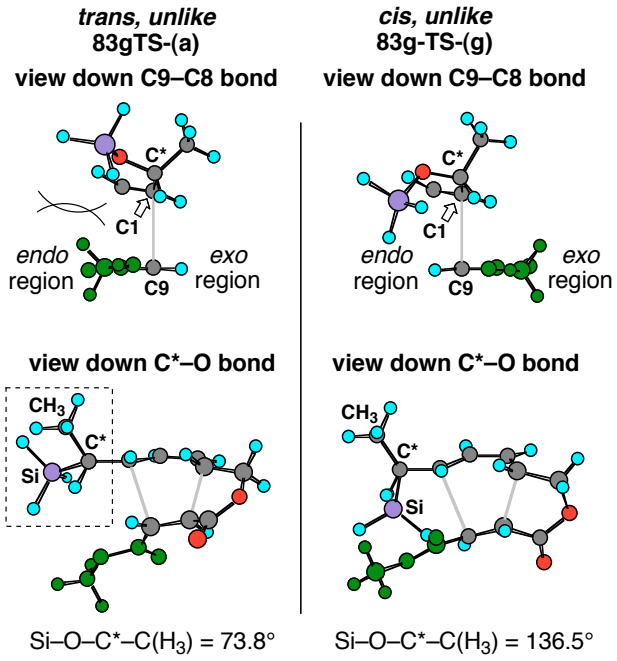


Figure 2.9 The two most stable (–$OSiH_3$ *inside,* –CH_3 *anti*) fumarate TSs leading to the *trans, unlike* (left) and *cis, unlike* (right) adducts. TS (g) is energetically favored over TS (a). Top: views down the C9–C8 axis (C3 – C8 are omitted for clarity); bottom: views down the C*–O bond. The *gauche* interaction between the SiH_3 and CH_3 groups is highlighted in the dashed box. This conformation is brought about by the steric (and possibly electronic) destabilization in the *endo* region in TS (a) indicated in the top left depiction. The CO_2CH_3 group is coloured green throughout.

2.7 Conclusions

The synthetic scope and limitations of the IMDA allylic stereocontrol method have been investigated with respect to allylic substituents and dienophile geometry, and theoretical models have been devised to explain these findings. The computational results offer unprecedented insights into the subtle stereocontrolling influences at play in these synthetically important reactions, and point the way forward for future investigations into additions to chiral allylic systems. The *unlike* π-diastereofacial selectivity observed

in these reactions comes about through the preference for a reactive conformation about the bond connecting the diene and the stereocentre in which the silyloxy group adopts an *inside* orientation, as summarized in Figure 2.10. The dienophile reacts at the more accessible π-face of the diene; in the absence of overriding electronic effects, this will be on the side of the diene in which the smaller substituent resides.

A particularly important finding from both experimental and computational studies is the requirement for the C*–oxygen atom to be electron rich, thereby strengthening its preference for the inside position by stabilizing electrostatic interactions with the diene C2H group. Thus, the silyloxy group is much superior to hydroxy, alkoxy and ester groups in its stereocontrolling ability.

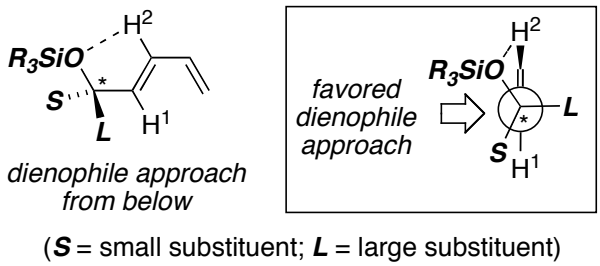


Figure 2.10 Theoretical model for π-diastereofacial selectivity in addition reactions to chiral allylic silyloxy systems.

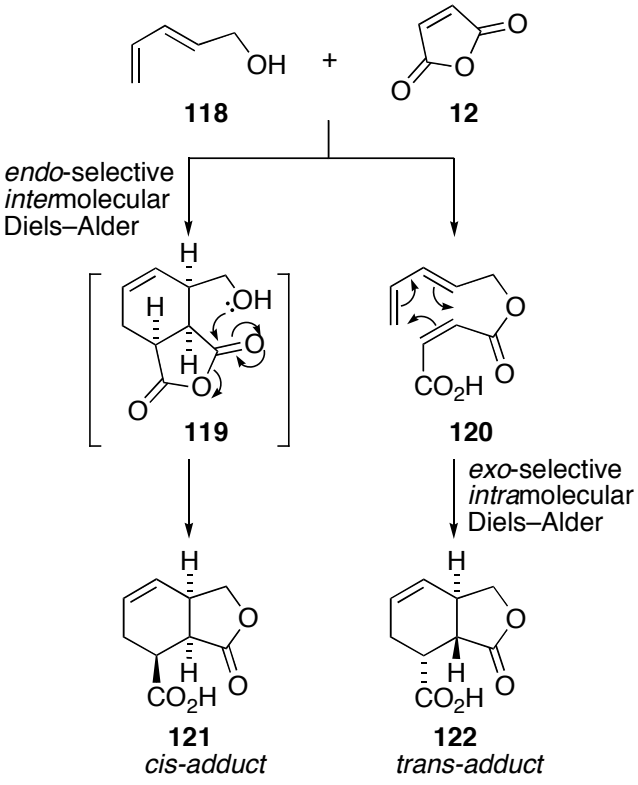
The enantiomerically pure cycloadducts formed in these reactions are rich in functionality, which invites further transformation into structures common with natural products.

3 Enhanced Stereocontrol in Diels–Alder Reactions of Chiral Dienols

3.1 Background

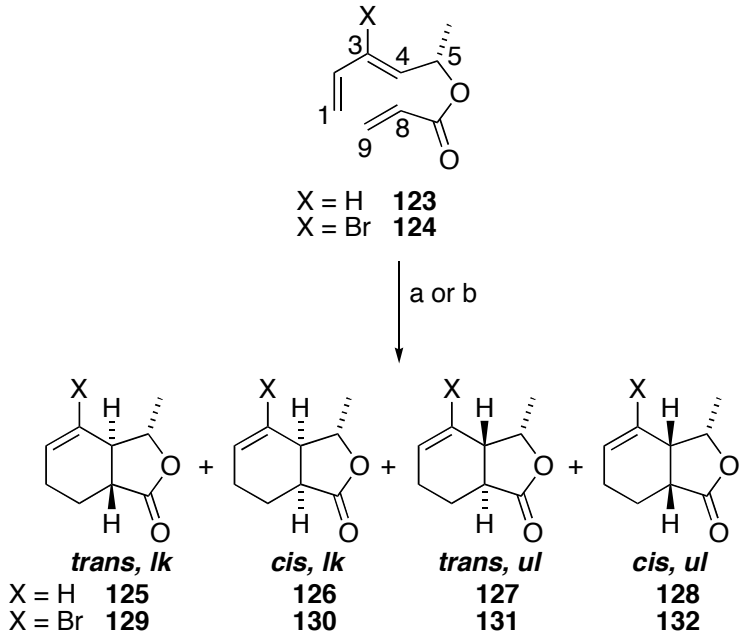
The Diels–Alder reaction is by no means fully understood and fully optimised since it commonly delivers more than one stereoisomeric product and, furthermore, methods to effect a switch in stereoselectivity are rare.[110]

It was recently reported that reactions between conjugated dienols **118** and maleic anhydride **12** (Scheme 3.1) provide either *cis*-fused **121** or *trans*-fused **122** bicyclic products as major products, depending upon how the reaction is carried out.[111] When mixtures of the two reactants are heated, an *endo*-selective *inter*molecular Diels–Alder reaction gives putative hydroxy anhydride intermediate **119**, which rapidly undergoes intramolecular esterification to furnish *cis*-fused lactone acids **121**. Alternatively, the pre-formed maleate half-ester derivative **120** affords *trans*-fused lactone acids **122** in high selectivity by way of an *exo*-selective *intra*molecular Diels–Alder (IMDA) reaction.



Scheme 3.1 Diels-Alder reactions of dienols and maleic anhydride.

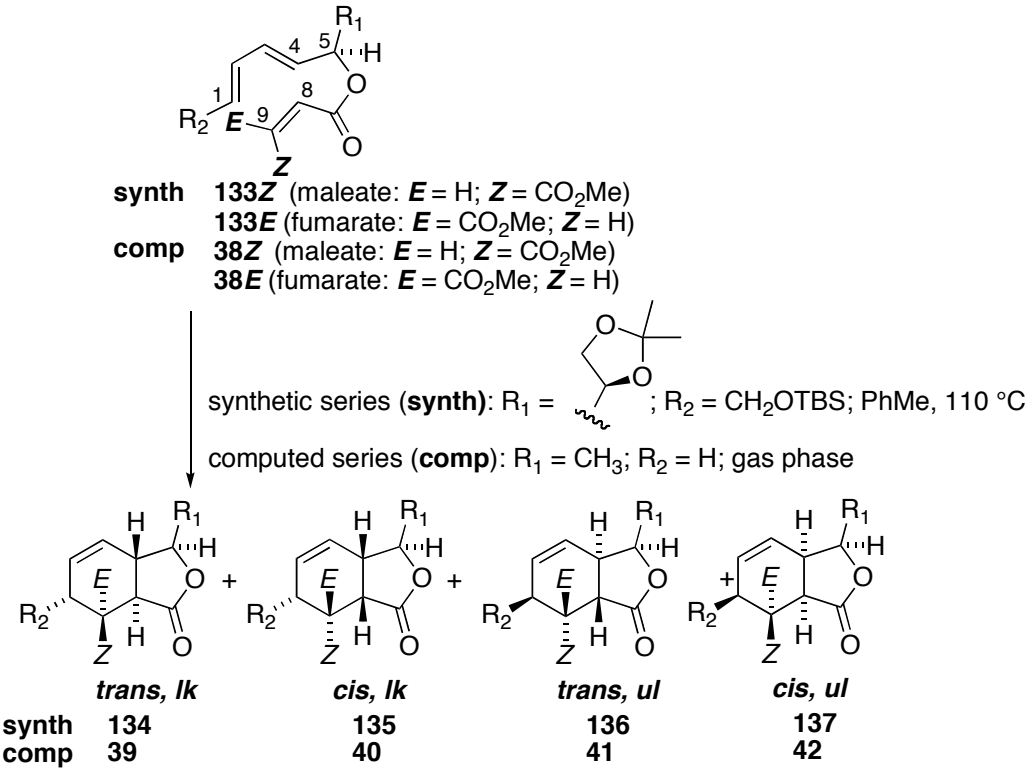
In a separate study the stereocontrolling influence of a removable bromine substituent upon the outcome of IMDA reactions of pentadienyl acrylates (Scheme 3.2; Table 3.1) was demonstrated.[85] Thus, compared with nonbrominated precursor **123**, the C3-bromine substituent in precursor **124** induces a dramatic improvement in both *trans/cis* stereoselectivity and π-diastereofacial selectivity. Detailed computational investigations identified destabilising torsional and steric strain operating in the transition structures (TSs) leading to cycloadducts **130**, **131** and **132**. The TS leading to the major cycloadduct **129** lacked such unfavourable interactions.



Scheme 3.2 *Reagents and conditions*: (a) X = H, 1,2-dichlorobenzene, 180 ^{o}C, 146 h, 59%; (b) X = Br, PhCl, 156 h, 83%.

Several groups have used a "steric directing group" strategy to control the outcome of IMDA reactions.[37,68,104] An investigation carried out in the Sherburn group focussed on the stereochemical outcome of IMDA reactions of C9-CO_2Me substituted trienes carrying a C5-dioxolanyl substituent and a C1-CH_2OTBS group (Scheme 3.3; Table 3.1).[58] The C9-*Z*-CO_2Me substrate, maleate **133*Z***, gave two of the four possible cycloadducts, namely *trans,lk*-**134*Z*** and *cis,lk*-**135*Z*** (86:14, respectively) in quantitative yield. The C9-*E*-CO_2Me substrate, fumarate **133*E***, gave three of the four possible adducts, *trans,lk*-**134*E***, *cis,lk*-**135*E***, and *cis,ul*-**137*E*** in a ratio of 72:17:11, respectively, in 90% yield. DFT calculations carried out on truncated maleate and fumarate model systems lacking the C1 substituent, and with the C5-dioxolane group replaced by a

methyl group, correctly predicted the *trans,lk*-adduct **39** as the major product with both ***E***- and ***Z***-dienophile geometries.



Scheme 3.3

Table 3.1 Synthetic and computed[a] product ratios for Schemes 3.2 and 3.3

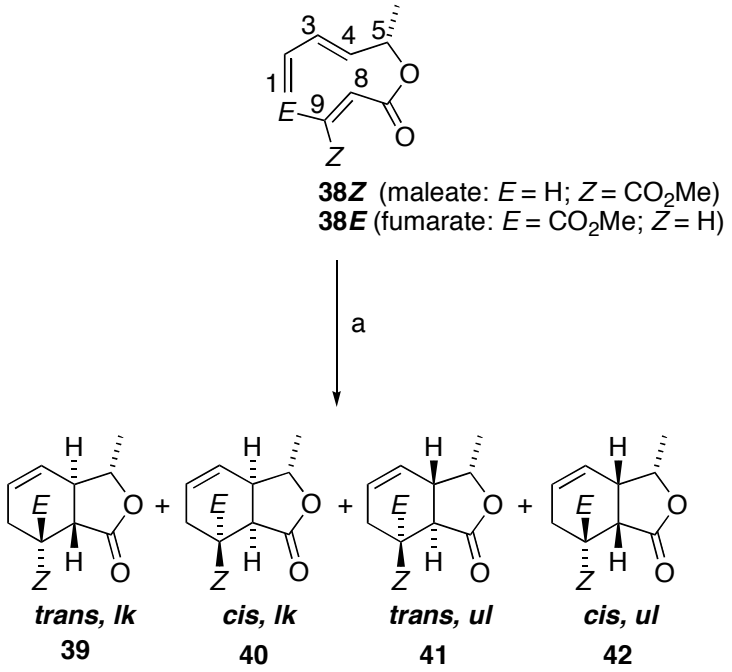
Entry	Triene	Time (h)	Yield (%)	Product ratio *trans,lk:cis,lk:trans,ul:cis,ul*	
1	**123**	146	59	**125:126:127:128**	
				synthetic	28:30:12:30
				computed	45:25:8:22
2	**124**	156	83	**129:130:131:132**	
				synthetic	81:19:0:0
				computed	91:8:0:1
3	**133*Z***	19	100	**134*Z*:135*Z*:136*Z*:137*Z***	
				synthetic	86:14:0:0
	38*Z*			**39*Z*:40*Z*:41*Z*:42*Z***	
				computed	85:2:12:1
4	**133*E***	39	90	**134*E*:135*E*:136*E*:137*E***	
				synthetic	72:17:0:11
	38*E*			**39*E*:40*E*:41*E*:42*E***	
				computed	62:14:10:14

[a]Populations at B3LYP/6-31+G(d) level.

Nevertheless, significant differences exist between experiment and theory in the distribution of the minor cycloadducts. In the maleate case, *cis,lk*-**135*Z*** is the only minor product observed in appreciable amounts from experiments, whereas theory

predicts that *trans,ul*-**136*Z*** should be the second most prevalent product. In the fumarate case, theory predicts a roughly even distribution of the three minor stereoisomeric cycloadducts, whereas experiments furnish only two. This unsatisfactory correlation could reflect unmodelled influences stemming from differences between the experimental and computed structures, or discrepancies in the theory (*i.e.* neglect of solvent effects). In order to identify the origin of the disagreement between theory and experiment, summarised in Scheme 3.3, the IMDA reactions of maleate **38*Z*** and fumarate **38*E*** were investigated.

In a study conducted by Cayzer[112] kinetically controlled *intra*molecular Diels–Alder reactions of the two triene precursors **38*Z*** and **38*E*** were carried out in dilute solutions of refluxing toluene. (Scheme 3.4; Table 3.2). Four cycloadducts were formed in both cases.



Scheme 3.4 *Reagents and conditions:* (a) PhMe, 110 °C.

Table 3.2 Synthetic and computed[a] product ratios for Scheme 3.4

Triene	Entry	Time (h)	Yield (%)	Product ratio *trans,lk:cis,lk:trans,ul:cis,ul*	
38*Z*	1	3	94	**39*Z*:40*Z*:41*Z*:42*Z***	
				synthetic[b]	68:9[c]:19:4
				computed[d]	85:2:12:1
38*E*	2	57	71	**39*E*:40*E*:41*E*:42*E***	
				synthetic[b]	55:13:16:16
				computed[d]	62:14:10:14

[a]Populations at B3LYP/6-31+G(d) level.

The IMDA reaction of maleate **38*Z*** exhibited strong *trans*-selectivity (87:13, *trans:cis*) and *like* π-diastereofacial preference (77:23, *like:unlike*). Fumarate **38*E*** also underwent a *trans*-selective (71:29, *trans:cis*) IMDA reaction with a *like* π-diastereofacial preference (68:32, *like:unlike*). The isolation of the *trans,like*-cycloadduct as the major product from both reactions is consistent with other reports with C5-substituted pentadienyl maleates and fumarates.[58,104] Arseniyadis and co-workers employed the IMDA reaction of the C5-*Et* counterpart of fumarate **38*Z*** as a key step in their synthesis of A-seco mevinic acid.[104] Compared to the C5-Me triene **38*Z*** in the present study, the C5-Et triene gave slightly higher *trans*-selectivity and slightly higher *like* π-diastereofacial selectivity (*trans,lk:cis,lk:trans,ul:cis,ul* = 74:4:7:15 [Et][104] *vs.* 62:14:10:14 [Me]). Evidently, the smaller methyl group has a slightly weaker stereocontrolling influence upon the IMDA reaction.

The identities of the four products from the IMDA reactions of **38*Z*** and **38*E*** were correctly predicted by theory with an impressive level of accuracy. Indeed, the experimental ratios of the three minor cycloadducts are in close agreement with calculated DFT Boltzmann distributions.

The order of product abundance in the IMDA reaction of maleate **38*Z***, namely *trans,lk* > *trans,ul* > *cis,lk* > *cis,ul*, can be rationalised by consideration of interactions in the C3–C5 region of the TSs (Figure 3.1). Two destabilising interactions can be identified, namely 1,3-allylic strain between C3-H and C5-CH_3 in the two *unlike* TSs, and an eclipsed C4–C5 bond in the two *cis*-TSs. These two interactions are absent in the *trans,lk*-TS, which leads to the major product from the reaction. They are both present in the *cis,ul*-TS, which leads to the least abundant product from the reaction. Of the two products formed in intermediate amount, the *trans,ul* cycloadduct is more abundant than the *cis,lk* product, which presumably indicates that the eclipsing interaction is more costly than allylic strain. It is noteworthy that the C5-*des*-methyl analogue of **38*Z*** undergoes a much less *trans*-selective reaction (58:42, *trans:cis*).[86] The enhanced *trans*-selectivity in the IMDA reaction of **38*Z*** can be ascribed to the destabilising interactions in TSs leading to the *cis*-isomers.

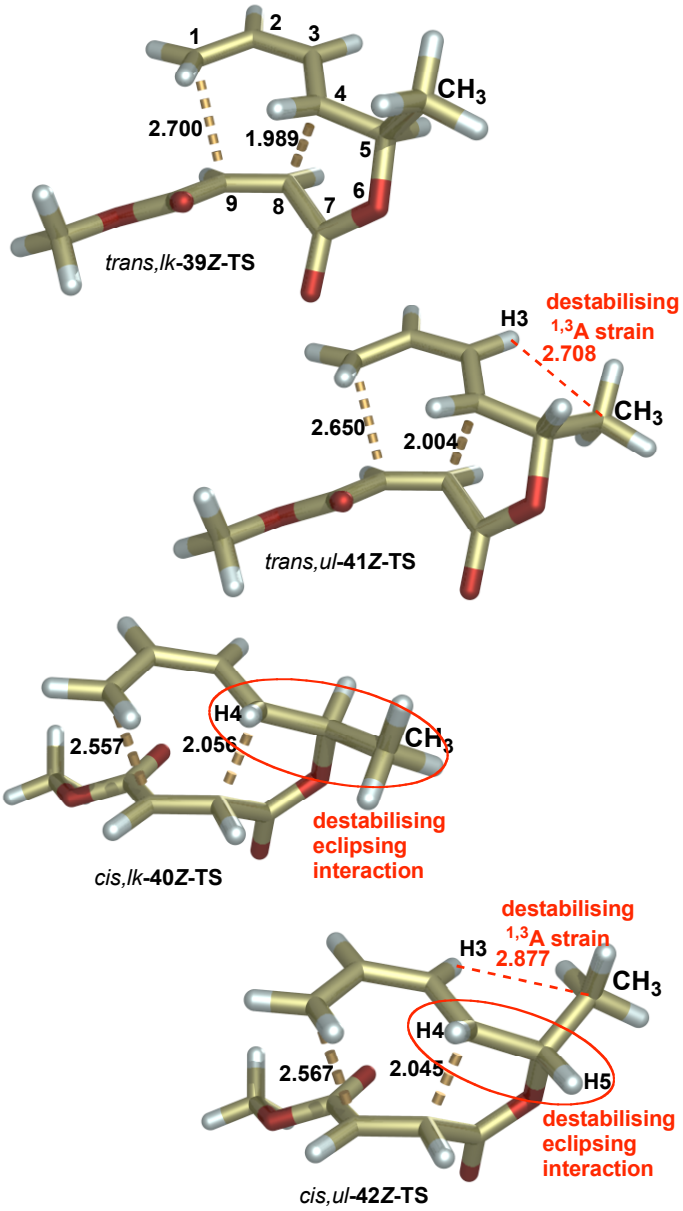


Figure 3.1 IMDA TSs from **38Z** with destabilising interactions identified.

With the fumarate precursor **38*E***, both experiments and calculations showed that the *trans,lk*-cycloadduct is the dominant product, with the remaining three isomers being formed in roughly equal amounts. The destabilising interactions are the same as those identified in the *Z*-TSs. In the case of the *E*-triene, there are negligible differences in the energies of the TS leading to the three minor products. Evidently, allylic strain and eclipsing interactions are finely balanced in this case.

Whilst these results confirmed the validity of the theoretical model, we were interested in developing a way to carry out these reactions in a more synthetically useful (i.e. a more stereoselective) manner.

3.2 Aims

The aim of this study is to enhance the stereoselectivity of maleate and fumarate IMDA reactions through incorporation of a C3-Br substituent and to investigate the influence of the bromine substituent upon the π-diastereofacial selectivity of *inter*molecular Diels–Alder reactions (Figure 3.2).

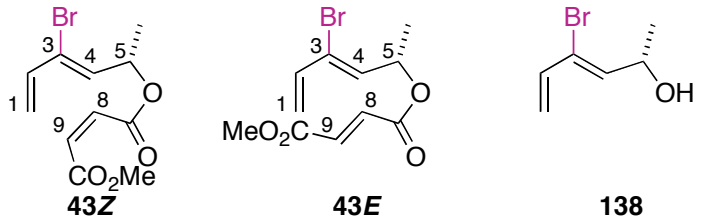
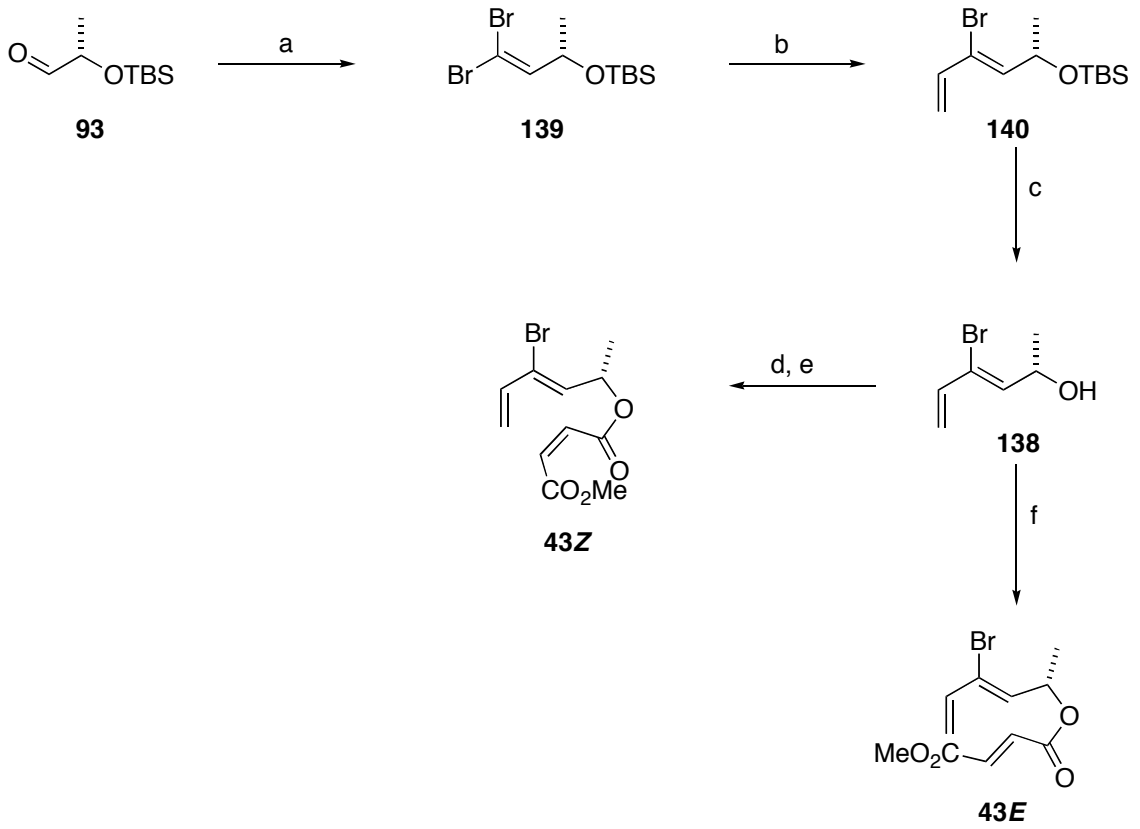


Figure 3.2 Enhanced stereocontrol through removable Br substituent?

3.3 Results and Discussion

3.3.1 Synthesis of the IMDA Precursors

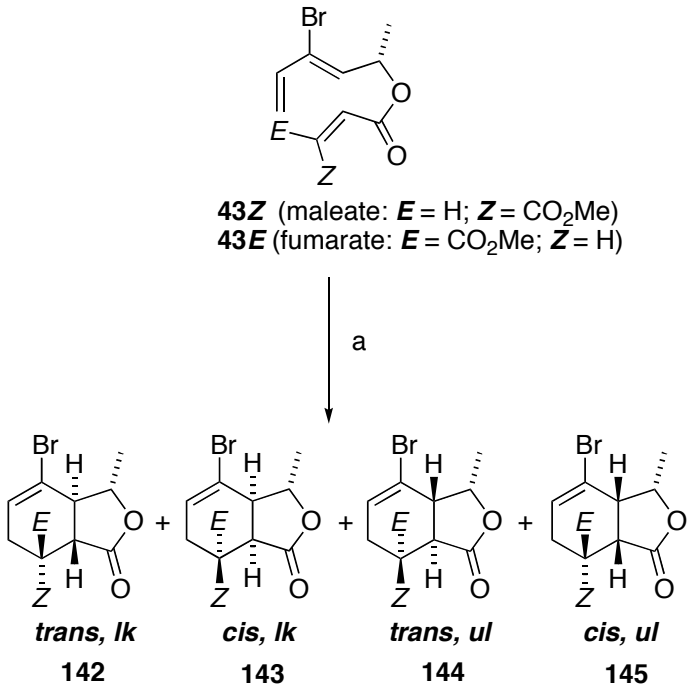
The maleate and fumarate IMDA precursors **43*Z*** and **43*E*** were synthesised according to Scheme 3.5. Corey-Fuchs dibromomethylenation[113] of aldehyde **93** gave **139**. Selective Stille reaction with tributyl(vinyl)tin using modified Farina conditions[114] gave the diene **140** in good yield. Removal of the silyl protecting group yielded the chiral dienol **138**.[85] Esterification with maleic anhydride followed by treatment with diazomethane gave the maleate IMDA precursor **43*Z***. Alternatively Steglich esterification of dienol **138** with *E*-methoxycarbonylacrylic acid gave the fumarate precursor **43*E***.



Scheme 3.5 *Reagents and conditions*: (a) PPh_3 (4.0 equiv), CBr_4 (2.0 equiv), CH_2Cl_2, 4 h, 76 %; (b) CH_2=$CHSnBu_3$ (1.05 equiv), Pd_2dba_3, $AsPh_3$, 50 ^oC, 83%; (c) TBAF, THF, 2.5 h, 84%; (d) Maleic anhydride, Et_3N, DMAP, CH_2Cl_2, 0 ^oC; (e) CH_2N_2, Et_2O, -78 ^oC; 40% over 2 steps; (f) *E*-methoxycarbonylacrylic acid, DCC, DMAP, Et_2O, RT, 63%.

3.3.2 IMDA Reactions of Maleate and Fumarate Precursors **43*Z*** *and* **43*E***.

The IMDA reactions of trienes **43*Z*** and **43*E*** were carried out in dilute solutions of refluxing toluene (Scheme 3.6). To our delight, a single isomer was generated from both reactions with complete stereoselectivity, within the limits of detection (Table 3.3). The products were tentatively assigned as the *trans,lk*-stereoisomer **142** on the basis of the large *trans*-diaxial coupling constants (J = 19.1-18.4 Hz).

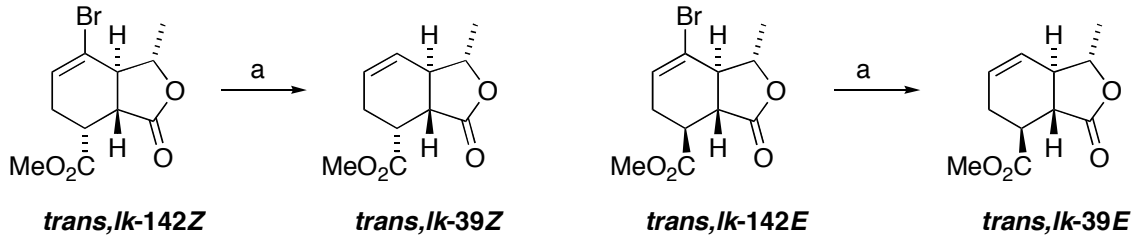


Scheme 3.6 *Reagents and conditions*: (a) PhMe, 100 ^{o}C.

Table 3.3 Synthetic and computed product ratios for Scheme 3.6

Entry	Triene	Time (h)	Yield (%)	Product ratio *trans,lk:cis,lk:trans,ul:cis,ul*	
1	**43*Z***	0.6	84	**142*Z*:143*Z*:144*Z*:145*Z***	
				synthetic	>98:0:0:0
				computed	99:1:0:0
2	**43*E***	10	77	**142*E*:143*E*:144*E*:145*E***	
				synthetic	>98:0:0:0
				computed	96:4:0:0

The bromine-containing cycloadducts **142*Z*** and **142*E*** were reductively debrominated under radical conditions to give samples which were identical to those obtained from the IMDA reactions of the non-brominated precursors **38*Z*** and **38*E*** (Scheme 3.7), whose structures had previously been determined by 2D NMR experiments.



Scheme 3.7 *Reagents and conditions*: (a) $HSnBu_3$, AIBN, PhMe, 80 ^{o}C , 3 h, 59 %.

The C3-Br IMDA precursors were also analysed computationally by Prof. Michael Paddon-Row (UNSW) (Table 3.3). Very high levels of stereoselectivity in favour of the *trans,lk*-adduct **142** were predicted in each case. The most obvious effect of the bromine in these TSs (Figure 3.3) is to enhance the magnitude of the destabilising ^{1,3}A-strain between the C3-substituent and the C5-methyl group. The *unlike*-TSs become prohibitively high in energy relative to the *like*-TSs and are, therefore, not populated to any significant extent. The H4•••CH_3 eclipsing interaction still destabilises the two *cis*-TSs. Indeed, the presence of the bromine has surprisingly little effect on the overall geometries of the TSs.

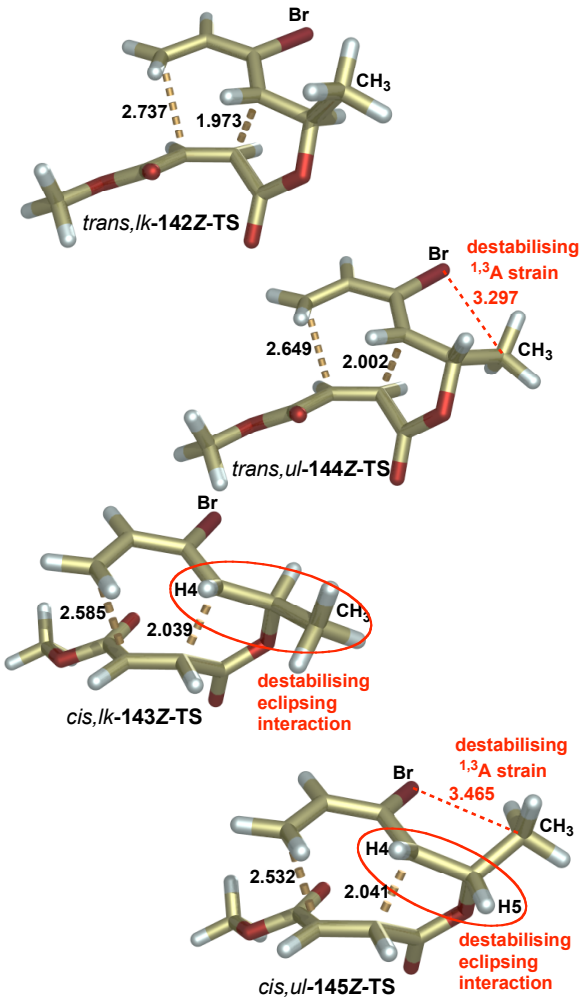
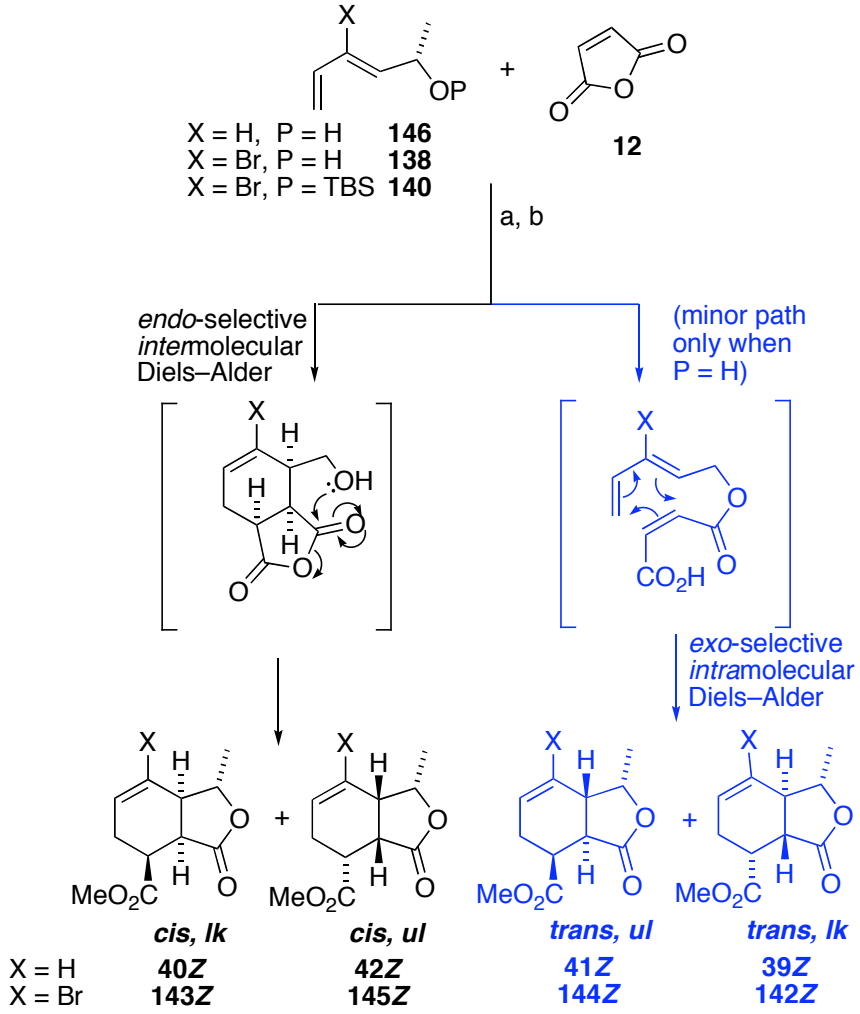


Figure 3.3 IMDA TSs from **43*Z*** with destabilising interactions identified. Distances between interacting atoms, and forming bond lengths are given in Angstroms (Å). The enantiomeric *lk*-TSs are depicted for ease of comparison.

3.3.3 *Intermolecular Diels-Alder Reactions of Dienol* ***138***

The dramatic improvement in stereoselectivity in these IMDA reactions brought about by the *cis*-C3-Br substituent led us to investigate the possibility of stereocontrol in *inter*molecular Diels–Alder reactions. The reaction between maleic anhydride and chiral dienol **146** (Scheme 3.8) as reported by Franck and coworkers[80] gave exclusively *cis*-adducts, with modest π-diastereofacial selectivity (*cis,lk*-**40*Z***:*cis,ul*-**42*Z*** = 73:27; Table 3.4, entry 1). When carried out by Cayzer this reaction furnished a mixture of four stereoisomeric cycloadducts (Table 3.4, entry 2). The *cis*-fused isomers – resulting from the *inter*molecular Diels–Alder pathway – are the dominant products but the *trans*-fused bicycles, accounting for about 10% of the product mixture, result from the competing esterification/IMDA pathway.[111] Nevertheless, a level of π-diastereofacial selectivity between the two *cis*-isomers that is consistent with the earlier report was observed.



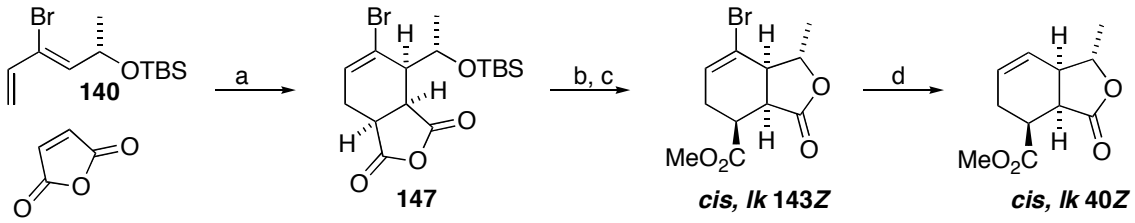
Scheme 3.8 *Reagents and conditions*: (a) PhMe, 110 °C; (b) P = H, CH_2N_2, Et_2O; P = TBS, i) CF_3CO_2H, CH_2Cl_2; ii) CH_2N_2, Et_2O.

Table 3.4 Experimental product ratios for Scheme 3.8

Entry	Diene	Time (h)	Yield (%)	Synthetic product ratio *trans,lk:cis,lk:trans,ul:cis,ul*	
1[a]	**146**	72	83	**39*Z*:40*Z*:41*Z*:42*Z***	0:73:0:27
2[b]	**146**	2	71	**39*Z*:40*Z*:41*Z*:42*Z***	10:57:1:32
3	**138**	5.5	58	**142*Z*:143*Z*:144*Z*:145*Z***	13:87:0:0
4[c]	**138**	74	58	**142*Z*:143*Z*:144*Z*:145*Z***	0:>98:0:0

[a] As reported by Franck *et al.* Reaction carried out at room temperature for 3 days.[12] [b] As reported by Cayzer. [c] Reaction conducted on **140**, the TBS ether of **138**.

Chiral bromodienol **138** reacts with maleic anhydride to give two of the four possible cycloadducts, *cis,lk*-**143*Z*** and *translk*-**142*Z***, in an 87:13 ratio (Scheme 3.8). Thus, complete π-diastereofacial selectivity is witnessed in this cycloaddition. That the minor, *trans*-isomer is the result of the esterification-IMDA pathway[111] is demonstrated by the reaction of the TBS ether derivative **140**. This protected alcohol undergoes *inter*molecular Diels–Alder reaction to give a single isomeric product, within the limits of detection. This product furnishes material identical in all respects to *cis,lk*-adduct **40*Z***, after silyl ether hydrolysis with concomitant lactonisation, methyl ester formation with diazomethane, and reductive debromination (Scheme 3.9). The very high level of *like* π-diastereofacial stereoselectivity witnessed here with a *removable* bromine substituent is comparable to that seen in Prein's investigations with methyl-substituted dienes.[79]



Scheme 3.9 *Reagents and conditions*: (a) PhMe, 110 ^{o}C, 74 h; (b) CF_3CO_2H, CH_2Cl_2, RT, 23h; (c) CH_2N_2, THF, -78 ^{o}C; 58% over 3 steps; (d) $HSnBu_3$, AIBN, PhMe, 80 ^{o}C, 3 h, 68 %

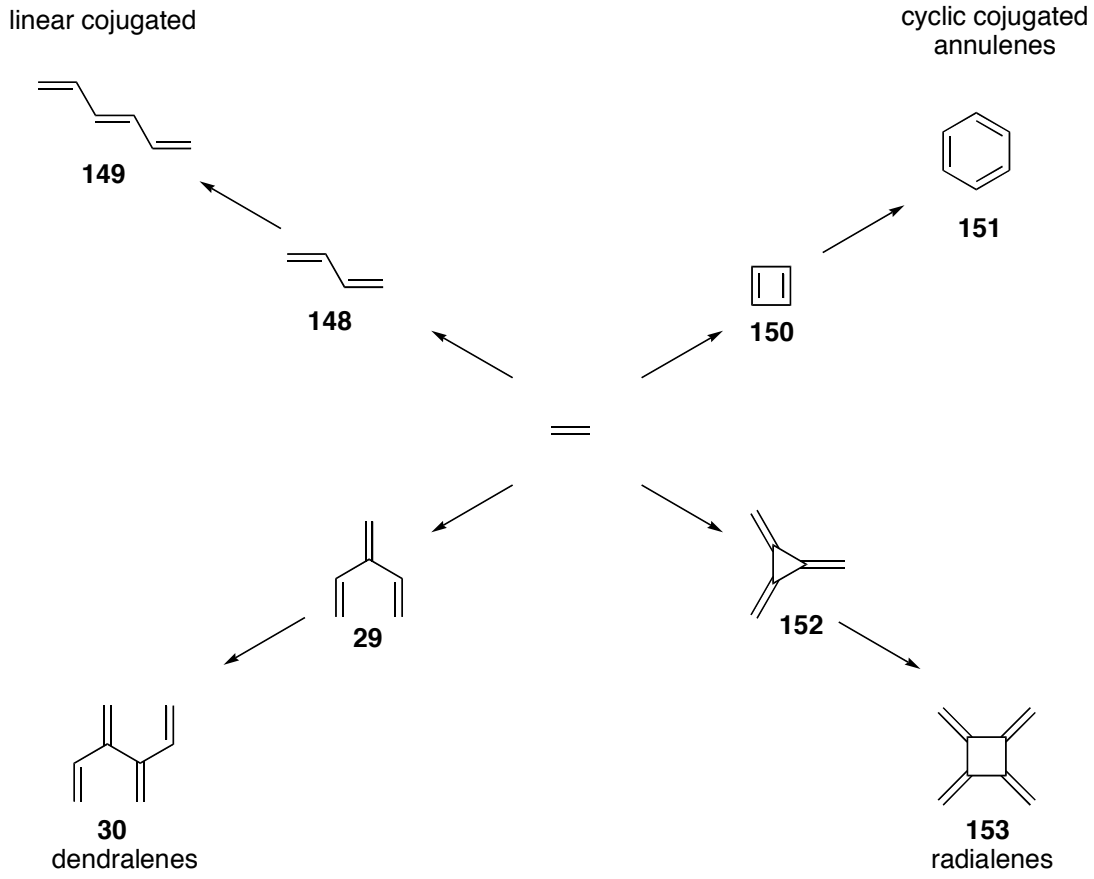
3.4 Conclusions

In summary, this work confirms the validity of the DFT model for pentadienyl maleate and fumarate IMDA reactions. The stereodirecting ability of a *cis*-bromine substituent in both *intra*molecular and *inter*molecular cycloaddition reactions of chiral dienols has been demonstrated. Thus, moderately stereoselective cycloaddition reactions are rendered *completely* stereoselective simply by the replacement of a hydrogen in the precursor by a bromine. Taken together with the ability to select either *cis* or *trans*-bicyclic lactone acids from simple dienols and maleic anhydride, operationally simple stereocontrolled approaches to enantiomerically pure bicyclic building blocks with complementary stereochemistries are now in hand. The use of a vinyl substituent in place of the bromine will be examined in the next chapter.

4 Chiral Dendralenes For Rapid Access To Enantiomerically Pure Polycycles

4.1 Background

The main classes of hydrocarbons that can be constructed using C=C bonds are illustrated in Scheme 4.1.[61] Diene **148** and triene **149** are the first two members of the linearly conjugated acyclic polyenes. Next are the cyclic conjugated polyenes also known as annulenes, of which **150** and **151** are the first two members. Compounds **152** and **153** are members of the radialene family of hydrocarbons, characterised by conjugated *exo*cyclic double bonds. The dendralenes **29** and **30** are acyclic cross-conjugated oligo-alkenes.



Scheme 4.1 The 4 main classes of hydrocarbon constructed from C=C bonds (modified from H. Hopf)[61]

Of the classes of hydrocarbons identified in Scheme 4.1, the linear acyclic conjugated polyenes and the annulenes have been extensively studied, while the dendralenes have remained somewhat neglected until recently. The preferred conformation of these hydrocarbons has caused much discussion in the literature. It is well established that the linear polyenes exist in a coplanar form to maximise overlap of the p-orbitals.[115] Their coplanar conformation is evident upon inspection of the UV absorption data for these compounds. The lower members of the annulenes, that is cycobutadiene **150** and benzene **151**, are also known to exist in planar form, while higher members of this class of hydrocarbons prefer a non-planar conformation for steric reasons.[61] Spectral data suggest that [3]radialenes (**152**) adopt planar conformations, as do [4]radialenes (**153**), provided there is no steric hinderance between the substituents.[116] For all known [5]- and [6]radialenes, steric hinderance between the substituents prevent them from adopting a planar conformation. The preferred conformation of the dendralenes is of particular interest.[60-62,117,118] Analysis of UV spectra show an absorption maximum in the same region as in simple 1,3-dienes, suggesting that they do not exist in a coplanar form. Further experimental studies and calculations show that there is in fact a dihedral angle of 40 ^{o} between the plane of the *s-trans*-1,3-butadiene and the remaining vinyl group in [3]dendralene **29** (Figure 4.1).[119]

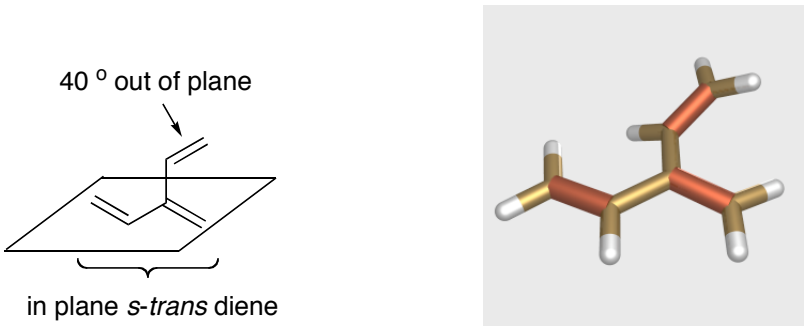
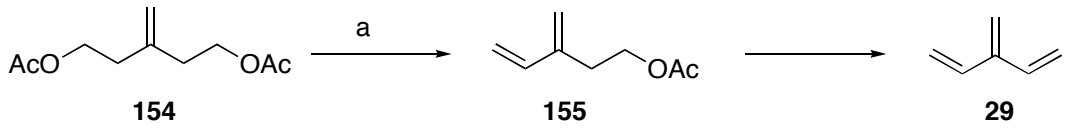


Figure 4.1 The preferred conformation of [3]dendralene.

The dendralenes are particularly attractive precursors for cycloaddition reactions with dienophiles, since they function as multi-dienes, thereby allowing rapid access to a variety of polycyclic frameworks. For this reason there has been much effort directed toward the synthesis of this class of compounds.

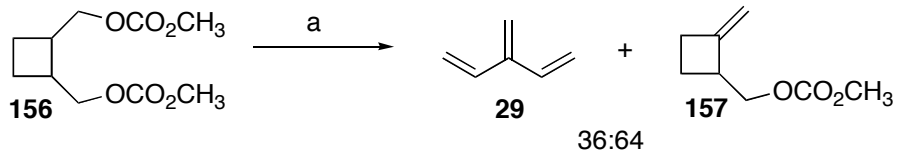
4.1.1 Previous Syntheses of Dendralenes

The first synthesis of the parent [3]dendralene **29** was reported in 1955 by Blomquist and Verdol.[65] Pyrolysis of 3-methylene-1,5-pentanediol diacetate **154** at 485 °C yielded [3]dendralene **29** (Scheme 4.2). It was reported that **29** was volatile and prone to dimerisation and polymerisation.[65]



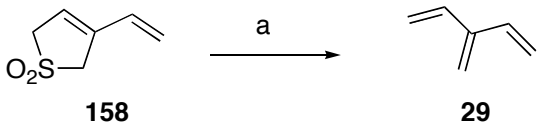
Scheme 4.2 *Reagents and conditions*: (a) 485 °C, 30%.

Bailey and Economy also reported a synthesis of the parent [3]dendralene **29** in 1955.[63] Thermal ring opening/elimination of 1,2-di(acetoxymethyl)cyclobutane **156** gave [3]dendralene **29** (Scheme 4.3).



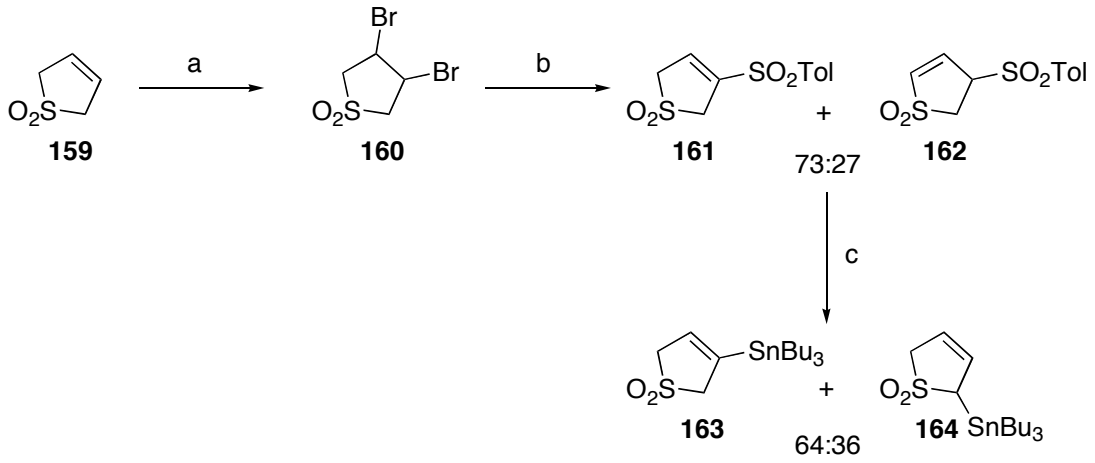
Scheme 4.3 *Reagents and conditions:* (a) 500 °C, 50%.

A more effective preparation of [3]dendralene **29** was reported by Cadogan in 1991 through cheleotropic elimination of sulphur dioxide from the sulfolene **158**.[120] However, six synthetic steps are involved, one of which is an oxidation that requires 46 days to go to completion (Scheme 4.4).



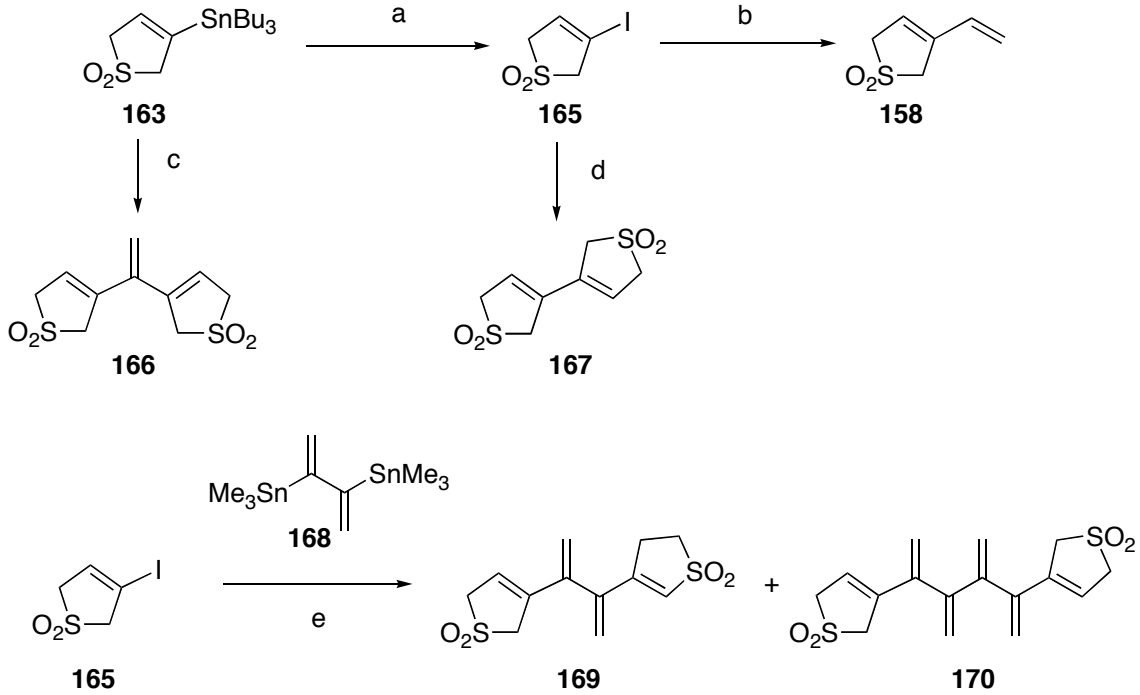
Scheme 4.4 *Reagents and conditions:* (a) 550 °C, 87%.

In 2000 Sherburn and Fielder reported a general route to the synthesis of the dendralene family.[66] The precursors to [3], [4], [5], [6] and [8]dendralene were synthesised from organotin and alkenyl halide building blocks. The key building block stannane **163** was synthesised in 3 steps from sulfolene **159** (Scheme 4.5).



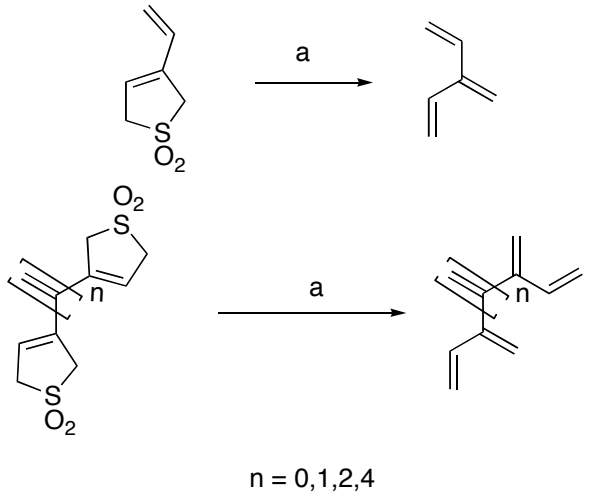
Scheme 4.5 *Reagents and conditions:* (a) Br_2, $CHCl_3$, 63 °C, 2 h, 80%; (b) $TolSO_2Na$, NaOH, MeOH, reflux, 5 h, 63%; (c) $HSnBu_3$, AIBN, PhH, 80 °C, 85%.

Stannane **163** was converted to iodide **165** which was coupled with vinyl tributyltin to give [3]dendralene precursor **158** (Scheme 4.6). Coupling of the stannane **163** with 1,1-dibromoethylene gave the [5]dendralene precursor **166** while the [4]dendralene precursor **167** was obtained through coupling of the stannane **163** and the iodide **165**. Finally, [6]dendralene precursor **169** and [8]dendralene precursor **170** were obtained through coupling of iodide **165** with 2,3-*bis*-trimethylstannyl-1,3-butadiene **168**.



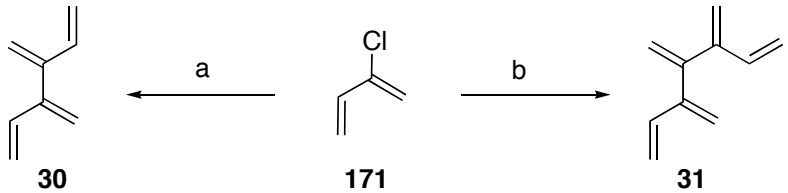
Scheme 4.6 *Reagents and conditions:* (a) CH_2Cl_2, I_2, 1 h, 80%; (b) $Bu_3SnCH{=}CH_2$, $[PdCl_2(CH_3CN)_2]$ (0.05 equiv), DMF, rt, 2 h, 92%; (c) $CH_2{=}CBr_2$ (0.5 equiv), $[PdCl_2(CH_3CN)_2]$ (0.05 equiv), DMF, 40 °C, 36 h, 11%; (d) **163**, $[PdCl_2(CH_3CN)_2]$ (0.05 equiv), DMF, rt, 18 h, 95%; (e) $[PdCl_2(CH_3CN)_2]$ (0.10 equiv), DMF, 60 °C, 72 h, 43% of **169** and 30% of **170**.

The [3], [4], [5], [6] and [8]dendralenes were then unmasked from the precursors **158**, **166**, **167**, **169** and **170** respectively through capillary pyrolysis (Scheme 4.7).



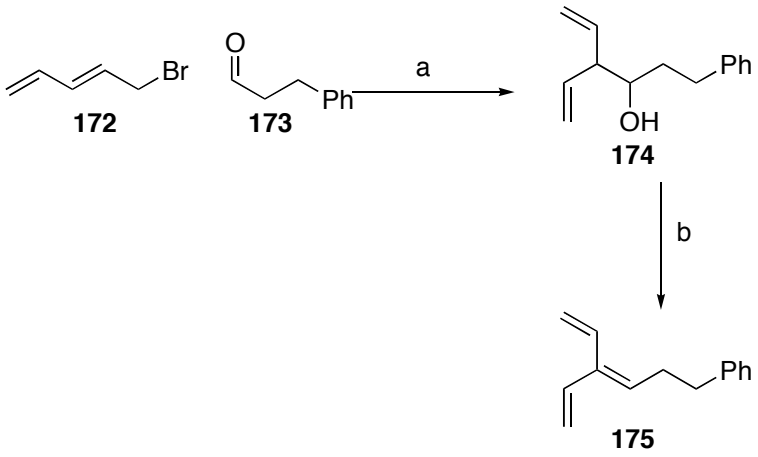
Scheme 4.7 *Reagents and conditions:* (a) capillary pyrolysis at 450 ^{o}C, 52-89%.

More recently, the Sherburn group has developed a highly efficient synthesis of the parent [4], [5], and [6]dendralenes.[121] The Grignard reagent derived from chloroprene undergoes oxidative coupling to give [4]dendralene **30** in 26% yield. This reaction has been carried out on large scale and 10 g batches of the dendralene can be readily synthesised. The Grignard reagent can also be used in a nickel catalysed Kumada coupling with vinylidene chloride to give [5]dendralene **31** in good yield.



Scheme 4.8 *Reagents and conditions*: (a) i) Mg, $ZnBr_2$, $(BrCH_2)_2$, THF; ii) CuCl, -78 ^{o}C; iii) $CuCl_2$.2LiCl, -78 ^{o}C, 26% overall; (b) i) Mg, $ZnBr_2$, $(BrCH_2)_2$, THF; ii) vinylidene chloride, Ni(dppe)Cl_2, THF, 65%.

There have been several syntheses of substituted [3]dendralenes reported in the literature. The most general method developed thus far for internally substituted trienes is the indium-mediated γ-pentadienylation of aldehydes and ketones reported by Fallis.[122] The reagent generated from the treatment of 5-bromo-1,3-pentadiene **172** with indium adds to aldehydes and ketones in a regioselective manner to give non-conjugated compounds of the type **174**. Dehydration of the diene **174** under Mitsunobu conditions generated the dendralene **175**.

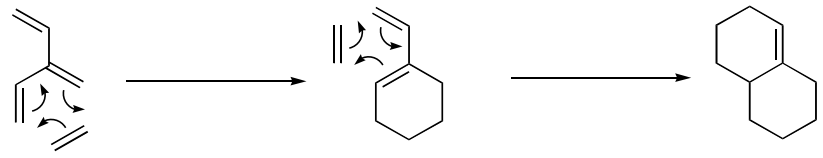


172 173 174 175

Scheme 4.9 *Reagents and conditions*: (a) In, H_2O, 16 h, 65%; (b) Ph_3P, DEAD, PhH, 80 ^oC, no yield reported.

4.1.2 Diene-Transmissive Diels-Alder Sequences

Diene-transmissive Diels-Alder (DTDA) sequences involve the addition of a dienophile to a dendralene, forming a new diene unit that may participate in a Diels-Alder reaction with a second dienophile (Scheme 4.10). This strikingly efficient process forms four C–C bonds and as many as eight stereocentres, yet it involves only two bond-forming events.



29 32 33

Scheme 4.10 Diene-transmissive Diels-Alder sequence.

As for all Diels-Alder reactions the issues of stereoselectivity, π-diastereofacial selectivity and regioselectivity must be considered (Section 1.1). In addition to this, if the [3]dendralene bears a substituent then the two diene units are no longer equivalent, raising the issue of site selectivity. If we consider an internally substituted [3]dendralene we can see that the *s-cis* conformation of one of the diene units is disfavoured due to steric interactions (Figure 4.2). This would result in the initial Diels-Alder reaction occurring at the diene more able to adopt the *s-cis* conformation.

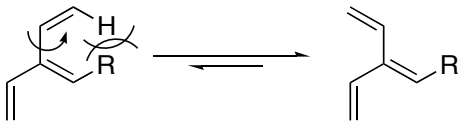


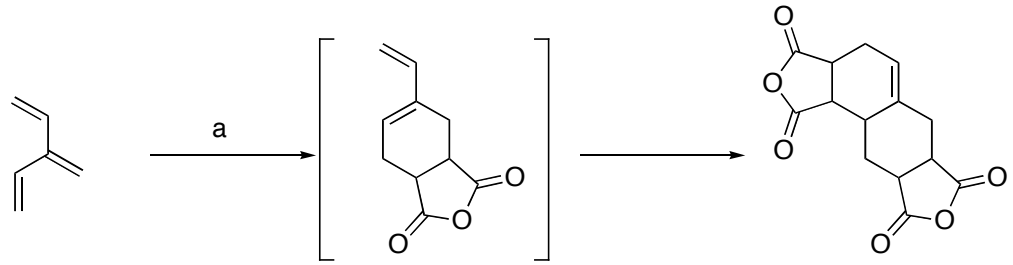
Figure 4.2 The preferred conformation of an *internally*-substituted [3]dendralene.

Ideally it would also be possible to control the selective formation of either the mono-adduct (ie. semicyclic diene **32**) or the bis-adduct (decalin **33**). If the DTDA sequence can be interrupted after the first cycloaddition a different dienophile could be used in the second Diels-Alder reaction giving access to a wider range of polycyclic skeletons.

There have been several examples of DTDA sequences reported in the literature. Both inter and intramolecular Diels-Alder reactions have been utilised as well as acyclic and cyclic dendralenes and dienophiles. The examples most relevant to this study are reviewed below.

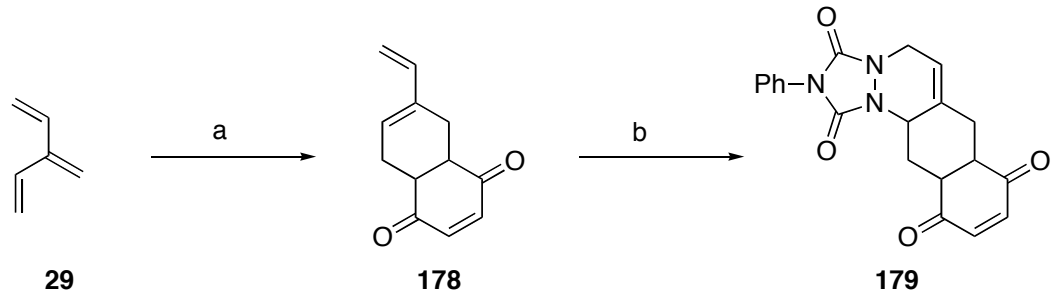
4.1.2.1 Inter/Intermolecular DTDA sequences of acyclic dendralenes.

The first DTDA sequence was reported in 1955 along with the first synthesis of the parent [3]dendralene (Scheme 4.11).[65] The structure of [3]dendralene **29** was confirmed through a DTDA sequence with two equivalents of maleic anhydride. Only the bis-adduct **177** was isolated and no stereochemistry was given.



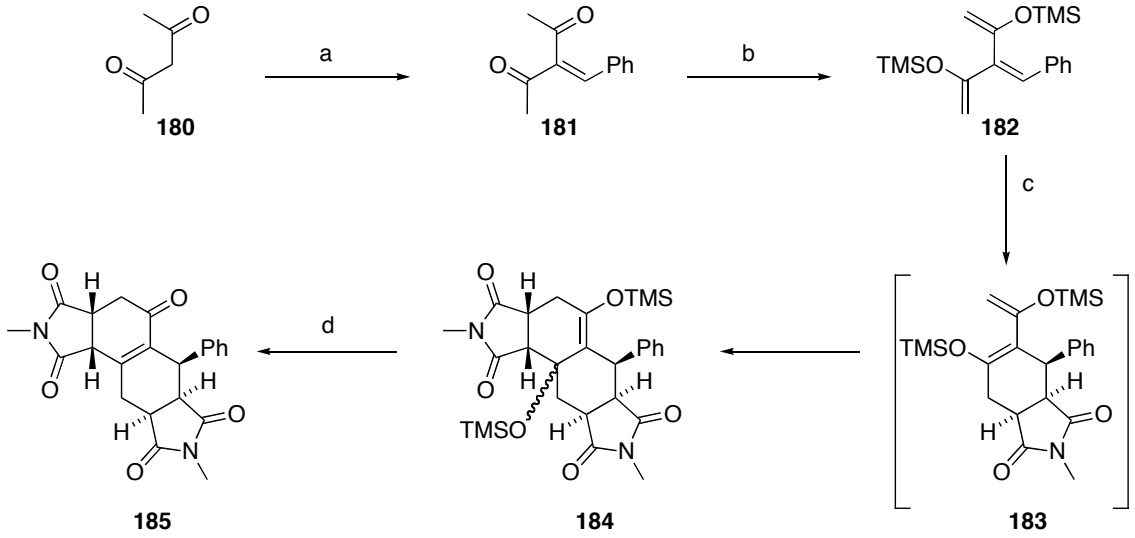
Scheme 4.11 *Reagents and conditions:* (a) maleic anhydride (2.1 equiv), PhH, 100 ^{o}C, 2h, 82%

The Cadogan group also provided examples of DTDA sequences involving the parent [3]dendralene **29** (Scheme 4.12).[120] They showed that a different dienophile may be used for the second Diels-Alder reaction in the sequence, resulting in the formation of mixed bis-adducts. Again, no stereochemistry was reported.



Scheme 4.12 *Reagents and conditions:* (a) *p*-benzoquinone, PhMe, 40 °C, 36 h, 90%; (b) *N*-phenyl-1,2,4-triazoline-3,5-dione, acetone, 40 °C, 2.5 h, 63%.

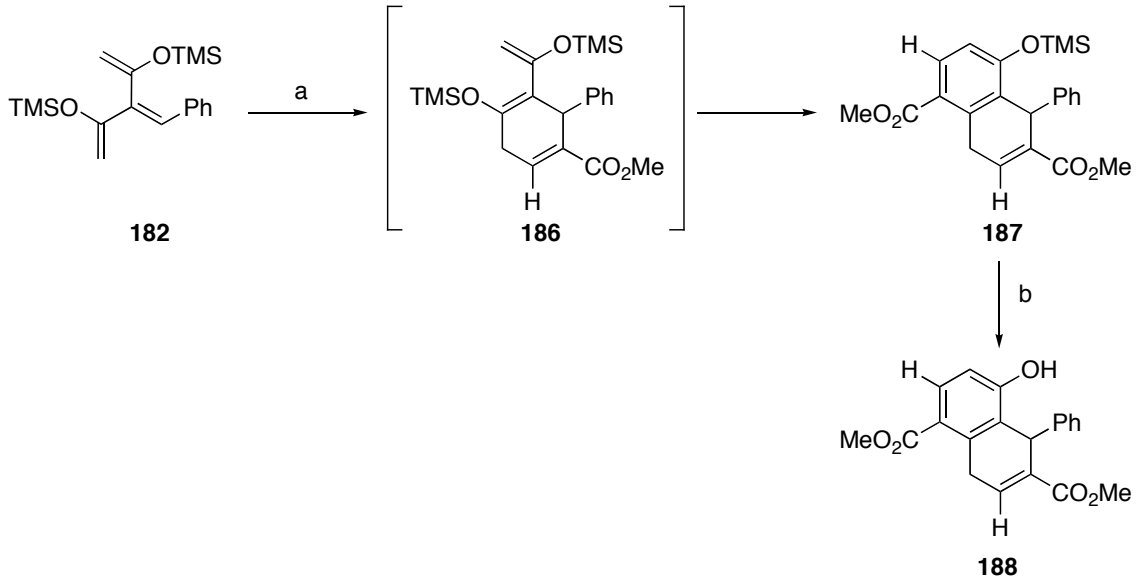
The Tsuge group have made a significant contribution to the area of DTDA chemistry. They have carried out a number of studies on inter/intermolecular DTDA sequences of substituted [3]dendralenes.[123-125] The [3]dendralene **182** was synthesised in two steps from benzaldehyde and 2,4-pentanedione (Scheme 4.13).[123] A phenyl substituent on the central C=C unit of the bis(trimethylsilyloxy)[3]dendralene **182** provides site selectivity for the first cycloaddition by disfavouring the *s*-cis conformation of one of the diene units. The phenyl group also influences π-diastereofacial selectivity in the second cycloaddition, with the dienophile approaching from the opposite π-diastereoface to that possessing the substituent.



Scheme 4.13 *Reagents and conditions:* (a) benzaldehyde, piperidine, PhH, 80 °C; (b) TMSCl, NEt_3, DMF, 90-95 °C, 48 h, 55%; (c) N-methylmaleimide (3 equiv), PhH, 80 °C, 72 h; (d) MeOH, rt, 18 h, 60% over 2 steps.

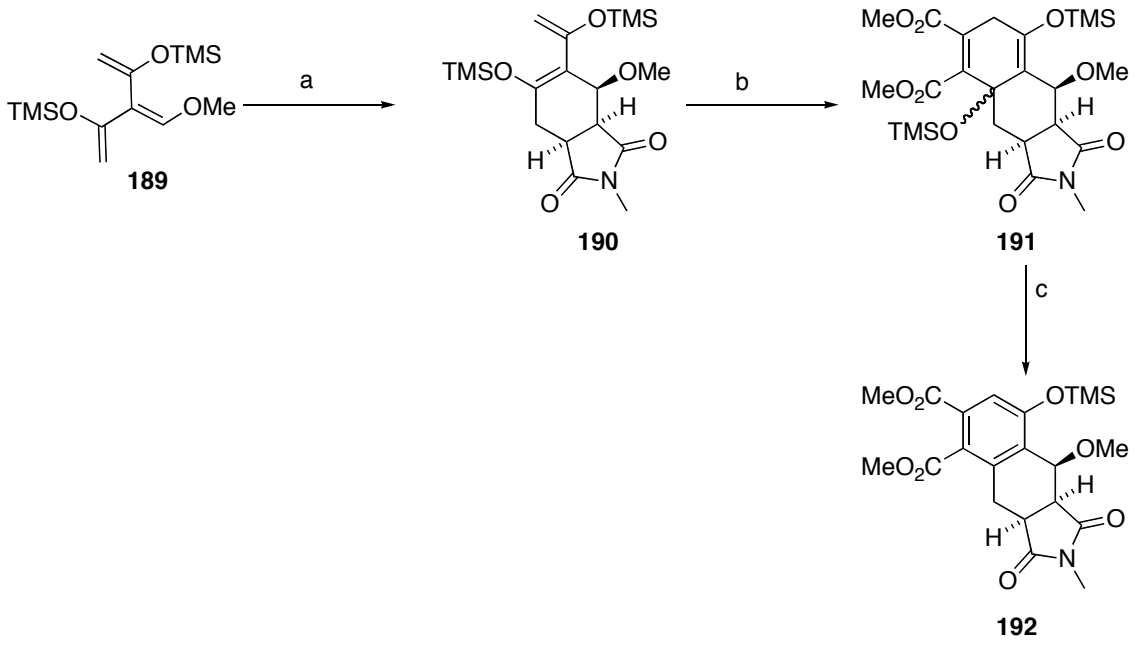
In the same study, dendralene **182** is also reacted with the unsymmetrical dienophile methyl propiolate, raising the issue of regioselectivity whilst removing the concern of stereoselectivity. When **182** was treated with an excess of methyl propiolate followed

by work up with methanol, the bicyclic product **188** was isolated in 47% yield (Scheme 4.14). The assignment of the product was based on spectral data. As only one product was formed, each Diels-Alder reaction has occurred in a highly regioselective manner. The regioselectivity is explained by the *ortho*-, *para*-orientation rule implied by the Woodward-Hoffman rules.[11,14]



Scheme 4.14 *Reagents and conditions*: (a) methyl propiolate, PhH, 80 ^{o}C; (b) methanol, 47% over 2 steps.

The methoxy substituted [3]dendralene **189** was synthesised in a similar manner to **182**.[126] The methoxy substituent at the central position of **189** also invokes site selectivity. The DTDA sequence can be interrupted after the first cycloaddition, allowing a different dienophile to be used for the second cycloaddition (Scheme 4.15).



Scheme 4.15 *Reagents and conditions:* (a) N-methylmaleimide (1.0 equiv), PhH, rt, 24 h; (b) dimethyl acetylenedicarboxylate (1.0 equiv), PhH, 80 ^{o}C, 20 h; (c) methanol, 41% 3 steps.

A DTDA sequence was also carried out using the 2-ethoxy substituted [3]dendralene **196**, synthesised from the Grignard reagent derived from chloroprene and 1-ethoxy-1,2-dibromoethane **194** (Scheme 4.16).[127] The authors had expected reaction to first occur at the more substituted diene. When **196** was reacted with *N*-methylmaleimide, however, the only product obtained was the bis-adduct **198**, resulting from the intermediate mono-adduct **197**. This result was explained on the basis of steric effects (Figure 4.3).

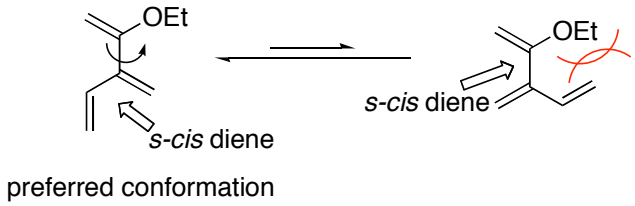
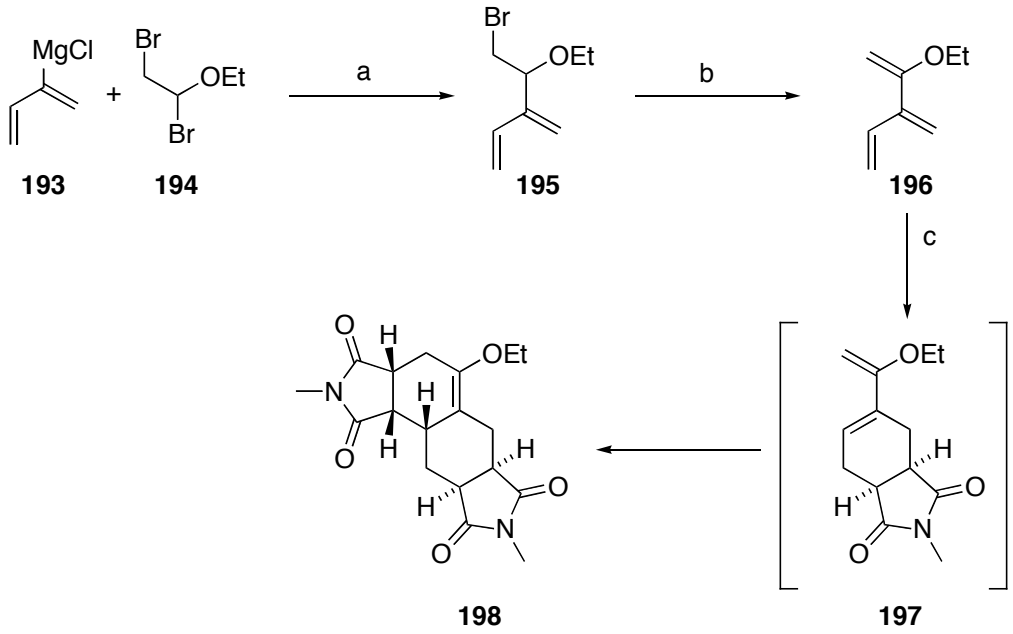
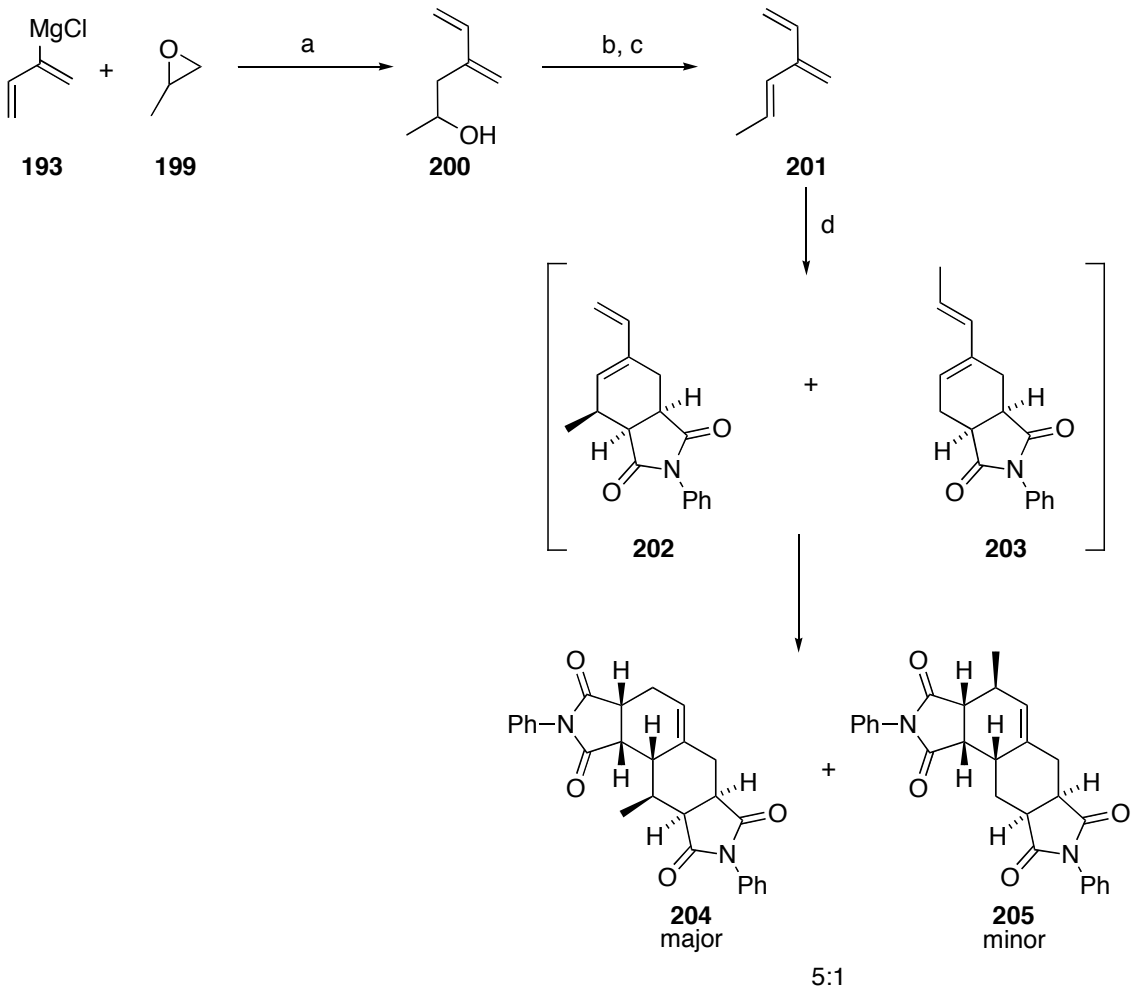


Figure 4.3 Preferred conformation of substituted [3]dendralene **196**



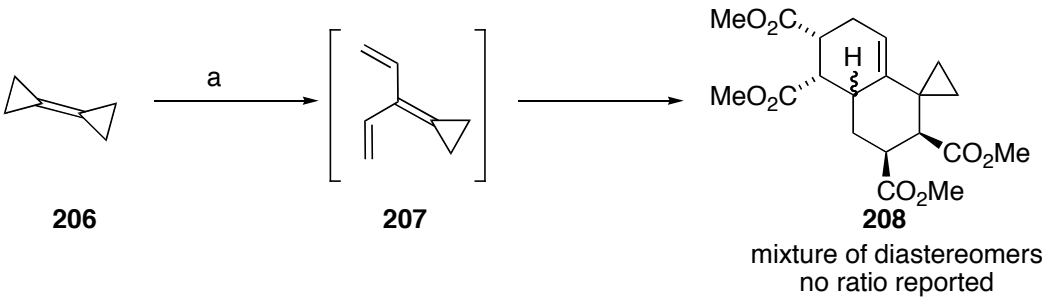
Scheme 4.16 *Reagents and conditions:* (a) THF, 0 ^{o}C, 6 h, 14%; (b) DBU, 100-110 ^{o}C, 2666 Pa, 82%; (c) N-methylmaleimide (2.4 equiv), PhH, rt, 2 h, 66%.

All DTDA sequences reviewed thus far exhibited near complete site and stereoselectivity. In contrast, the Diels-Alder reactions of terminally substituted [3]dendralene **201**, synthesised from Grignard reagent derived from chloroprene and methyl oxirane **199**, were less selective.[128] Reaction of **201** with *N*-phenylmaleimide results in the formation of the two cycloadducts **204** and **205** in a ratio of 5:1 respectively (Scheme 4.17).



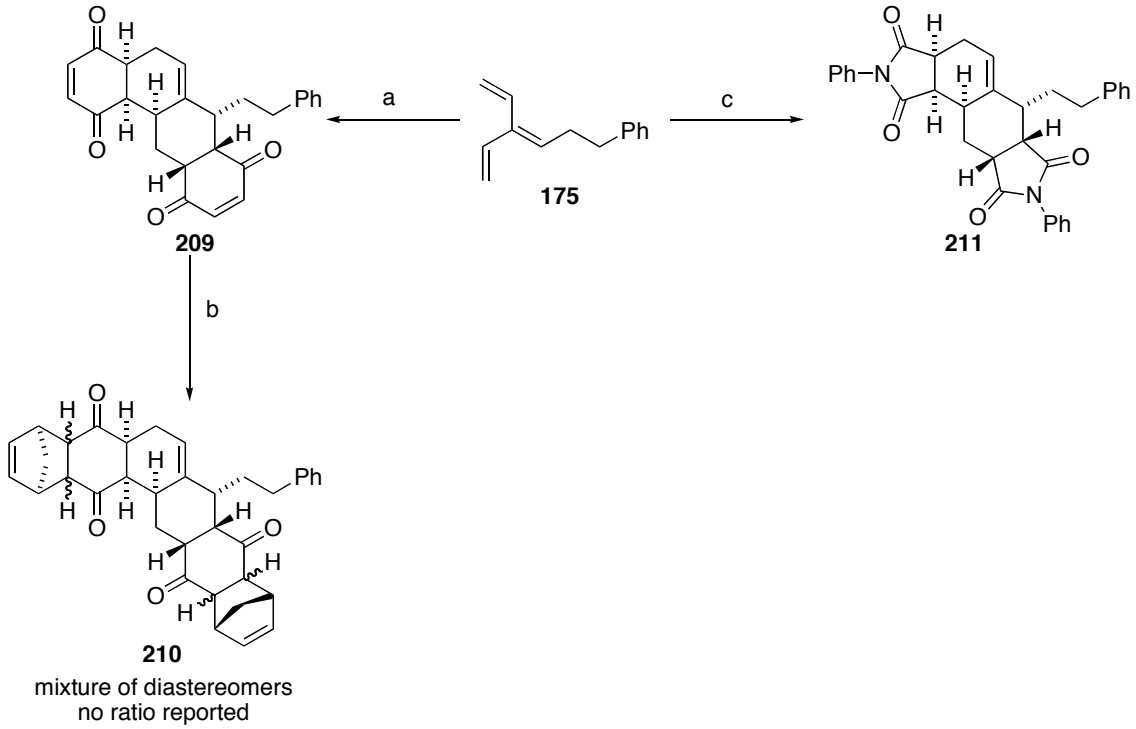
Scheme 4.17 *Reagents and conditions:* (a) 50-60 ^{o}C, THF, 2 h, 42%; (b) TsCl, pyridine, 36 h, 80%; (c) DBU, 110 ^{o}C, 20 mm/Hg, 30 min, 64%; (d) N-phenylmaleimide (1.1 equiv), PhH, rt, 20 h, 92%.

DTDA sequences have also been used as part of a larger domino sequence. de Meijere has reported a novel sequence involving a Heck reaction to form the substituted [3]dendralene **207** followed by a DTDA sequence to give the bis-adduct **208** as a mixture of diastereoisomers (Scheme 4.18).[129]



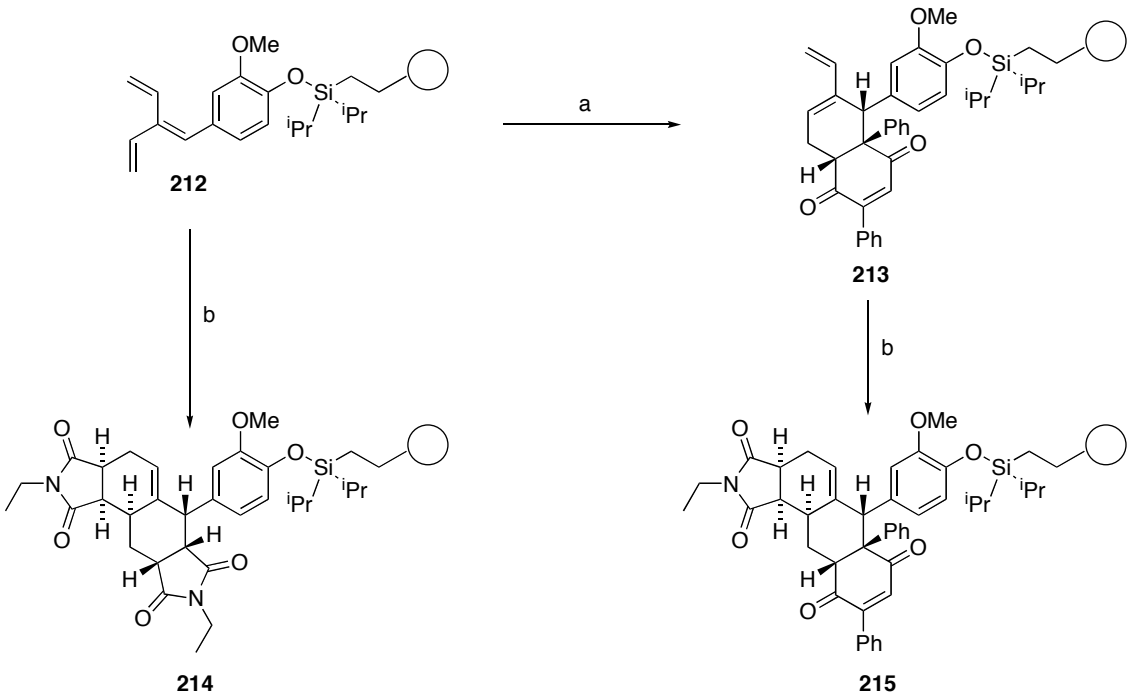
Scheme 4.18 *Reagents and conditions:* (a) vinyl iodide, dimethyl maleate, $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 75 ^{o}C, 20 h, 49%.

More recently, Fallis reported DTDA sequences involving the internally substituted [3]dendralene **175** (Scheme 4.19).[122] The bis-adducts **209** and **211**, arising from the addition of *p*-benzoquinone or *N*-phenylmaleimide, were synthesised with complete site and π-diastereofacial selectivity. Once again the site selectivity is a result of the substituent disfavouring the s-cis conformation of one of the diene units. The bis-adduct **209** was reacted further with an excess of cylopentadiene to give the octacyclic skeleton **210** as a mixture of diastereoisomers.



Scheme 4.19 *Reagents and conditions*: (a) *p*-benzoquinone, 21 °C, no yield reported; (b) cyclopentadiene, 21 °C, 16 h, 71%; (c) *N*-phenylmaleimide, 21 °C, 81%.

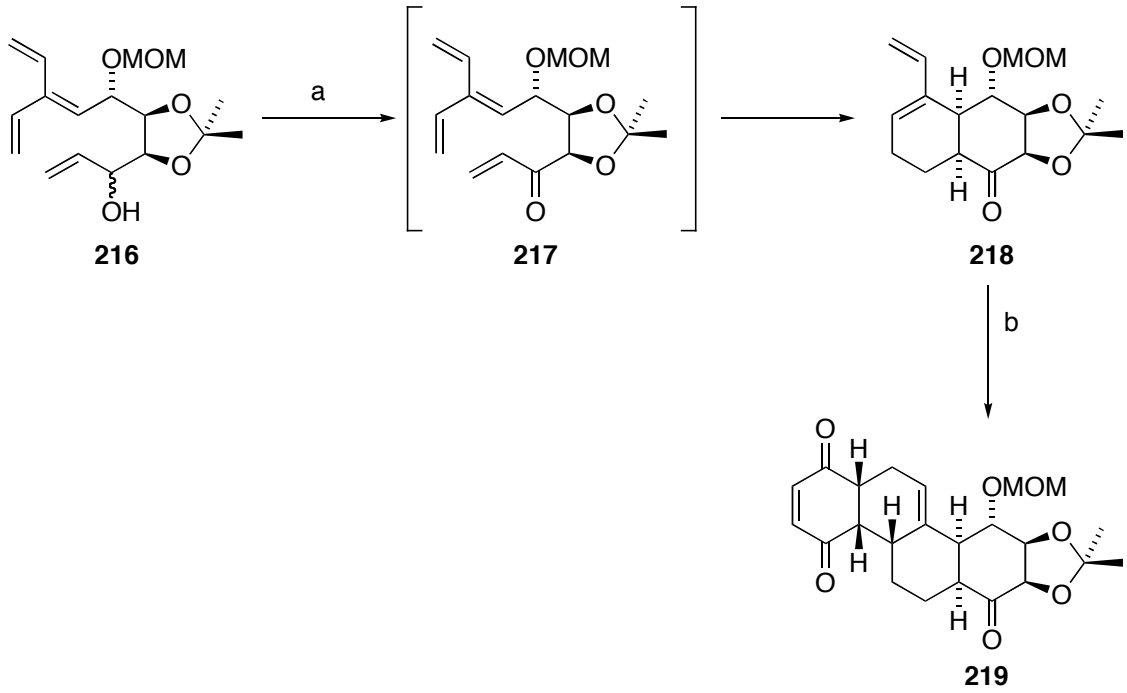
Schreiber used Fallis' method to synthesise 40 dendralenes from phenolic aldehyde-loaded macrobeads.[130] These dendralenes were used in the combinatorial synthesis of 29400 discrete polycyclic compounds comprising 10 different ring skeletons. It was reported that disubstituted dienophiles, such as *N*-ethylmaleimide, underwent double cycloaddition to give the bis-adducts while tri- or tetrasubstituted dienophiles only underwent mono addition. The monoadducts were then reacted further with a second dienophile (Scheme 4.20).



Scheme 4.20 *Reagents and conditions*: (a) 2,5-diphenyl-*p*-benzoquinone, PhMe; (b) *N*-ethylmaleimide, PhMe.

4.1.2.2 Intra/Intermolecular DTDA sequences

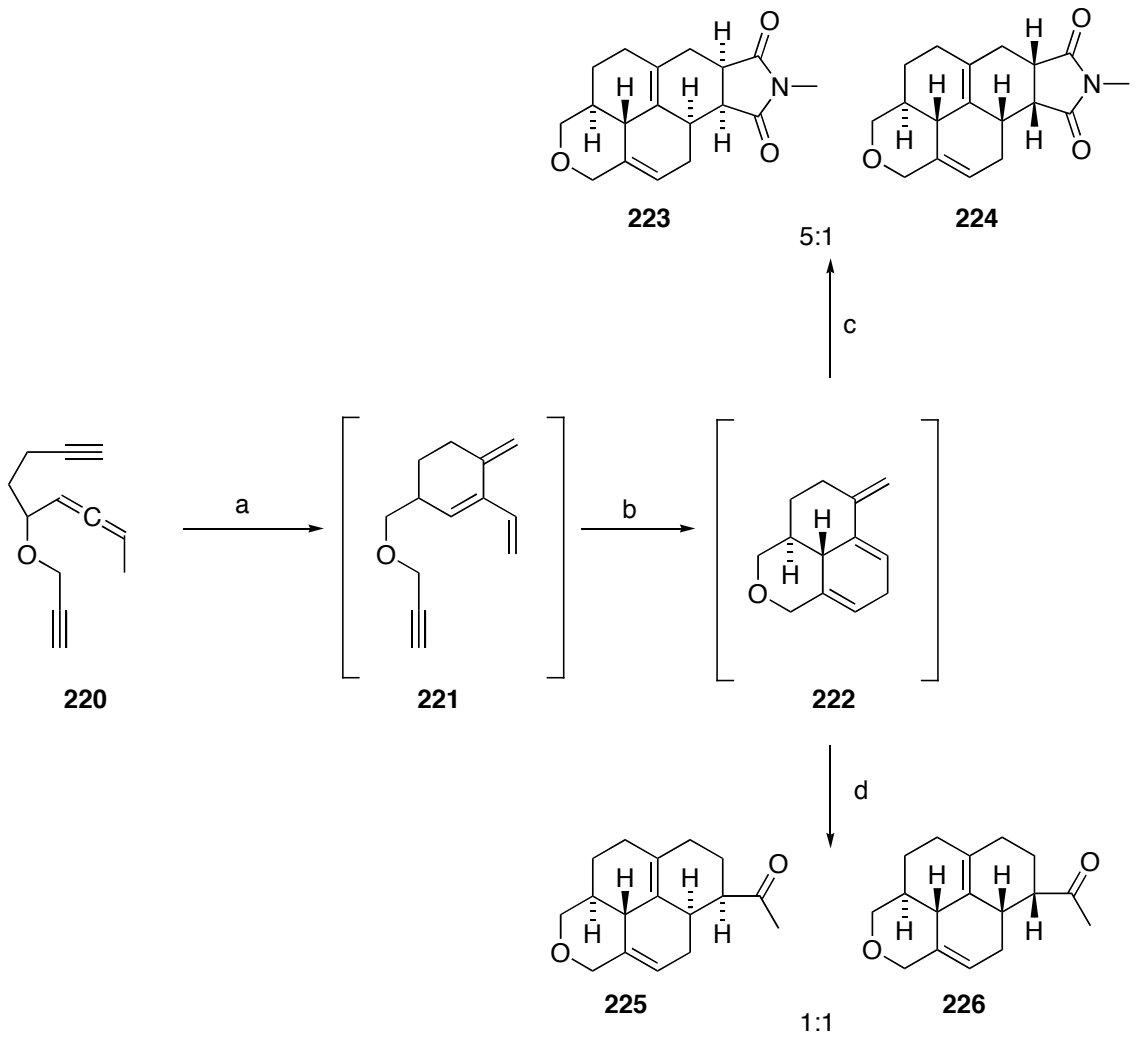
In addition to his work on inter/intermolecular DTDA sequences, Fallis has also reported an intra/intermolecular DTDA sequence.[131] The [3]dendralene **216** was synthesised in eight steps from L-arabinose. Oxidation of the alcohol resulted in spontaneous IMDA reaction to give the semi-cyclic diene **218** in 78% yield. The *cis*-fused isomer is formed through the *endo*-transition state which is favoured for steric reasons. Intermolecular Diels-Alder reaction with *p*-benzoquinone gave the nor-triterpenoid **219** as a single product. Single crystal X-ray analysis confirmed that the dienophile had approached the diene from the more accessible convex face in an *endo*-orientation.



216 **217** **218** **219**

Scheme 4.21 *Reagents and conditions*: (a) $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, -78 ^oC, 78%; (b) *p*-benzoquinone, PhH, 21 ^oC, 3 d, 85%.

Recently a domino sequence involving a Rh-catalysed Alder-ene reaction followed by an inter/intramolecular DTDA transformation was reported.[132] The best result obtained involved the one-pot conversion of dialkynylallene **220** into tetracycles **223** and **224** in a 5:1 ratio respectively, when N-methylmaleimide was used as the dienophile. The intramolecular Diels-Alder reaction proceeds with complete site and stereoselectivity to give a single isomer, while the intermolecular Diels-Alder reaction gives the two *endo*-products resulting from addition of the dienophile to either π-diastereoface of **222**. The use of an unsymmetrical dienophile for the intermolecular Diels-Alder reaction resulted in the formation of the two diastereoisomers **225** and **226** in a 1:1 ratio. The reaction did, however, proceed with complete regioselectivity.



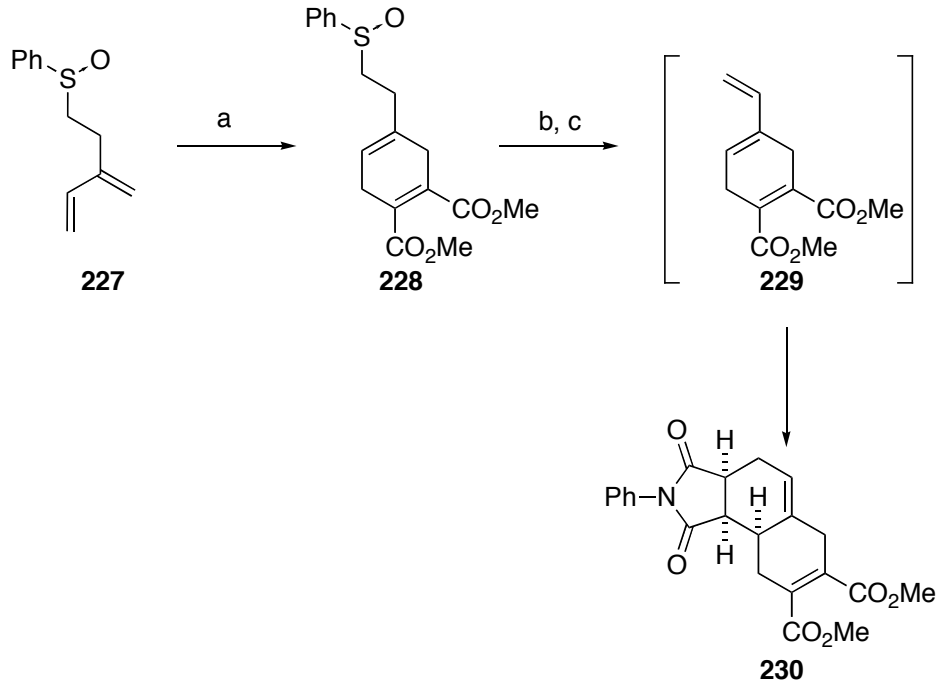
Scheme 4.22 *Reagents and conditions:* (a) $[Rh(CO)_2Cl]_2$ (0.05 equiv), DCE, rt, 1 h; (b) $[Rh(dppe)Cl]_2$ (0.05 equiv), $AgSbF_6$ (0.10 equiv), DCE, 30 min; (c) N-methyl maleimide, 24 h, 82%; (d) methyl vinyl ketone, 12 h, 75%.

4.1.2.3 Sequential Diels-Alder reactions using [3]dendralene equivalents

In order to address the issue of site selectivity, a number of groups have carried out Diels-Alder reactions on masked dendralenes. This involves a Diels-Alder reaction followed by a transformation, often an elimination, to unmask a second diene, followed by another Diels-Alder reaction.

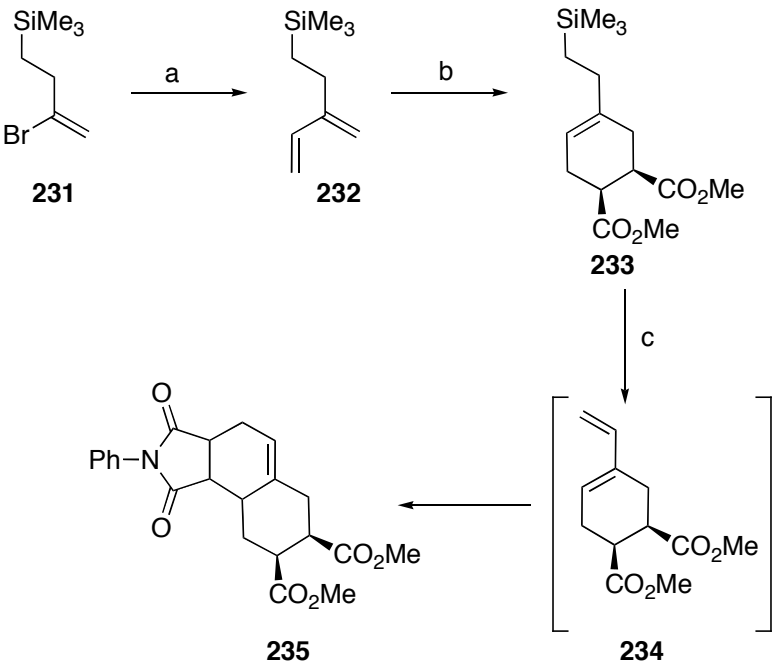
The Tsuge group have made contributions to this area also, firstly with examples of masked equivalents of the parent [3]dendralene.[133] Thus, diene **227** readily reacts with a variety of dienophiles to give cycloadducts of the type **228** (Scheme 4.23). Thermal elimination followed by Diels-Alder reaction with the newly formed diene gives the bis-adduct **230**. This example was published before Cadogan's work[120] (Scheme 4.12) and

was the first example of the parent dendralene or an equivalent being reacted with two different dienophiles to give mixed bis-adducts.



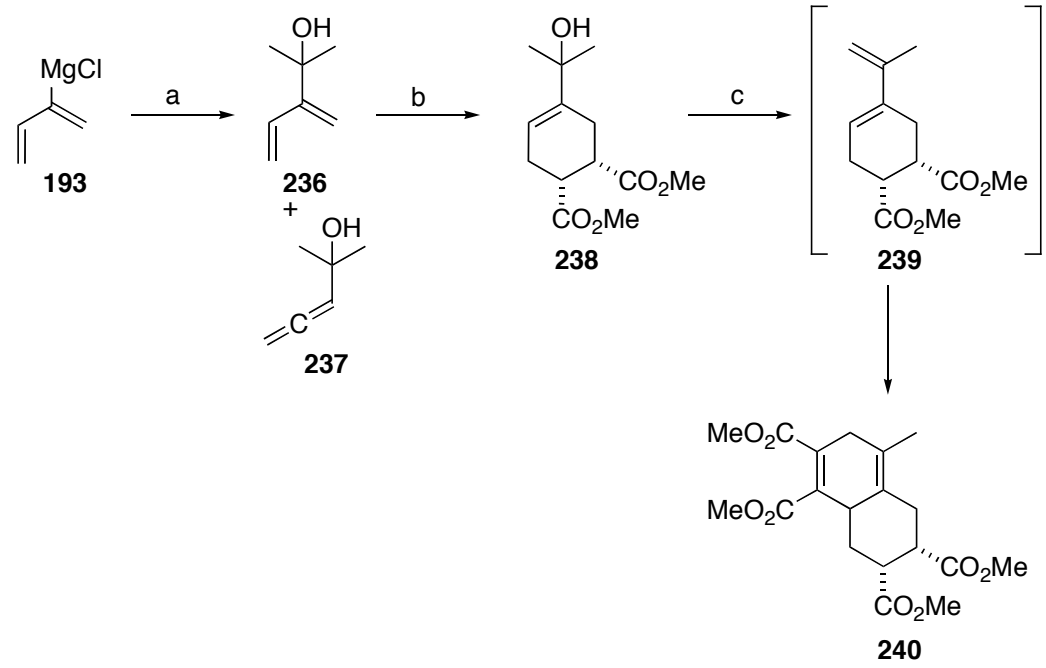
Scheme 4.23 *Reagents and conditions*: (a) DMAD, $EtAlCl_2$ (2.0 equiv), CH_2Cl_2, rt, 24 h, 52%; (b) PhMe, 110 ^oC, 22 h; (c) N-phenylmaleimide, 76%.

The Hosomi group reported the use of 2-trimethylsilylethyl-1,3-butadiene **232** as a synthetic equivalent to the parent [3]dendralene **29**.[134] Diels-Alder reaction between **232** and dimethyl maleate give cycloadduct **233** in 85% yield. Elimination followed by Diels-Alder reaction gives the tetracycle **235** in 79% yield. Product stereochemistry was not reported in this publication.



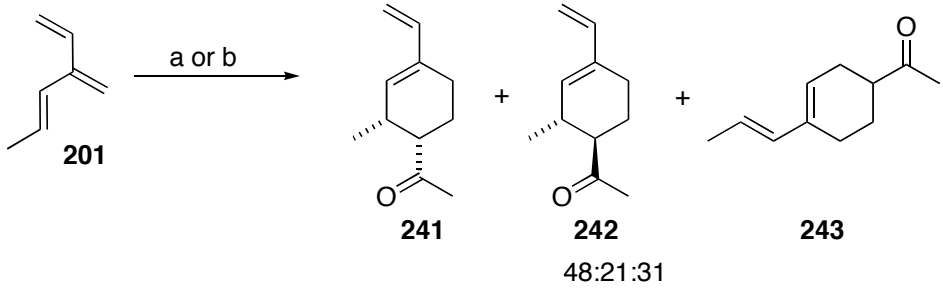
Scheme 4.24 *Reagents and conditions*: (a) i) Mg, THF; ii) CH_2=CHBr, Ni(dppp)Cl_2, 88%; (b) dimethyl maleate, 130 ^oC, 24 h, 85%; (c) i) $Ph_3C^+BF_4^-$, MeCN, rt, 5 h; ii) PhMe, 110 ^oC, 36 h, 79%.

There are also examples of equivalents of substituted [3]dendralenes undergoing sequential Diels-Alder reactions. The Grignard reagent derived from chloroprene was reacted with acetone to give a mixture of the two alcohols **236** and **237** in a 3:1 ratio (Scheme 4.25).[135] This mixture was heated with dimethyl maleate to give the cycloadduct **238**. Dehydration and the second Diels-Alder reaction could be achieved in one pot by adding molecular sieves and an excess of dimethyl acetylenedicarboxylate to **238**. The bis-adduct **240** was obtained in 63% yield.



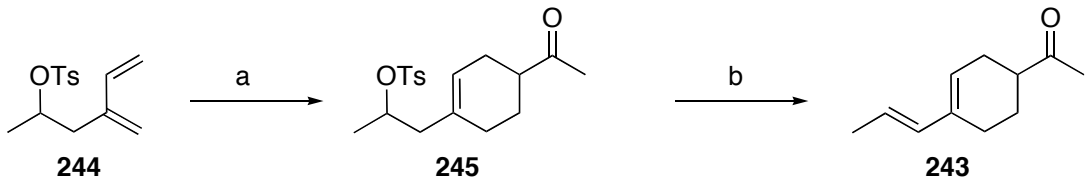
Scheme 4.25 *Reagents and conditions:* (a) Acetone in THF, no yield given; (b) dimethyl maleate, PhMe, 110 ^{o}C, 95%; (c) 5Å molecular sieves, dimethyl acetylenedicarboxylate (3 equiv), PhH, 80 ^{o}C.

Reaction of [3]dendralene **201** with the unsymmetrical dienophile methyl vinyl ketone at room temperature gave a mixture of the three mono-adducts **241**, **242** and **243** in a ratio of 48:21:31 respectively (Scheme 4.26).[128] The use of a Lewis acid improved the *endo*/*exo* selectivity while it had no effect on the site selectivity, resulting in a product ratio of 71:2:26.



Scheme 4.26 *Reagents and conditions:* (a) methyl vinyl ketone (2.2 equiv), PhH, rt, 2 h, 76%; (b) methyl vinyl ketone, $EtAlCl_2$, PhMe, -78 ^{o}C, 0.5 h, 46%.

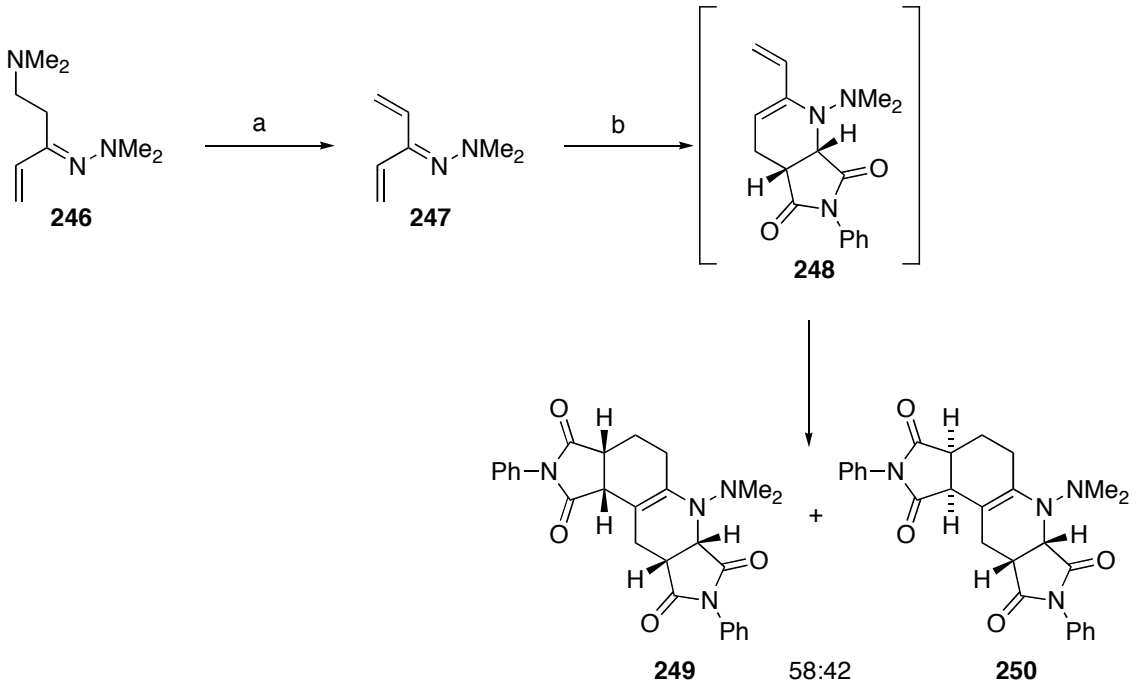
Diels-Alder reaction was then carried out between tosylate **244**, a synthetic equivalent of [3]dendralene **201** and methyl vinyl ketone in the presence of ethylaluminum dichloride to give **245** as a single product. Subsequent elimination gave the diene **243**, previously obtained as the minor product in Scheme 4.25, thus illustrating the advantages of this method.



Scheme 4.27 *Reagents and conditions*: (a) methyl vinyl ketone, $EtAlCl_2$, PhMe, -78 °C, 1h, 67%; (b) DBU, PhMe, 110 °C, 12 h, 66%.

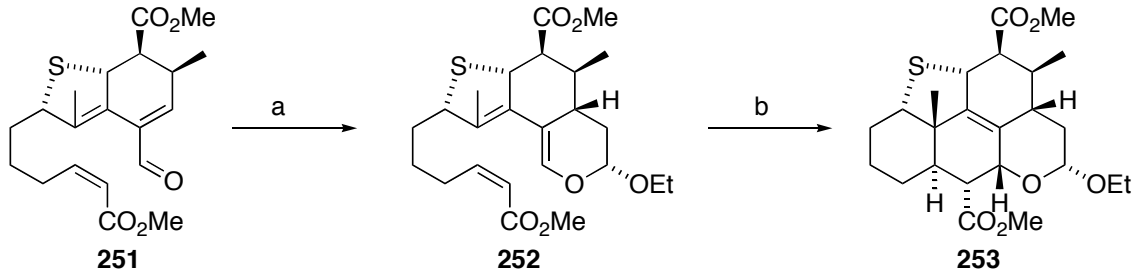
4.1.2.4 DTDA reactions involving heteroatom-containing equivalents of [3]dendralenes

There are many examples of a heteroatom-containing equivalent of a dendralene being used in a DTDA sequence. An example of a nitrogen-containing [3]dendralene equivalent undergoing an intermolecular/intermolecular DTDA was reported in 1991.[136] A mixture of two bis-adducts **249** and **250** was obtained after **247** was treated with N-phenylmaleimide followed by subsequent migration of the double bond to the more substituted position.



Scheme 4.28 *Reagents and conditions*: (a) KOH, isopropanol, 60 °C, 40 min, 79%; (b) N-phenylmaleimide, CH_2Cl_2, rt, 48 h, 31% of **249** and 43% of **250**.

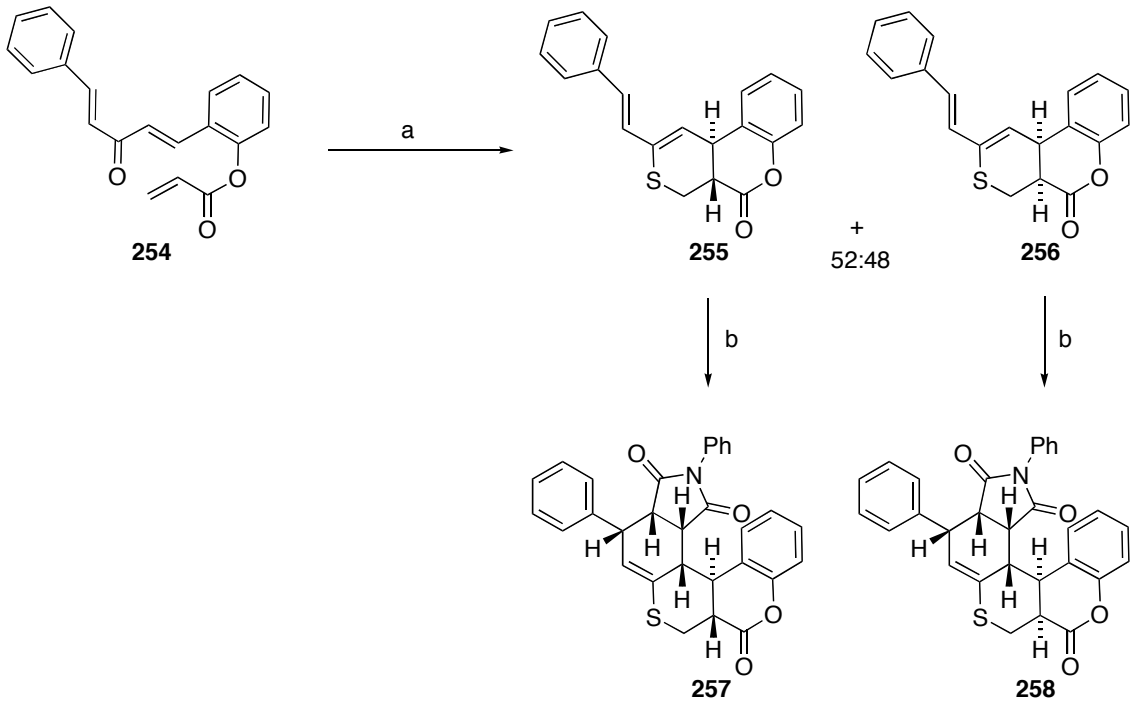
The Spino group have published several papers on a DTDA strategy involving an intermolecular hetero Diels-Alder followed by an intramolecular Diels-Alder reaction to synthesise the quassinoid skeleton.[137-140] They recently reported the synthesis of an advanced intermediate to the quassinoids in 14 steps from tetrahydrofuran (Scheme 4.26).[141] Hetero-Diels-Alder reaction between [3]dendralene equivalent **251** and ethylvinyl ether proceeds via an *endo*-transition state with the dienophile approaching the less hindered π-diastereoface of **251** to give **252**. The intramolecular Diels-Alder reaction also proceeds through an *endo*-transition state to give pentacycle **253** as a single isomer.



251 **252** **253**

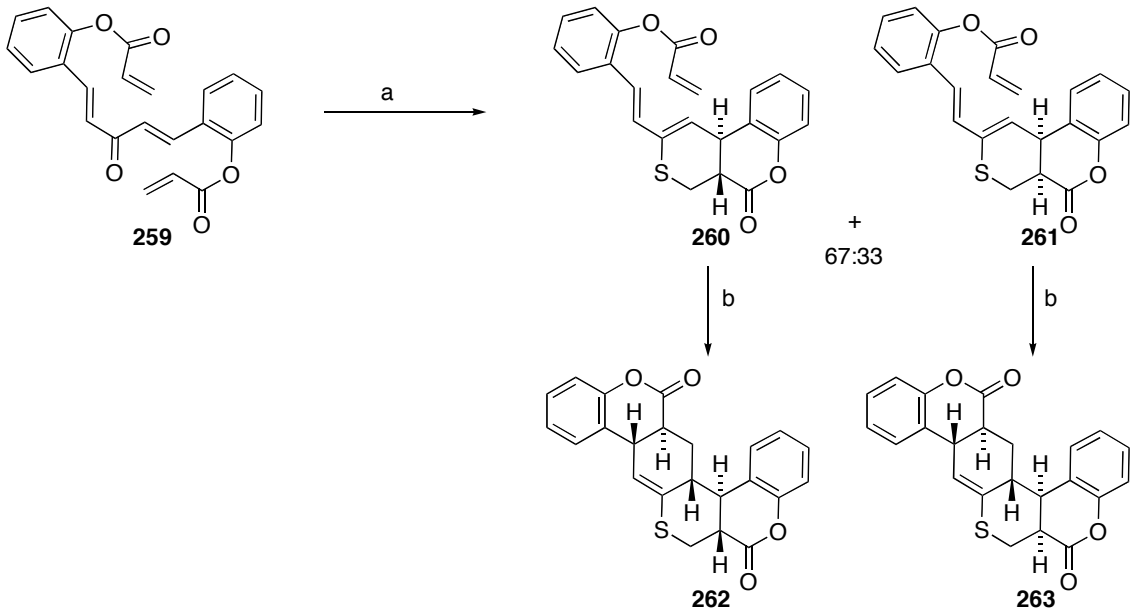
Scheme 4.29 *Reagents and conditions*: (a) ethylvinyl ether, $Yb(fod)_3$, 76%; (b) PhMe, 250 ^{o}C, 50%.

The Saito group have reported examples of heteroatom containing dendralene equivalents undergoing both intra/intermolecular DTDA sequences and intramolecular/intramolecular DTDA sequences.[142] When ketone **254** was treated with Lawesson's reagent the resulting thioketone underwent rapid IMDA reaction to give the cycloadducts **255** and **256** in a ratio of 52:48. Intermolecular Diels-Alder reaction between each of the mono-adducts **257** and **258** and N-phenyl maleimide proceeded with a high level of *endo*- and π-diastereofacial selectivity to give a single product in each case.



Scheme 4.30 *Reagents and conditions:* (a) Lawesson's reagent, PhH, 80 ^{o}C, 0.5 h, 80%; (b) N-phenylmaleimide, xylene, 140 ^{o}C, 3 h, 88% for **257**, 28 h, 84% for **258**.

Similarly, when ketone **259** was treated with Lawesson's reagent, the intermediate thioketone underwent rapid IMDA reaction to give the cycloadducts **260** and **261** in a ratio of 67:33 (Scheme 4.31). After separation each of the mono-adducts **260** and **261** were heated in xylene to effect the second IMDA cyclisation with a high level of *exo*-selectivity to give **262** and **263** respectively.



Scheme 4.31 *Reagents and conditions*: (a) Lawesson's reagent, PhH, 80 ^{o}C, 1 h, 94%; (b) xylene, 140 ^{o}C, 7 h, 81% for **262**, 14 h, 54% for **263**.

4.2 Aims

While several examples of the DTDA sequence have been reported in the literature, until now the control of chemo-, regio- and stereoselectivity during intermolecular "diene-transmissive" cycloaddition sequences has not been reported. Furthermore, no general synthetic approach to substituted cross-conjugated systems has been reported.

We aim to develop a straightforward method for the preparation of substituted chiral dendralenes (Figure 4.4). This new approach will demonstrate that substitution can be tolerated at all available positions of the triene-framework.

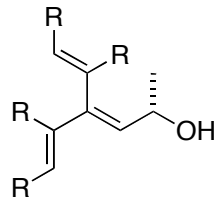
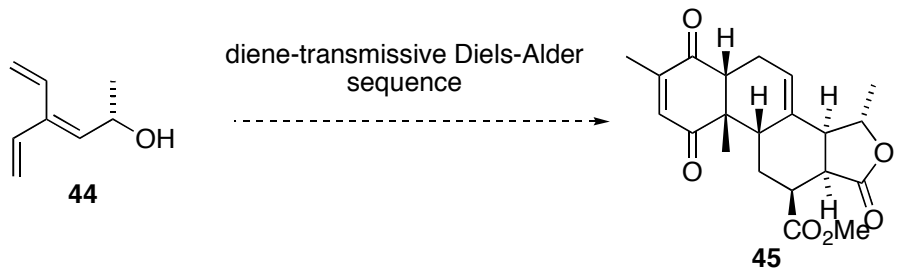


Figure 4.4 Chiral dendralenes where R = H or alkyl groups.

We will also demonstrate the involvement of one of the simplest chiral [3]dendralenes in highly chemo-, regio- and stereoselective diene-transmissive Diels–Alder (DA) sequences to form enantiomerically pure polycyclic frameworks (Scheme 4.32).



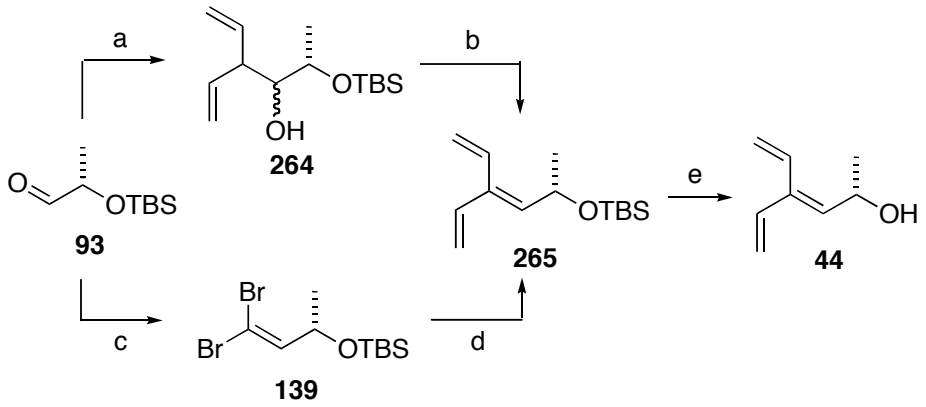
Scheme 4.32 The rapid construction of fused polycycles.

4.3 Results and Discussion

4.3.1 Synthesis of Substituted Chiral Dendralenes

*4.3.1.1 Synthesis of a simple chiral [3]dendralene **44***

Applying Fallis' indium-mediated coupling protocol to simple chiral aldehyde **93** gave the alcohol **264** as a 1:1 mixture of diastereoisomers. Elimination under Mitsunobu conditions furnished triene silyl ether **265** in 25% overall yield (Scheme 4.33). A slightly higher yield was obtained using mesylation of the alcohols followed by elimination. The modest yield for this transformation led us to develop an alternative route. Thus, Corey-Fuchs dibromomethylenation[113] of aldehyde **93** gave **139**,[91] which underwent twofold Stille or Negishi couplings to furnish triene **265** in up to 51% overall yield from **93**. Deprotection of the silyl ether gave alcohol **44**. Trienes **265** and **44** are easily purified and stored and require no special handling techniques.

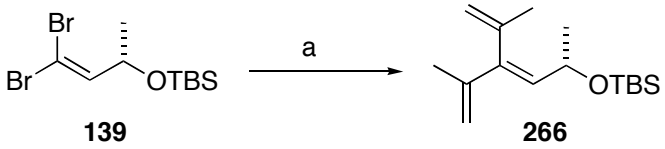


Scheme 4.33 *Reagents and conditions*: (a) CH_2=CH-CH=$CHCH_2Br$ (**172**) (1.2 equiv), In (1.1 equiv), DMF, 25 °C, 16 h, 54%; (b) PPh_3 (2.0 equiv), DEAD (2.0 equiv), THF, reflux, 3.25 h, 46%; (c) PPh_3 (4.0 equiv), CBr_4 (2.0 equiv), CH_2Cl_2, 25 °C, 4 h, 76 %. (d) CH_2=$CHSnBu_3$ (2.5 equiv), $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.10 equiv), CH_3CN, 60 °C, 26 h, 61 % or CH_2=$CHMgBr$ (3.33 equiv), $ZnBr_2$ (3.47 equiv), $Pd(PPh_3)_4$ (0.03 equiv), THF, 25 °C, 48 h, 67 %. (e) TBAF (2.0 equiv), THF, 25 °C, 2.5 h, 86 %.

4.3.1.2 Other chiral dendralenes

In contrast to Fallis' seminal nucleophilic addition–dehydration approach to [3]dendralenes, the route that we have developed is by no means limited to the synthesis of trienes substituted at the central methylene unit. In order to demonstrate the generality of this new approach, several other dendralenes with different substitution patterns were synthesised.

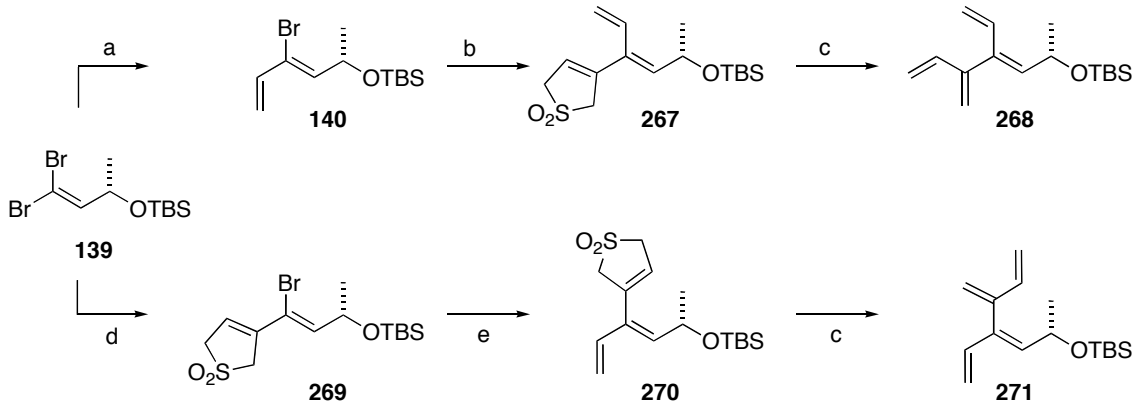
[3]dendralene **266** was synthesised to show that substitution can be tolerated at the 2 position of the triene framework (Scheme 4.34). Thus dibromide **139** was reacted with an excess of isopropenyl zinc bromide in a Negishi coupling to give the dendralene **266** in good yield.



139 **266**

Scheme 4.34 *Reagents and conditions*: (a) $H_2C{=}C(CH_3)ZnBr$ (5.0 equiv), $Pd(PPh_3)_4$ (0.05 equiv), THF, RT, 18 h, 83%

The route also lends itself to the highly stereoselective synthesis of both geometrical isomers of unsymmetrically–substituted systems. This was exemplified by the synthesis of the first chiral [4]dendralenes, **268** and **271 (**Scheme 4.35**)**.



Scheme 4.35 *Reagents and conditions*: (a) $H_2C{=}CHSnBu_3$ (1.05 equiv), $Pd_2(dba)_3$ (0.025 equiv), $AsPh_3$ (0.10 equiv), THF, 50 °C, 10 h, 85 %; (b) 3-(tributylstannyl)-3-sulfolene (1.2 equiv), $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.10 equiv), CH_3CN, 60 °C, 48 h, 90%; (c) PhCl, 132 °C, 1.5 h, 90% for **268**, 69% for **271**; (d) 3-(tributylstannyl)-3-sulfolene (1.0 equiv), tri(2-furyl)phosphine (0.15 equiv), $Pd_2(dba)_3$ (0.025 equiv), PhMe, 55 °C, 55%; (e) $H_2C{=}CHSnBu_3$ (2.0 equiv), $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.10 equiv), CH_3CN, 60 °C, 18 h, 92%.

Stille couplings between *gem*-dibromoalkenes and one equivalent of a vinyl stannane have been shown to proceed with *trans*-selectivity.[143] Thus, dibromide **139** was selectively coupled with tributyl(vinyl)tin following the procedure of Wong to give the *Z*-bromodiene **140** with greater than 20:1 selectivity.[85] A second Stille coupling using a slight excess of 3-(tributylstannyl)-3-sulfolene **163**[66] resulted in clean inversion of configuration[144] to give [4]dendralene precursor **267** as a single product. The

configuration of **267** was determined through 2D NMR experiments. A NOESY cross peak between H-2 and H-5 shows that inversion of configuration has occurred (Figure 4.5).

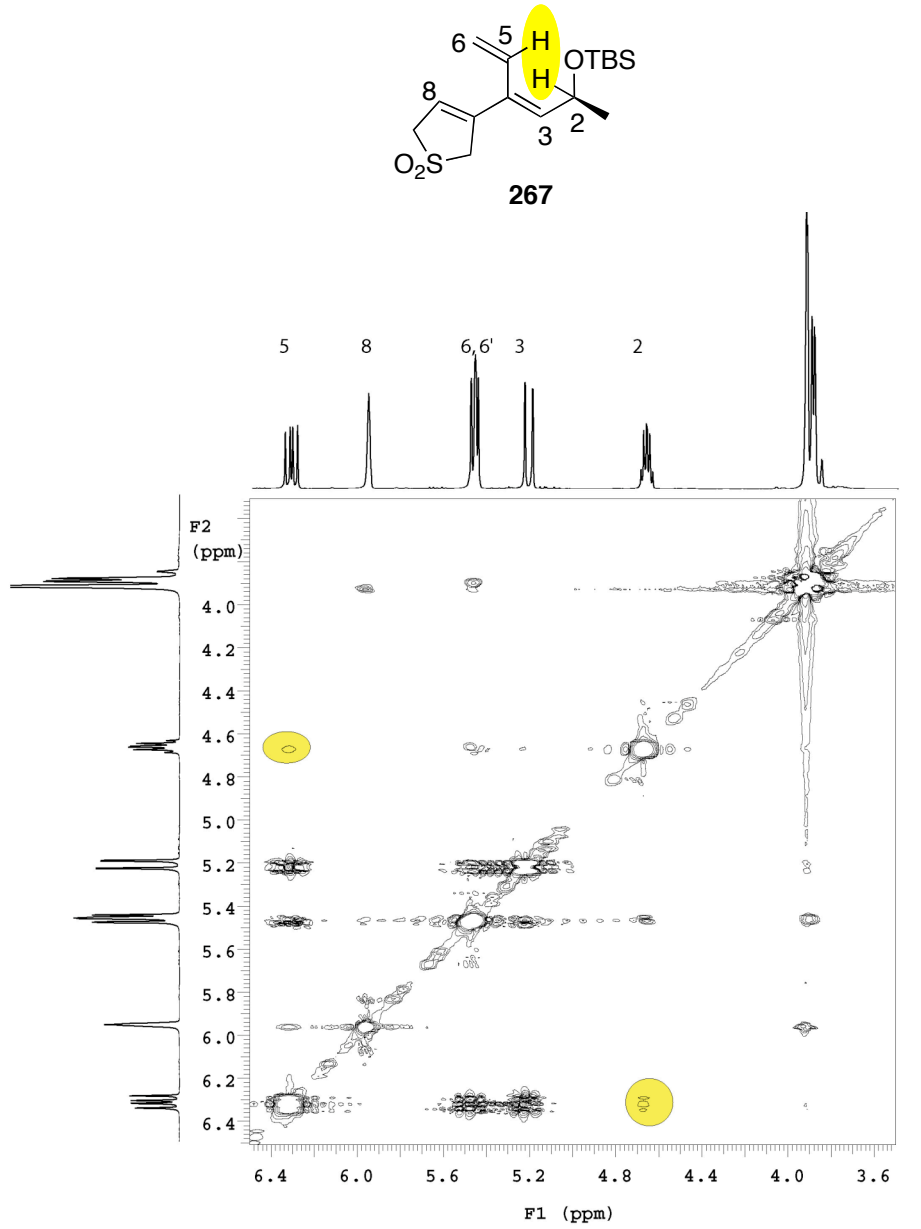
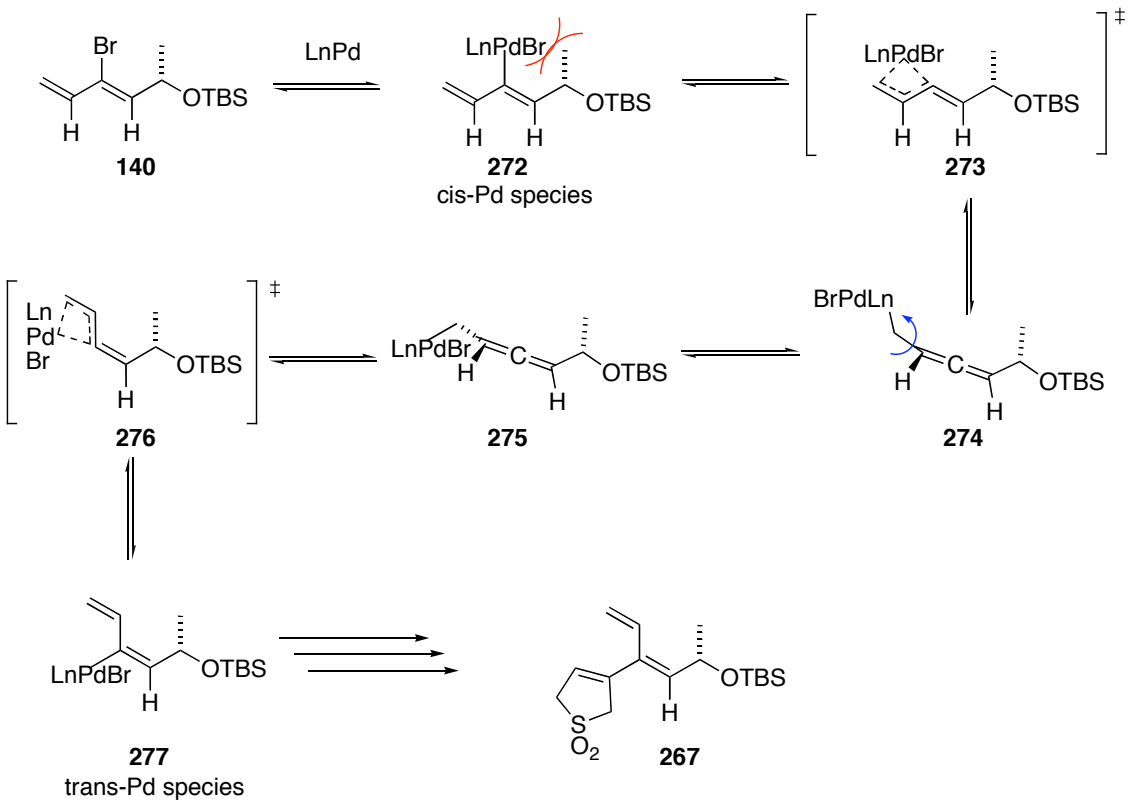


Figure 4.5 NOESY spectrum of [4]dendralene precursor **267**

This unusual inversion of configuration has been seen in the coupling of organozinc compounds with 2-bromo-1,3-butadienes and is thought to proceed via the mechanism shown in Scheme 4.36.[144] It is proposed that steric repulsion between Pd and the *cis* substituent in the Pd-complex **272** is reduced via the allene species **274** leading to the

trans-Pd species **277**. The *trans*-Pd complex would then undergo transmetallation and reductive elimination to give the observed product.



Scheme 4.36 Proposed mechanism of inversion of configuration at the sp^2 centre.

The geometrical isomer of [4]dendralene precursor **267** could be synthesised by reversing the order of the two palladium catalysed coupling steps. Once again, reaction between bromide **269** and tributyl(vinyl)tin proceeded with clean inversion of configuration to give the [4]dendralene precursor **270**. The configuration of the central alkene of **270** was also determined through 2D NMR experiments. NOESY cross-peaks between H-8 and H-2 confirm that inversion of configuration has occurred.

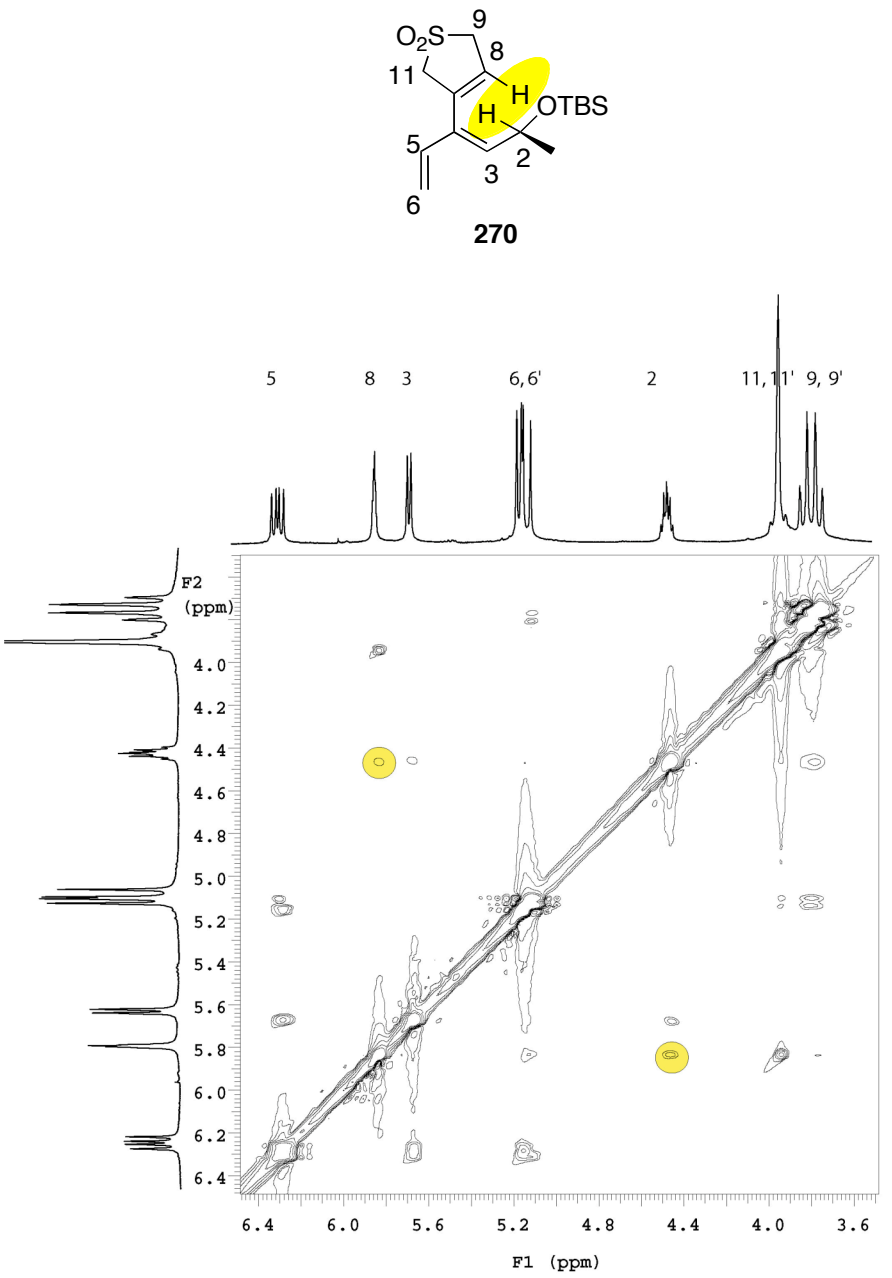


Figure 4.6 NOESY spectrum of [4]dendralene precursor **270**.

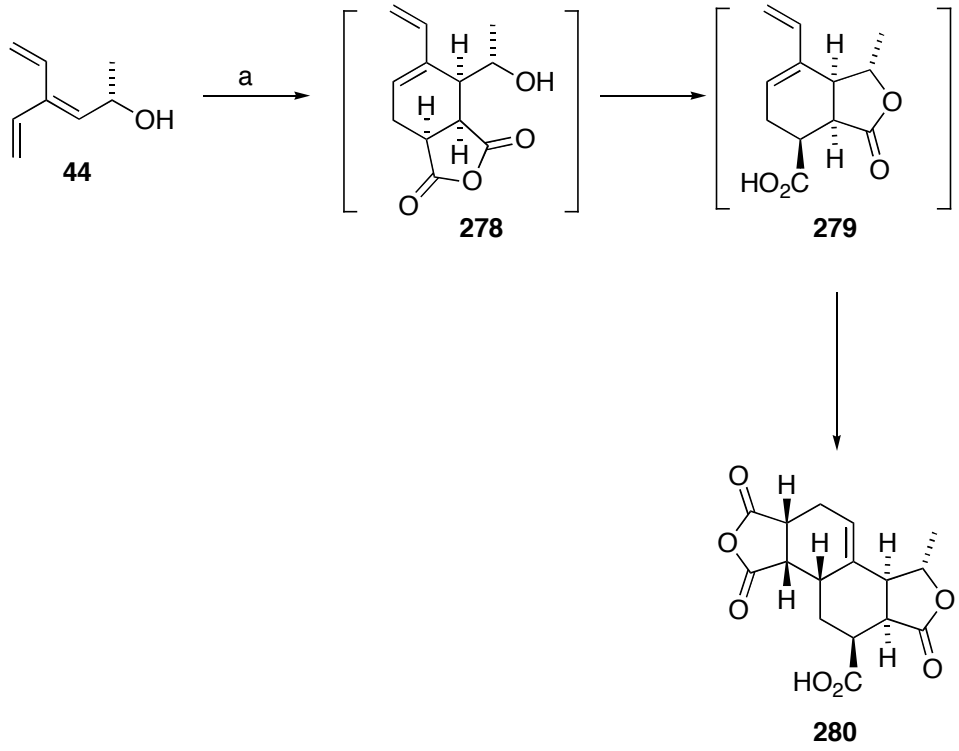
The [4]dendralene precursors **267** and **270** underwent cheleotropic extrusion of sulfur dioxide when heated to give the [4]dendralenes **268** and **271** respectively.

*4.3.2 DTDA Reactions Involving Chiral [3]Dendralene **44***

In order to demonstrate that these chiral substituted dendralenes could be used in DTDA sequences to form enantiomerically pure polycyclic frameworks we elected to carry out reactions using the simplest chiral [3]dendralene **44**.

4.3.2.1 Double cycloadditions of chiral [3]dendralene and maleic anhydride

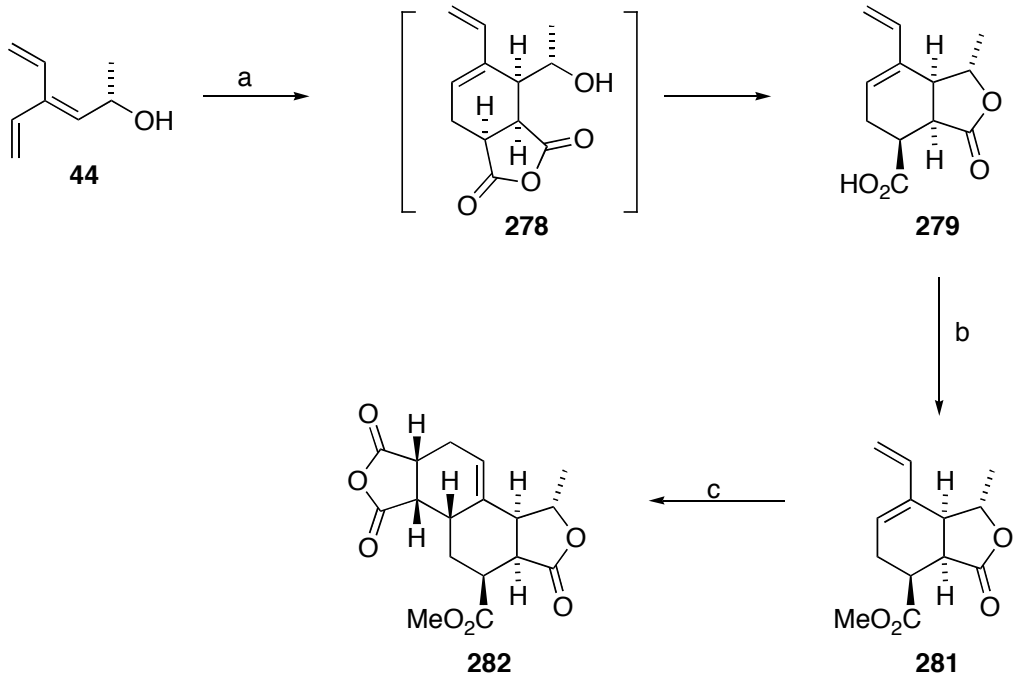
A mixture of chiral [3]dendralene **44** and maleic anhydride (2 equiv) in acetonitrile at room temperature gave tetracyclic lactone acid **280** in high yield (Scheme 4.37). The transformation presumably proceeds[111,112] by way of the short lived hydroxy anhydride **278**, which cyclizes rapidly to bicyclic lactone acid **279**, which in turn reacts with maleic anhydride to form **280**. Both cycloaddition steps are highly stereoselective, with **280** being formed as a single diastereomer, the stereochemistry of which was determined after subsequent experiments. The intermediate mono-adduct **279** remains a minor component throughout the course of the transformation, demonstrating that the second cycloaddition is more facile than the first. There are traces of minor products resulting from the competing esterification/IMDA pathway (Scheme 3.1).



Scheme 4.37 *Reagents and conditions*: (a) maleic anhydride (2.0 equiv), CD_3CN, 25°C, 60 h, >90%

The cascade sequences depicted above are agreeably effective ways to form new fused ring systems in a stereocontrolled manner. Nevertheless, a sequence that could be interrupted after the cycloaddition would offer significantly greater synthetic versatility.

Gratifyingly, this outcome was achieved in a very straightforward manner, by simply carrying out the reaction between alcohol **44** and maleic anhydride in benzene (Scheme 4.38). The same highly stereoselective cycloaddition–lactonization sequence carried out in benzene gave lactone acid **279**, which is insoluble in benzene and precipitates from solution as it forms; the product is isolated in pure form simply by filtration.



Scheme 4.38 *Reagents and conditions*: (a) maleic anhydride, (1.05 equiv), C_6D_6, 25°C, 48 h, 83%; (b) CH_2N_2, Et_2O/THF, –78°C, 15 min, 70%; (c) maleic anhydride (1.5 equiv), C_6D_6, 80°C, 18 h, 67%.

Esterification of **279** with diazomethane gave the corresponding methyl ester **281**. Reaction of **281** with a second equivalent of maleic anhydride gave **282** as a single diastereomer. The clean conversion of bicycle **281** into the tetracycle **282** could be tracked by ^{1}H NMR. Figure 4.7 shows ^{1}H NMR spectra of the reaction between **281** and maleic anhydride at time = 0 h, 1 h, 4 h, 7 h and finally 18 h. The disappearance of the signal due to the C1-H in the starting material (highlighted in purple) and the formation of the corresponding peak in the product (highlighted in green) provide a good

indication of how far the reaction has progressed. As can be seen in the spectrum taken at 18 h, there is a single alkenic peak due to the product (highlighted in blue).

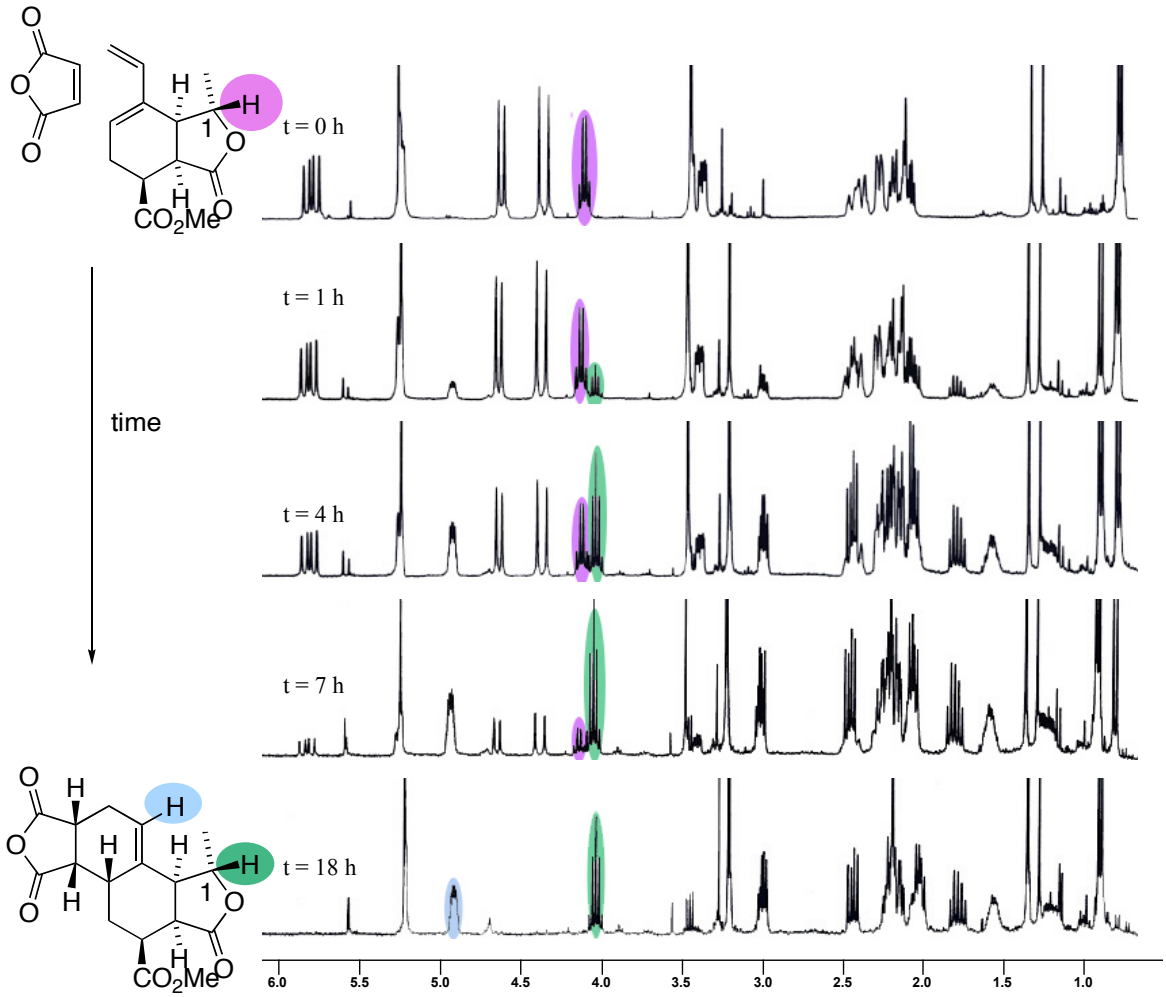
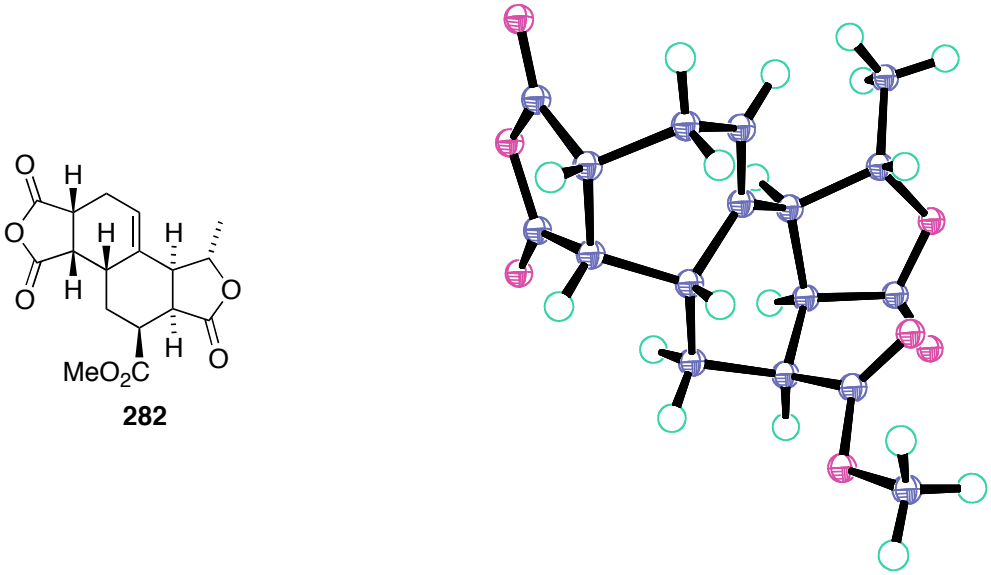


Figure 4.7 NMR spectra for the conversion of **281** to **282**.

Attempts were made to determine the stereochemistry of tetracycle **282** using 2D NMR techniques. While a solvent was found that separated all of the peaks of interest, the stereochemistry at the three new stereocentres relative to the existing stereocentres could not be unequivocally proven. Thus, single crystal X-ray analysis was used to confirm the stereochemistry of the tetracyclic product (Figure 4.8).



282

Figure 4.8 Thermal ellipsoid diagram of **282**. Ellipsoids show 30% probability levels.

It was thought that the high level of stereoselectivity observed in the first cycloaddition reaction could be result of hydrogen bonding between the free alcohol and maleic anhydride.[79] As a result of [1,3]A strain, there are two likely preferred conformations about the C1-C2 bond as depicted in Figure 4.9. In the conformation on the left, the H is in the most sterically hindered *inside* position, the CH_3 in the *outside* position and the OH in the *anti* position. If this is the preferred conformation, the maleic anhydride would be expected to approach the dendralene from the top face as drawn to maximise hydrogen bonding. In the conformation on the right, the H is still in the most sterically hindered *inside* position, while the CH_3 in the *anti* position and the OH is in the *outside* position. If this is the preferred conformation, the maleic anhydride would approach the dendralene from above since the bottom face is blocked by the methyl group.

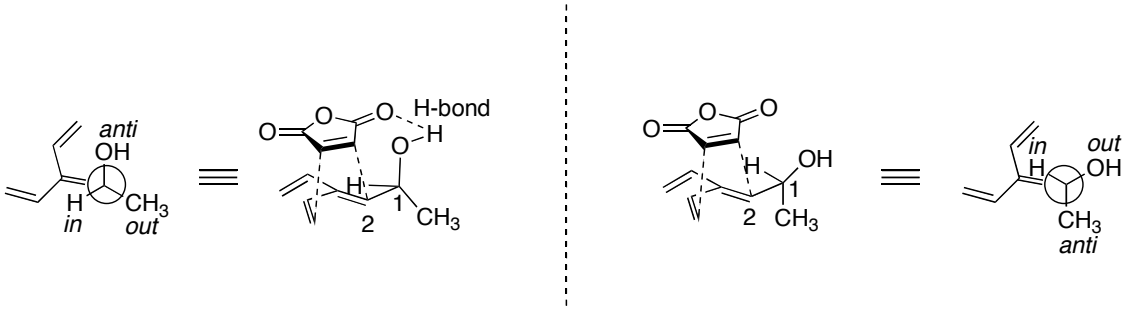
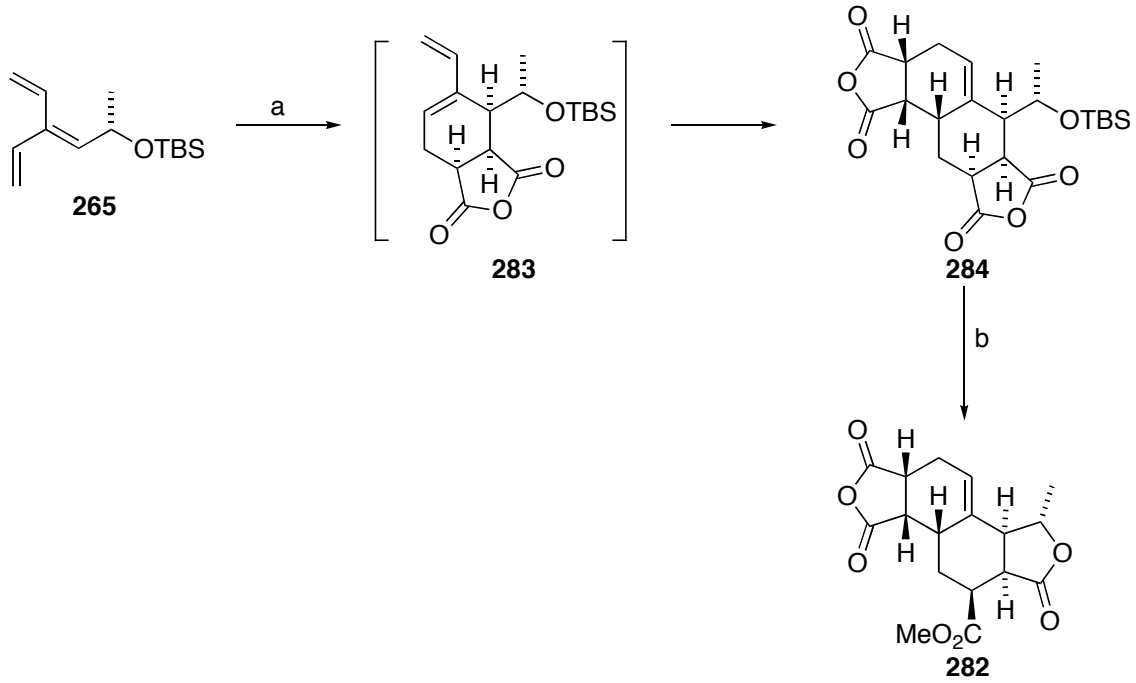


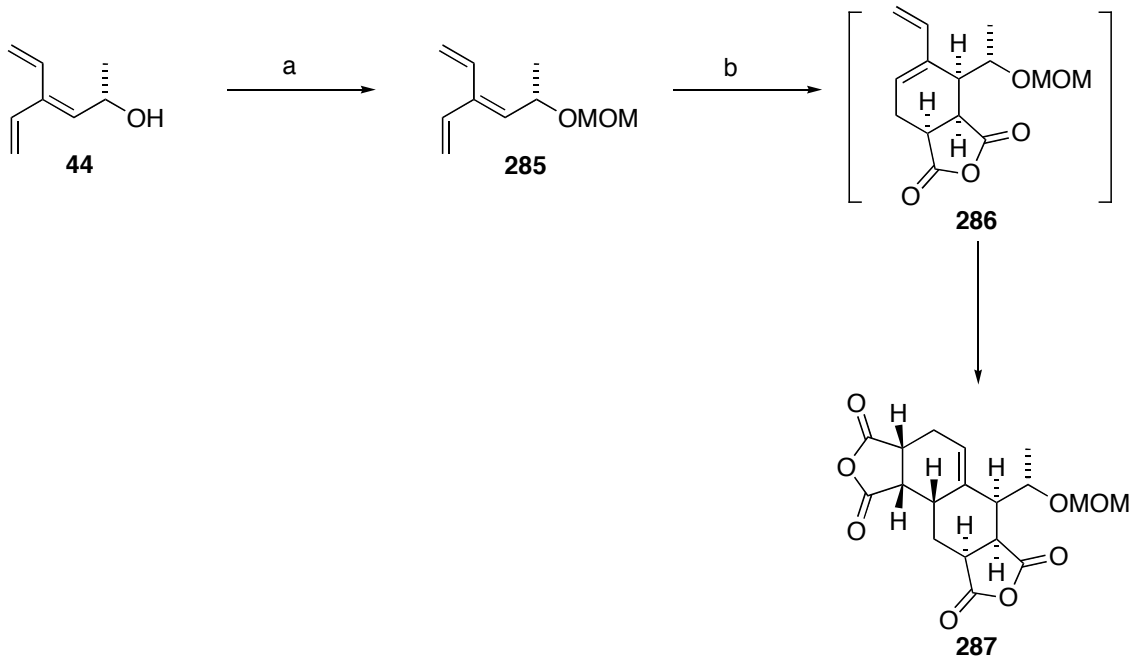
Figure 4.9 The preferred conformations about the C1-C2 bond

To determine if hydrogen bonding was the reason for the high level of stereoselectivity, the protected analogues of [3]dendralene **44**, namely silyl ether **265** and MOM ether **285**, were reacted with maleic anhydride (2 equiv). It was envisaged that if hydrogen bonding was not possible, the maleic anhydride would approach the dendralene from both π-diastereofaces and a mixture of products would be obtained.

In the event, both the silyl ether **265** and MOM ether **285** underwent highly stereoselective domino cycloadditions to give tetracyclic *bis*-anhydrides **284** and **287** as sole products in high yields (Scheme 4.39 and Scheme 4.40). The second DA reaction in the diene-transmissive sequence occurred faster than the first. That the protected alcohols **265** and **285** give the same stereoisomeric double cycloadducts as alcohol **44** was confirmed by the conversion of **284** into **282**, and the X-ray crystal structures of **282** and **287**.



Scheme 4.39 *Reagents and conditions*: (a) maleic anhydride (2.0 equiv), C_6D_6, 25°C, 48 h, 97%; (b) CF_3CO_2H, CH_2Cl_2, 25°C, 16 h then CH_2N_2, Et_2O/THF, –78°C to 25°C, 0.25 h, 81%.



Scheme 4.40 *Reagents and conditions*: (a) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 18 h, 60%; (b) maleic anhydride (2.0 equiv), C_6D_6, 25°C, 72 h, 100%

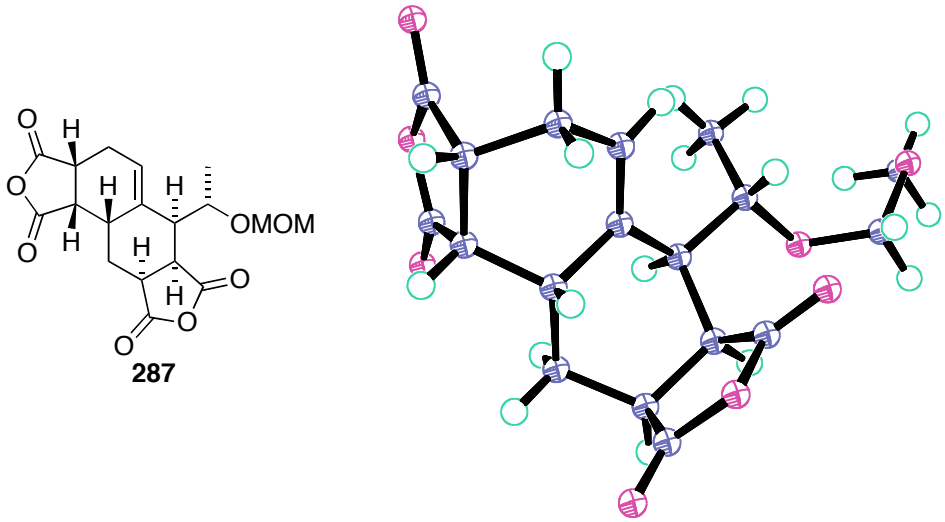
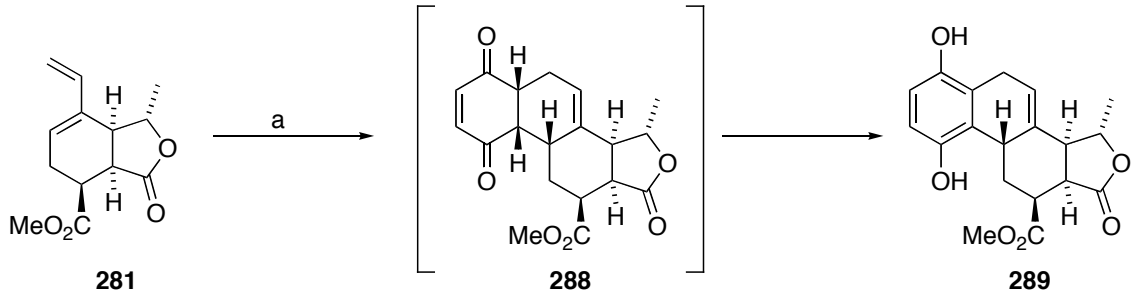


Figure 4.10 Thermal ellipsoid diagram of **287**. Ellipsoids show 30% probability levels.

4.3.2.2 Cycloadditions with benzoquinones

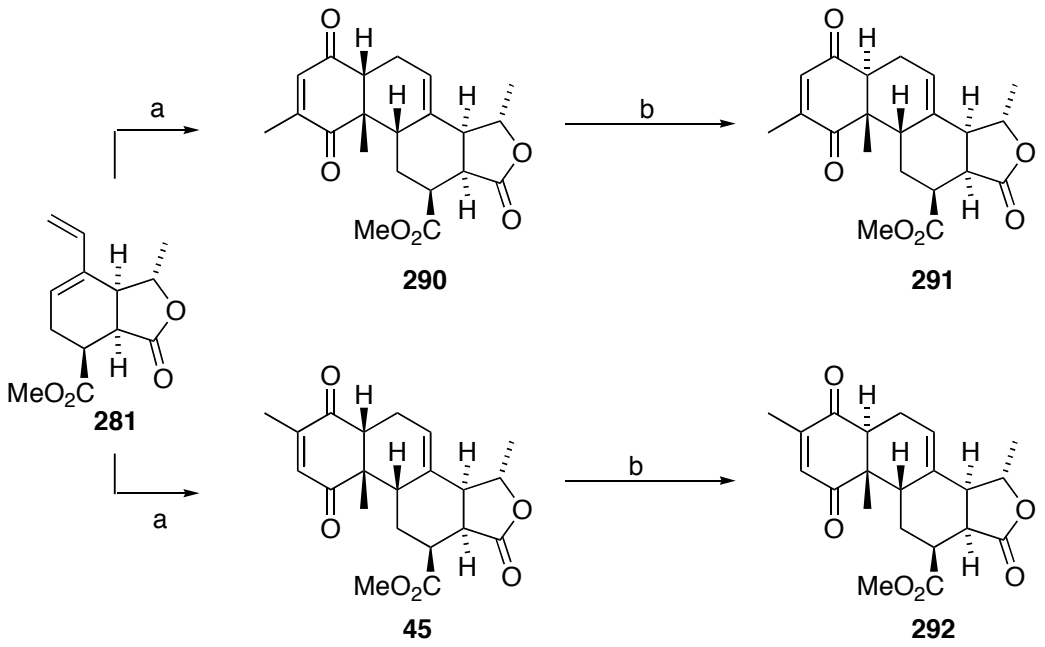
As the DTDA sequence with alcohol **44** is easily interrupted after the first cycloaddition (Scheme 4.38), different dienophiles could be used for the second Diels-Alder reaction in the sequence. Thus, methyl ester **281** underwent a highly selective cycloaddition with *p*-benzoquinone (Scheme 4.41). With the unsubstituted dienophile, attempts to purify the initial cycloadduct by column chromatography were met with aromatisation to **289**.



281 **288** **289**

Scheme 4.41 *Reagents and conditions*: (a) *p*-benzoquinone (1.0 equiv), C_6D_6, 80°C, 48 h then SiO_2, CH_2Cl_2, 70% overall.

Aromatisation could be prevented by using 2,6-dimethyl-*p*-benzoquinone or 2,5-dimethyl-*p*-benzoquinone. These dienophiles also incorporate angular methyl groups into the tetracyclic product, a feature common to many natural products. One major cycloadduct was formed in very high regio- and diastereoselectivity by reaction of diene **281** with each of the dimethyl-*p*-benzoquinones (Scheme 4.42). In both cases, epimerisation occurred upon exposure of the initial cycloadducts **290/45** to flash silica, leading separately to **291** and **292**, the stereochemistries of which were confirmed by single crystal X-ray analyses (Figure 4.11).



Scheme 4.42 *Reagents and conditions*: (a) 2,5- or 2,6-dimethyl-*p*-benzoquinone (1.2 equiv), [D_8]toluene, 110°C, 125 h, 78% (for **290**), 76% (for **45**); (b) SiO_2, CH_2Cl_2, 8 h, 100% (for **291**), 4 h, 100% (for **292**)

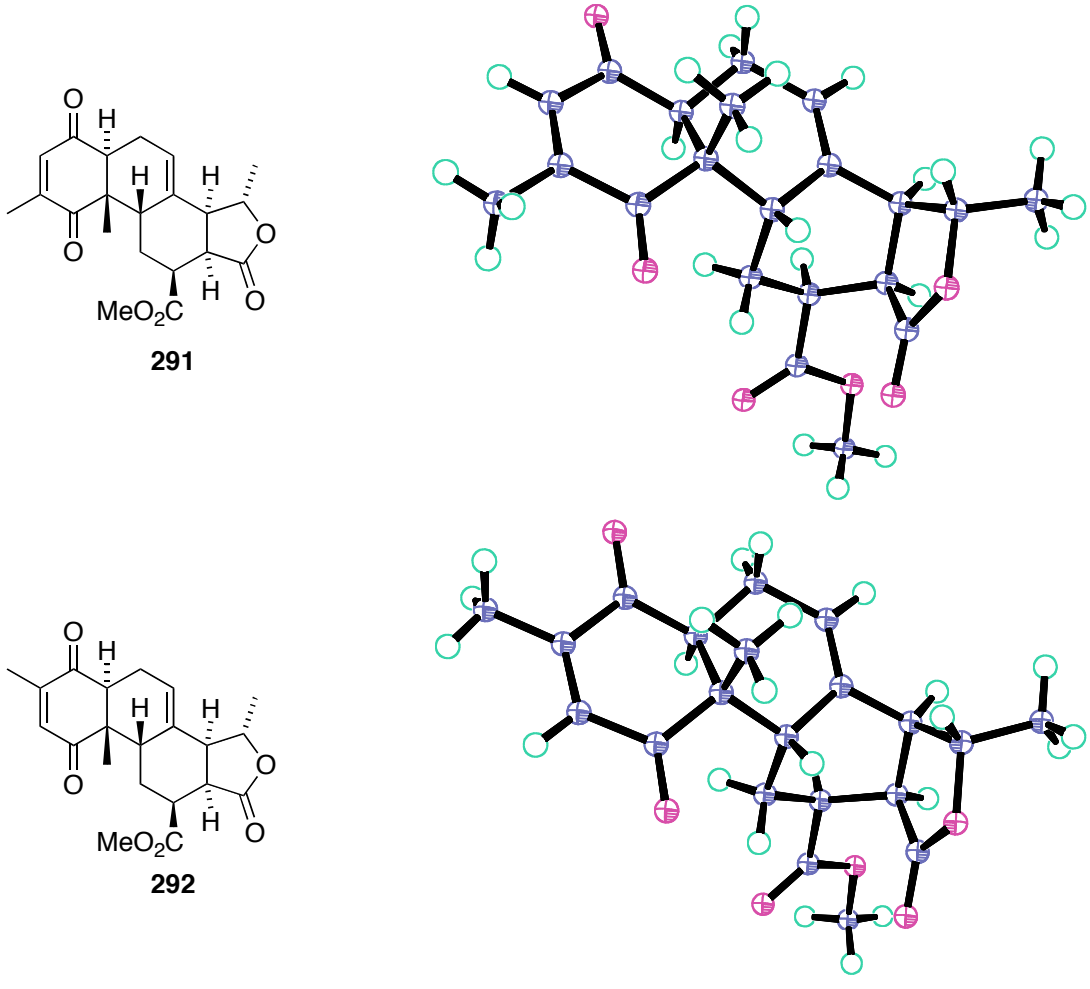
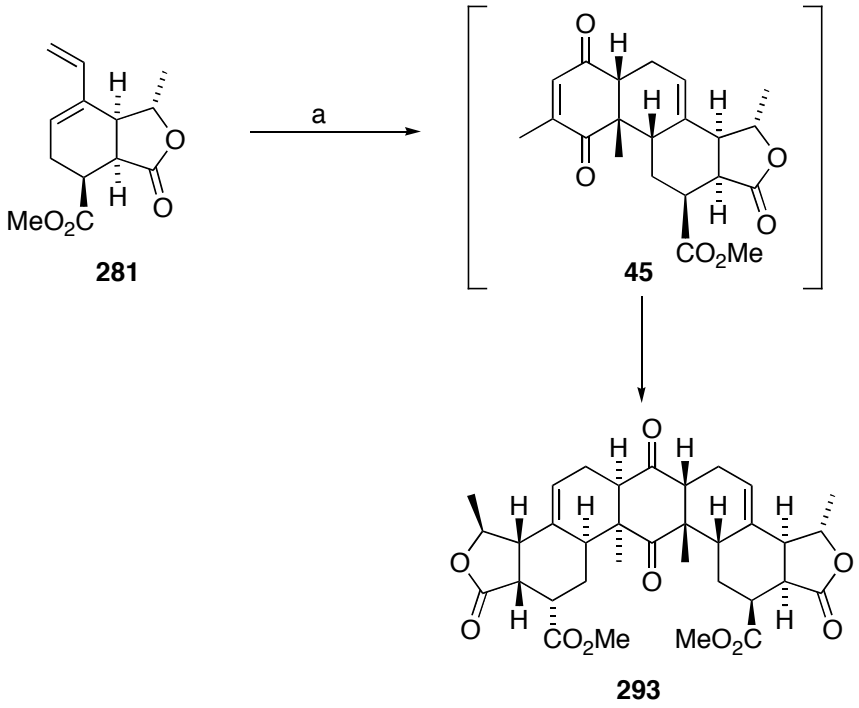


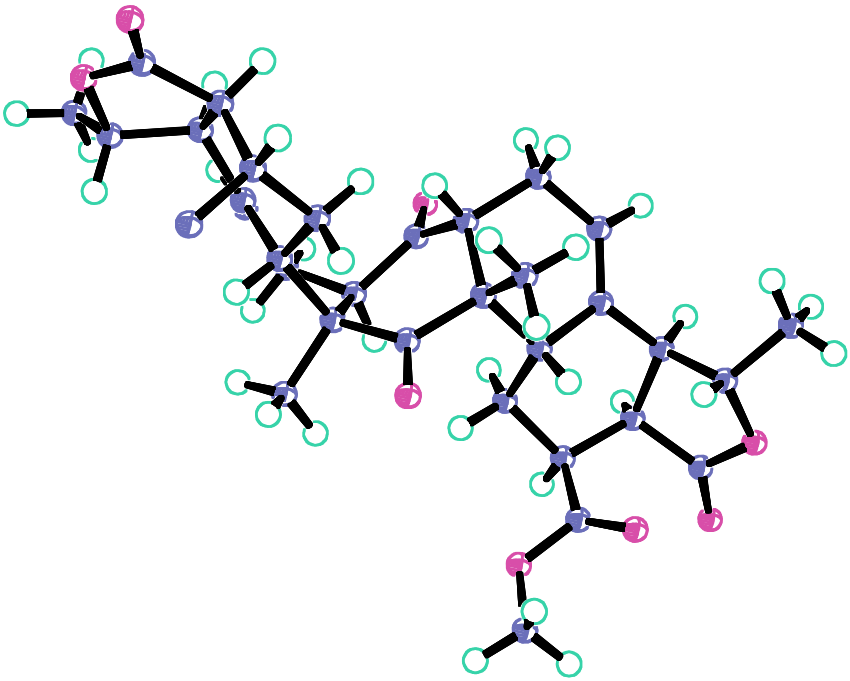
Figure 4.11 Thermal ellipsoid diagram of **291** and **292**. Ellipsoids show 30% probability levels.

Finally, semicyclic diene **281** participated in a highly selective double cycloaddition reaction with 2,6-dimethyl-*p*-benzoquinone to form heptacycle **293** in high yield (Scheme 4.43). The reaction proceeds via the tetracyclic intermediate **45,** which acts as a dienophile in the second Diels-Alder reaction. The heptacyclic product has as axis of symmetry, as evident by the ^{1}H and ^{13}C NMR spectra. The structure of **293** was confirmed by single crystal X-ray analysis (Figure 4.12). This last example demonstrates the extraordinary ease by which enantiomerically pure fused polycyclic structures can be prepared: structure **293** was assembled in three synthetic steps from dendralene **44**.



281 **45** **293**

Scheme 4.43 *Reagents and conditions*: **(**a) 2,6-dimethyl-*p*-benzoquinone (0.5 equiv), CH_2Cl_2, 25°C, 19 kbar, 72 h, 85%.



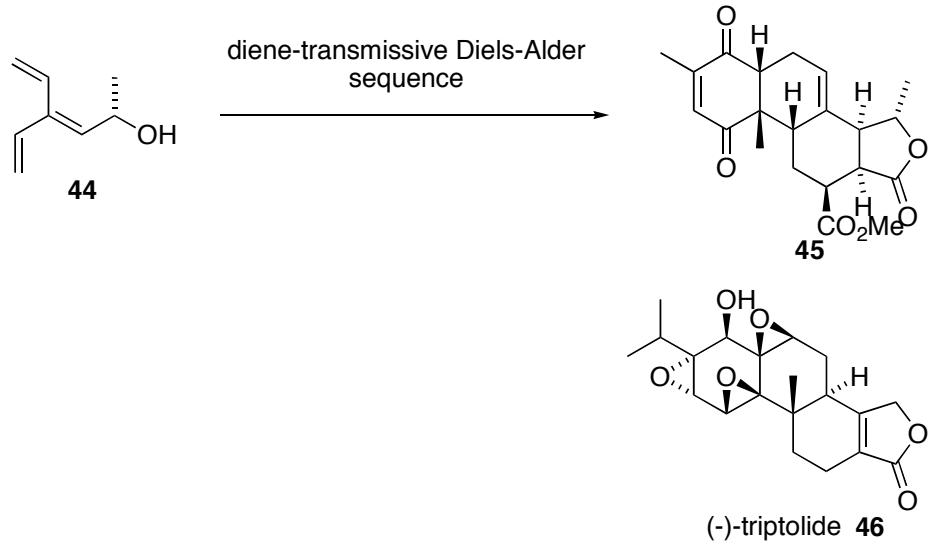
293

Figure 4.12 Thermal ellipsoid diagram of **293**. Ellipsoids show 30% probability levels.

4.4 Conclusions

A variety of substituted chiral dendralenes have been synthesised from a simple chiral dibromoalkene. Considering the functional group tolerance of both the Corey-Fuchs dibromomethylenation of aldehydes and metal–catalyzed cross couplings, the scope of this approach for the synthesis of cross–conjugated systems – and polycyclic systems derived therefrom – is vast.

The next chapter builds upon these findings in a formal total synthesis of the biologically active natural product triptolide.



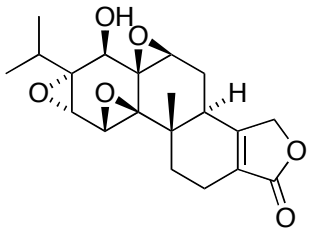
Scheme 4.44 A diene-transmissive Diels-Alder sequence to give tetracyclic frameworks common to natural products.

5 The Formal Total Synthesis of (±)-Triptolide

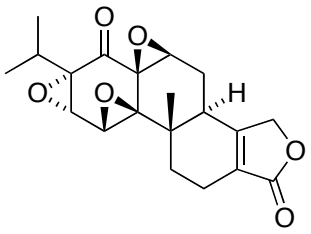
5.1 Background

5.1.1 Isolation and Biological Activity

Extracts of the plant *Tripterygium wilfordii* Hook F have been used in traditional Chinese medicine for many years. In 1972 Kupchan reported the isolation of triptolide **46** and triptonide **294** from the vine like plant (Figure 5.1).[145] These compounds represent the first known diterpenoid triexpoxide natural products.



(-)-triptolide **46**

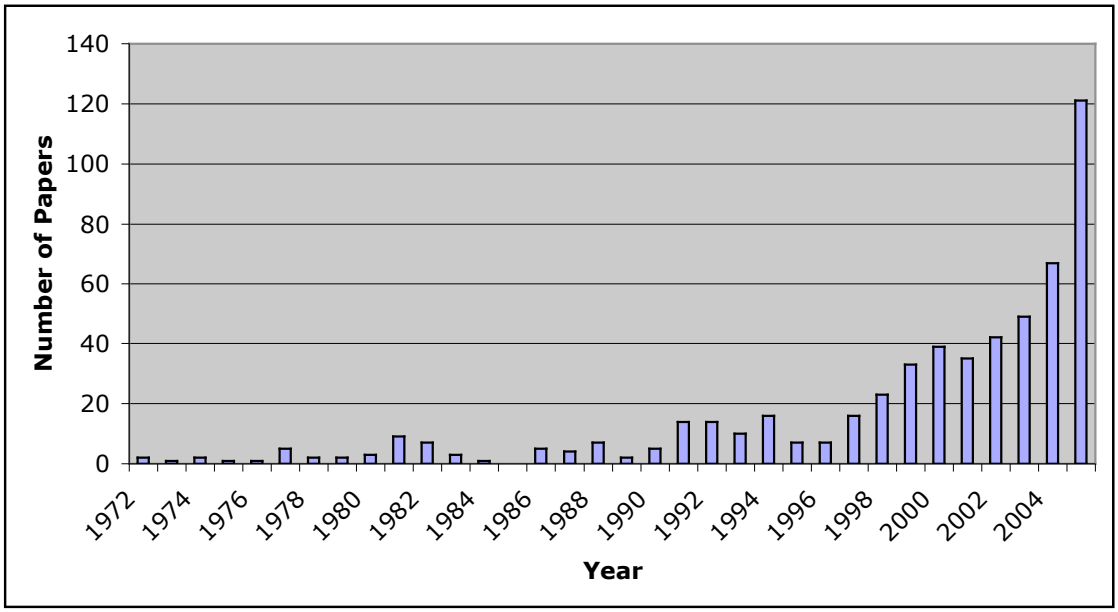


(-)-triptonide **294**

Figure 5.1 Diterpenoid triepoxide natural products

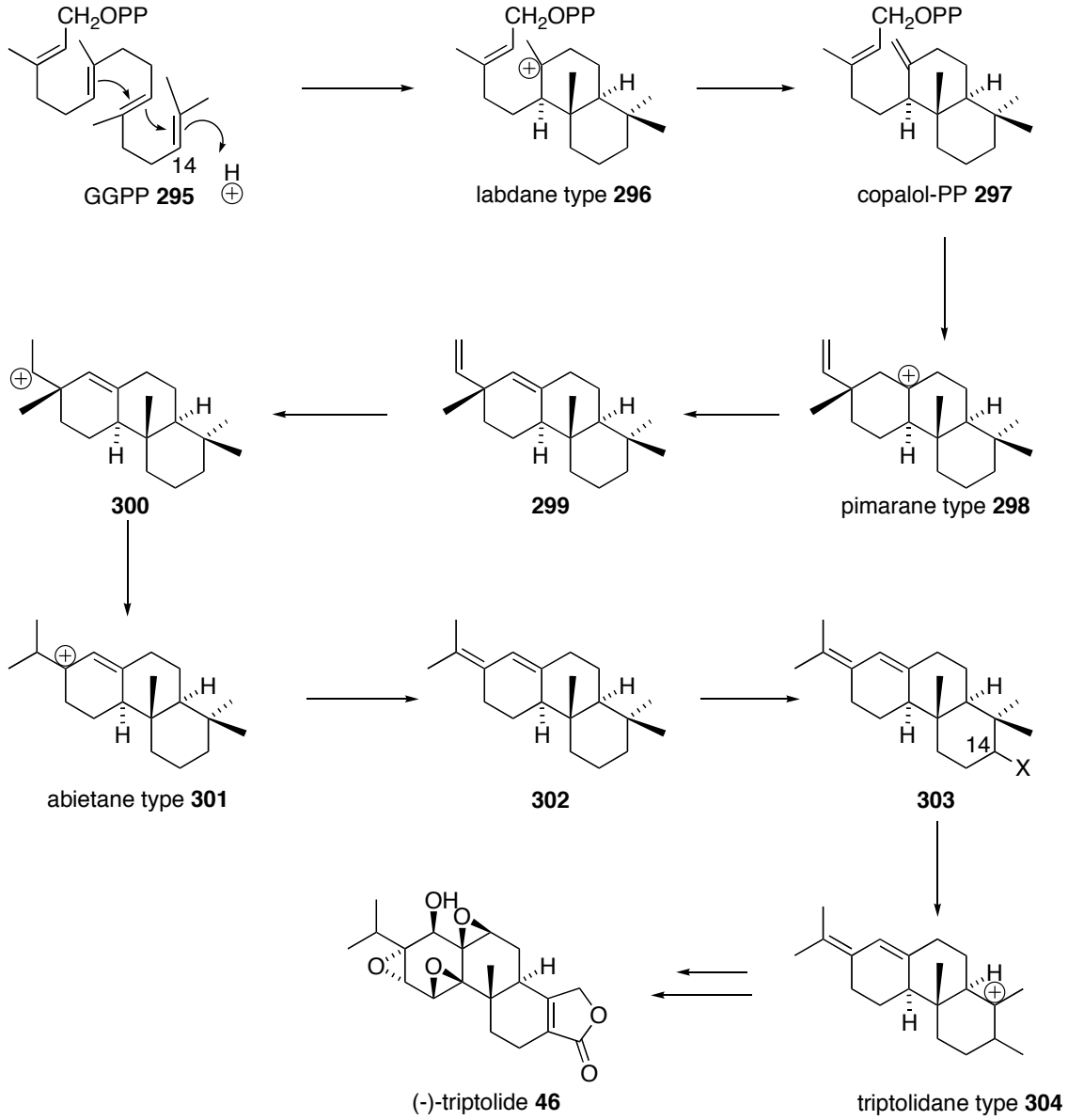
Triptolide **46** and triptonide **294** and their derivatives have displayed potent antiluekemic and antitumour activity.[145-149] They exhibit antiinflammatory[146,150,151] and immunosuppressive[150-155] properties as well as having a potential use as a male contraceptive.[156] The number of papers published relating to the biological activity of triptolide has risen dramatically over the last decade (Figure 5.2).

Figure 5.2 Scifinder Scholar search results of papers on the synthesis and biological activity of triptolide.



5.1.2 Biosynthesis

Electrophilic addition to the C14-C15 olefinic linkage in geranylgeraniol pyrophosphate (GGPP) **295** triggers a cyclisation leading to the bicyclic labdane type intermediate **296** (Scheme 5.1).[157] This cationic structure and the derived copalyl pyrophosphate **297** are involved in the biosynthesis of most terrestrial diterpenoids. Loss of pyrophospate ion and cyclisation gives pimarane type intermediate **298**. A suggested link between the pimarane and abietane type structures is shown in Scheme 5.1. The abietane type diterpenoid **301** can be transformed into the triptolidane type **304**, a precursor of triptolide **46**, through introduction of a leaving group at C14 followed by loss of the leaving group and methyl migration.



Scheme 5.1 The biosynthesis of triptolide

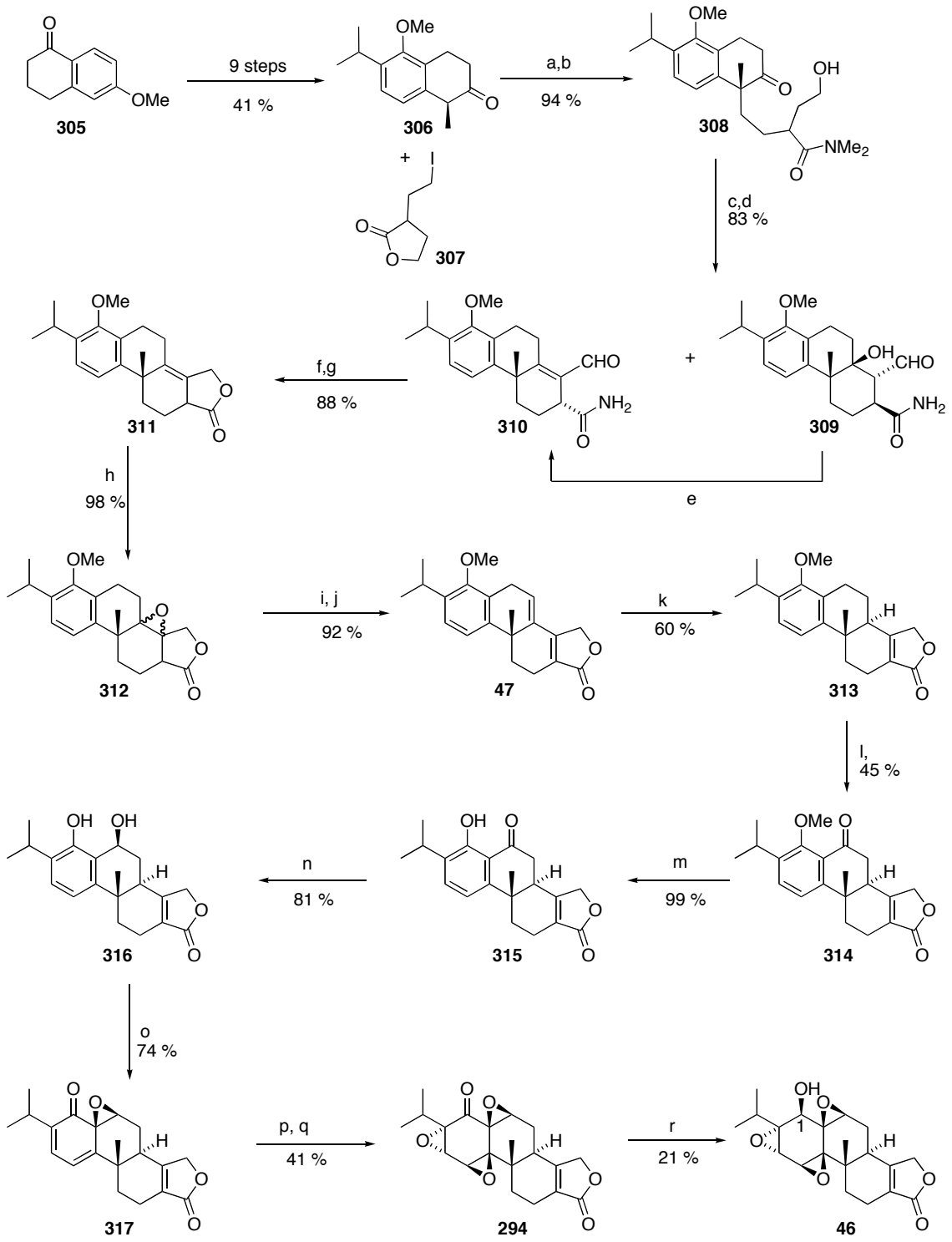
5.1.3 Previous Syntheses

Due to the significance of its biological activity and its unusual triepoxide skeleton, triptolide has been to focus of much synthetic effort. Berchtold reported initial studies on the synthesis of triptolide in 1977, three years before publishing a completed total synthesis in 1980. A revised total synthesis was published in 1982 (Scheme 5.2).[158-160]

6-Methoxy-1-tetralone **305** was converted to the ketone **306** *via* a nine step procedure. The enolate of **306** was alkylated with **307** before the lactone was cleaved with Me_2NH to give a 1:1 mixture of diastereomers **308**. Oxidation to the aldehyde followed by Al_2O_3-catalysed aldol condensation gave a 1:1 mixture of **309** and **310**. The mixture was heated with acid to effect dehydration of **309**. Aldehyde reduction and acid catalysed lactonisation during work up gave **311** as a single isomer.

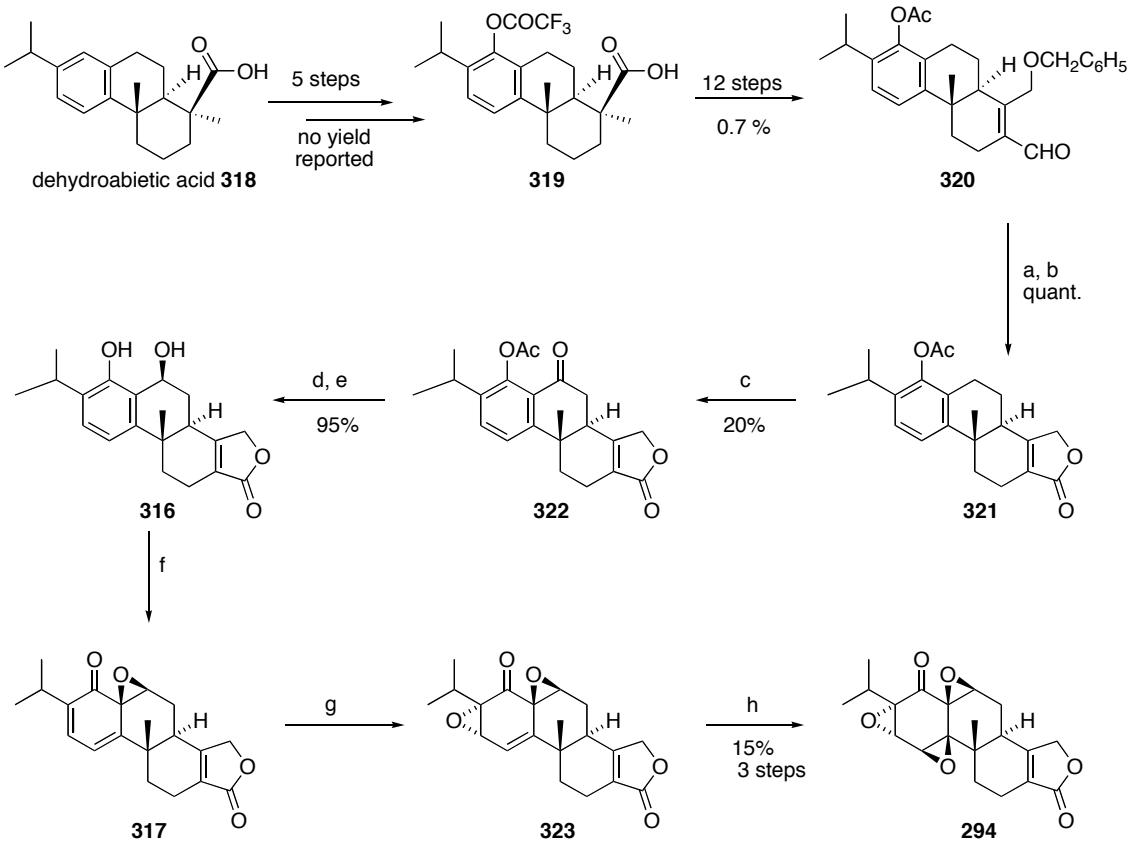
It was originally reported that methoxide-catalysed isomerization of **311** gave **313** directly. In a subsequent publication, however, it was reported that a mixture of the trans (40%) and cis (60%) isomers is obtained after 15 minutes, with the cis isomer being the sole product of the base-catalysed reaction after 48 h. To avoid this problem, an alternative route was developed. Thus, peracid epoxidation of **311** gave epoxides **312**, which were dehydrated to give the diene **47**. Hydrogenation gave the trans-fused product **313** as the major product (60% after recrystallisation).

Benzylic oxidation and ether cleavage lead to phenol **315**. Subsequent reduction of the ketone gave **316** which underwent the Alder periodate reaction to give the epoxy dienone **317**. Reaction of **317** with *m*CPBA followed by treatment with H_2O_2/OH^- gave triptonide **294**. Sodium borahydride reduction of triptonide **294** gave triptolide **46** in 21% yield along with 68% of C1 epitriptolide.



Scheme 5.2 *Reagents and conditions:* (a) NaH, DMF, 12 h; (b) Me_2NH, 12 h; (c) CrO_3.py, CH_2Cl_2, 15 min; (d) grade 3 neutral alumina, EtOAc, 48 h; (e) *p*-TsOH, C_6H_6, reflux, 2 h; (f) $NaBH_4$, EtOH, 2 h; (g) aq. HCl (work-up); (h) *m*-CPBA, CH_2Cl_2, 18 h; (i) NEt_3, CH_2Cl_2, 18 h; (j) 2,4,6-trimethylpyridine, MsCl, DMF; (k) Pd/C, 50 psi H_2, EtOAc, 1.5 h; (l) CrO_3, HOAc-H_2O (9:1), 6 h; (m) BBr_3, CH_2Cl_2, 10 h; (n) $NaBH_4$, EtOH, 1h; (o) $NaIO_4$, aq. MeOH, 5 h; (p) *m*-CPBA (3 equiv), CH_2Cl_2, reflux, 20 h then rt 18 h; (q) 30% H_2O_2 (1.75 equiv), 1 M aq. NaOH (1.3 equiv), MeOH, 20 h; (r) $NaBH_4$, EtOH, 1 h.

van Tamelen reported the formal synthesis of the natural enantiomer of triptolide in 1980.[161] The trifluoroacetate **319**, derived from dehydroabietic acid **318**, was converted to **320** through a twelve-step sequence. Oxidation of **320** to the carboxylic acid followed by hydrogenolysis of the benzyloxy group led to spontaneous lactonisation to give butenolide **321** in quantitative yield. In a sequence similar to that used by Berchtold **3221** was converted to the epoxy dienone **317**. Nucleophilic epoxidation with H_2O_2-KOH then peracid epoxidation gave *l*-triptonide **294** in 15% yield, thus completing the formal total synthesis of *l*-triptolide.



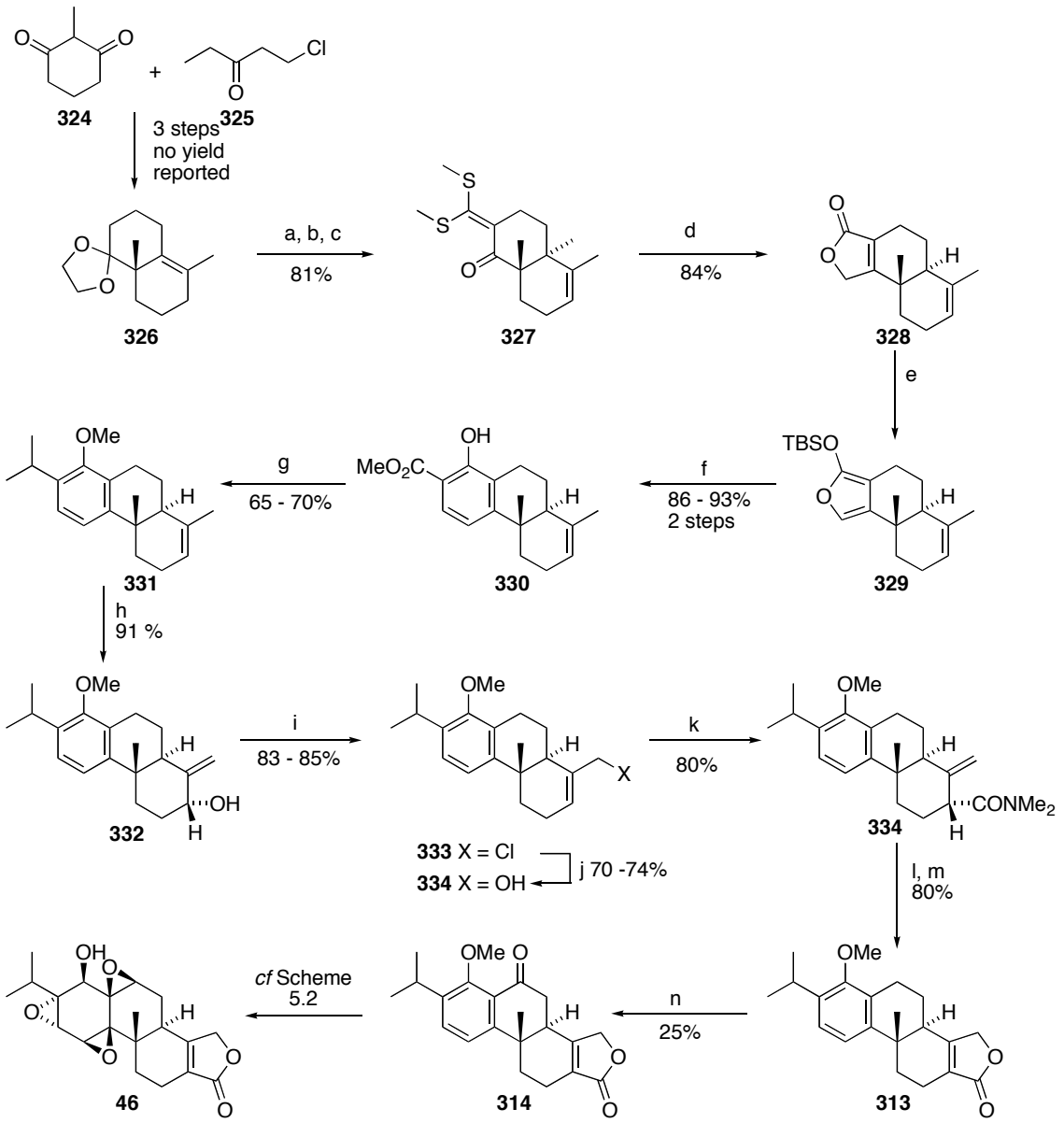
Scheme 5.3 *Reagents and conditions:* (a) $NaClO_2$-$HOSO_2NH_2$, dioxane-H_2O; (b) H_2, Pd/C, EtOH; (c) CrO_3, AcOH-H_2O, 40 ^oC; (d) KOH, MeOH-H_2O; (e) $NaBH_4$, EtOH; (f) $NaIO_4$, MeOH-H_2O; (g) H_2O_2-KOH, MeOH; (h) 3,5-$(NO_2)_2C_6H_3CO_3H$-Na_2HPO_4, CH_2Cl_2.

In 1982, van Tamelen and co workers reported two further syntheses of racemic triptolide.[162,163] The first of these had an overall yield 40 to 50 times greater than their earlier synthesis.[162] The bicyclic diketone monoethylene ketal **326** was converted to the ketene dithioacetal **327** through a high yielding sequence. Treatment of **327** with dimethylsulfonium methylide followed by acid hydrolysis gave the unsaturated lactone **328**.

Butenolide **328** was converted into the α-(*tert*-butyldimethylsilyl)furan **329**, which then underwent a Diels-Alder reaction with methyl acrylate to give **330** after acid mediated aromatisation of the cycloadduct. Methylation of the phenol followed by the addition of methyl lithium formed the tertiary alcohol, which was deoxygentated to give **331**, a key intermediate in the synthesis.

Epoxidation followed by base-promoted ring opening gave the allylic alcohol **332**. Thionyl chloride induced rearrangement of **332** gave the allylic chloride **333**. Conversion to the alcohol **334** followed by Eschenmoser-Claisen rearrangement resulted in the formation of the allylic amide **335**.

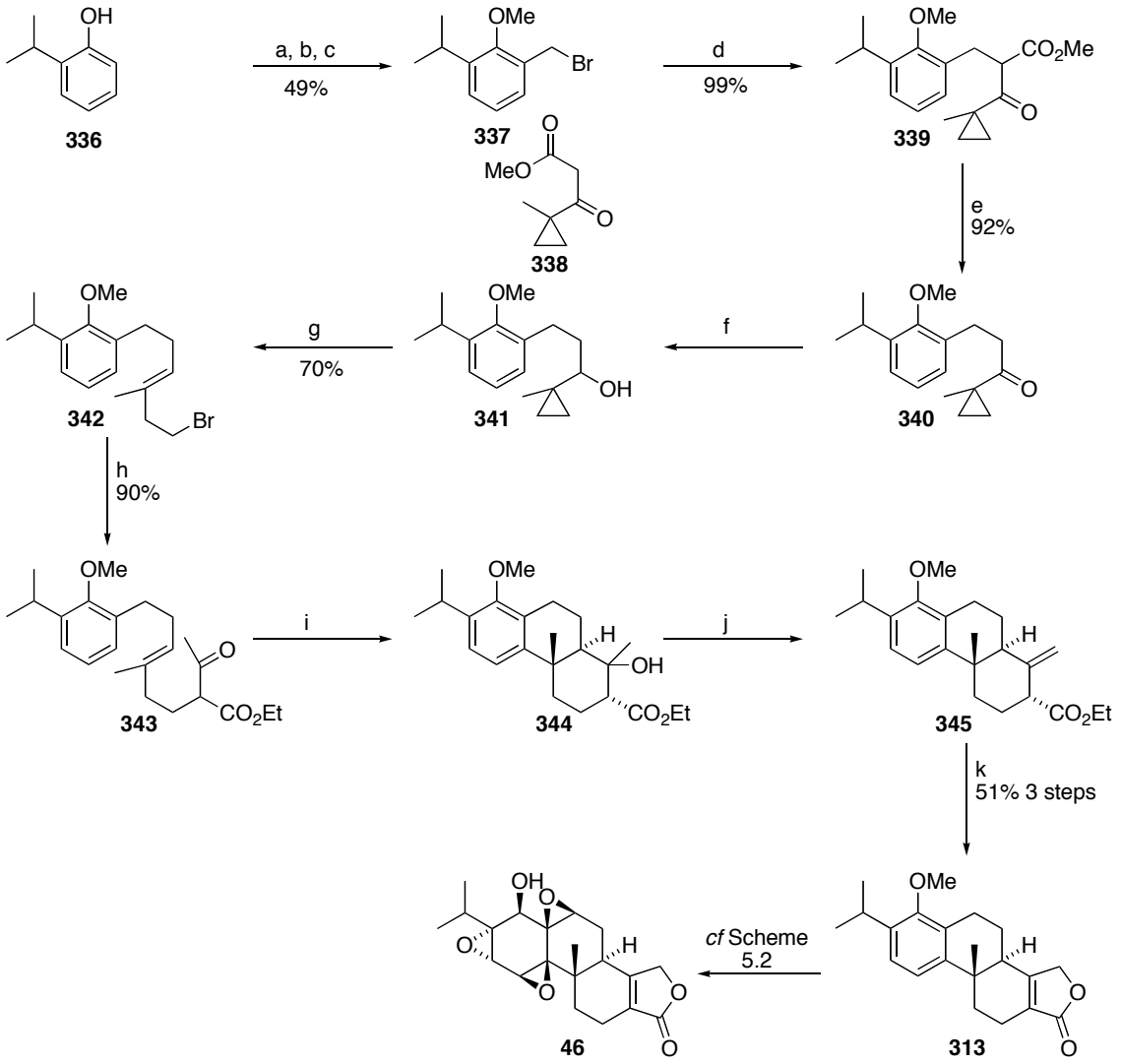
Epoxidation of **335** followed by β-elimination gave the intermediate α,β-unsaturated amide, which underwent acid hydrolysis to give the butenolide **313**. Finally, benzylic oxidation gave **314**, an intermediate used in a Berchtold's synthesis of (±)-triptonide (Scheme 5.2).



Scheme 5.4 *Reagents and conditions:* (a) Li/NH_3, THF, 0.8 equiv *t*-BuOH, - 78 ^oC 15 min; diethyl chlorophosphate, THF, 0 ^oC, 30 min; Li, $EtNH_2$, THF, *t*-BuOH, 0 ^oC, 12h; (b) 3M H_2SO_4, THF, 25 ^oC, 24 h; (c) CS_2, lithium 4-methyl-2,6-di-*tert*-butylphenoxide, THF, 48 h then MeI, THF, 24 h; (d) dimethylsulfonium methylide, 1:1 DMSO/THF then 1:6 6M aq HCl/MeOH, 15 h; (e) LDA/HMPA, THF, 25 min then TBSCl, 1h; (f) methyl acrylate, C_6H_6, 65 – 70 ^oC, 48 h then 5:1 MeOH/6M HCl, 25 ^oC, 1h; (g) MeI, NaH, THF, 25 ^oC, 48 h; MeLi, THF, -15 ^oC, 5 min; MsCl, NEt_3, CH_2Cl_2, 0 – 25 ^oC, 1 h; Li/NH_3, THF, -78 ^oC, 15 min; (h) *m*-CPBA, CH_2Cl_2, 25 ^oC, 6 h; LDA, THF, 25 ^oC, 24 h; (i) $SOCl_2$, pyridine, EtO_2, 0 ^oC, 2 h; (j) KOAc, DMSO, 70 – 75 ^oC, 24 h; NaOMe, MeOH, 25 ^oC, 2 h; (k) dimethylformamide dimethylacetal, xylene, reflux, 4 Å sieves, 3 days; (l) *m*-CPBA, CH_2Cl_2, 25 ^oC, 30 h; (m) lithium hexamethyldisilazide, THF, 0 ^oC then 25 ^oC for 2 h; 1 M HCl, 10 min; (n) CrO_3, 80% AcOH-H_2O, 35 – 40 ^oC, 2 – 3 h.

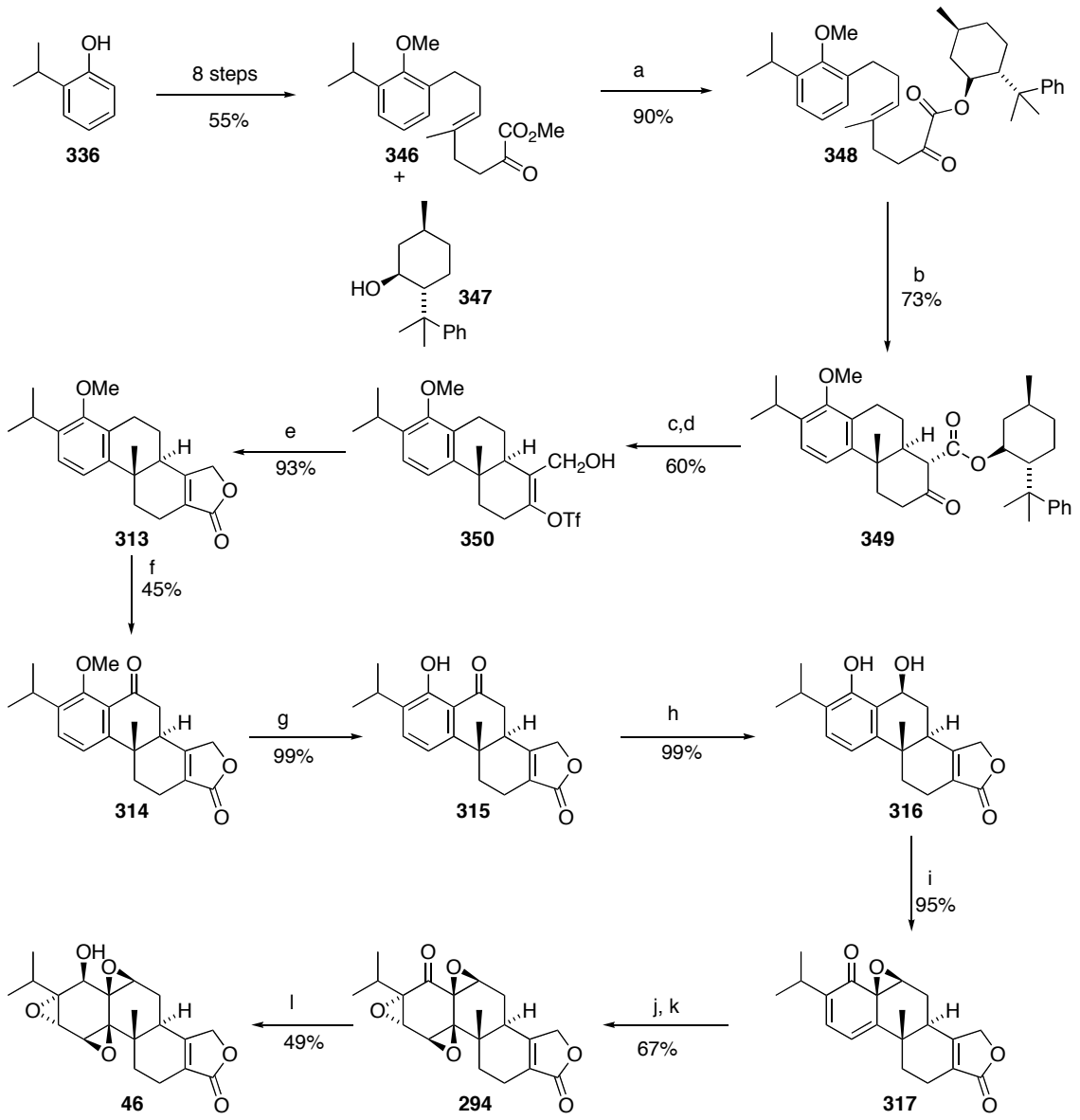
The second synthesis reported by van Tamelen in 1982 differed from previous approaches in that it uses a biomimetic strategy (Scheme 5.5).[163] 2-Isopropylphenol **336** was converted to the benzyl bromide **337** through a three step sequence. Alkylation of the cyclopropyl β-ketoester **338** with bromide **337** gave **339** in near quantative yield. Hydrolysis and decarboxylation of the ester and reduction of the ketone gave the cyclopropyl carbinol **341**, which was converted to the homoallylic bromide **342** in 70% yield. Ethyl acetoacetate was alkylated with bromide **342** to give the cyclisation precursor **343**.

Upon treatment with $SnCl_4$, **343** underwent the biomimetic cationic bicyclization to give tricycle **344**, which was converted to the unsaturated ester **345** without purification. The crude ester **345** was epoxidised before base-promoted elimination to form the tetracycle **313**, an intermediate used in Berchtold's previous syntheses of (±)- triptolide (Scheme 5.2).



Scheme 5.5 *Reagents and conditions:* (a) NaH, MeI, THF, rt; (b) *n*-BuLi, TMEDA, CHO; (c) PBr_3, Et_2O, 0 ^oC; (d) NaH, THF, 0 ^oC; (e) $Ba(OH)_2$, H_2O/Et_2O, 90 ^oC 17 h; (f) LAH, Et_2O, 0 ^oC; (g) LiBr, PBr_3, collidine in Et_2O, then $ZnBr_2$ in Et_2O, 0 ^oC; (h) ethyl acetoacetate, LiH, DMF, 75 ^oC; (i) $SnCl_4$, CH_2Cl_2, 0 ^oC; (j) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 ^oC; (k) *m*-CPBA, CH_2Cl_2 then LDA, -78 ^oC.

In 1999 Yang reported a diastereoselective synthesis of (-)-triptolide, (-)-triptonide and the related natural products (+)-triptophenolide and (+)-triptoquinonide (Scheme 5.6).[164,165] A strategy similar to van Tamelen's second synthesis was used, with the two central rings being formed through a biomimetic type bicyclisation, albeit via a radical intermediate. 2-Isopropylphenol **336** was converted into ketoester **346** through an eight step sequence. Transesterification with (+)-8-phenylmenthol **347** gave the acyclic chiral precursor **348**. $Yb(OTf)_3/Mn(OAc)_3$-promoted radical bicyclisation of **348** gave the tricyclic product **349** as the major diastereomer (38:1 dr).

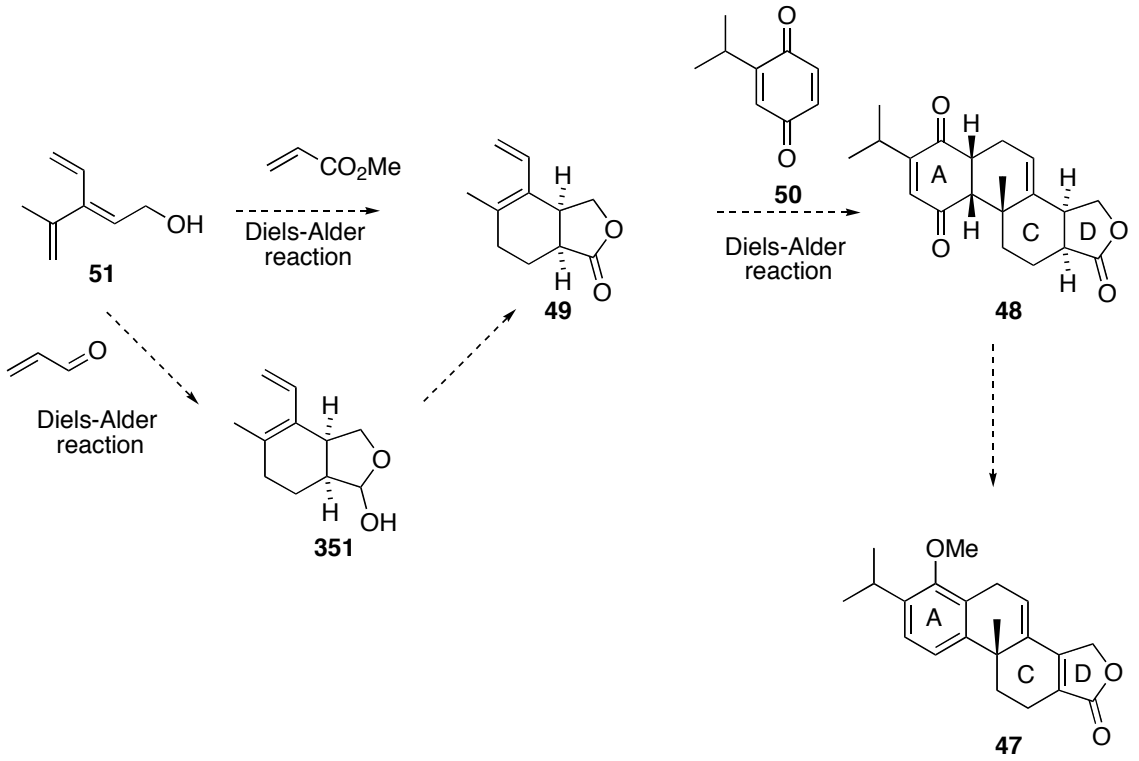


Scheme 5.6 *Reagents and conditions*: (a) DMAP, PhMe, reflux; (b) $Mn(OAc)_3.2H_2O$, $Yb(OTf)_3$, CF_3CH_2OH, -5 ^oC, 5 h; (c) KHMDS, THF, -78 to 20 ^oC, then $PhNTf_2$, -78 ^oC to rt; (d) DIBAL-H, CH_2Cl_2, -78 ^oC to -30 ^oC, 20 h; (e) Bu_3N, $Pd(PPh_3)_4$, LiCl, CO (1 atm), CH_3CN, 65 ^oC, 12 h; (f) CrO_3, aq. HOAc, rt; (g) BBr_3 CH_2Cl_2, -78 ^oC to rt; (h) $NaBH_4$, CH_3OH, 0 ^oC, 2h; (i) $NaIO_4$, 3:1 MeOH:H_2O, 0 to 25 ^oC, 1 h; (j) CF_3COCH_3, Oxone, $NaHCO_3$, 3:2 CH_3CN:aq $Na_2(EDTA)$, 25 ^oC, 4 h; (k) H_2O_2, NaOH, MeOH, 25 ^oC 3h; (l) $Eu(fod)_3$, $NaBH_4$, CH_3OH.

After preparation of vinyl triflate, the ester was reduced to the alcohol **350** using an excess of DIBAL-H. Carbonylation of **350** led to methyl ether **313**, an intermediate common to earlier syntheses of (-)-triptolide. This was converted to (-)-triptolide though a sequence similar to that developed by Berchtold (Scheme 5.2). The overall yield, however, was greatly improved.

5.2 Aims

The previous syntheses of triptolide have either been multistep approaches, where one ring is constructed at a time, or they have involved a biomimetic approach to form two rings in one step. In Chapter 4, we demonstrated that a DTDA sequence could be used for the rapid assembly of tetracyclic systems common to diterpenoid natural products. The aim of the work described herein is to synthesise the tetracyclic compound **47**, a key intermediate from previous syntheses of (-)-triptolide,[160] through a DTDA approach (Scheme 5.7).



Scheme 5.7 Proposed synthesis of triptolide

The proposed synthesis requires the preparation of the unsymmetrically substituted dendralene **51** in synthetically useful amounts. Investigations will initially be carried out in order to optimise the synthesis of this dendralene.

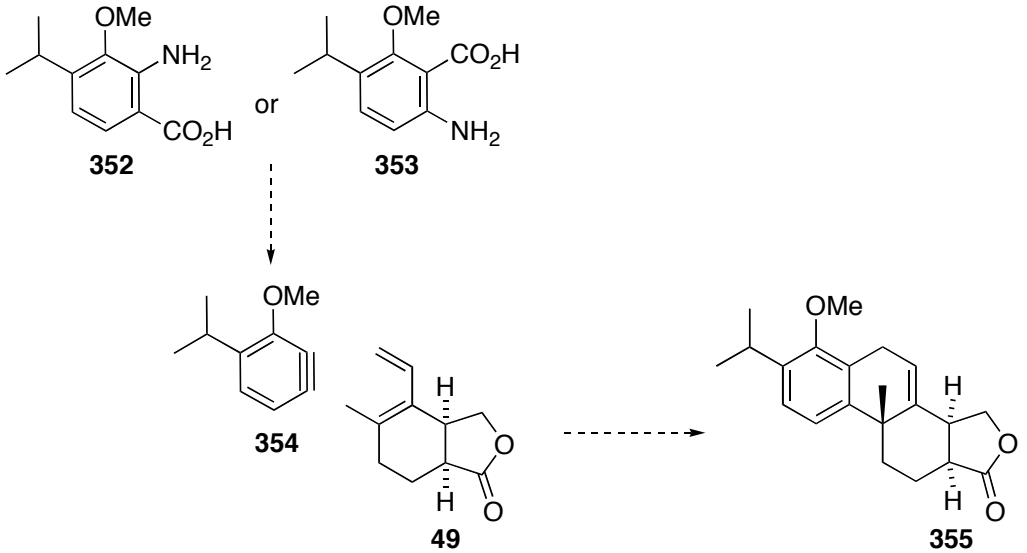
The first Diels-Alder reaction in the DTDA sequence could either be carried out with methyl acrylate to give the lactone **49** directly or with acrolein forming the lactol **351**, which would then be oxidised to form the lactone **49**. Both of these Diels-Alder reactions should proceed via an *endo* transition state to give the *cis*-fused cycloadducts. The initial reaction should also be site selective as one of the diene units in the

dendralene is more able to adopt the required *s-cis* conformation. It is envisaged that these Diels-Alder reactions could be carried in an enantioselective manner by using a chiral catalyst. The reactions are also predicted to give the desired regiochemical outcome by the *ortho*-, *para*-orientation rule implied by the Woodward-Hoffman rules.[11,14]

The second Diels-Alder reaction in the sequence should also proceed via an *endo* transition state with the dienophile approaching the diene from the less hindered π-diastereoface. According to literature precedent[166] the Diels-Alder reaction should also proceed to give the desired regiochemical outcome.

Once the tetracyclic core is in place, one of the ketones on the A ring (**48** in Scheme 5.7) must be converted to a methyl ether, while the other needs to be removed. The last step required is a dehydrogenation across the C/D ring junction to give the α,β-unsaturated lactone.

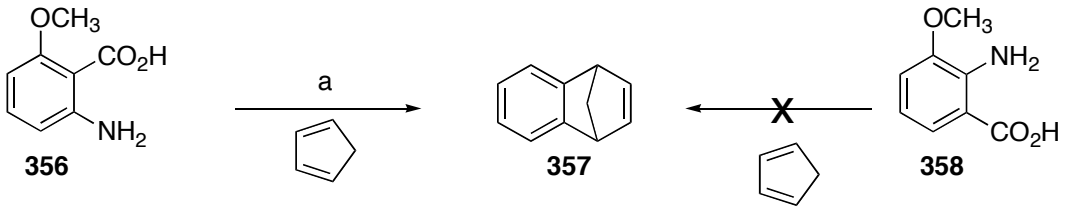
The possibility of carrying out a Diels-Alder reaction between semicyclic diene **49** and the substituted benzyne **354** to give tetracycle **355** directly was also considered (Scheme 5.8).



Scheme 5.8 Benzyne approach to triptolide

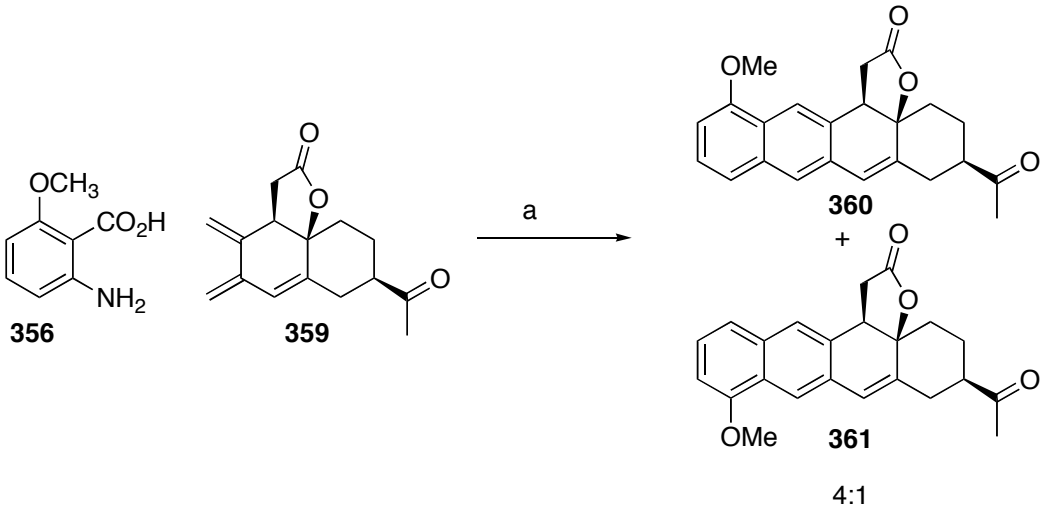
There are several methods available for the generation of benzynes, however, many of them involve the use of strong bases. Since the benzyne **354** would need to be generated in the presence of the lactone **49**, non-nucleophilic conditions would be required. It was

therefore decided to investigate the synthesis of anthranilic acid precursors for the benzyne **354**. For substituted benzynes such as **354**, there are two possible regioisomeric anthranilic acid precursors, that is, with the amino group *ortho* (**352**) or *meta* (**353**) to the methoxy substituent. Paquette has shown that for benzyne generation to occur the amino group must be positioned *meta* to the methoxy substituent (Scheme 5.9).[167]



Scheme 5.9 *Reagents and conditions*: (a) *i*$C_5H_{11}ONO$, 57%.

A search of the literature also revealed that Diels-Alder reactions of similar substrates do not proceed with a high level of regioselectivity and the yield for such reactions is quite low (Scheme 5.10).[168]



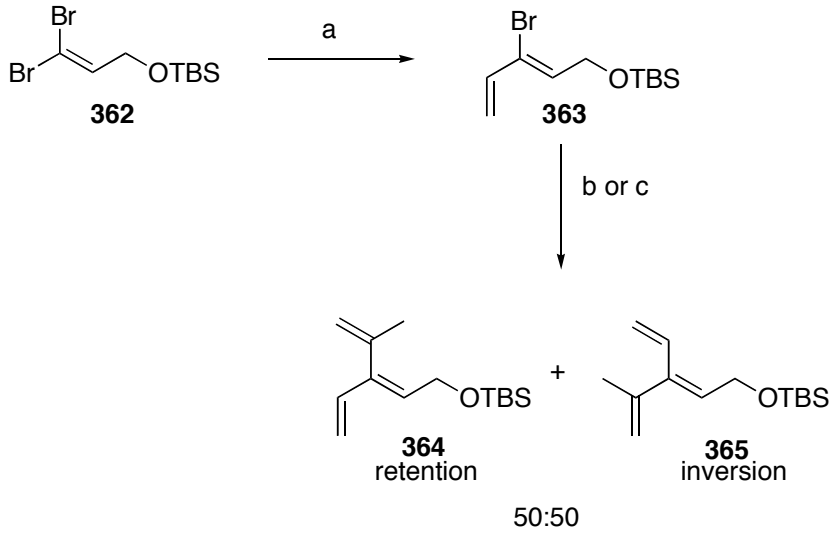
Scheme 5.10 *Reagents and conditions:* (a) pentyl nitrile, dioxane, 70 ^{o}C, 35%.

The synthesis of the required regioisomer of the anthranilic acid precursor would take several steps to complete. In addition, the regiochemical outcome of the Diels-Alder reaction could not be predicted and the overall yield for the sequence was anticipated to be quite low. The benzyne approach was, therefore, abandoned in favour of the quinone route.

5.3 Results and Discussion

*5.3.1 Synthetic Approaches to Substituted [3]Dendralene **365** by Stille Coupling*

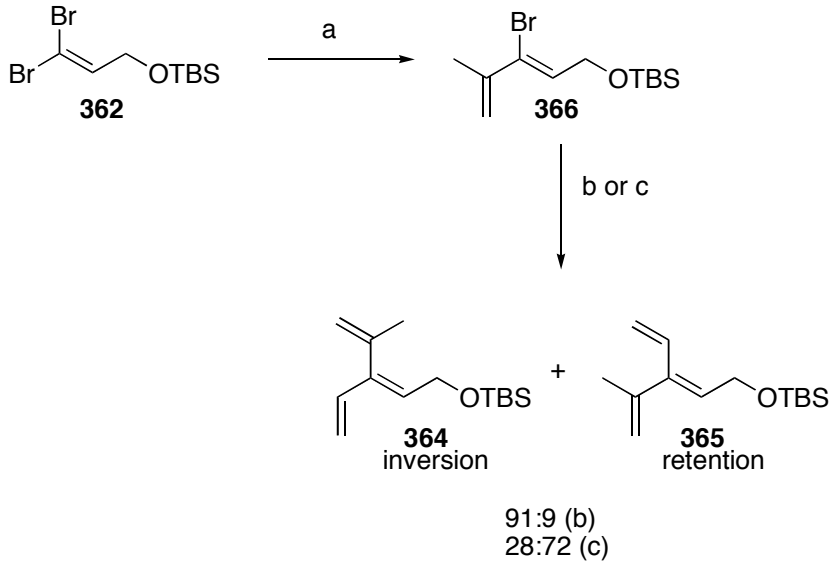
As observed earlier, palladium catalysed cross-couplings of 2-bromo-1,3-butadienes often proceed with clean inversion of configuration (Scheme 4.36). Thus, a Stille coupling between the known dibromoolefin **362**,[85,169] synthesised in three steps from ethyl glycolate, and tributyl(vinyl)tin was carried out to give **363** (Scheme 5.11).[85] The Stille coupling between **363** and tributyl(prop-1-en-2-yl)stannane was expected to occur with clean inversion of configuration at the sp^2 centre.[144] After several attempts, however, the best result obtained was a 50:50 ratio of the products due to inversion and retention of configuration.



Scheme 5.11 *Reagents and conditions:* (a) tributyl(vinyl)tin (1.05 equiv), $Pd_2(dba)_3$ (0.025 equiv), Ph_3As (0.10 equiv), THF, 55 ^{0}C, 18 h, 66%; (b) tributyl(prop-1-en-2-yl)stannane (2.0 equiv), PPh_3 (0.1 equiv), $Pd(OAc)_2$ (0.05 equiv), CH_3CN, 60 ^{o}C, 48 h, 49% of a 50:50 mixture of **364** and **365**; or tributyl(prop-1-en-2-yl)stannane (2.0 equiv), CsF (2.0 equiv), CuI (0.08 equiv), $PdCl_2$ (0.04 equiv), *t*Bu_3P (0.08 equiv), DMF, 45 ^{o}C, 24 h, 44% of 50:50 mixture of **364** and **365**.

While this study was being conducted, it was reported in the literature that certain conditions for coupling reactions resulted in the retention of configuration of the starting materials.[170] Therefore, the bromodiene **366** was synthesized through a Negishi coupling between dibromoolefin **362**[85,169] and isopropenyl magnesium bromide (Scheme 5.12). Stille reaction between bromodiene **366** and tributyl(vinyl)tin under the conditions of Baldwin,[171] using *t*Bu_3P as the ligand, proceeded cleanly to give two

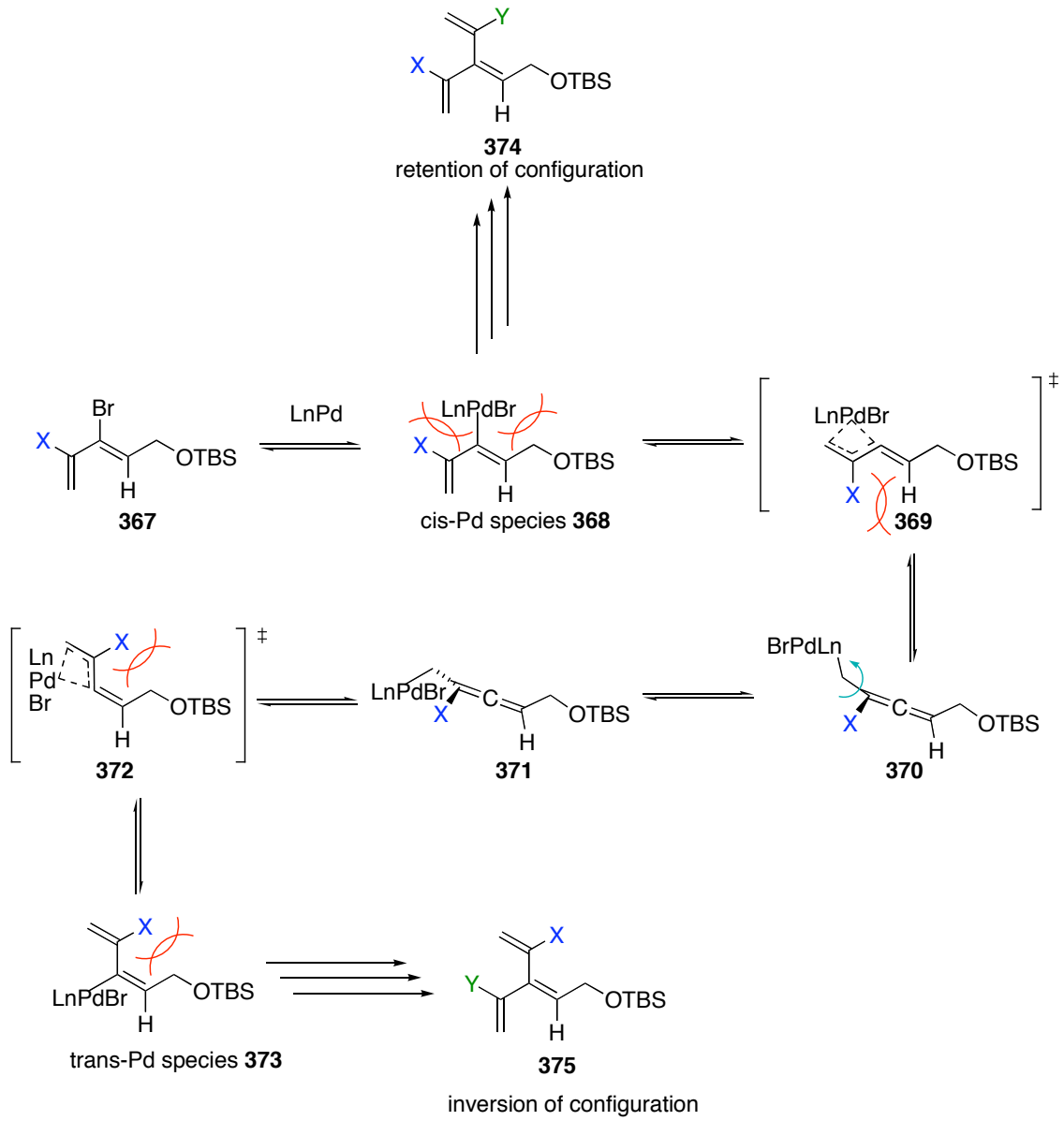
dendralenes in a 91:9 ratio. 2D NMR experiments, however, showed that the major product resulted from inversion of configuration, not retention as expected.[170] It was hoped that if these same conditions were applied to a coupling between **363** and tributyl(prop-1-en-2-yl)stannane, clean inversion would also occur. Unfortunately, this was not the case and once again a mixture products was obtained (Scheme 5.11).



Scheme 5.12 *Reagents and conditions:* a) isopropenyl magnesium bromide, $ZnBr_2$, THF, rt, 45 min, 78%; (b) tributyl(vinyl)tin (2.0 equiv), CsF (2.0 equiv), CuI (0.08 equiv), $PdCl_2$ (0.04 equiv), tBu$_3$P (0.08 equiv), DMF, 45 ^oC, 24 h, 50% conversion, 69% yield based on recovered s.m. (c) vinyl tributyltin(2.0 equiv), PPh_3 (0.1 equiv), $Pd(OAc)_2$ (0.05 equiv), CH_3CN, 60 ^oC, 18 h, 46%

Finally, bromodiene **366** was coupled with an excess of tributyl(vinyl)tin under the conditions that gave complete inversion of configuration during the synthesis of the chiral [4]dendralene precursors (Scheme 4.35). To our surprise the two dendralenes **364** and **365** were formed in a 72:28 ratio, with the major product resulting from retention of configuration (Scheme 5.12).

The unexpected results obtained from the coupling reactions could be the result of finely balanced competing steric interactions (Scheme 5.13 *cf* Scheme 4.36). Steric interactions include those between the Pd ligands and the substrate (**368**) and between the substituent X and other parts of the substrate (**369**, **372** and **373**). A change in substitution or ligand will determine which of these steric interactions are dominant.



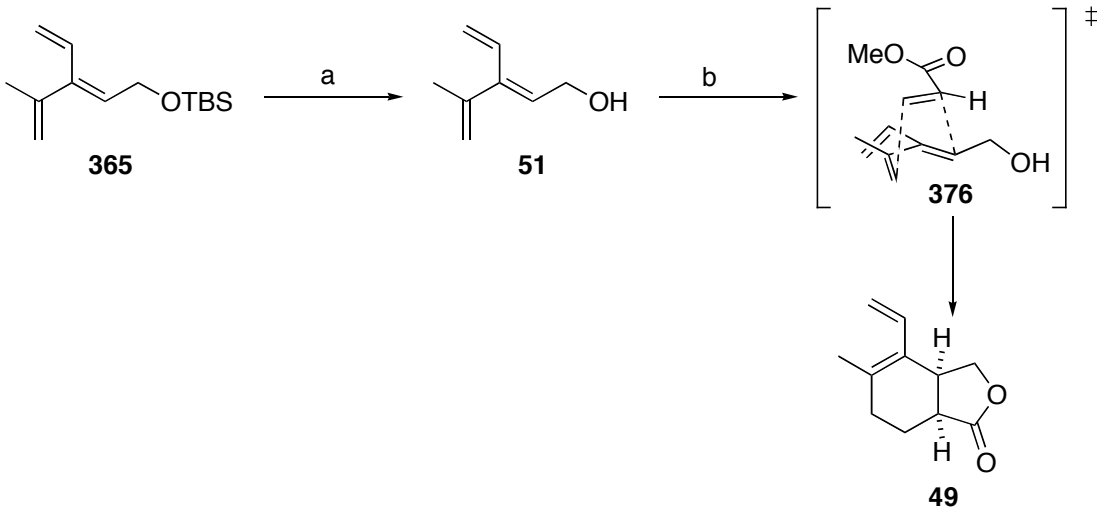
Scheme 5.13 Steric interactions during the palladium catalysed coupling reactions leading to retention or inversion of configuration.

As a 72 :28 ratio of the dendralenes **365** and **364** was the best result obtained, this mixture was carried on to the next step of the synthesis.

*5.3.2 Synthesis of the Bicyclic Intermediate **49***

5.3.2.1 A dendralene approach

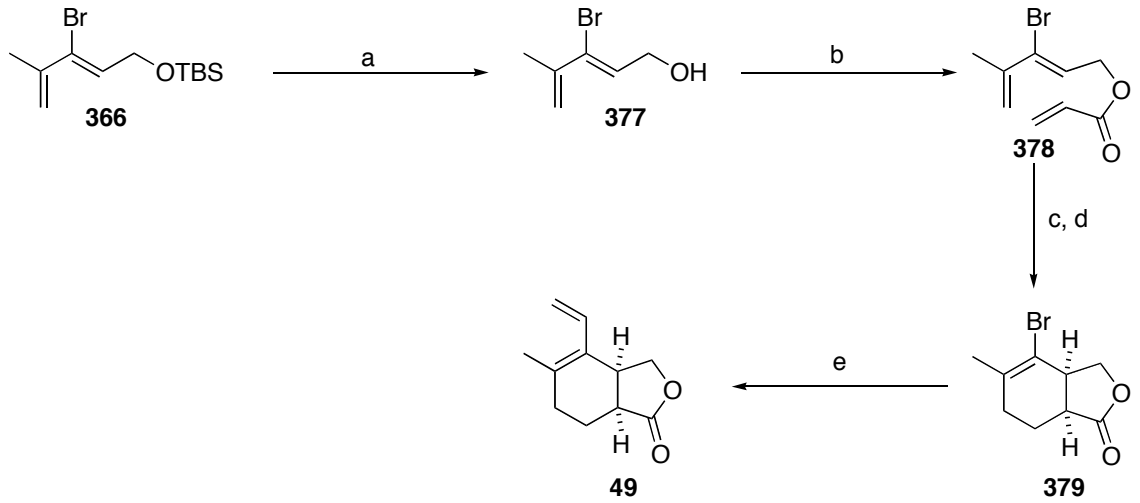
Deprotection of dendralene **365** gave the alcohol **51** (Scheme 5.14). When heated in a sealed tube with methyl acrylate, **51** underwent a stereoselective and regioselective Diels-Alder reaction through the transtion state **376** depicted in Scheme 5.14 to give the desired product. As the overall yield for this sequence was disappointingly low, however, an alternative route to the key intermediate **49** was sought.



Scheme 5.14 *Reagents and conditions:* (a) TBAF, THF, 2.5 h; (b) methyl acrylate, PhMe, 100 ^{o}C, 18 h, 30% for 2 steps.

5.3.2.2 An IMDA approach

As sufficient quantities of the desired [3]dendralene **51** could not be synthesised, an alternative route to the key bicyclic intermediate **49** was designed (Scheme 5.15). Treatment of bromodiene **366** with tetrabutyl ammonium fluoride resulted in removal of the silyl group to give alcohol **377**. The alcohol **377** was esterified with acryloyl chloride to form the IMDA precursor **378**.



Scheme 5.15 *Reagents and conditions:* (a) TBAF, THF, 1h, 80%; (b) acryloyl chloride, NEt_3, CH_2Cl_2, 0 ^oC, 1.5 h, 85%; (c) $C_6H_4Cl_2$, 180 ^oC, 72 h; (d) DBU, CH_2Cl_2, 40 ^oC, 2.5 h, 40% over 2 steps; (e) tributyl(vinyl)tin, $PdCl_2(CH_3CN)_2$, DMF, 100 ^oC, 6 d, 36%.

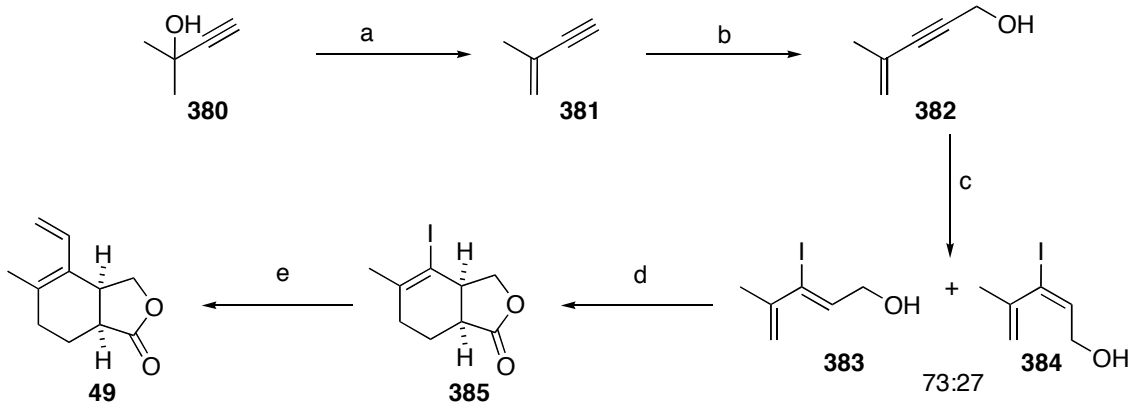
Cyclisation of triene **378** occurred after prolonged heating at 180 ^oC to give a mixture of the *cis* and *trans* fused cycloadducts. After removal of the dichlorobenzene by distillation under reduced pressure, the crude product mixture was treated with DBU to give exclusively the *cis* fused bicyclic product **379**. The low yield for this sequence (40%) has been attributed to the volatility of the cycloadducts, since GC analysis of the distilled dichlorobenzene showed the presence of the cycloadducts.

Stille reaction between bromide **379** and tributyl(vinyl)tin under optimised conditions occurred in a disappointingly low yield of 36% after six days. As this route was very low yielding overall and sufficient quantities of material could not be made it was abandoned.

5.3.2.3 An intermolecular approach

Since Stille reactions are known to occur with iodides much more readily than they do with bromides, the bicyclic iodide **385** was synthesised (Scheme 5.16). Dehydration of 2-methyl-3-butyn-2-ol **380** according to a literature procedure gave 2-methyl-1-buten-3-yne **381** in 50% yield.[172] Reaction of **381** with ethyl magnesium bromide and paraformaldehyde gave the alcohol **382**.[173] Treatment of **382** with lithium aluminium hydride followed by iodine gave the iodides **383** and **384**.[174] The mixture of isomers was then heated with methyl acrylate in a sealed tube at 100 ^oC for 18 h. The *Z* isomer underwent a regioselective Diels-Alder reaction followed by spontaneous lactonisation

to give the bicyclic lactone **385** in 61% yield. Finally, Stille reaction between **385** and tributyl(vinyl)tin gave the desired bicyclic intermediate **49** in very good yield.

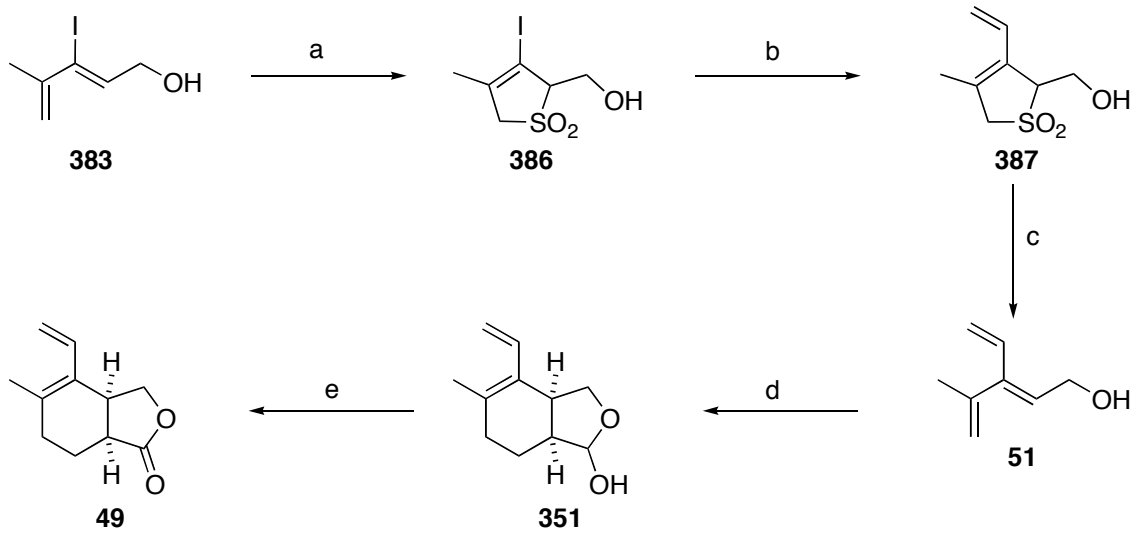


Scheme 5.16 *Reagents and conditions:* (a) Acetic anhydride, pTsOH, 50%; (b) EtMgBr, $(CH_2O)_n$, THF, 56%; (c) LiAlH, I_2, -78 - 0 ^oC, 42% (*E/Z* 2.75:1); (d) methyl acrylate, PhMe, 100 ^oC, 18 h, 61%; (e) tributyl(vinyl)tin, $Pd_2(dba)_3$, tri(2-furyl)phosphine, PhMe, 60 ^oC, 24 h, 86 %.

5.3.2.4 A new dendralene approach

As large amounts of the iodide **383** were now readily available, an alternative route to the dendralene **51** was considered. Protection of the butadiene as its sulfolene derivative would prevent inversion of configuration in subsequent palladium catalysed coupling reactions. Cheleotropic extrusion of sulphur dioxide would then give the dendralene.

Thus, iodide **383** was reacted with an excess of sulphur dioxide in a sealed tube for six days to give **386** (Scheme 5.17). Stille coupling between **386** and tributyl(vinyl)tin gave the [3]dendralene precursor **387** in good yield.



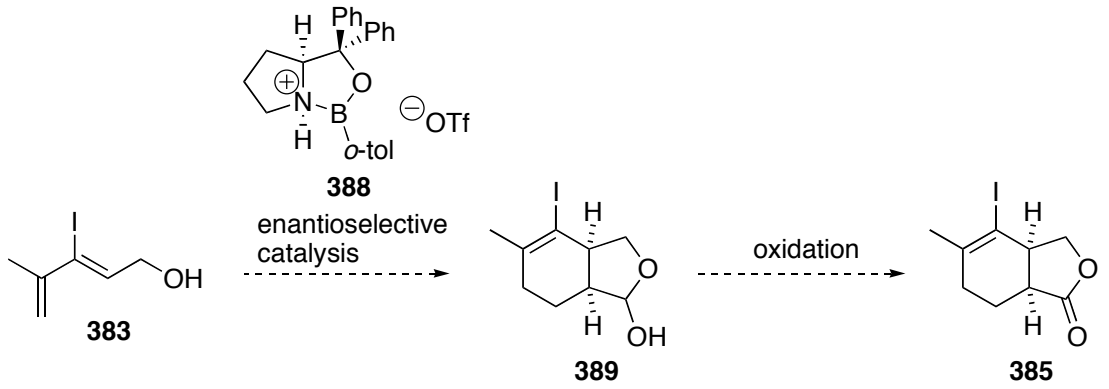
Scheme 5.17 *Reagents and conditions:* (a) SO_2, MeOH/Et_2O, 1:1, rt, 6 d, 51%; (b) tributyl(vinyl)tin, $PdCl_2(CH_3CN)_2$, DMF, 100 ^oC, 75%; (c) 230 ^oC, 100 mm/Hg, 16%; (d) acrolein, MeOH/H_2O 95:5, 24 h, 29%; (e) PCC, NaOAc, $NaHCO_3$, CH_2Cl_2, 18 h, 93%.

Sulfolene **387** was expected to readily undergo cheleotroplic elimination of sulphur dioxide when heated, as is the case for most such substances.[175,176] Intriguingly, no reaction was observed when solutions of **387** in chlorobenzene or dimethyl sulfoxide were heated to reflux. Finally, heating **387** to 230 ^oC at 100 mm/Hg resulted in the formation of the dendralene **51**, albeit in low yield. It is thought that conjugation of the 3,4-alkene slows the rate of cheleotropic elimination.

Reaction of dendralene **51** and acrolein proceeded at room temperature to give the lactol **351** and subsequent oxidation gave the lactone **49**. Optimisation of this sequence was not carried out as we already had a shorter and higher yielding route available.

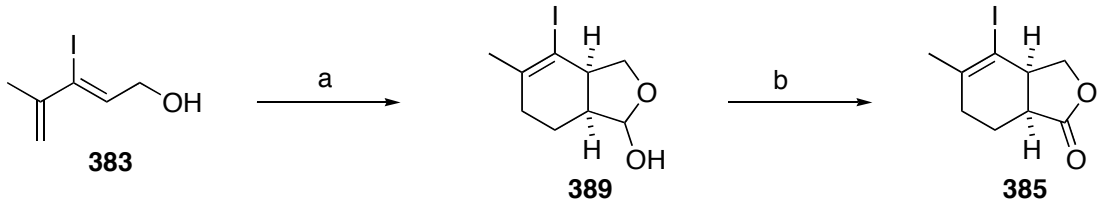
*5.3.2.5 Attempted enantioselective synthesis of the bicyclic intermediate **385***

In recent years there has been much interest in catalysed enantioselective Diels-Alder reactions. It was envisaged that a Diels-Alder reaction between dienol **383** and acrolein could be carried out using Corey's chiral, cationic oxazaborolidine catalyst **388**[6] to enantioselectively give the lactol **389** (Scheme 5.18). The lactol **389** could then be oxidised to give the bicyclic lactone **385**.



Scheme 5.18 Enantioselective route to **385**.

Before any enantioselective reactions were attempted, the uncatalysed Diels-Alder reaction between dienol **383** and acrolein was first carried out (Scheme 5.19). Reaction occurred at room temperature to give the lactol **389** in good yield. Oxidation was then accomplished using PCC.



Scheme 5.19 *Reagents and conditions:* (a) acrolein, MeOH/H_2O 95:5, rt, 6 d, 66 %; (b) PCC, NaOAc, $NaHCO_3$, CH_2Cl_2, 18 h, 84%.

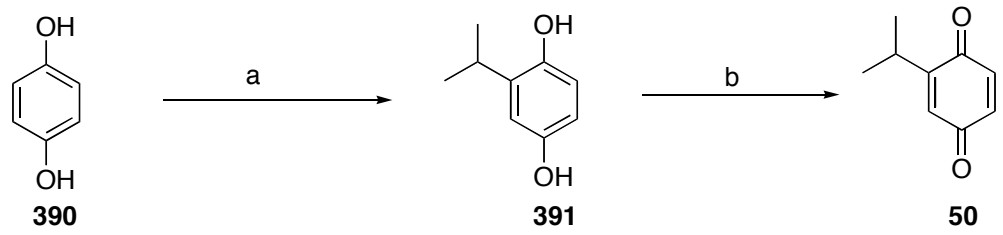
Reactions between dienol **383** and acrolein, ethyl acrylate and triflouroethyl acrylate in the presence of **388** were attempted. At best, only trace amounts of the desired product were formed. Chiral HPLC analysis of the products showed little to no *ee*. In order to determine if the catalyst was being formed an example from Corey's paper was carried out. As this reaction was successful, we conclude that even though the catalyst **388** is reported to be of broad applicability, it was not useful for our diene.

Due to time constraints, exploration of alternative catalysts was postponed and the synthesis of racemic triptolide was investigated.

5.3.3 Completion of the Synthesis of (±)-Triptolide

*5.3.3.1 Formation of the dienophile **50***

The requisite dienophile **50** was synthesised according to literature procedures (Scheme 5.20).[177] Friedel-Crafts reaction of hydroquinone and one equivalent of isopropanol gave a mixture of starting material, the desired product **391** and 2,5-diisopropylhydroquinone. 2-isopropylhydroquinone **391** was obtained after recrystallisation. Subsequent oxidation gave 2-isopropyl-*p*-benzoquinone **50**. The yield for this sequence is very low (7%) but compares well with that reported in the literature (11%). Nevertheless, substantial amounts of the desired product could be obtained as the reactions can be carried out on large scale and inexpensive starting materials are used.

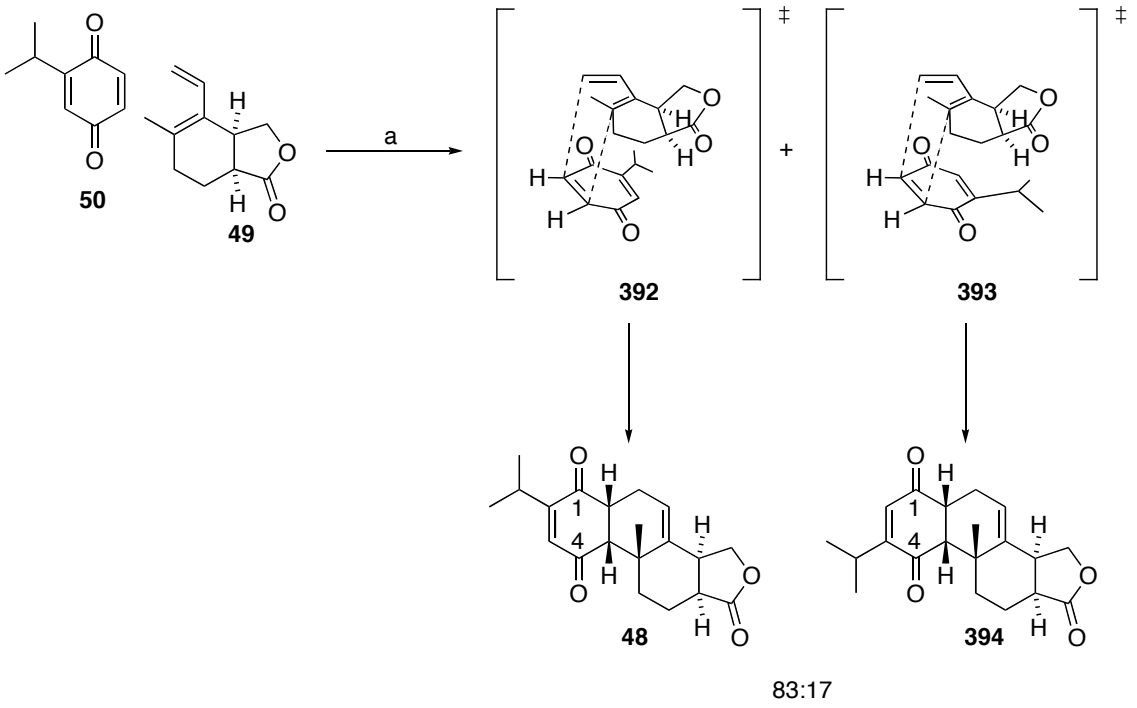


390 **391** **50**

Scheme 5.20 *Reagents and conditions:* (a) *i*-PrOH, $ZnCl_2$, HCl, H_2O, 98 ^oC, 18 h; (b) $KBrO_3$, H_2SO_4, H_2O, dioxane, 70 ^oC, 5 min, 7% over 2 steps.

5.3.3.2 Formation of the tetracyclic core

As the diene **49** and dienophile **50** were now in hand, a Diels-Alder reaction could be carried out. A solution of diene **49** and a slight excess of dienophile **50** in dichloromethane was compressed at 19 kbar pressure for seven days to give two products in a 83:17 ratio (Scheme 5.21). Single crystal X-ray analysis confirmed that the major product was indeed the desired tetracycle **48** (Figure 5.3). Due to striking similarities between the ^1H NMR and ^{13}C NMR spectra for both isomers, it is thought that the minor product is the regioisomer where the isopropyl group is in the C3 position, however, this is yet to be confirmed.



Scheme 5.21 *Reagents and conditions:* (a) **50** (1.2 equiv), 19 kbar, CH_2Cl_2, 7 d, 50% of **48**.

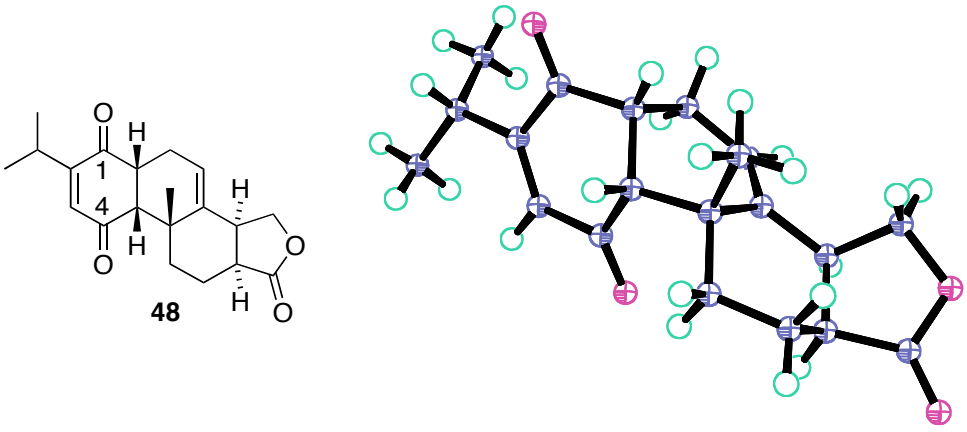
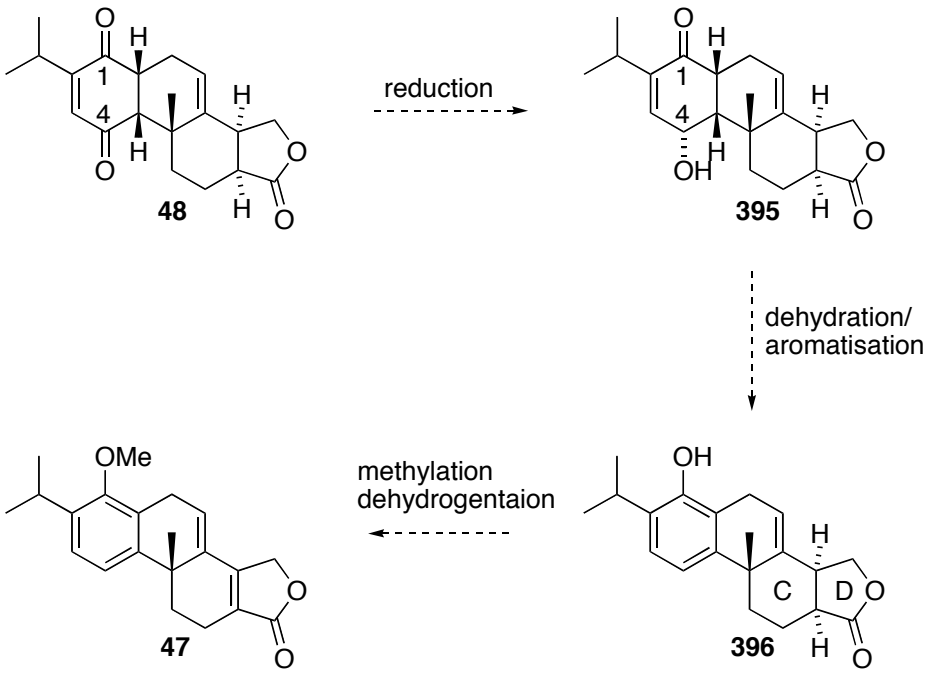


Figure 5.3 Thermal ellipsoid diagram of **48**. Ellipsoids show 30% probability levels.

The Diels-Alder reaction proceeded with a high level of stereoselectivity and regioselectivity. The major product is a result of the dienophile approaching the convex face of the bicyclic diene **49** in an *endo* orientation as depicted in **392** (Scheme 5.21). The regioselectivity observed is presumably a result of steric forces.

5.3.3.3 Synthetic strategy I

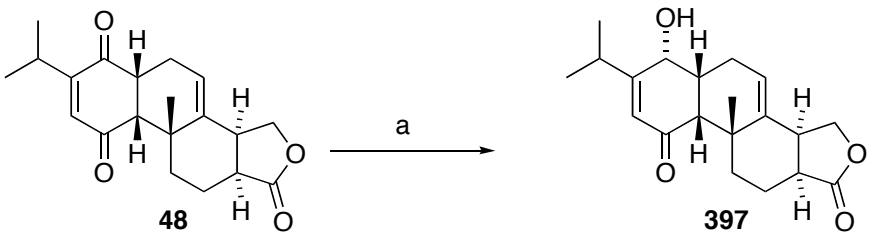
With the tetracyclic core now in place, some functional group interconversions were required to complete the synthesis (Scheme 5.22). We planned to carry out a regioselective reduction of the ketone at C4, followed by dehydration and aromatisation to give phenol **396**. Methyl ether formation followed by dehydrogenation across the C/D ring junction (*cf* **396**) would give **47**, thus completing the formal total synthesis of triptolide.



Scheme 5.22 Synthetic strategy

5.3.3.3.1 Reduction of diketone **48**

Treatment of the diketone **48** with 0.8 molar equivalents of sodium borohydride resulted in the formation of a single product in quantitative yield (Scheme 5.23). Single crystal X-ray analysis revealed that the ketone next to the isopropyl group had been reduced (C1) (Figure 5.4). This result was unexpected since the isopropyl group was expected to inhibit approach of the nucleophile to the adjacent C=O group. Analysis of the crystal structure of the diketone **48**, however, reveals that the C4 ketone is in a significantly more hindered position than the C1 ketone.



Scheme 5.23 *Reagents and conditions:* (a) $NaBH_4$ (0.8 equiv), THF, H_2O, 0 ^oC, 30 min, 99%.

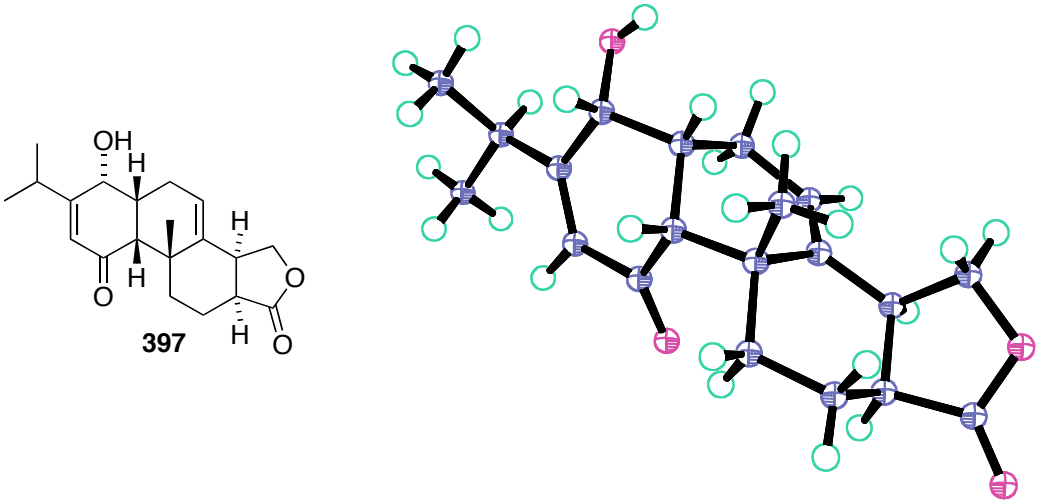
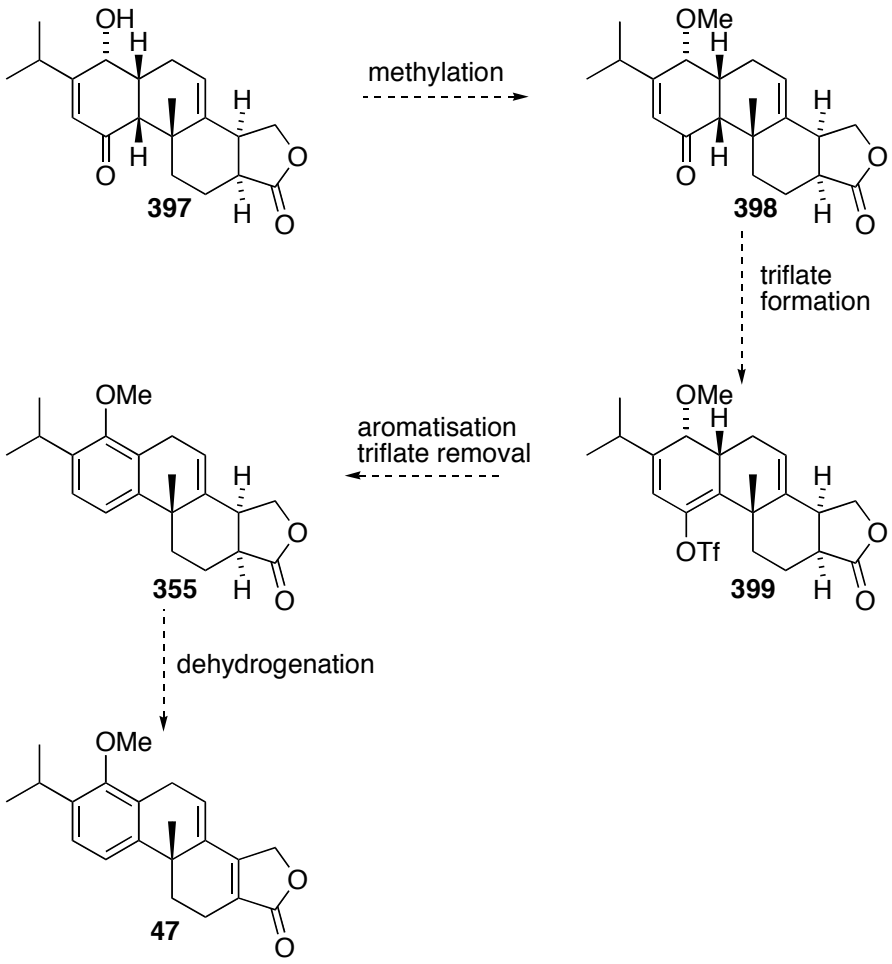


Figure 5.4 Thermal ellipsoid diagram of **397**. Ellipsoids show 30% probability levels.

5.3.3.4 Synthetic strategy II

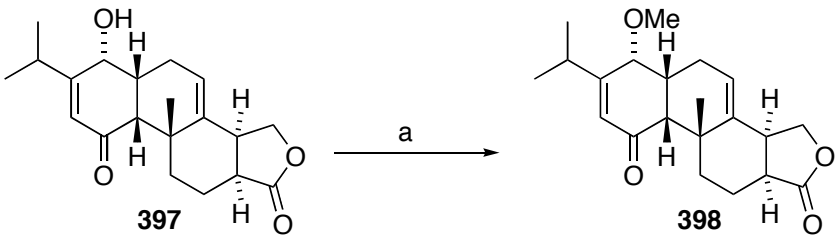
As the reduction occurred at the C1 ketone in preference to the C4 ketone, a new strategy was required. We envisaged a five step sequence to convert **397** into **47** which involved methylation to give **398**, formation the vinyl triflate **399** followed by careful aromatisation then palladium-catalysed reductive removal of the triflate group to give **355**. Finally, dehydrogenation would give **47** (Scheme 5.24).



Scheme 5.24 Revised strategy

5.3.3.4.1 Methyl ether formation

As there are epimerisable positions in **397**, a strong base could not be used to form the methyl ether **398**. Thus, methylation was first attempted using conditions reported to prevent epimerisation.[178] Alcohol **397** was treated with 30 equivalents of 2,6-di-*tert*-butylpyridine and 15 equivalents of methyl triflate. No reaction was observed under these conditions. A base could be avoided altogether by using methyl iodide and silver oxide, however only a trace amount of the desired methyl ether **398** was formed when a solution of alcohol **397** in dichloromethane was treated with methyl iodide and silver oxide.[179] Gratifyingly when the reaction was carried out with 10 equivalents of silver oxide and using methyl iodide as the solvent, the desired product **398** was obtained in near quantitative yield (Scheme 5.25). Single crystal X-ray analysis confirmed that epimerisation had not occurred (Figure 5.5).



Scheme 5.25 *Reagents and conditions:* (a) MeI, Ag_2O, 41 ^{o}C, 18 h, 99%.

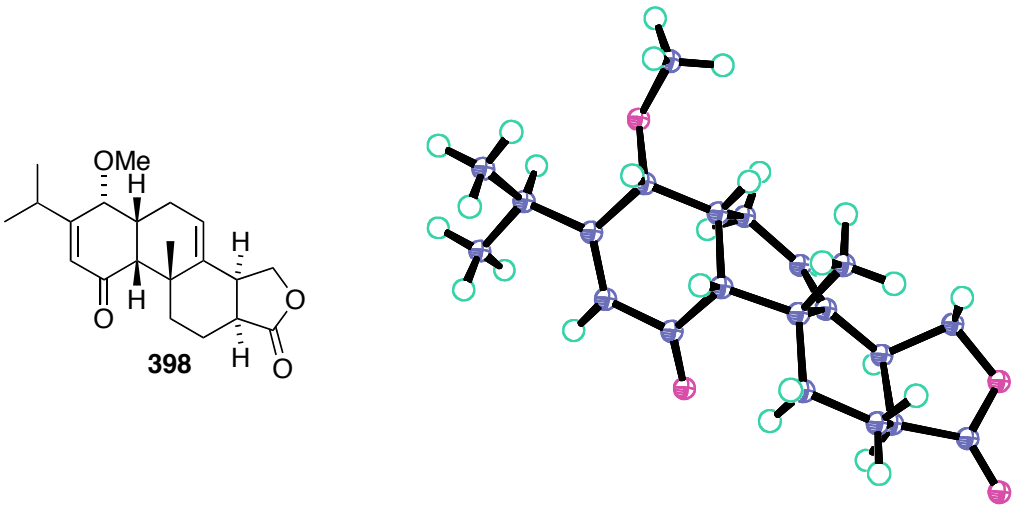
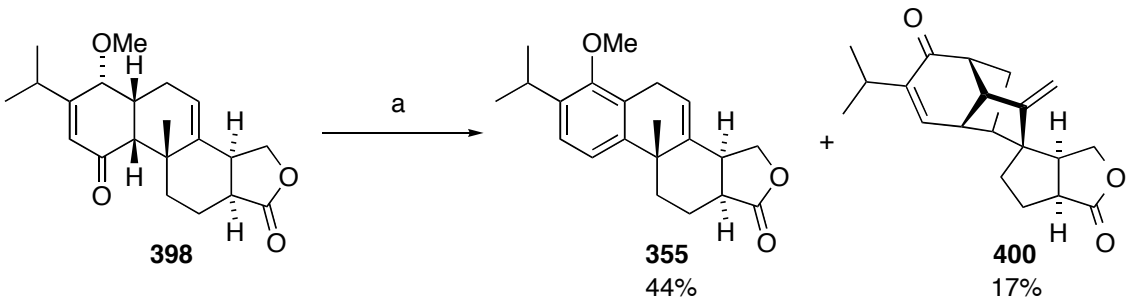


Figure 5.5 Thermal ellipsoid diagram of **398**. Ellipsoids show 30% probability levels.

5.3.3.4.2 Unexpected results from reaction of **398** with triflic anhydride

Treatment of ketone **398** with 1.2 equivalents of 2,6-di-*tert*-butyl-4-methylpyridine and 1.1 equivalents of triflic anhydride[180] did not give any on the expected vinyl triflate **399** and instead two other products were obtained (Scheme 5.26). The products were separated by column chromatography. ^{1}H NMR analysis suggested that one of the products was in fact the penultimate target **355**. This was confirmed by single crystal X-ray analysis (Figure 5.6). The identity of the other major product was more elusive. ^{1}H NMR analysis showed no peak due to the methyl ether or the methyl group at the ring junction. ^{13}C NMR spectroscopy showed that only one carbon atom had been lost. This was confirmed by high resolution mass spectrometry. Finally, single crystal X-ray analysis showed that **398** had undergone extensive rearrangement under the reaction conditions to form a novel ring system **400** (Figure 5.6).



Scheme 5.26 *Reagents and conditions:* (a) Tf_2O (1.1 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.2 equiv), CH_2Cl_2, -78 ^oC-rt, 48 h.

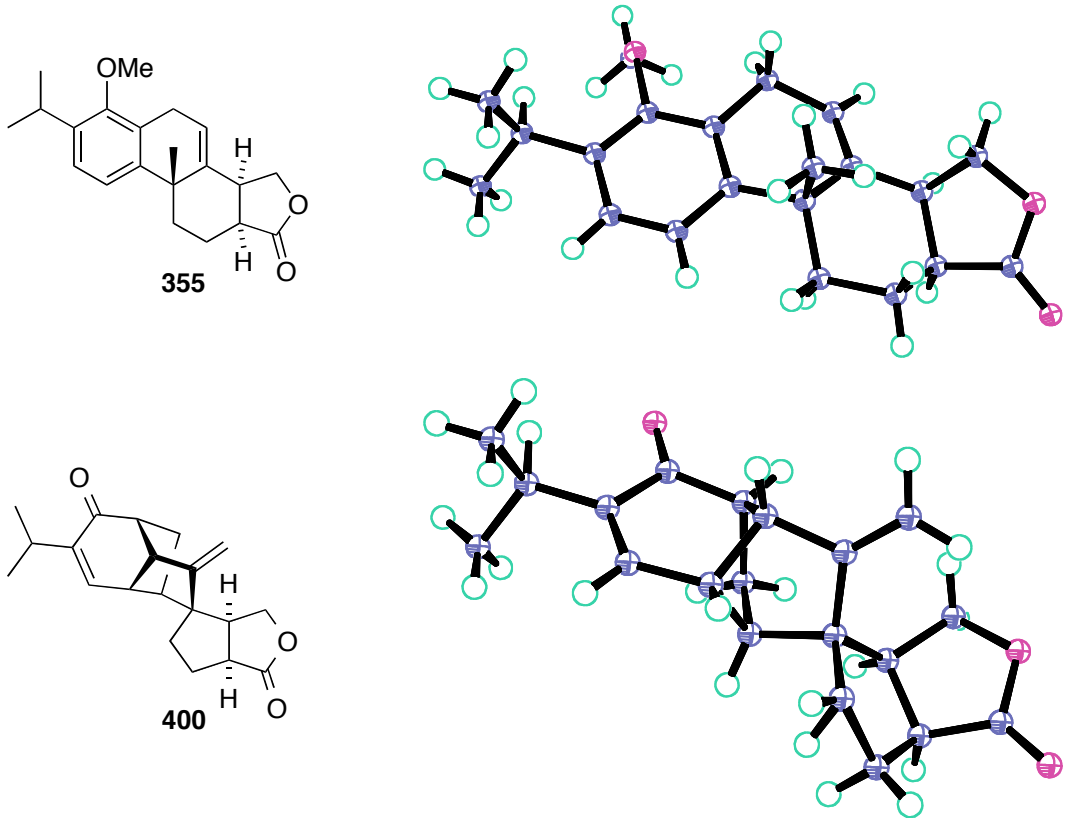
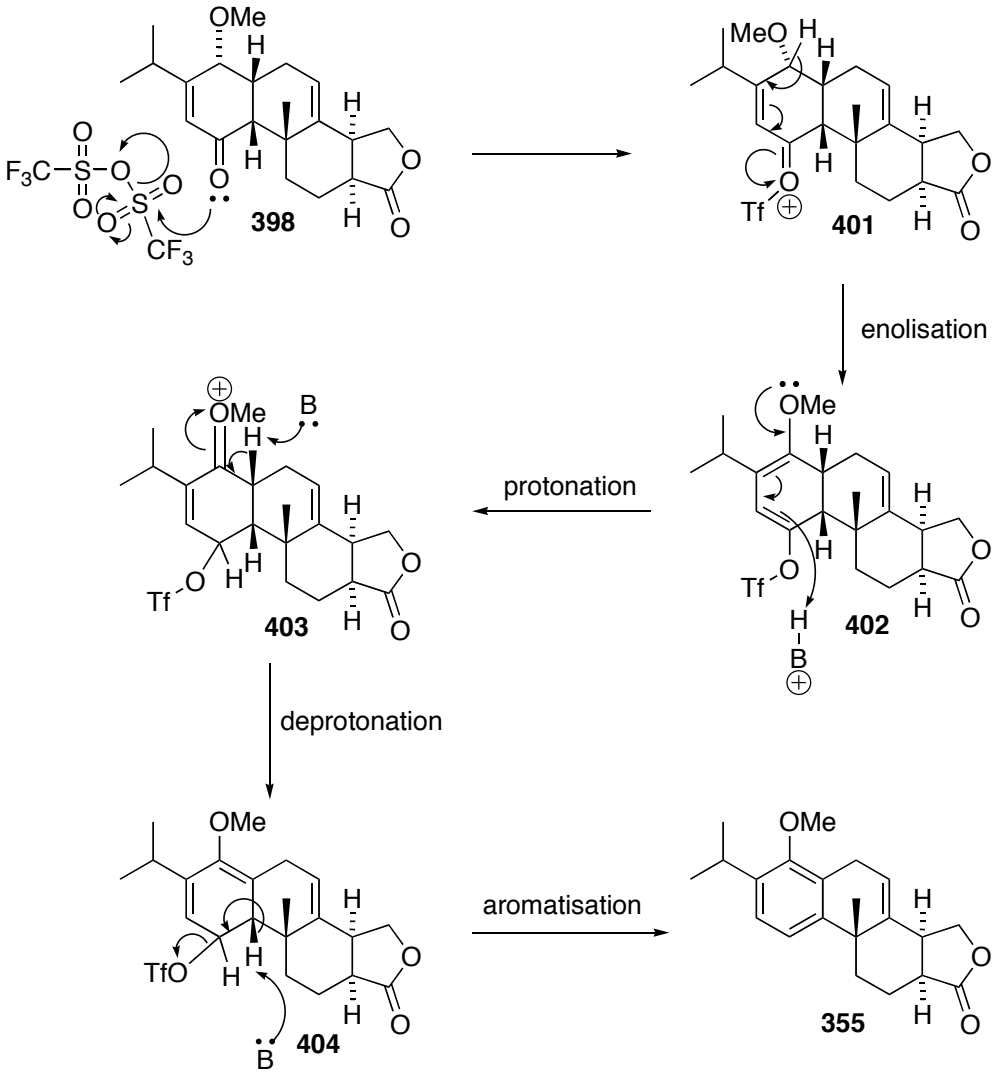


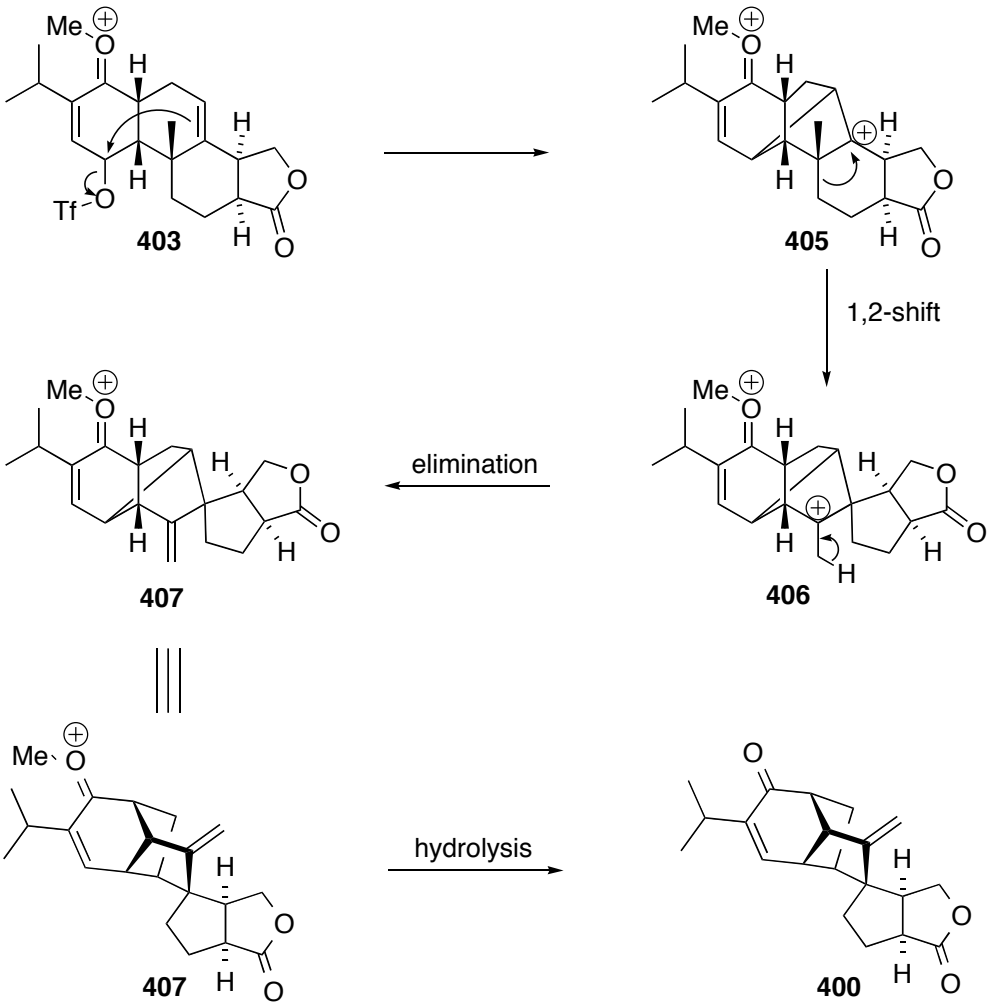
Figure 5.6 Thermal ellipsoid diagrams for **355** and **400**. Ellipsoids show 30% probability levels.

The mechanism for the formation of **355** possibly proceeds *via* the path shown in Scheme 5.27. Formation of the triflate followed by enolisation gives **402**. Protonation and deprotonation gives **404**, which is then able to undergo elimination of triflic acid to give the product **355**.



Scheme 5.27 A possible mechanism for the formation of **355**

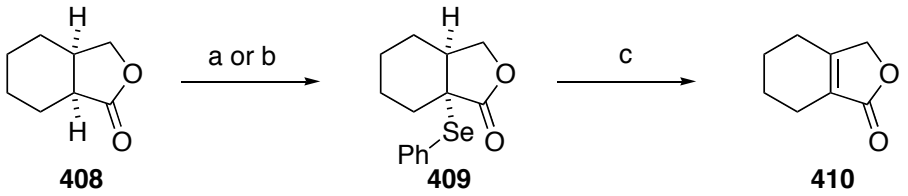
A proposed mechanism for the formation of the rearranged product **400** is drawn in Scheme 5.28. The generation of a new five membered ring from the common intermediate **403** results in the formation of a stable tertiary carbocation **405**. A 1,2-shift gives the spirocyclic ring system **406** while forming a new tertiary carbocation. Elimination gives the exocyclic double bond and hydrolysis gives the rearranged product **400**.



Scheme 5.28 A possible mechanism for the formation of **400**

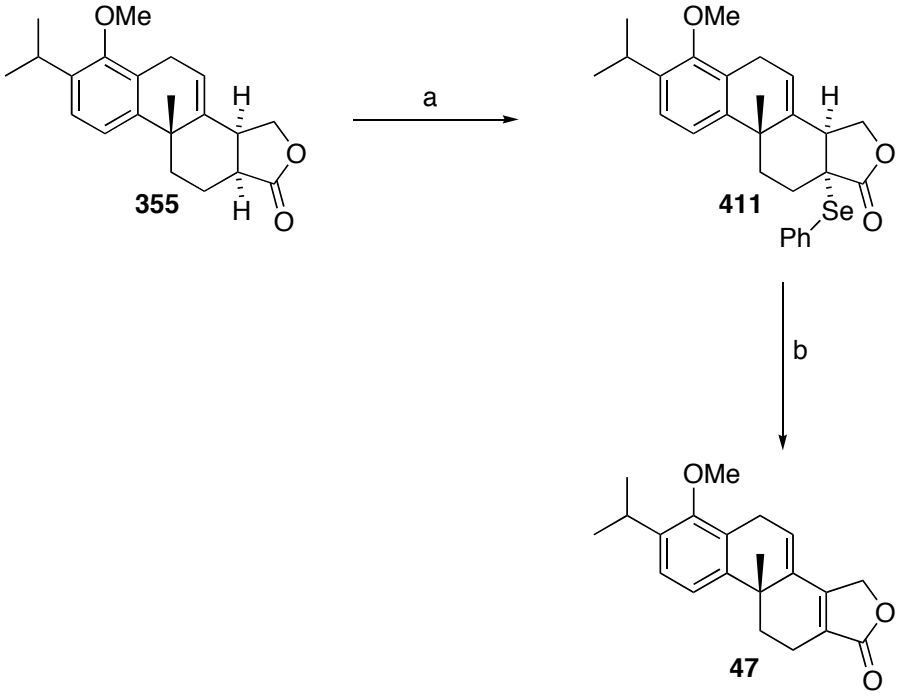
5.3.3.4.3 Dehydrogentation of **355**

Several options were available for the dehydrogenation of **355** to form the α,β-unsaturated lactone **47**. Studies on the model compound **408** showed that treatment with an excess of potassium hexamethyldisilazide, diphenyl diselenide and HMPA gave the intermediate selenide **409**.[181] Elimination across the ring junction to give the more substituted double bond (**410**) was accomplished in good yield using aqueous hydrogen peroxide (Scheme 5.29). Unfortunately, these conditions led to decomposition of the starting material when applied to **355**.



Scheme 5.29 *Reagents and conditions:* (a) PhSeSePh (3.25 equiv), KHMDS (3.25 equiv), HMPA, THF, -78 ^{o}C, 2 h; (b) TIPSOTf (2.0 equiv), NEt_3 (3.0 equiv), PhSeCl (3.0 equiv), CH_2Cl_2, rt, 10 min; (c) H_2O_2, CH_2Cl_2, 0 ^{o}C, 2 h, 66%.

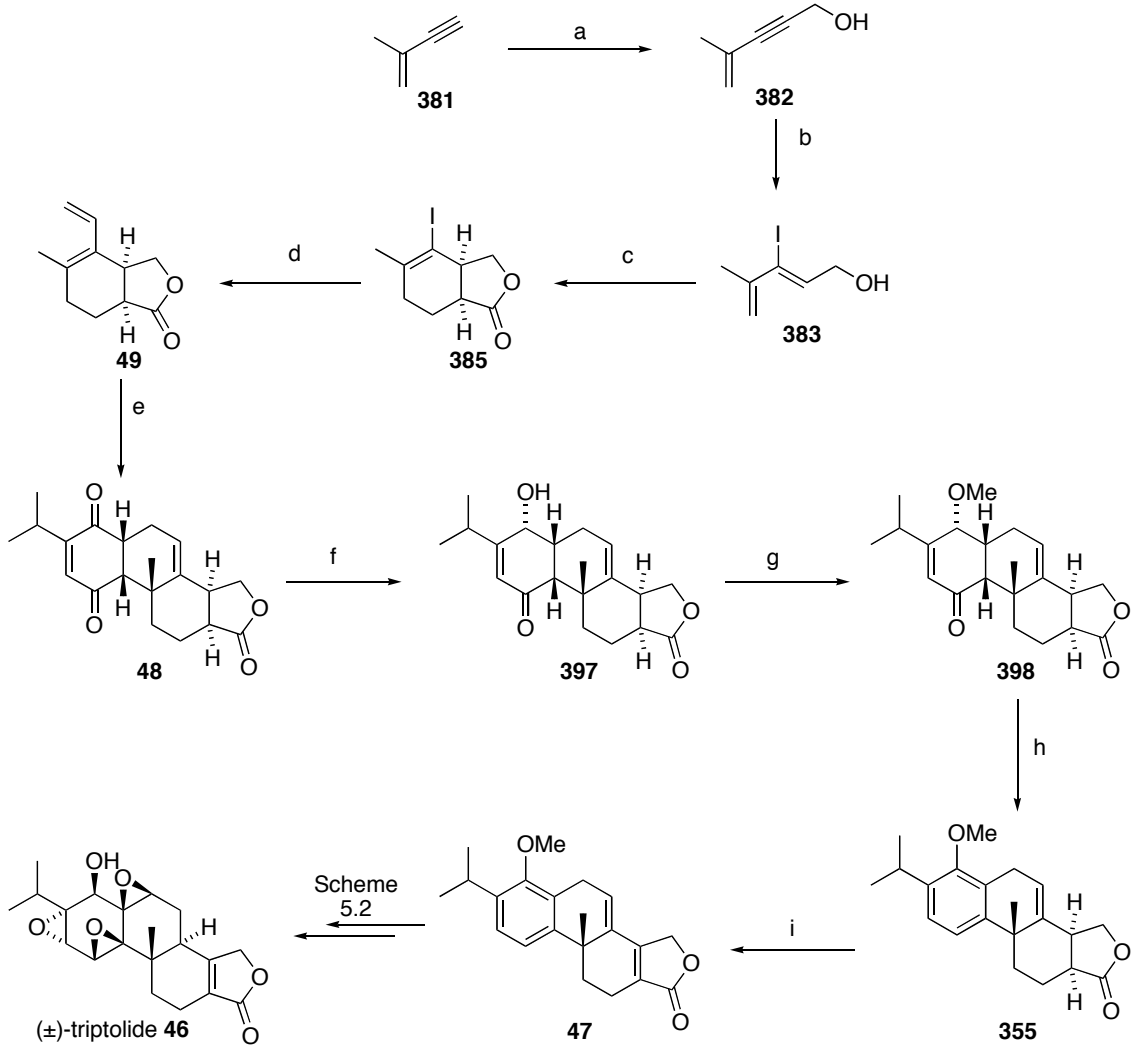
Alternative conditions that did not require the use of a strong base were sought. Treatment of the model compound **408** with an excess of triisopropylsilyl triflate and triethylamine resulted clean conversion to the corresponding silyl ketene acetal. All attempts to isolate the silyl ketene acetal were met with hydrolysis back to **408**. Thus, the silyl enol ether was formed *in situ* then treatment with phenylselenyl chloride gave selenide **409**. Gratifyingly, when these conditions were applied to the real system **355**, selenide **411** was generated. Treatment of a solution of the crude selenide in dichloromethane with aqueous hydrogen peroxide resulted in elimination across the ring junction to give **47**, thus completing the formal total synthesis of (±)-triptolide (Scheme 5.30). Unfortunately, due to time constraints, conditions for this reaction could not be optimised.



Scheme 5.30 *Reagents and conditions:* (a) TIPSOTf (6.0 equiv), NEt_3 (8.0 equiv), PhSeCl (8.0 equiv), CH_2Cl_2, rt, 10 min; (b) H_2O_2, CH_2Cl_2, 0 ^{o}C, 2 h, 50% by NMR.

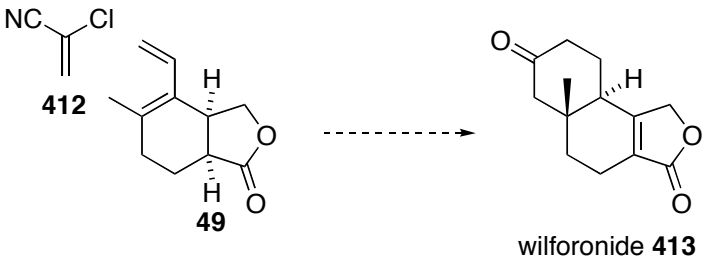
5.4 Conclusions and Future Work

A concise formal total synthesis of (±)-triptolide was completed (Scheme 5.31). The iodide **383** was formed in two steps from commercially available material, following literature procedures. Regioselective and stereoselective Diels-Alder reaction with methyl acrylate gave the bicylic iodide **385**. This was converted to the semi-cyclic diene **49** *via* a Stille coupling. A second Diels-Alder reaction gave the tetracyclic intermediate **48**. In just four more synthetic steps the tetracyclic target **47** was obtained. This intermediate has previously been converted to triptolide through an eight step sequence.



Scheme 5.31 *Reagents and conditions*: (a) EtMgBr, $(CH_2O)_n$, THF, 56%; (b) LiAlH, I_2, -78 - 0 ^oC, 42% (*E/Z* 73:27); (c) methyl acrylate, PhMe, 100 ^oC, 18 h, 61%; (d) tributyl(vinyl)tin, $Pd_2(dba)_3$, tri(2-furyl)phosphine, PhMe, 60 ^oC, 24 h, 86 %; (e) **50** (1.2 equiv), 19 kbar, CH_2Cl_2, 7 d, 50%; (f) $NaBH_4$ (0.8 equiv), THF, H_2O, 0 ^oC, 30 min, 99%; (g) MeI, Ag_2O, 41 ^oC, 18 h, 99%; (h) Tf_2O (1.1 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.2 equiv), CH_2Cl_2, -78 ^0C-rt, 48 h; (i) TIPSOTf (6.0 equiv), NEt_3 (8.0 equiv), PhSeCl (8.0 equiv), CH_2Cl_2, rt, 10 min; then H_2O_2, CH_2Cl_2, 0 ^oC, 2 h, 50% by NMR.

The possibility of carrying out the first Diels-Alder reaction in the presence of a suitable catalyst to selectively give either enantiomer of triptolide remains. The stereocentres formed during the first Diels-Alder reaction would be used to stereoselectively control the formation of the quaternary stereocentre present in the target compound. If successful, this would be the first catalytic enantioselective synthesis of the natural product. While the use of Corey's catalyst does not look promising there are many other catalysts available, such as MacMillan's organocatalyst. The methods developed could also be applied to the synthesis of related natural products such as wilforinide **413** (Scheme 5.32).



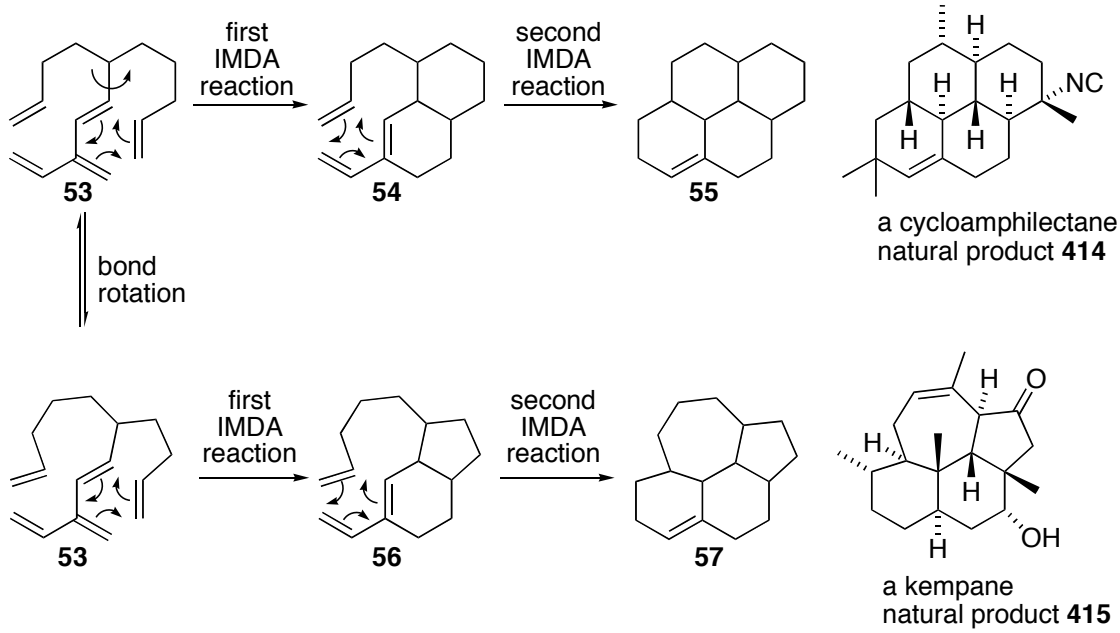
Scheme 5.32 Possible synthesis of wilforonide

6 Diene-Transmissive Diels-Alder Approaches to Tetracyclic Natural Product Frameworks

6.1 Introduction

With the growing interest in cascade sequences, many groups have recognised the power of the intramolecular Diels-Alder (IMDA) reaction. There is only one previous example, however, of a diene-transmissive Diels-Alder (DTDA) sequence that involves two consecutive IMDA reactions (see Scheme 4.31).[142]

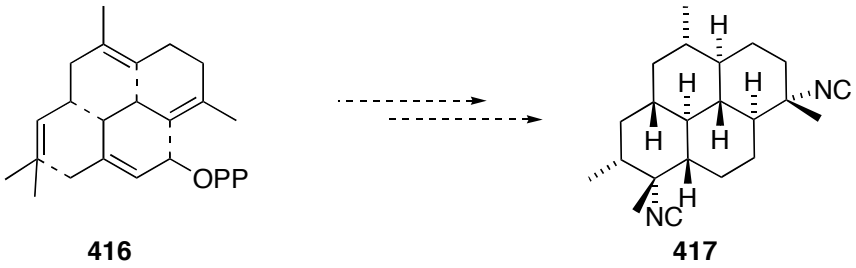
There are several different ways in which two dienophiles can be connected to a [3]dendralene, to allow a sequence of two IMDA reactions. A DTDA sequence of precursor **53** could produce either the carbon skeletons **55** or **57**, depending on the order of the cycloadditions (Scheme 6.1).



Scheme 6.1 Diene-transmissive sequences to give carbon skeletons **55** and **57**.

6.1.1 Perhydropyrene Ring System

Diisocyanoadociane, the first example of a diterpene containing a perhydropyrene ring system, was isolated from a marine sponge of the genus *Amphimedon* (ex. *Adocia*) in 1976.[182] The skeleton is unusual in that it contains no angular methyl substituents. It's biosynthesis might involve a unique tetracyclisation along with a single methyl migration (Figure 6.1).[157]



416 **417**

Figure 6.1 Possible biosynthesis of 7,20-Diisocyanoadociane.

Examples of related natural products isolated from marine sponges are illustrated in Figure 6.2. Many display significant and selective *in vitro* antimalarial activity.[183]

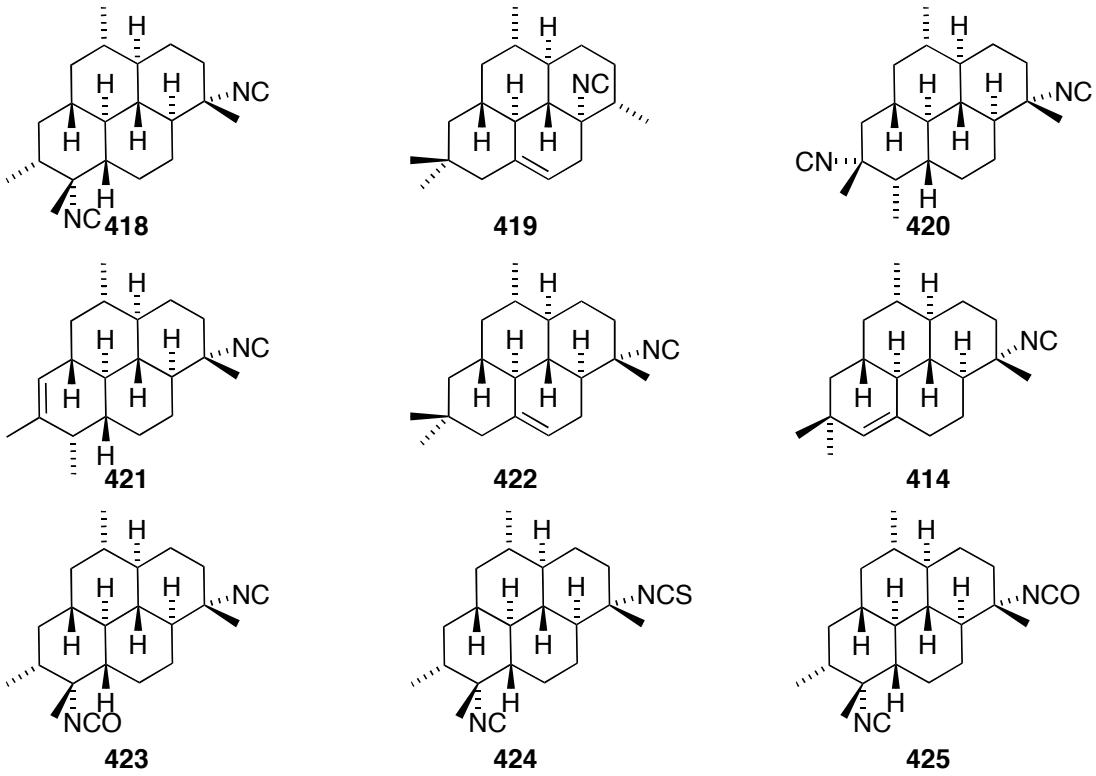


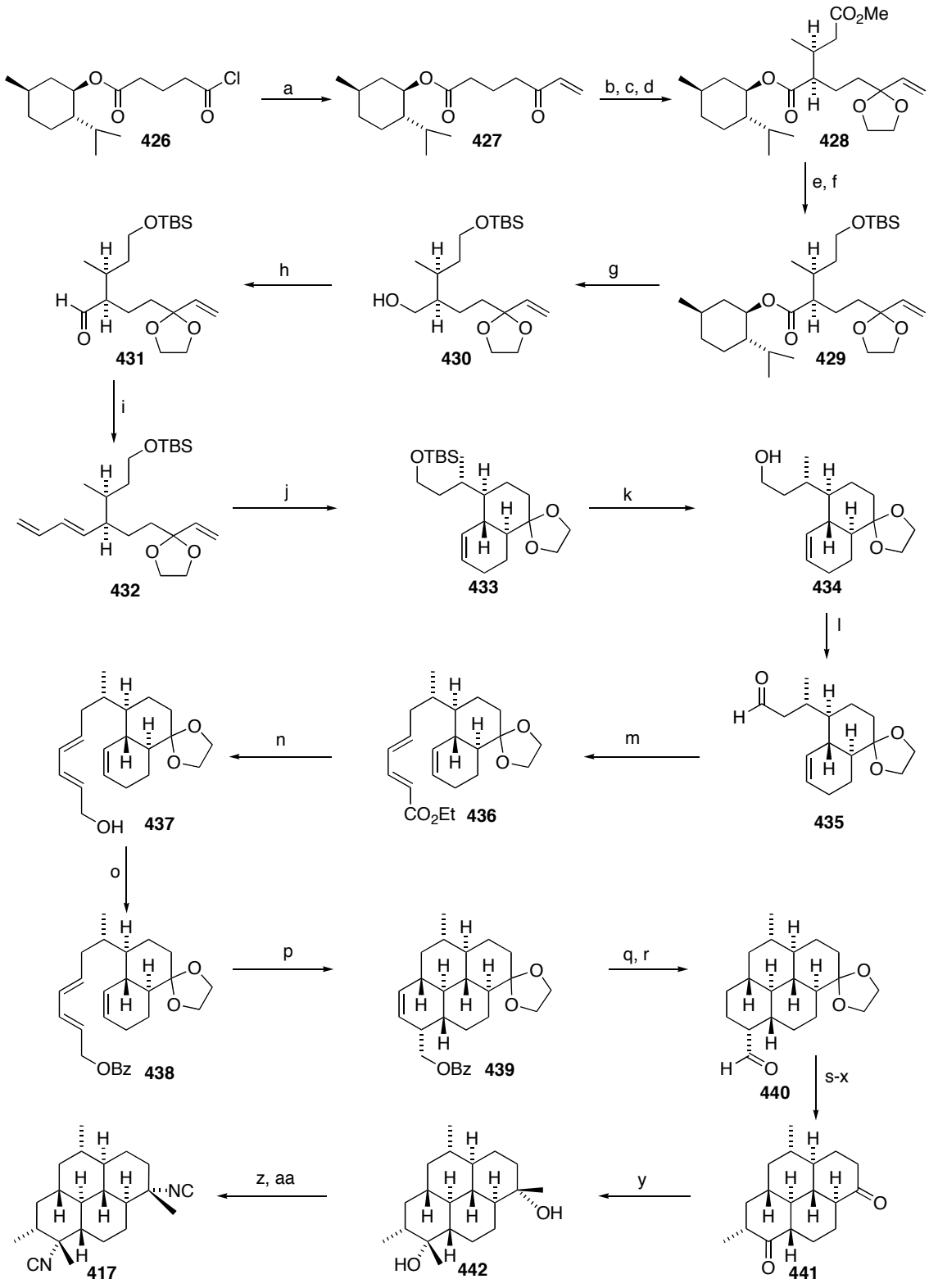
Figure 6.2 Tetracyclic diterpenes isolated from marine sponges *Amphimedon* sp. and *Cymbastela hooperi.*

Several studies have been carried out on the biosynthesis of 7,20-diisocyanoadociane **417**.[184-188] Only one total synthesis[189] and one formal total synthesis has been reported.[190] In 1987, Corey reported a synthesis of a single enantiomer of the natural product, allowing the assignment of the absolute configuration of **417** (Scheme 6.2).[189]

The vinyl ketone **427**, synthesised in three steps from menthol and glutaric acid, was transformed into the ethylene ketal by a two step sequence. Reaction with LDA and methyl crotonate gave the Michael adduct **428** as a 8:1 mixture of diastereomers. After removal of the auxiliary by reduction with $LiAlH_4$, the resulting alcohol was converted to the *E*-diene by a two step sequence. The triene **432** underwent IMDA reaction upon heating in toluene at 150 ^{o}C for 20 hours to give the *trans*-fused adduct **433** in 90% yield. The free enone corresponding to ketal **432** undergoes an IMDA reaction rapidly at or below room temperature to give the *cis*-fused adduct exclusively. It is thought that steric interactions involving the ketal unit in **432** disfavour the *endo* transition state.

The bicyclic product **433** was converted to a second IMDA precursor through a five step sequence. Triene **438** was heated in toluene at 185 ^{o}C for 36 hours to give the desired adduct **439** in 54% yield along with 36% of a diastereomeric adduct. Removal of the benzyl group followed by oxidation gave aldehyde **440**, which was converted to the all *trans*-fused ketone **441**.

Finally, the two isocyanide groups were installed through a single "biomimetic" operation. A mixture of four diastereomeric isocyanides was obtained. Separation of the mixture by HPLC gave 7,20-diisocyanoadociane **417**.


426
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430
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k
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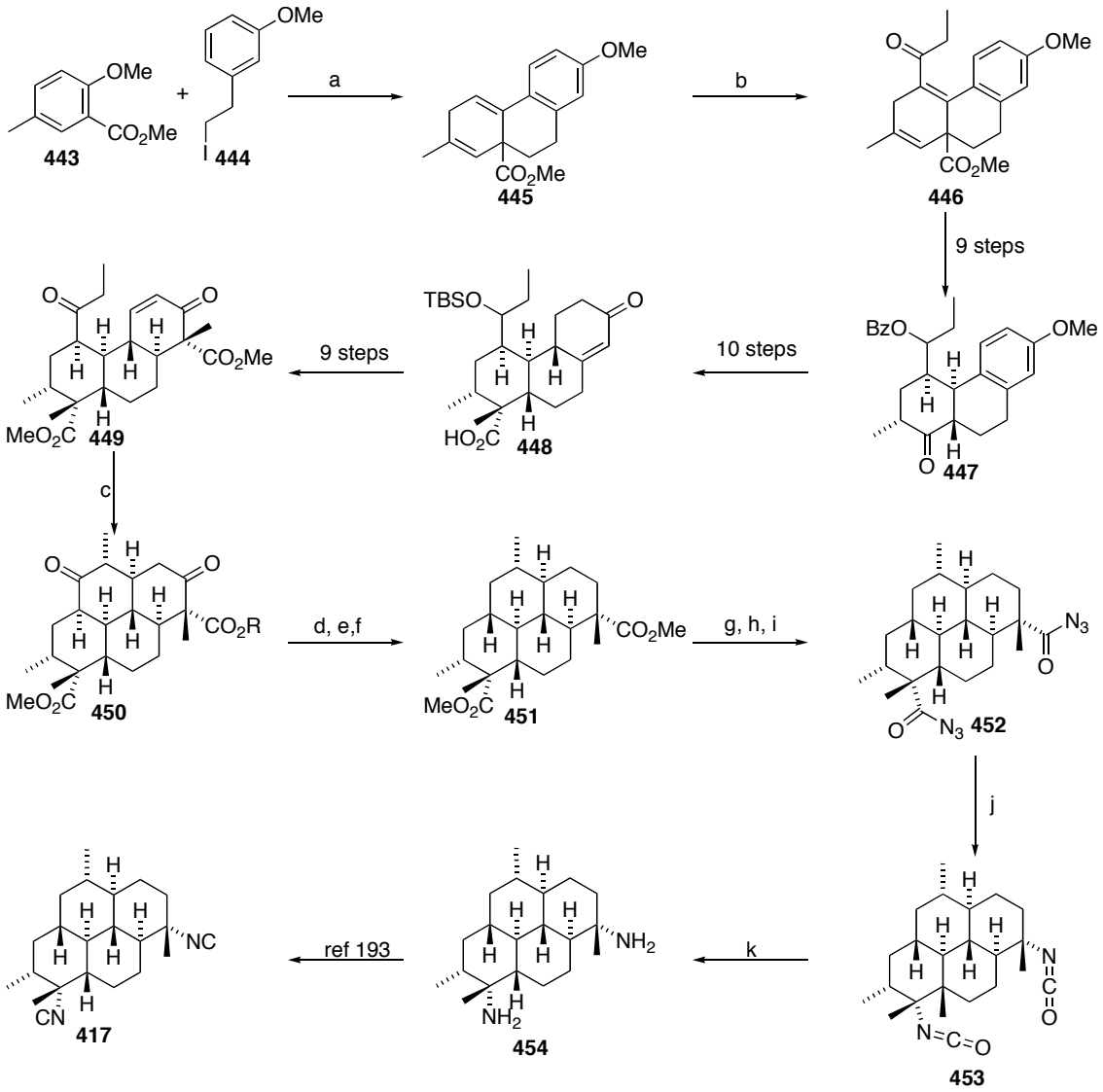
435
m
436
n
437
o
438
p
439
q, r
440
s-x
441
y
442
z, aa
417

Scheme 6.2 *Reagents and conditions:* (a) 1.1 equiv tributyl(vinyl)tin, 0.34 mol% $Pd(PPh_3)_4$, THF, 70 ^oC, 2 h, 90%; (b) 1.3 equiv $PhSeSiMe_3$, 5 equiv ethylene glycol, 0.025 equiv I_2, $CHCl_3$, 65 ^oC, 4h, 99%; (c) 1.5 equiv *m*CPBA, CH_2Cl_2, -20 ^oC, 15 min then 0.8 equiv DMS, 3 equiv DIPA, 60 ^oC, 6.5 h, 90%; (d) LDA, 1.1 equiv methyl crotonate, - 78 ^oC, 1 h, 80% (threo/erythro 8:1, ca. 60%*ee*); (e) 2.3 equiv $NaAl(CH_3OCH_2CH_2O)_2H_2$, Et_2O, -40 ^oC, 1.5 h; (f) 1.05 equiv TBSCl, 1.2 equiv NEt_3, 0.4 equiv DMAP, CH_2Cl_2, 30 min, 85% for 2 steps; (g) 0.4 M $LiAlH_4$, Et_2O, 1.5 h, 90 %; (h) 3 equiv PDC, 4 Å molecular sieves, CH_2Cl_2, 30 min; (i) 1.2 equiv methylallyldiphenylphosphonium bromide, 1.1 equiv KO-*t*-Bu, THF, 0 ^oC, 45 min, 75% for 2 steps; (j) PhMe, 150 ^oC, 20 h, 90%; (k) Bu_4NF, THF, 1.5 h; (l) PDC, 4 Å molecular sieves, CH_2Cl_2, 30 min, 82% 2 steps; (m) triethyl lithio-4-phosphono-*E*-crotonate, THF -78 ^oC – rt, 1 h, 70%; (n) 2.2 equiv DIBAL-H, PhMe, -20 ^oC, 10 min; (o) 4 equiv NaH, 1.4 equiv BnBr, DMSO, 30 min, 89% 2 steps; (p) 0.04 M sol in PhMe, 185 ^oC, 36 h, 54% desired adduct, 36% diastereomeric adduct; (q) 1 atm H_2, Pd-C, ethanol, 4.5 h, 80 %; (r) PDC, 4 Å molecular sieves, CH_2Cl_2, 30 min, 80%; (s) pyrrolidine, *p*TsOH, C_6H_6, 10 h, 90%; (t) ruthenium tetroxide, CCl_4, 0 ^oC, 5 min; (u) 1 M NaOMe in MeOH, 2 min, 75%; (v) 1.05 equiv LDA, 5 equiv MeI, -78 – 23 ^oC over 20 min; (w) 0.5 M NaOMe in 1:1 THF/MeOH, 12 h, 90%; (x) 0.5 M HCl in 50% aq, acetone, 99%; (y) 4.8 equiv MeLi, 5 equiv $CeCl_3$, THF, -78 - 0 ^oC, 1.5 h, 92%; (z) 3 equiv trifluoroacetic anhydride, 5 equiv pyridine, CH_2Cl_2, 0 ^oC, 20 min, 95%; (aa) 15 equiv TMSCN, 20 equiv $TiCl_4$, CH_2Cl_2, 3.5 h, 70 % of 4 diastereomeric isocyanides.

Recently, Mander reported a total formal synthesis of racemic 7,20-diisocyanoadociane **417** (Scheme 6.3).[190] Birch reduction of 2-methoxy-5-methylbenzoate **443** and in situ alkylation followed by Friedel-Crafts cyclisation gave **445**. $AlCl_3$-catalyzed acylation of the styrene double bond with propionyl chloride gave the key intermediate **446**.

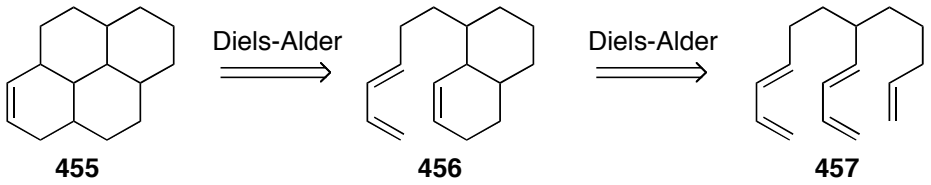
A nine-step sequence involving reduction, protection, oxygenation and a retro-Claisen reaction led to **447**. From this point, a ten-step sequence, including another Birch reduction, led to the next key intermediate **448**. After another nine steps **449** was obtained. This compound has both quaternary centres in place and is the precursor for the final cyclisation.

Following the intramolecular Michael reaction to give the tetracyclic intermediate **450**, reduction gave the diol. Conversion to the dixanthate and subsequent Barton-McCombie deoxygenation gave the tetracycle **451**. Demethylation of the ester groups preceeded preparation of the diacyl azide **452**. Curtius rearrangement to **453** was achieved by heating in toluene at reflux. Finally, hydrolysis in concentrated HCl gave the diamine **454**, thus completing the formal total synthesis of 7,20-diisocyanoadociane **417**.



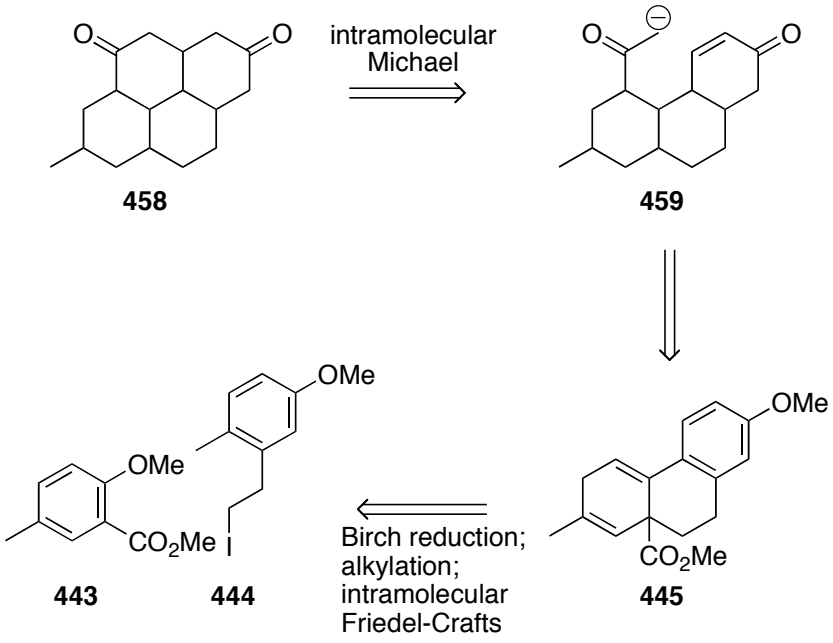
Scheme 6.3 *Reagents and conditions:* (a) i) Li, NH_3; ii) $BF_3.Et_2O$, 85%; (b) EtCOCl, $AlCl_3$, 75%; (c) NEt_3, $HOCH_2CH_2OH$, 70 ^oC, 4 days, 71% (4:3 mixture R = CH_2CH_2OH to R = Me); (d) $NaBH_4$, $CeCl_3$; (e) NaHMDS, CS_2, MeI; (f) *n*-Bu_3SnH, AIBN, 47% 3 steps; (g) *n*-PrSNa, 87%; (h) $(COCl)_2$; (i) NaN_3; (j) PhMe, 110 ^oC; (k) concd HCl, 39% 4 steps.

When the two previous syntheses are analysed retrosynthetically, it can be seen that they have little in common. In Corey's synthesis, the key ring forming steps are two IMDA reactions where the double bond formed in the first IMDA acts as the dienophile in the second IMDA reaction (Scheme 6.4). While this approach is very elegant, several manipulations are carried out between the two Diels-Alder reactions.



Scheme 6.4 Key disconnections in Corey's synthesis

In Mander's synthesis, the key ring forming events are: (a) a Birch reduction with in situ alkylation and cyclisation and, (b) an intramolecular Michael reaction (Scheme 6.5).



Scheme 6.5 Key disconnections in Mander's synthesis

Both of these elegant syntheses are landmark achievements. Nevertheless, they involve long linear sequences of either 26 steps (Corey) or 40 steps (Mander). A short synthetic route to a cycloamphilectane natural product would represent a significant new contribution to this area.

6.1.2 Cembrene-Derived Carbon Skeletons

The defence secretions of soldier termites from the Nasutitermitinae subfamily have been found to contain a variety of structurally complex diterpenes.[191] Many of these are based on the kempane **460** or rippertane **461** skeletons, which are formed from a common precursor, cembrene A **462** (Figure 6.3).

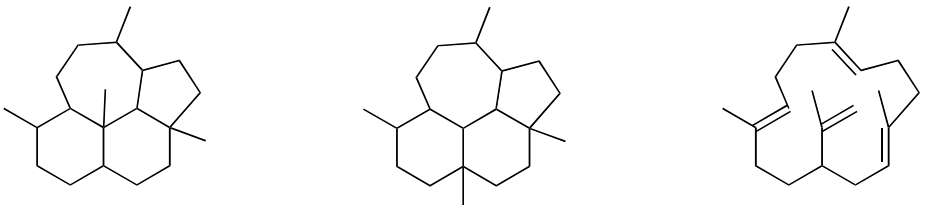


Figure 6.3 The kempane and rippertane skeletons

After the isolation of these unusual diterpenes, the defence secretions of other South American termites were investigated[192] and several other related tetracyclic natural products were isolated (Figure 6.4).

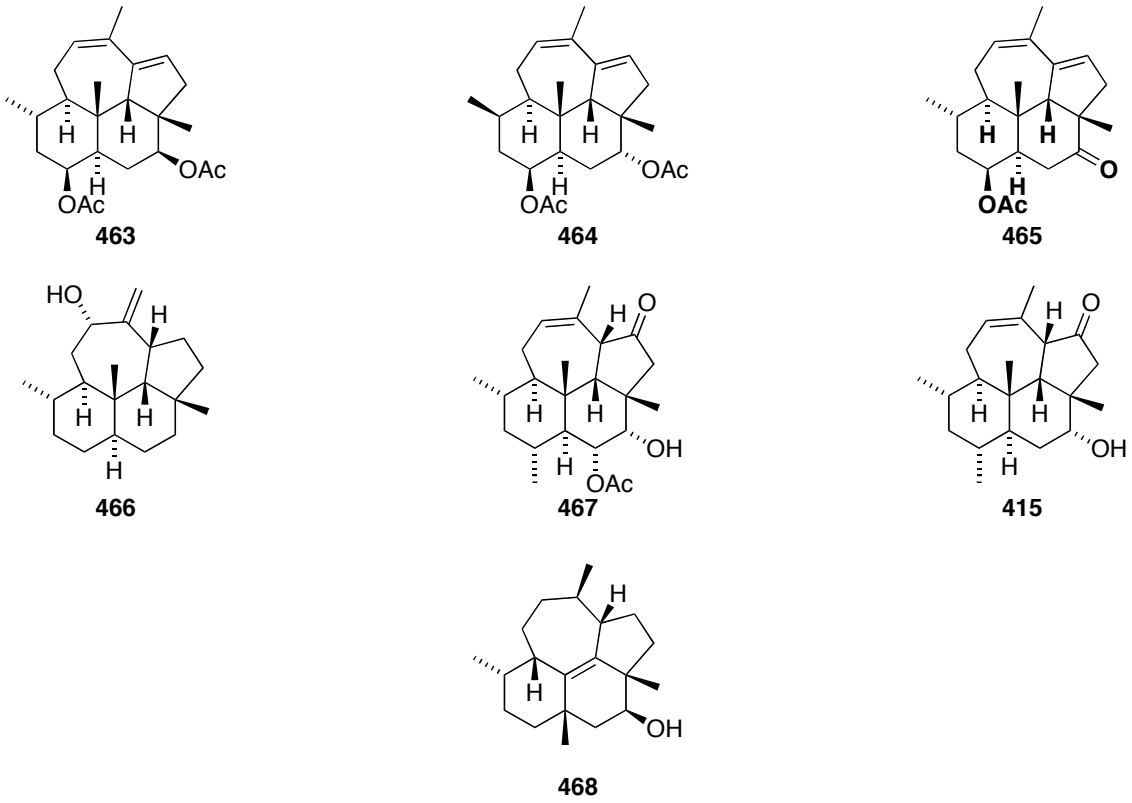
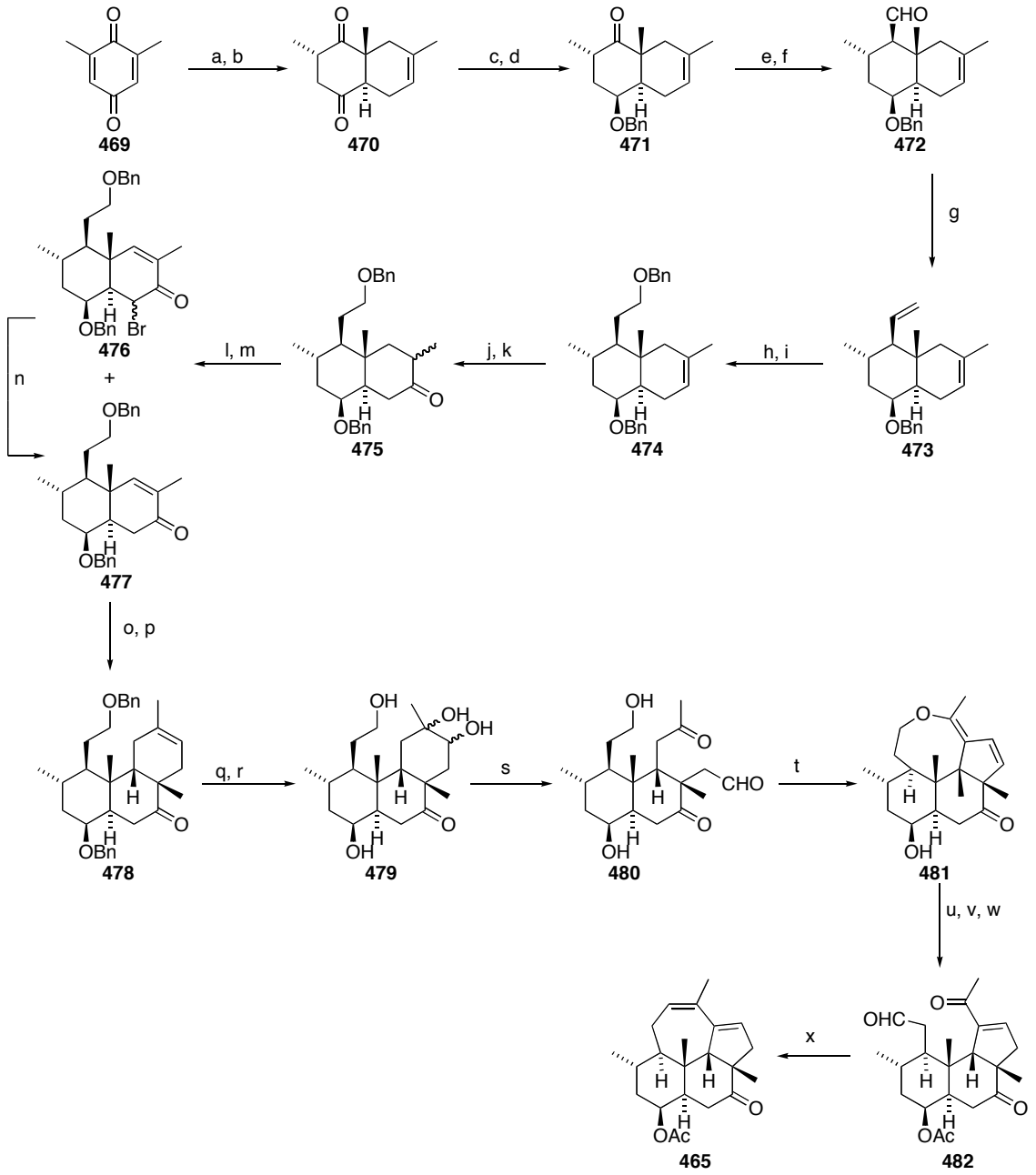


Figure 6.4 Kempane and rippertane natural products

Several groups have attempted the synthesis of kempane diterpenes, with varying levels of success.[193-203] In 1991, Dauben reported the total synthesis racemic kempene-2 **465** (Scheme 6.6). This remains the only successful synthesis of a natural product from this class.[193] The first step of the synthesis involved a Lewis-acid catalysed Diels-Alder reaction between 2,6-dimethylbenzoquinone and isoprene to give a mixture of regioisomeric products. Reduction of the quinone double bond under equilibrating conditions gave **470** in 13% yield. The less hindered carbonyl group was reduced with L-Selectride to give the axial alcohol as a single isomer. After protection of the alcohol as the benzyl ether **471**, the remaining carbonyl was converted into a vinyl group **473** by a 3 step sequence. Selective hydroboration followed by oxidative work-up gave the primary alcohol which was then converted into the benzyl ether **474**. Hydroboration followed by oxidation gave ketone **475** as a mixture of diastereomers. The mixture was treated with pyridinium bromide perbromide, with the resulting bromides being subjected to elimination conditions to give **477**, a key intermediate in the synthesis.

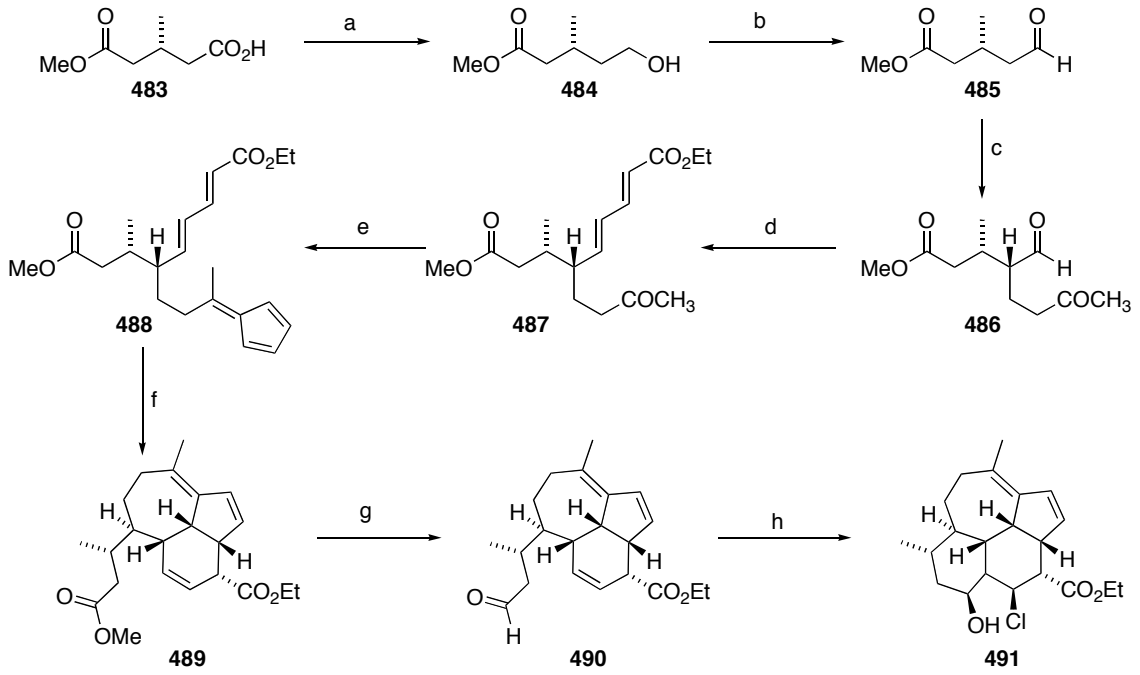
A second Lewis-acid catalysed Diels-Alder reaction with isoprene gave **478** as the major cycloadduct. Dihydroxylation and removal of the benzyl protecting groups gave the tetrol **479** as a mixture of isomers. Glycol cleavage and treatment with acid yielded the dienol ether **481**. Acetylation, hydrolysis of the enol ether and oxidation of the primary alcohol gave enone aldehyde **482**.

The final step of the synthesis was Ti^0-induced McMurry coupling to form the tetracyclic skeleton, yielding (±)-kempene-2 **465** in 24 steps and 0.04% overall yield.



Scheme 6.6 *Reagents and conditions:* (a) $BF_3.Et_2O$, isoprene, 96 h; (b) Zn, HOAc, reflux, 18 h, 13% over 2 steps; (c) L-Selectride, THF, -78 °C then 0 °C, NaOH, H_2O_2, 82%; (d) NaH, BnBr, Bu_4NI, THF, 72 h, 83%; (e) CH_3OCH_2TMS, *sec*-BuLi, THF, -60 °C to -20 °C, 1 h, then **471**, -40 °C, 30 min; (f) HCO_2H, EtOH, 73% 2 steps; (g) CH_3PPh_3I, KO*t*Bu, THF, 0 °C, 1 h, then **472**, rt, 18 h, 78%; (h) $HB(sia)_2$, THF, 40 °C, 72 h then 0 °C, NaOH, H_2O_2, 82%; (i) NaH, BnBr, Bu_4NI, THF, 48 h, 98%; (j) BH_3.THF, 0 °C, 6 h then NaOH, H_2O_2, 77%; (k) $(COCl)_2$, DMSO, CH_2Cl_2, 90%; (l) py.HBr.Br_2, THF, -78 °C, 30 min; (m) LiBr, Li_2CO_3, DMF, 120 °C, 16 h, 60% of **477** and 23% of **476**; (n) Bu_3SnH, AIBN, C_6H_6, reflux, 24 h, 53%; (o) $EtAlCl_2$, PhMe, 5 min then isoprene, 80 °C, sealed tube, 24 h, 66%; (p) HPLC; (q) Cat OsO_4, $(CH_3)_2CO/H_2O$, 95%; (r) H_2, 10% Pd/C, AcOEt, 88%; (s) $NaIO_4$, dioxane/H_2O, 81% (t) Cat TsOH.H_2O, C_6H_6, 80 °C, 2h, 61%; (u) Ac_2O, pyridine, DMAP, 66%; (v) HCl, EtOH, 80 °C, 68%; (w) PCC/Al_2O_3, hexane/CH_2Cl_2, 57%; (x) $TiCl_3(DME)_{1.5}$, Zn-Cu, DME, reflux, 4h, then **482** added over 12 h, 2 h reflux, 32%.

While other groups have successfully synthesised the tetracyclic kempane/rippertane framework[194,195,203-206] the synthesis of most relevance to this study involves an IMDA reaction of a fulvene (Scheme 6.7).[201] Selective reduction of **483** followed by oxidation with PCC gave aldehyde **485**. Stereoselective Michael addition of **485** and methyl vinyl ketone gave **486** in 73% yield as a 3:1 diastereomer ratio. Horner-Wadsworth-Emmons Olefination, followed by condensation of the ketone with cyclopentadiene gave fulvene **488**. Heating **488** in toluene resulted in an IMDA reaction to give the tricyclic product **489**. Reduction of the methyl ester **489** to the alcohol, followed by oxidation gave the aldehyde **490**. Finally, Prins reaction of **490** with $TiCl_2(i\text{-}OPr)_2$ gave the tetracyclic skeleton **491**.



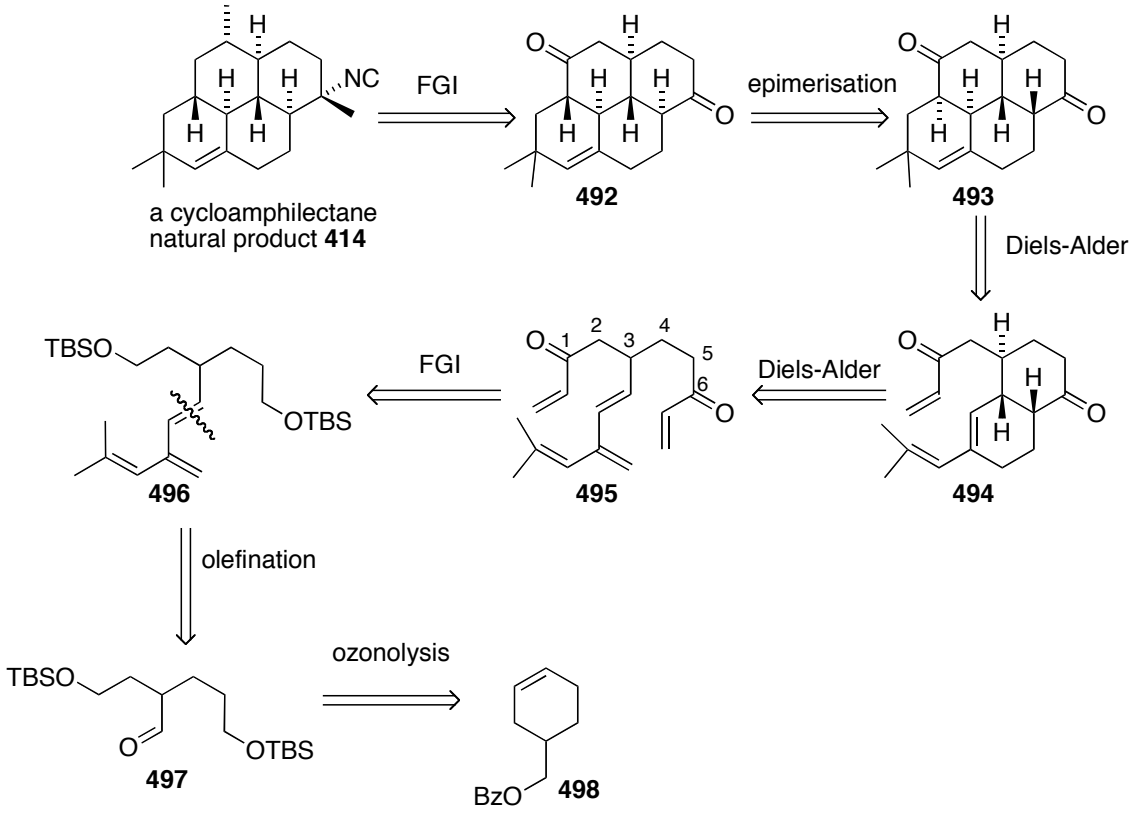
Scheme 6.7 *Reagents and conditions:* (a) BH_3-SMe_2, 84%; (b) PCC, 81%; (c) MVK, THF, HFIP, (R)-2-Benzhydryipyrolidine, 73%; (d) LDA, THF, $(EtO)_2P(O)CH_2CH{=}CHCO_2Et$, 69%; (e) cyclopentadiene, pyrrolidine, MeOH, 85%; (f) PhMe, 110 ^oC, 71%; (g) i) DIBALH, THF; ii) DMP, CH_2Cl_2, 71%; (h) $TiCl_2(i\text{-}OPr)_2$, CH_2Cl_2, 82%.

The tetracyclic framework **491** was synthesised though a concise and impressive sequence that involves just eight linear steps.

6.2 Aims

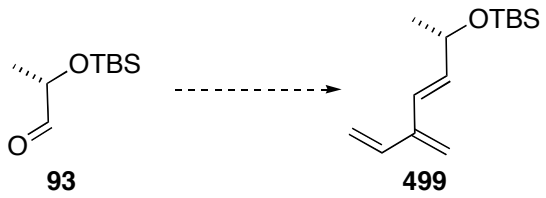
We have demonstrated that diene-transmissive Diels-Alder (DTDA) sequences involving *internally*-substituted [3]dendralenes are useful for the rapid assembly of fused tetracyclic frameworks common to many natural products (Chapter 4). We now aim to synthesise the tetracyclic cycloamphilectane and kempane frameworks through DTDA sequences involving a *terminally*-substituted [3]dendralenes (Scheme 6.1).

We aim to demonstrate that a DTDA sequence can be used for the rapid construction of the cycloamphilectane framework. It is envisaged that the all-*trans* stereochemistry in the target could be obtained via epimerisation of the tetracyclic adduct **493** (Scheme 6.8). The use of internally activated dienophiles would result in carbonyl groups being in ideal locations for both the epimerisations and the other functional group interconversions. So, an efficient route to the DTDA precursor **494** is required. The [3]dendralene moiety will be installed through an olefination reaction while the 1,6-dioxygenation of the DTDA precursor invokes ozonolysis of a cyclohexene as the first step.



Scheme 6.8 Retrosynthesis of a cycloamphilectane natural product

A reliable method for the synthesis of *terminally*-substituted [3]dendralenes must be developed. Since chiral aldehyde **93** was readily available from earlier studies (Chapter 2, 3 and 4), model studies will be directed towards the synthesis of simple chiral [3]dendralene **499** (Scheme 6.9).

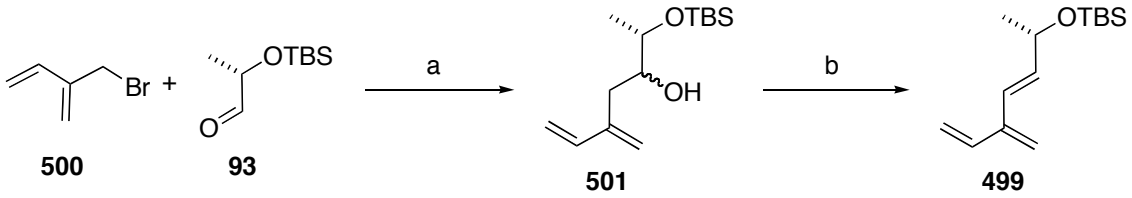


Scheme 6.9 A simple chiral *terminally*-substituted [3]dendralene

6.3 Results and Discussion

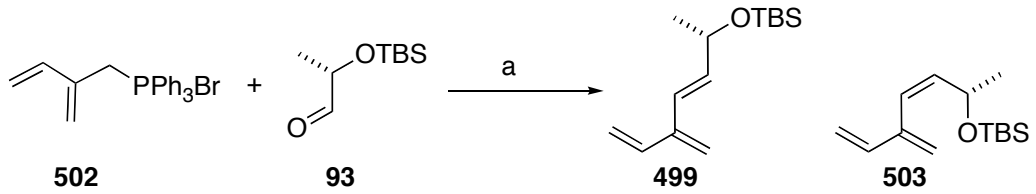
6.3.1 Synthesis of a Terminally-Substituted [3]Dendralene

We initially attempted the synthesis of the *terminally*-substituted [3]dendralene **499** by applying a similar method to that developed by Fallis for the synthesis of internally substituted [3]dendralenes (Scheme 4.9).[122] Thus, the known bromide **500**, generated in three steps from isoprene,[207] was used in an indium-mediated coupling[208] with aldehyde **93** (Scheme 6.10). The resulting mixture of diastereomeric alcohols **501** were dehydrated under Mitsunobu conditions to give the [3]dendralene **499** in a disappointing yield of 26%. The overall low yield for this sequence prompted us to investigate an alternative path.



Scheme 6.10 *Reagents and conditions:* a) In (1.1 equiv), DMF, rt, 18 h, 58%; b) PPh_3 (2.0 equiv), DEAD (2.0 equiv), THF, reflux, 5 h, 26%.

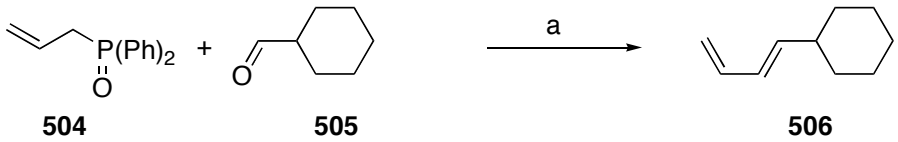
The phosphonium salt **502**,[209] synthesised from the bromide **500**, was used in a Wittig reaction with aldehyde **93** (Scheme 6.11). Several attempts were made to optimise this reaction by varying the solvent, temperature and time but the best result obtained was a 37% yield of a mixture of *E/Z* isomers of **499** and **503**.



502 **93** **499** **503**

Scheme 6.11 *Reagents and conditions:* a) *n*-BuLi (1.0 equiv), THF, -78 ^{o}C – rt, 1.5 h, 37%.

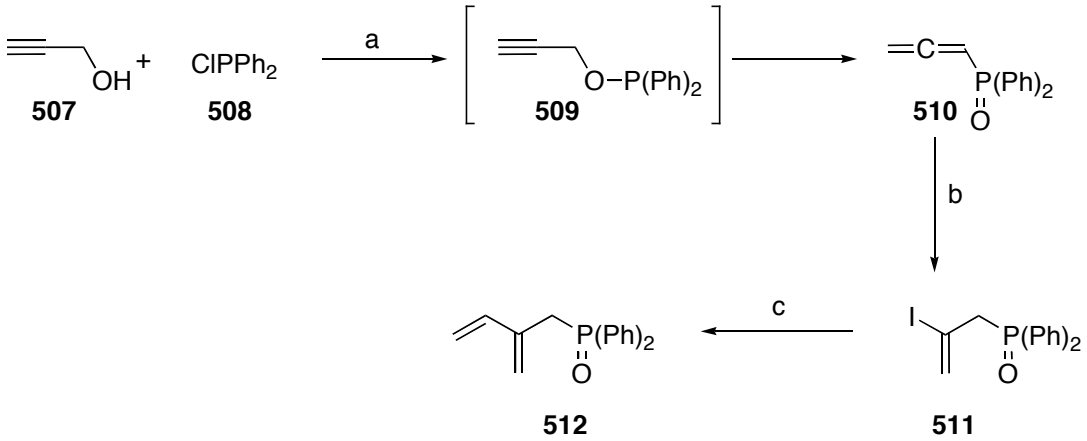
Yamamoto has reported that allyldiphenylphosphine oxide **504** undergoes highly *E*-selective Horner-Emmons type couplings with several different aldehydes (Scheme 6.12).[210,211]



504 **505** **506**

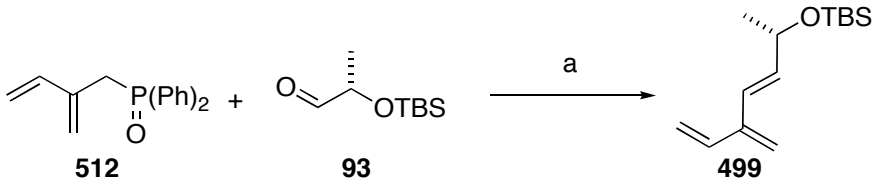
Scheme 6.12 *Reagents and conditions:* a) *n*-BuLi (1.0 equiv), HMPA (2.0 equiv), THF, -78 ^{o}C – rt, 4 h, 82% (*E*/*Z* 90:10).

It was anticipated that a vinyl substituent (compare **504** Scheme 6.12 with **512** Scheme 6.13) would not alter the reactivity of the phosphine oxide. Thus, the phosphine oxide **512** was synthesised according to Scheme 6.13. Propargyl alcohol was reacted with diphenylphosphine chloride according to the procedure of Brandsma.[212] The intermediate alkyne **509** undergoes a spontaneous rearrangement to give the allene **510**. Reaction with sodium iodide in acetic acid gave the iodide **511**.[213] Stille reaction between iodide **511** and tributyl(vinyl)tin gave the desired phosphine oxide **512** in good yield. Negishi and Suzuki reactions were also attempted without success, presumably on account of the base sensitive nature of the substrate.



Scheme 6.13 *Reagents and conditions:* a) NEt_3 (1.1 equiv), CH_2Cl_2, -80 °C, 5 min, 100%; b) LiI, AcOH, 100 °C, 18 h, 81%; c) tributyl(vinyl)tin (1.2 equiv), $Pd(CH_3CN)_2Cl_2$ (0.05 equiv), DMF, rt, 3 h, 72%.

Gratifyingly, reaction between phosphine oxide **512** and aldehyde **93** yielded the chiral [3]dendralene **499** as a single isomer in acceptable yield (Scheme 6.14). With a reliable method for the preparation of *terminally*-substituted dendralenes now available, we turned our attention to the synthesis of a DTDA precursor.

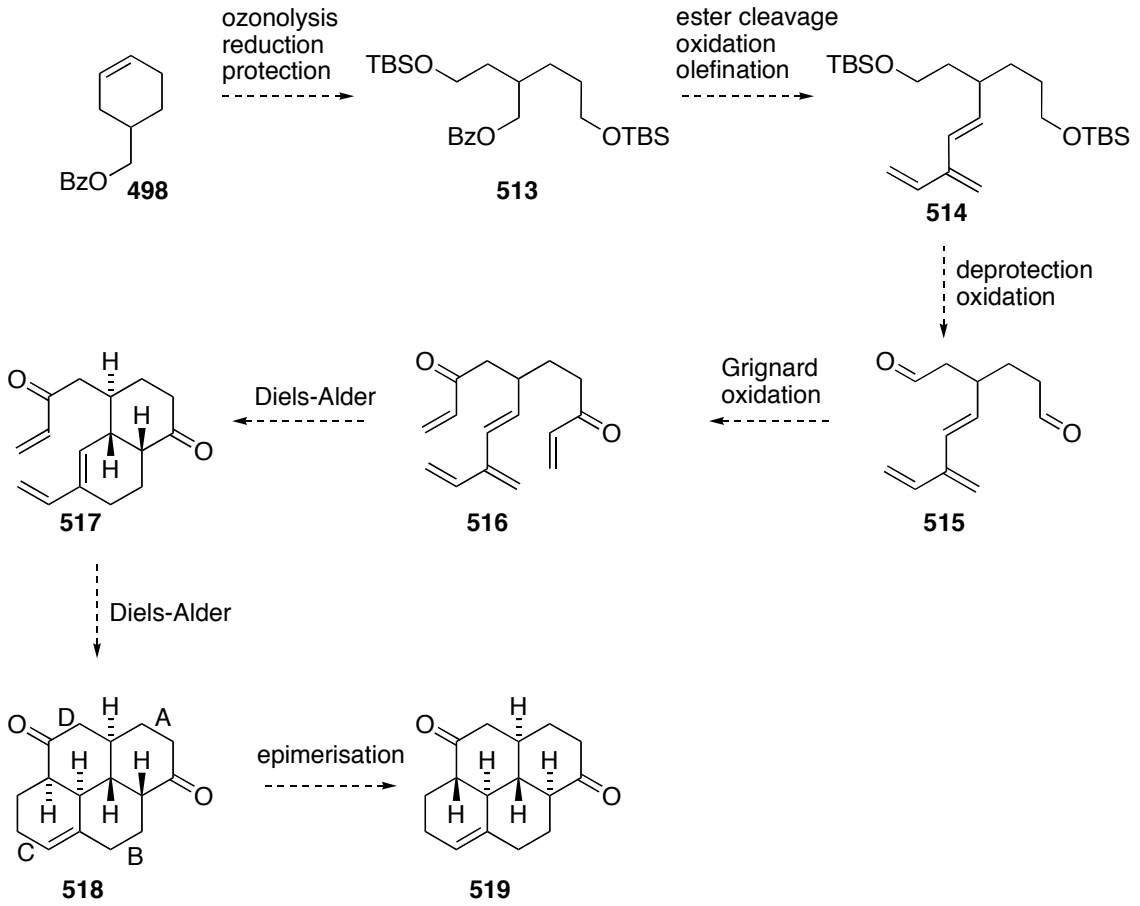


Scheme 6.14 *Reagents and conditions:* a) nBuLi (1.2 equiv), HMPA (2.4 equiv), THF, -78 °C – rt, 4 h, 55%.

6.3.2 Synthesis of the Tetracyclic Framework

6.3.2.1 Synthetic Strategy

The pseudo-symmetrical nature of the DTDA precursor lends itself to an efficient two directional[214] synthesis (Scheme 6.15). Ozonolysis of (cyclohex-3-enyl)methyl benzoate **498** with *in situ* reduction should give a 1,6-diol. Protection of the diol followed by ester cleavage and oxidation is expected to give the aldehyde. After the dendralene is installed through the Horner-Emmons-type Olefination, the two dienophile units can be constructed. We aim to do this through a four step sequence involving deprotection, oxidation, Grignard reaction and oxidation.

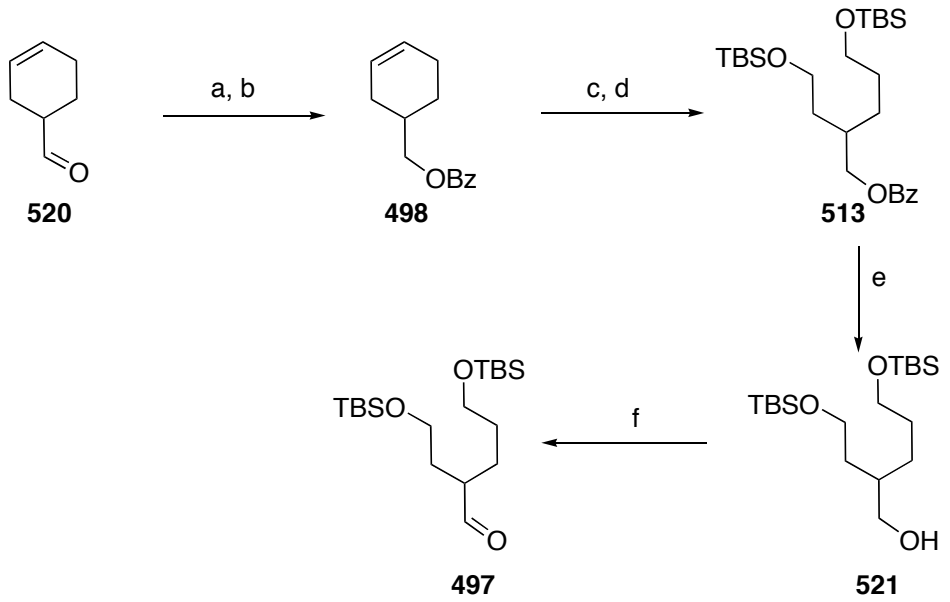


Scheme 6.15 Synthetic strategy

It is anticipated that the first Diels-Alder reaction (**516** to **517**, Scheme 6.15) would occur *via* an *endo* transition state to give a *cis* ring junction,[189] with the dienophile-containing side chain in an equatorial position. The second Diels-Alder reaction is also expected to proceed *via* an *endo* transtion state, with the dienophile approaching the diene from the less hindered π-diasteroface, resulting in a *trans* fusion between the D and B rings (**518**, Scheme 6.15). Base-promoted epimerisation should give the most thermodynamically stable all *trans* ring system required for the natural product.

*6.3.2.2 Synthesis of aldehyde **497***

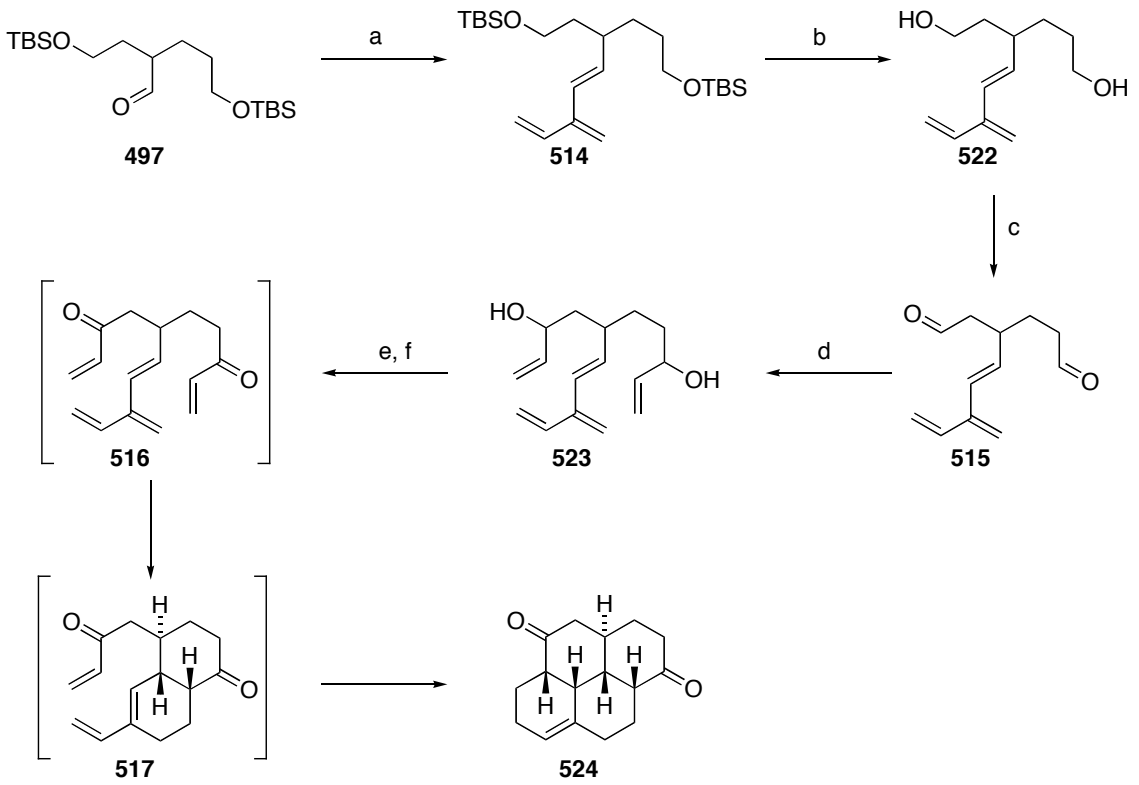
1,2,3,6-Tetrahydrobenzaldehyde **520** was reduced with lithium aluminium hydride and the subsequent alcohol was protected as the benzoate to give **498** in high yield (Scheme 6.16). Ozonolysis and in situ reduction with sodium borahydride followed by protection of the resulting diol gave the differentially protected triol **513**. Removal of the benzoate protecting group was achieved with sodium hydroxide in methanol. Finally, Swern oxidation gave the required aldehyde **497**.



Scheme 6.16 *Reagents and conditions:* a) $LiAlH_4$ (1.2 equiv), Et_2O, 0 °C, 1 h, 100%; b) NEt_3 (1.2 equiv), BzCl (1.2 equiv), CH_2Cl_2, rt, 18 h, 84%; c) O_3, $NaHCO_3$, $NaBH_4$, CH_2Cl_2, MeOH; d) imidazole (3.0 equiv), TBSCl (2.5 equiv), DMF, 1.5 h, 80% over 2 steps; e) NaOH, MeOH, 18 h, rt, 77%; f) $(COCl)_2$ (1.2 equiv), DMSO (2.0 equiv), NEt_3 (4.0 equiv), CH_2Cl_2, -78 °C – rt, 1.5 h, 76%.

6.3.2.3 DTDA sequence

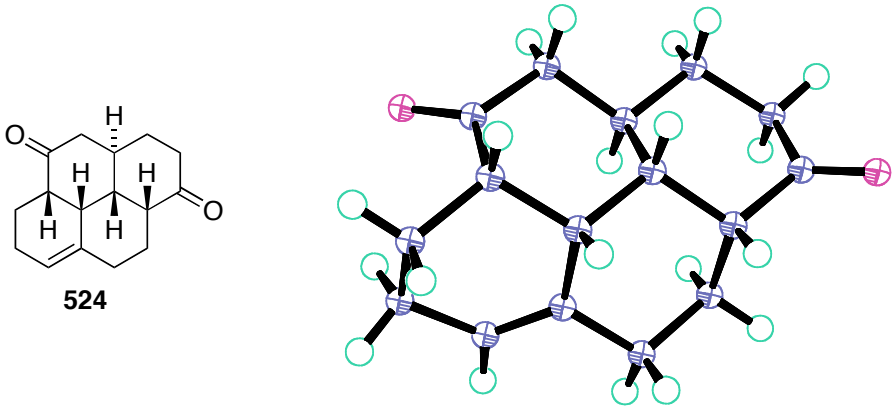
To our delight, the Horner-Emmons-type reaction between aldehyde **497** and phosphine oxide **512** resulted in an 86% yield of the *terminally*-substituted [3]dendralene **514** (Scheme 6.17). The *Z*-isomer of the dendralene was not detected. Removal of the silyl protecting groups with tetrabutyl ammonium flouride gave the diol **522**. Oxidation to the dialdehyde **515** occurred under Swern reaction conditions. The dialdehyde **515** was not purified as it was feared it would not be stable towards column chromatography. Instead, the crude dialdehyde **515** was treated with an excess of vinyl magnesium bromide to give the diol **523**. The crude diol **523** was then oxidised under Swern conditions to give the DTDA precursor **516**. This product was not isolated and instead, the reaction was worked up in the usual manner and a small amount of triflouroacetic acid was added. After 48 h at room temperature the reaction mixture was concentrated *in vacuo*. ^{1}H NMR analysis of the crude product revealed that there was one major product from the reaction. High resolution mass spectrometry suggested that the desired product had in fact been formed.



Scheme 6.17 *Reagents and conditions:* a) **512** (1.1 equiv), *n*-BuLi (1.2 equiv), HMPA (2.4 equiv), THF, -78 °C – rt, 86%; b) TBAF (3.0 equiv), THF, rt, 2 h, 76%; c) $(COCl)_2$ (2.4 equiv), DMSO (4.0 equiv), NEt_3 (8.0 equiv), CH_2Cl_2, -78 °C – rt, 1.5 h; d) vinyl magnesiumbromide (1.0 M, 5.1 equiv), THF, 1 h; e) $(COCl)_2$ (2.4 equiv), DMSO (4.0 equiv), NEt_3 (8.0 equiv), CH_2Cl_2, -78 °C – rt, 1.5 h; f) TFA (5 equiv), 48 h, 3% over 4 steps.

The tetracycle **524** was purified by semi-preprative HPLC to give a small amount of pure material, representing a 3% yield from the diol **523**. Optimisation of the yield was deferred until the stereochemistry of the product could be determined. The 800 MHz ^{1}H NMR spectrum for **524** is very complicated, with 19 signals appearing between 1.2 and 2.8 ppm and only one alkenic signal. Thus, NMR techniques could not be used to determine the stereochemistry.

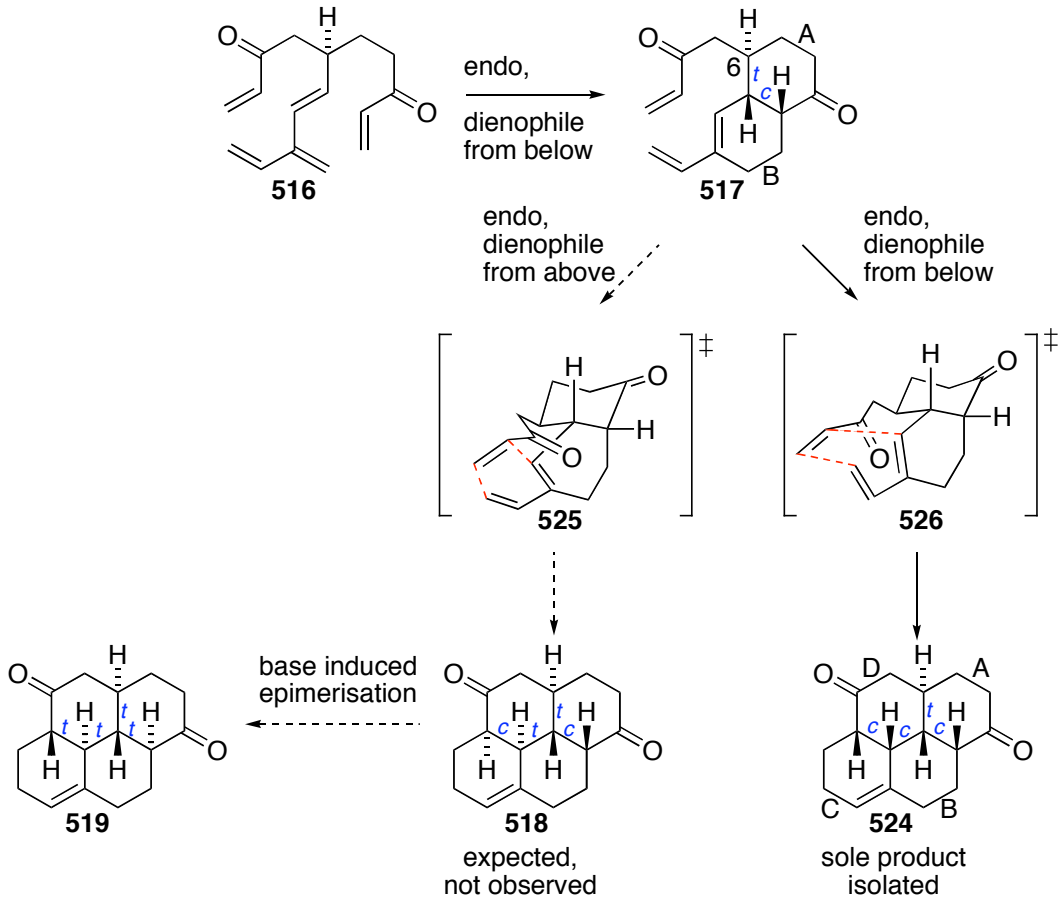
Single crystal X-ray analysis revealed the stereochemistry of the tetracycle **524** is as depicted in Figure 6.5.



524

Figure 6.5 Thermal ellipsoid diagram of **524**. Ellipsoids show 30% probability levels.

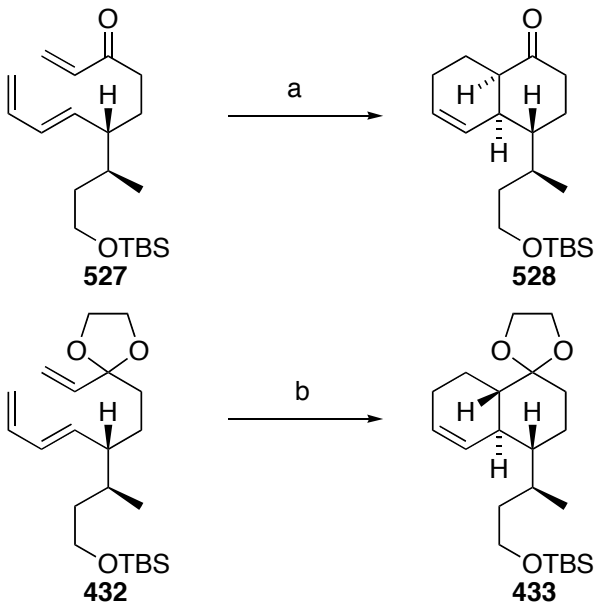
Disappointingly, this is not the stereochemistry required for the synthesis of the target natural product **414** (see Scheme 6.1). As predicted, the first Diels-Alder reaction proceeds via an *endo* transition state with the dienophile approaching the diene from below. The second Diels-Alder reaction also proceeds via an *endo* transition state with the dienophile once again approaching the diene from below (**526**, Scheme 6.18). This sequence results in a fixed *cis* fusion between rings B and D (**524**, Scheme 6.18). This result was unexpected due to the stereochemistry at C6 relative to that at the AB ring junction (**517**, Scheme 6.18). The side-chain containing the dienophile is pointing up, therefore it was expected to approach the diene from above. Inspection of a Drieding model of the bicyclic intermediate, however, suggests that the dienophile can only approach the diene from below. In order to get the required *trans* ring fusion, the second Diels-Alder reaction would have to proceed via an *endo* transition state with the dienophile approaching the diene from above.



Scheme 6.18 Stereoselectivity in the DTDA sequence

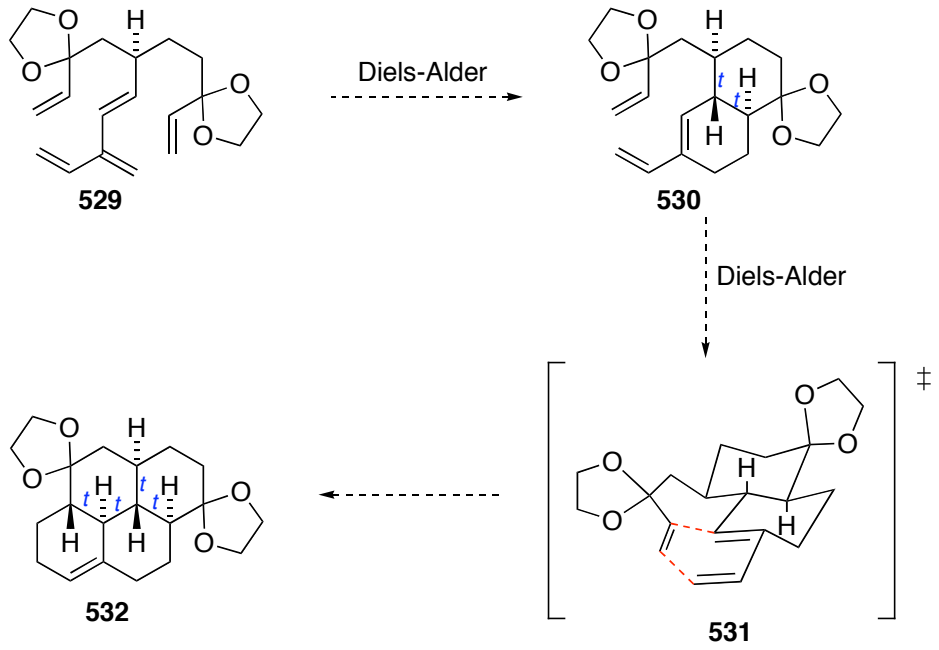
6.4 Conclusions and Future Work

The tetracycle **524**, possessing the carbon skeleton common to several cycloamphilectane natural products, was obtained through a short synthetic sequence of 11 steps. As the tetracycle with the required stereochemistry could not be obtained, an alternative approach must be devised. In his synthesis of 7,20-diisocyanoadociane **417,** Corey noted that the intramolecular Diels-Alder reaction of ketone **527** proceeded rapidly at room temperature or below to give the *cis* fused adduct **528** resulting from an *endo* mode of cyclisation (Scheme 6.19).[189] In contrast, the corresponding ketal **432** undergoes a Diels-Alder reaction under more forcing conditions to give the *trans* fused adduct **433** resulting from the *exo* mode of cyclisation. The reversal in selectivity is thought to be brought about by the ketal unit, which disfavours the *endo* transition state relative to the *exo* transition state.



Scheme 6.19 *Reagents and conditions:* a) rt; b) PhMe, 185 ^{o}C, 36 h, 54%.

It is envisaged that we could take advantage of this reversal of selectivity by synthesising the DTDA precursor **529** (Scheme 6.20). Cyclisation should lead first to the *trans*-fused bicylic intermediate **530**. Models suggest that the second Diels-Alder reaction should proceed through an *exo*-transition state with the dienophile approaching the diene from above, as depicted in **531**. This would give the tetracycle **532**, possessing the same relative stereochemistry as that observed in the natural products of interest.



Scheme 6.20 Proposed synthesis of a tetracycle with the correct relative stereochemistry.

Once a tetracycle with the correct relative stereochemistry is synthesised, simple functional group interconversions would lead to natural products of the cycloamphilectane class. Studies into the possibility of controlling the order of the cycloadditions in the DTDA sequence, to gain access to the kempane class of natural products, are currently underway.

7 Experimental

7.1 General Methods

NMR spectra were recorded at 298K using a Varian Unity INOVA 500 MHz, Bruker DPX/DRX 400 Mhz or a Varian Unity INOVA 300 MHz spectrometer. Residual acetone (δ2.04 ppm), benzene (δ7.15 ppm), chloroform (δ7.26 ppm), and methanol (δ3.31 ppm) were used as internal references for ^{1}H NMR spectra measured in these solvents. Residual acetone (δ29.8 ppm , 206.8 ppm), benzene (δ128.1 ppm), chloroform (δ77.1 ppm), and methanol (δ49.0 ppm) were used as internal references for ^{13}C NMR spectra. Assignment of proton signals was assisted by ^{1}H–^{1}H COSY and NOESY experiments when necessary. IR spectra were recorded on a Perkin–Elmer 1600 F.T.I.R,, a Perkin–Elmer Spectrum One spectrometer or a Perkin-Elmer Paragon 1000 FT-IR spectometer as neat films on NaCl plates for oils or as KBr pellets for solid products. Low resolution mass spectra were recorded on a Finnigan PolarisQ ion trap mass spectrometer using electron impact (EI) ionisation mode at 40 or 70 eV. Low resolution electrospray ionisation spectra were recorded on a Finnigan LCQ ion trap mass spectrometer. High resolution mass spectra were recorded on a VG Autospec mass spectrometer operating at 70 eV. High resolution electrospray ionisation spectra were recorded on a Bruker BioApex FTICR with an Analytica ESI source, operating at 4.7 T. Melting points were measured on a Reichert melting point stage and are uncorrected. Optical rotations were measured with an Optical Activity Polaar 2001, Perkin Elmer 241 optical polarimeter or an Optical Activity Limited AA-100 polarimeter. HPLC was performed using a Shimadzu LC-10ADVP pump with a Shimadzu SIL-10ADVP autoinjector or a Shimadzu LC-8A preprative pump monitored by a Shimadzu SPD-PAVP UV detector at $\lambda = 254$ nm and a Shimadzu RID-10A refractive index detector or a Waters 510EF chromatograph pump and Waters U6K injector monitored by an Waters Lambda-Max 481 UV spectrophotometer at $\lambda = 254$ nm and an Erma ERC-7512 refractive index detector or a Waters 510EF chromatograph pump and Waters U6K injector monitored by an ISCO 226 UV spectrophotometer at $\lambda = 254$ nm and a Waters R403 refractive index detector. GC measurements were recorded on an Agilent 6850 gas chromatograph with a split/splitless capillary inlet and FID detector or GC measurements were recorded on a Hewlett Packard 5890A gas chromatograph with a split/splitless capillary inlet and FID detector. GC data was processed using Hewlett Packard ChemStation software. Analytical TLC was performed with Merck silica gel

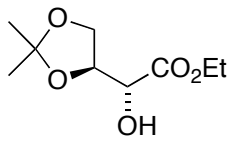
plates, precoated with silica gel 60 F254 (0.2 mm). Flash chromatography employed Merck Kiesegel 60 (230–400 mesh) silica gel.

Reactions were conducted under a positive pressure of dry argon or nitrogen. Benzene, diethyl ether, toluene and tetrahydrofuran were dried over sodium wire and distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Chlorobenzene was purified by the method of Perrin and Armarego.[215] Commercially available chemicals were purified by standard procedures or used as purchased.

7.2 Chapter 2

7.2.1 Chiral Dienols

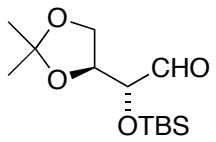
Ethyl (2*R*, 3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate **84**



84

L-ascorbic acid (100g, 0.57 mol) was protected based on the method of Jung and Shaw[87] to give 5,6-*O*-isopropylidene-L-ascorbic acid (93.6 g, 0.43 mol, 76%) as a white crystalline solid. Oxidative cleavage of 5,6-*O*-isopropylidene-L-ascorbic (93.6 g, 0.43 mol) acid and esterification of the resulting potassium salt was based on the method of Abushanab *et al*[88,89] to give ethyl (2*R*, 3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate **84** (69.0 g, 0.33 mol, 78%) as a yellow oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

(2*R*,3*S*)-3,4-*O*-Isopropylidene-2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxybutanal **85**

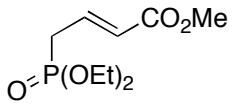


85

The TBS ether of ethyl (2*R*,3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate **84** (10.2 g, 50 mmol) was synthesised according to the procedure of Lilly.[216,217] Distillation gave ethyl (2*R*,3*S*)-3,4-*O*-isopropylidene-2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxybutanoate (10.8 g, 30 mmol, 68%) as a colourless oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

Reduction of ethyl (2*R*,3*S*)-3,4-*O*-isopropylidene-2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxybutanoate (10.8 g, 34 mmol) was carried out according to Lilly's procedure Distillation gave (2*R*,3*S*)-3,4-*O*-Isopropylidene-2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihy-droxybutanal **85** (7.97 g, 29 mmol, 86%) as a colourless oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

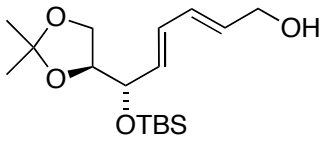
Triethyl phoshonocrotonate **95**



95

This product was formed following literature procedure.[92] Methyl 4-bromocrotonate (11.28 g, 63 mmol, 1.0 equiv) was added to triethyl phosphite at such a rate that the temperature remained at 130 ^{o}C. The mixture was stirred at this temperature for 1 h 25 min. The mixture was cooled to RT and unreacted triethyl phosphite was removed under reduced pressure to give triethyl phoshonocrotonate **95** (14.88 g, 63 mmol, 100%) as a yellow oil. ^{1}H NMR data for this compound was consistent with that reported in the literature.[92]

(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-Isopropylidene-3-((*tert*-butyldimethylsilyl)oxy)-4,6-octadien-1,2,8-triol **86**



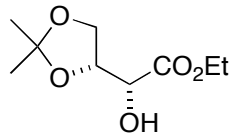
86

To a stirred solution of lithium hexamethyldisilazide, prepared from hexamethyldisilazane (2.28 mL, 19.0 mmol, 1.8 equiv) and *n*-butyllithium (10.34 mL of a 1.66 M solution in hexanes, 15.5 mmol, 1.47 equiv) in tetrahydrofuran (20 mL) at –78 °C under nitrogen, was added phosphonate **95** (3.49 g, 14.8 mmol, 1.4 equiv) in tetrahydrofuran(10 mL). The reaction mixture was warmed to –40 °C and a solution of (2*R*,3*S*)-3,4-*O*-isopropylidene-2-((*tert*-butyl-dimethylsilyl)oxy)-3,4-dihydroxybutanal **85** (2.89g, 10.6 mmol, 1.0 equiv) in tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was warmed to rt and stirring was continued for 1.5 h. The mixture was concentrated *in vacuo* and the residue was portioned between water (100 mL) and ether (3 x 20 mL). The combined organic layers were washed with 1 M HCl (40 mL), dried and concentrated *in vacuo*. Chromatography of the crude product on silica

(hexanes/ethyl acetate 93:7) gave ethyl (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)-oxy)-7,8-dihydroxy-2,4-octadienoate (2.60 g, 5.2 mmol, 49%) as a colourless oil.

To a stirred solution of ethyl (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadienoate (853 mg, 2.4 mmol, 1.0 equiv) in diethyl ether (5 mL) at 0 °C under nitrogen was added DIBAL-H (1.0 M solution in hexanes, 5.10 mL, 5.10 mmol, 2.1 equiv). After 1 h 45 minutes the reaction mixture was added dropwise, *via* cannula, to a stirred solution of sodium potassium tartrate tetrahydrate in ice/water (50 mL) and dichloromethane (50 mL). The emulsion was stirred at room temperture for 2 h. After separation of the phases the aqueous layer was extracted with ether (3 x 20 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (20 mL), brine (20 mL), dried and concentrated *in vacuo*. Chromatography of the crude product on silica (hexanes/ethyl acetate 80:20) gave (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-((*tert*-butyldimethylsilyl)oxy)-4,6-octadien-1,2,8-triol **86** (724 mg, 2.2 mmol, 92%) as a colourless oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

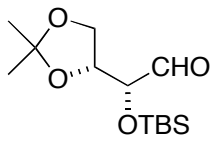
Ethyl (2*R*, 3*R*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate **87**



87

Isoascorbic acid was converted into the monoacetonide before oxidative cleavage with potassium carbonate and hydrogen peroxide in water. The resulting potassium carboxylate was treated with ethyl iodide to give ethyl (2*R*, 3*R*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate **87** following the method of Abushanab *et al.*[88,89]

(2*R*,3*R*)-3,4-*O*-Isopropylidene-2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxybutanal **88**

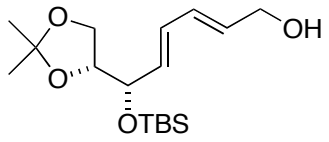


88

To a stirred solution of **87** (4.5 g, 22.2 mmol, 1.0 equiv) in DMF (5mL) at 0°C under argon was added imidazole (1.82 g, 26.7 mmol, 1.2 equiv) and *tert*-butyldimethylsilyl chloride (3.69 g, 24.5 mmol, 1.1 equiv). On completion of the addition the resulting solution was allowed to warm to rt and stirred for 30min. The reaction mixture was partitioned between water (50mL) and ethyl acetate (3 x 50mL) and the combined extracts were dried, filtered and evaporated to give the crude product as a yellow oil. Column chromatography gave ethyl (2*R*,3*R*)-3,4-*O*-isopropylidene-2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxybutanoate (6.44 g, 20.2 mmol, 91 %) as a colourless oil that was used directly in the next step.

To a stirred solution of ethyl (2*R*,3*R*)-3,4-*O*-isopropylidene-2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxybutanoate (5.86 g, 18.4 mmol, 1.0 equiv) in dichloromethane (50 mL) at -98 °C under nitrogen was added DIBAL-H (1.0 M in hexanes, 27.6 mmol, 27.6 mL, 1.5 equiv) dropwise over 45 minutes. The reaction mixture was stirred at this temperature for a further 15 minutes before being quenched with 2 % aqueous sodium hydroxide (15 mL). The reaction mixture was allowed to warm to room temperature and water (50 mL) and dichloromethane (50 mL) were added resulting in an emulsion, which was eliminated by the stepwise addition of sat. aqueous potassium sodium (+)-tartrate. The aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were dried and concentrated *in vacuo*. Chromatography of the crude product on silica (hexanes/ethyl acetate 95:5) gave (2*R*,3*R*)-3,4-*O*-isopropylidene-2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihy-droxybutanal **88** (2.94 g, 10.7 mmol, 58%) as a colourless oil. $[\alpha]_D^{25} = +15.79$ (c = 2.66, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.64 (1H, d, *J* = 1.8 Hz,), 4.22 (1H, dd, *J* = 6.1, 6.1 Hz), 4.04 (1H, dd, *J* = 6.3, 1.9 Hz), 4.00 (1H, dd, *J* = 8.3, 6.3 Hz), 3.90 (1H, dd, *J* = 8.3, 5.8 Hz), 1.41, 1.32 (6H, 2 x s), 0.89 (9H, s), 0.08, 0.07 (6H, 2 xs) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 201.5, 109.9, 78.0, 75.9, 65.9, 26.6, 25.7, 25.3, 18.3, -4.5, -4.9 ppm . IR (thin film): ν = 2955, 2931, 2858, 1737 cm^{-1}. EIMS (70 eV) *m/z* (%): 259 (10), 217 (40), 159 (80), 101 (95) 75 (100); HRMS: calcd for $C_{12}H_{23}O_4Si$ [M-CH_3]: 259.1366; found: 259.1363.

(2*R*,3*S*,4*E*,6*E*)-1,2-*O*-Isopropylidene-3-((*tert*-butyldimethylsilyl)oxy)-4,6-octadien-1,2,8-triol **89**



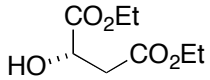
89

To a stirred solution of lithium hexamethyldisilazide, prepared from hexamethyldisilazane (3.05 mL, 14.0 mmol, 1.8 equiv) and *n*-butyllithium (6.92 mL of a 1.66 M solution in hexanes, 11.5 mmol, 1.47 equiv) in tetrahydrofuran (20 mL) at –78 °C under nitrogen, was added phosphonate **95** (2.58 g, 10.9 mmol, 1.4 equiv) in tetrahydrofuran (10 mL). The reaction mixture was warmed to –40 °C and a solution of (2*R*,3*R*)-3,4-*O*-isopropylidene-2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxybutanal **88** (2.14 g, 7.8 mmol, 1.0 equiv) in tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirring was continued for 1.5 h. The mixture was concentrated *in vacuo* and the residue was portioned between water (100 mL) and ether (3 x 20 mL). The combined organic layers were washed with 1 M HCl (40 mL), dried and concentrated *in vacuo*. Chromatography of the crude product on silica (hexanes/ethyl acetate 93:7) gave ethyl (2*E*,4*E*,6*S*,7*R*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)-oxy)-7,8-dihydroxy-2,4-octadienoate (1.94 g, 5.4 mmol, 70%) as a colourless oil. $[\alpha]_D^{25} = -8.13$ (c= 0.16, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (1H, dd, *J* = 16.5, 11.8 Hz), 6.37 (1H, dd, *J* = 14.6, 11.3 Hz), 6.11 (1H, dd, *J* = 15.1, 5.8 Hz), 5.88 (1H, d, *J* = 15.1 H), 4.21 (1H, dt, *J* = 5.7, 1.1 Hz), 4.01-3.81 (3H, m), 3.73 (3H, s), 1.40, 1.32 (6H, 2 x s), 0.89 (9H, s), 0.07, 0.01 (6H, 2 x s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 143.9, 142.4, 128.8, 121.3, 109.6, 78.8, 73.2, 66.3, 51.6, 26.7, 25.8, 25.4, 18.2, -4.2, -4.7 ppm. IR (thin film): ν = 2987, 2954, 2858, 1723, 1649, 1619 cm^{-1}. EIMS (70 eV) *m/z* (%): 356 (5), 341 (50), 299 (10), 241 (35), 101 (100) ; HRMS: calcd for $C_{18}H_{32}O_5Si$ [M^+]: 356.2019; found: 356.2023.

To a stirred solution of ethyl (2*E*,4*E*,6*S*,7*R*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)-oxy)-7,8-dihydroxy-2,4-octadienoate (2.55 g, 7.1 mmol, 1.0 equiv) in diethyl ether (5 mL) at 0 °C under nitrogen was added DIBAL-H (1.0 M solution in hexanes, 15.2 mL, 15.2 mmol, 2.1 equiv). After 1 h 45 minutes the reaction mixture was added dropwise, *via* cannula, to a stirred solution of sodium potassium tartrate tetrahydrate (7.72 g, 27.4 mmol, 3.7 equiv) in ice/water (50 mL) and dichloromethane (50 mL). The emulsion was stirred at rt for 2 h. After separation of the phases the aqueous layer was extracted with ether (3 x 20 mL). The combined organic extracts

were washed with sat. $NaHCO_3$ (20 mL), brine (20 mL), dried and concentrated *in vacuo*. Chromatography of the crude product on silica (hexanes/ethyl acetate 80:20) gave (2*R*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-((*tert*-butyldimethylsilyl)oxy)-4,6-octadien-1,2,8-triol **89** (1.88 g, 5.72 mmol, 80%) as a colourless oil. $[\alpha]_D^{25} = -2.88$ (c= 3.64, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.25 (2H, m), 5.84 (1H, m), 5.67 (1H, m), 4.19 (2H, d, J = 5.1 Hz), 4.15 (1H, t, J = 5.8 Hz), 3.96 (2H, m), 3.88 (1H, dt, J = 5.4, 1.9 Hz), 1.41 (3H, s), 1.33 (3H, s), 0.89 (9H, s), 0.08 (3H, s), 0.03 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.6, 132.4, 130.8, 130.6, 109.4, 79.1, 73.5, 66.2, 63.2, 26.7, 25.9, 25.8, 18.2, -4.1, -4.7 ppm . IR (thin film): ν = 3436, 2955, 2931, 2858 cm^{-1}. EIMS (70 eV) *m/z* (%): 328 (20), 313 (25), 275 (30), 101 (100), 75 (70), 73 (75); HRMS: calcd for $C_{17}H_{32}O_4Si$ [M^+]: 328.2070; found: 328.2075.

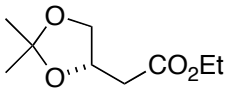
Diethyl-L-malate



diethyl malate

The title compound was synthesised from L-malic acid (27 g, 0.20 mol) according to the procedure of Seebach. Distillation gave diethyl-L-malate (39 g, 0.20 mol, 100%) as a colourless oil.[218] ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

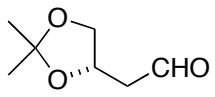
Ethyl (3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate **90**



90

Regiochemical reduction of diethyl L-malate (18.0 g, 95 mmol, 1.0 equiv) and protection of the resulting diol was based on the method of Saito *et al*[90] to give ethyl (3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate **90** (12.4 g, 66 mmol, 84%) as a colourless oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

(3*S*)-3,4-*O*-Isopropylidene-3,4-dihydroxybutanal **91**

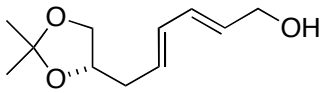


91

To a stirred solution of ethyl (3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate **91** (12.4 g, 66 mmol, 1.0 equiv) in tetrahydrofuran (180 mL) at 0˚C under argon was added lithium aluminium hydride (6.25g, 160 mmol, 2.5 equiv.). The solution was stirred at this temperature for 2 h. The reaction mixture was diluted with dichloromethane (150 mL) and the excess lithium aluminium hydride was quenched with tetrahydrofuran:water (1:1, 50 mL). The reaction mixture was filtered through celite (20g) which was rinsed with dichloromethane (3 x 300mL), then the combined extracts were dried, filtered and evaporated to give (2*S*)-1,2-*O*-isopropylidene-1,2,4-butanetriol (8.34g, 57 mmol, 86%) as a colourless oil.

To a stirred solution of oxalyl chloride (2.24 mL, 26 mmol, 1.5 equiv) in dichloromethane (230 mL) at -78 ^{o}C was added dimethyl sulfoxide (3.65 mL, 50 mmol, 3.0 equiv). After 5 minutes a solution of (2*S*)-1,2-*O*-Isopropylidene-1,2,4-butanetriol (2.5 g, 17 mmol, 1.0 equiv) in dichloromethane (100 mL) was added. The resulting solution was stirred at -78 ^{o}C for 1.5 h before the addition of triethylamine (16 mL). The reaction mixture was then gradually warmed to rt. Sat. aq. NH_4Cl (200 mL) was added. The aqueous layer was extracted with diethyl ether (2 x 100 mL) and ethyl acetate (100 mL). The combined organic layers were dried and concentrated *in vacuo* to give (3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanal **91** (2.46 g, 17 mmol, 100%) as a colourless oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

(2*S*,4*E*,6*E*)-1,2-*O*-Isopropylidene-4,6-octdadiene-1,2,8-triol **92**



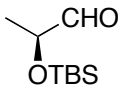
92

To a stirred solution of lithium hexamethyldisilazide, prepared from hexamethyldisilazane (3.93 mL, 19 mmol, 1.1 equiv) and *n*-butyllithium (7.3 mL of a 2.46 M solution in hexanes, 18 mmol, 1.05 equiv) in tetrahydrofuran (30 mL) at –78 °C under nitrogen, was added phosphonate **95** (4.24 g, 18 mmol, 1.05 equiv) in tetrahydrofuran (10 mL). The reaction mixture was warmed to –40 °C and a solution of (3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanal **91** (2.46 g, 17 mmol, 1.0 equiv) in tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was warmed to rt and

stirring was continued for 1.5 h. The mixture was concentrated *in vacuo* and the residue was portioned between water (100 mL) and ether (3 x 20 mL). The combined organic layers were washed with 1 M HCl (40 mL), dried and concentrated *in vacuo*. Chromatography of the crude product on silica (hexanes/ethyl acetate 85:15) gave (2*E*,4*E*,7*S*)-7,8-*O*-isopropylidene-7,8-dihydroxy-2,4-octadienoate (798 mg, 3.5 mmol, 21%) as a colourless oil.

To a stirred solution of ethyl (2*E*,4*E*,7*S*)-7,8-*O*-isopropylidene-7,8-dihydroxy-2,4-octadienoate (610 mg, 2.7 mmol, 1.0 equiv) in dichloromethane (26 mL) at –78 °C was added DIBAL-H (1.0 M solution in hexanes, 5.93 mL, 5.93 mmol, 2.2 equiv). Stirring was continued at this temperature for 1.5 h before addition to stirred solution of sodium potassium tartrate tetrahydrate (2.86 g, 10.08 mmol, 3.75 equiv) in ice/water (100 mL) and dichloromethane (100 mL). The emulsion was stirred at rt for 1.5 h. The aqueous layer was extracted with ether (3 x 50 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (50 mL), brine (50 mL), dried and concentrated *in vacuo* to give (2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-4,6-octdadiene-1,2,8-triol **92** (498 mg, 2.5 mmol, 93%) as a colourless oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]propanal **93**

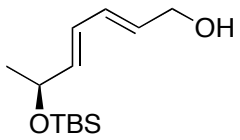


93

Protection of (*S*)-ethyl lactate (11.5 mL, 101 mmol, 1.0 equiv) was carried out according to literature procedures[91,169,219] to give ethyl (*S*)-2-[(*tert*-butyldimethylsilyl)oxy]propanoate (20.02 g, 85 mmol, 85 %) as a colourless oil, distilling at 42-50 ^{o}C/ 1-1.5 mmHg. ^{1}H NMR data for this compound was consistent with that reported in the literature.[91]

Reduction of of ethyl (*S*)-2-[(*tert*-butyldimethylsilyl)oxy]propanoate (13.1 g, 57 mmol, 1.0 equiv) was carried out according to literature procedures[91,169,219] to give ethyl (*S*)-2-[(*tert*-butyldimethylsilyl)oxy]propanoate **93** (6.93 g, 37 mmol, 65 %) as a colourless oil distilling at 78 ^{o}C /25 mmHg. ^{1}H NMR data for this compound was consistent with that reported in the literature.[91]

(2*E*,4*E*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)hepta-2,4-dien-1-ol **94**



94

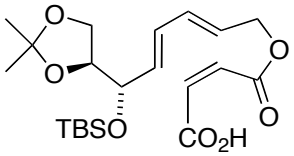
To a stirred solution of lithium hexamethyldisilazide, prepared from hexamethyldisilazane (6.55 g, 41 mmol, 1.29 equiv) and *n*-butyllithium (21.4 mL of 1.58 M solution in hexanes, 34 mmol, 1.07 equiv) in tetrahydrofuran (56 mL) at –78 ˚C under argon was added phosphonate **95** (7.51 g, 32 mmol, 1.0 equiv) in tetrahydrofuran (9.5 mL). The mixture was warmed to –40 ˚C and aldehyde **93** (5.94 g, 32 mmol, 1.0 equiv) in tetrahydrofuran (6 mL) was added dropwise. The reaction mixture was warmed to rt and concentrated *in vacuo*. The residue was partitioned between water (100 mL) and ether (20 mL). The aqueous phase was extracted with ether (3 x 20 mL). The combined extracts were washed with 1M HCl (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography over silica gel (hexane/ethyl acetate 95:5) gave methyl (2*E*,4*E*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hepta-2,4-dienoate (2.80 g, 10.2 mmol, 32%) as a colourless oil. [α] = - 1.57 (c = 4.35, dichloromethane) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (1H, dd, *J* = 15.4, 11.3 Hz), 6.29 (1H, ddd, *J* = 15.2, 11.0, 0.7 Hz), 6.08 (1H, ddd, *J* = 15.2, 4.9, 0.7 Hz), 5.84 (1H, d, *J* = 15.4 Hz), 4.38 (1H, dq, *J* = 12.23, 6.11 Hz), 3.70 (3H, s), 1.21 (3H, d, *J* = 6.6 Hz), 0.87 (9H, s), 0.04 , 0.02 (6H, 2 x s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 167.4 (Q), 147.1, 144.4, 125.7, 120.4, 68.4, 51.4, 25.8, 24.0, 18.2 (Q), -4.8, -4.8 ppm . IR (thin film): *ν* = 2954, 2929, 2886, 2857 (C-H), 1723 (C=O), 1649, 1618cm^{-1} (C=C). EIMS (70 eV) *m/z* (%): 213 (35) $[M\text{-}C_4H_9]^+$, 131 (100), 75 (95); HRMS: calcd for $C_{10}H_{17}O_3Si$ $[M\text{-}C_4H_9]^+$:213.0947; found: 213.0948.

To a stirred solution of DIBAL-H (1.5 M solution in toluene, 10.22 mL, 15.3 mmol, 2.1 equiv) at 0 ˚C under argon was added a solution of methyl (2*E*,4*E*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hepta-2,4-dienoate (1.97 g, 7.3 mmol, 1.0 equiv) in dry diethyl ether (3 mL). After 45 min the reaction mixture was added dropwise, *via* cannula, to a stirred solution of sodium potassium tartrate tetrahydrate (7.72g, 27.4 mmol, 3.75 equiv) in ice/water (50 mL) and dichloromethane (20 mL). The emulsion was stirred at room temperature for 2 h. After separation of the phases the aqueous layer was extracted with ether (3 x 10 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (15 mL), sat. NaCl (15 mL) and dried ($MgSO_4$). The filtered solution was then concentrated *in vacuo* to give (2*E*,4*E*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hepta-2,4-

dien-1-ol **94** (1.55 g, 6.3 mmol, 88%) as a colourless oil. $[\alpha] = +3.59$ (c = 0.835, dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.23 (1H, ddt, *J* = 14.9, 10.5, 1.2 Hz), 6.16 (1H, ddd, *J* = 14.4, 10.5, 1.0 Hz), 5.80 (1H, dt, *J* = 14.7, 5.9 Hz), 5.71 (1H, dd, *J* = 14.7, 5.6 Hz, 4.34 (1H, dq, *J* = 6.4, 6.4 Hz), 4.16 (2H, dd, *J* = 5.9, 1.2 Hz), 1.22 (3H, d, *J* = 6.6 Hz), 0.89 (9H, s), 0.06, 0.05 (6H, 2 x s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 131.3, 131.3, 127.3, 68.9, 63.5, 26.0, 24.5, 18.4, -4.5, -4.7 ppm. IR (thin film): ν = 3331(OH), 2955, 2857 cm^{-1} (C-H). EIMS (70 eV) *m/z* (%): 224 (70), 167 (60), 159 (100), 149 (65).

7.2.2 The Ascorbate Series

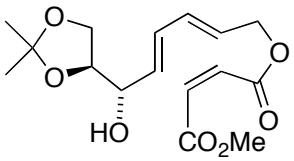
(2*E*,4*E*,6*S*,7*S*)-7,8-*O*-Isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl hydrogen maleate **96**



96

The title compound was synthesised from (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-((*tert*-butyldimethylsilyl)oxy)-4,6-octadien-1,2,8-triol **86** (124 mg, 0.38 mmol, 1.0 equiv) according to the procedure of Lilly to give (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl hydrogen maleate **96** (161 mg, 0.38 mmol, 100%) as a pale yellow oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

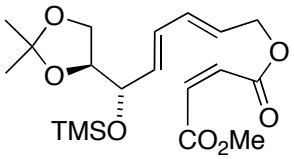
(2*E*,4*E*,6*S*,7*S*)-7,8-*O*-Isopropylidene-6,7,8-trihydroxy-2,4-octadien-1-yl methyl maleate **78a**



78a

The title compound was synthesised from (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl hydrogen maleate **96** (161 mg, 0.38 mmol, 1.0 equiv) according to the procedure of Lilly to give **78a** (50 mg, 0.15 mmol, 39%). ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

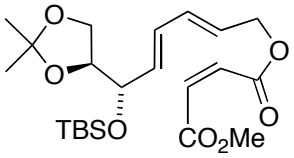
(2*E*,4*E*,6*S*,7*S*)-7,8-*O*-Isopropylidene-6-((trimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78b**



78b

The title compound was synthesised from (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6,7,8-trihydroxy-2,4-octadien-1-yl methyl maleate **78a** (12 mg, 0.04 mmol, 1.0 equiv) according to the procedure of Lilly to give (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((trimethylsilyl)oxy)-7,8-dihy-droxy-2,4-octadien-1-yl methyl maleate **78b** (7.7 mg, 0.02 mmol, 59%) as a colourless oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

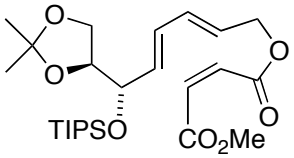
(2*E*,4*E*,6*S*,7*S*)-7,8-*O*-Isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78c**



78c

The title compound was synthesised form (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-((*tert*-butyldimethylsilyl)oxy)-4,6-octadien-1,2,8-triol **86** (110 mg, 0.35 mmol, 1.0 equiv) according to the procedure of Lilly to give (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78c** (77 mg, 0.17 mmol, 50%) as a pale yellow oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

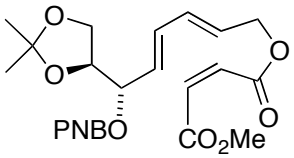
(2*E*,4*E*,6*S*,7*S*)-7,8-*O*-Isopropylidene-6-((triisopropylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78d**



78d

To a stirred solution of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6,7,8-trihydroxy-2,4-octadien-1-yl methyl maleate **78a** (15 mg, 0.05 mmol, 1.0 equiv) in dichloromethane (1 mL) at 0 °C was added 2,6-lutidine (15 μL, 0.14 mmol, 3.0 equiv) and triisopropylsilyl trifluorometanesulphonate (22 μL, 0.08 mmol, 1.8 equiv). The reaction was warmed to rt and stirring was continued for 30 min. The reaction mixture was diluted with diethyl ether (20 mL) and portioned against sat. $NaHCO_3$ (20 mL). The aqueous layer was extracted with diethyl ether (2 x10 mL) and the combined extracts were washed with sat. NaCl (10 mL), dried, filtered and concentrated *in vacuo*. After column chromatography on silica (hexanes/ethyl acetate 85:15) (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((triisopropylsilyl)oxy)-7,8-dihy-droxy-2,4-octadien-1-yl methyl maleate **78d** (20 mg, 0.05 mmol, 91%) was obtained a colourless oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

(2*E*,4*E*,6*S*,7*S*)-7,8-*O*-Isopropylidene-6-(4-nitrobenzoyloxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78e**

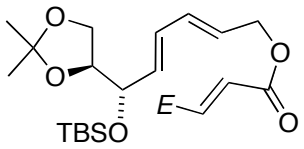


78e

To a stirred solution of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6,7,8-trihydroxy-2,4-octadien-1-yl methyl maleate **78a** (33 mg, 0.10 mmol, 1.0 equiv) in dichloromethane (5 mL) was added pyridine (82 μL, 1.01 mmol, 10.0 equiv), 4-nitrobenzoyl chloride (47 mg, 0.25 mmol, 2.5 equiv) and DMAP (13 mg, 0.10 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 18 h before being diluted with diethyl ether (20 mL) and portioned against 2M HCl (10 mL), water (10 mL) and brine (10 mL). The organic layer was then dried and concentrated *in vacuo.* After column chromatography (dichloromethane/ethyl acetate) **78e** (37 mg, 0.08 mmol, 82%) was obtained as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (4H, m), 6.47 (1H, dd, *J* = 15.0, 10.6 Hz), 6.32 (1H, m), 6.27 (1H, m), 5.89 (1H, dt, *J* = 15.0, 6.8 Hz), 5.76 (1H, dd, *J* =

15.0, 7.7 Hz), 5.60 (1H, t, *J* = 6.8 Hz), 4.73 (2H, d, *J* = 6.4 Hz), 4.38 (1H, q, *J* = 6.3 Hz), 4.09 (1H, ddd, *J* = 8.7, 6.6, 1.0), 3.85 (1H, ddd, *J* = 8.9, 5.7, 0.9 Hz), 3.78 (3H, s), 1.47 (3H, s), 1.38 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 164.8, 163.9, 150.7, 135.6, 134.7, 132.8, 130.9, 130.1, 129.6, 128.9, 127.5, 123.6, 110.4, 76.5, 76.4, 65.8, 65.0, 52.3, 26.6, 25.3 ppm. IR (thin film): ν = 2989, 2953, 1728, 1647, 1608, 1529 cm^{-1}. EIMS (70 eV) *m/z* (%): 460 (40), 417 (15), 245 (35), 150 (100), 101 (75); HRMS: calcd for $C_{22}H_{22}NO_{10}$ [M-CH_3]: 460.1244; found: 460.1238

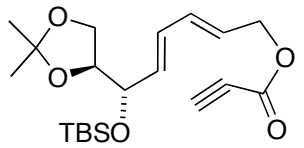
(2*E*,4*E*,6*S*,7*S*)-7,8-*O*-Isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl fumarate **78f**



78f $E = CO_2Me$

The title compound was synthesised from (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-((*tert*-butyldimethylsilyl)oxy)-4,6-octadien-1,2,8-triol **86** (171 mg, 0.52 mmol, 1.0 equiv) according to the procedure of Lilly to give (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl fumarate **78f** (204 mg, 0.46 mmol, 89%) as a colourless oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

(2*E*,4*E*,6*S*,7*S*)-7,8-*O*-Isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl propiolate **78g**

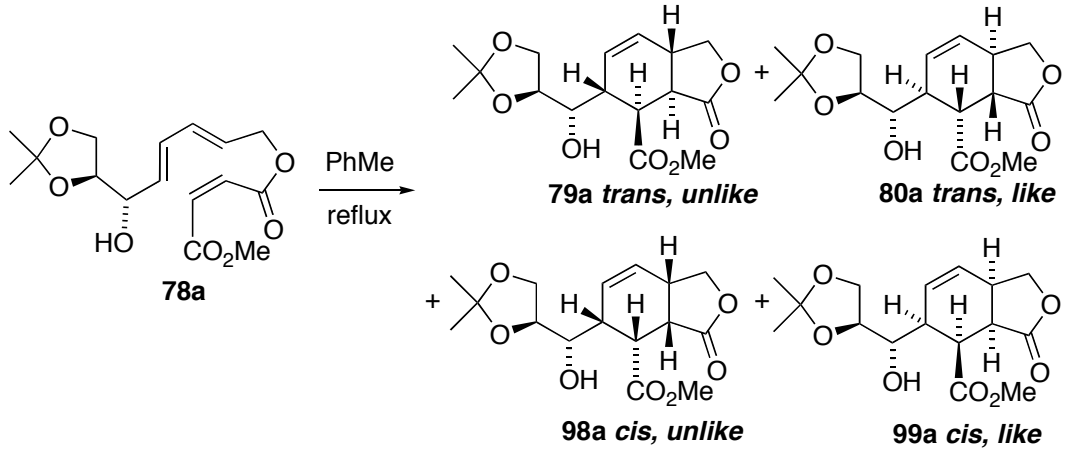


78g

The title compound was synthesised from (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-((*tert*-butyldimethylsilyl)oxy)-4,6-octadien-1,2,8-triol **86** (27 mg, 0.08 mmol, 1.0 equiv) according to the procedure of Lilly to give (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl propiolate **78g** (13 mg, 0.03 mmol, 42%) as a colourless oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

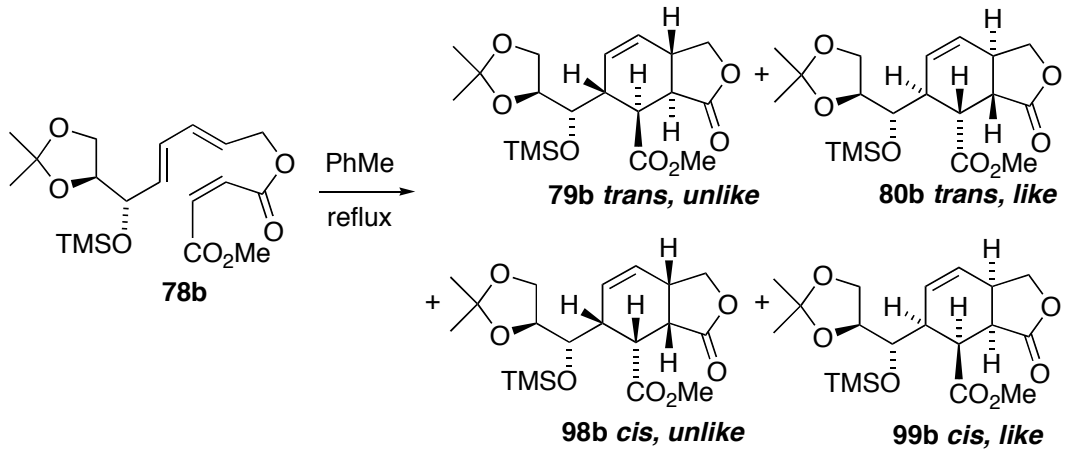
*7.2.2.1 IMDA reactions of **78***

IMDA reaction of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6,7,8-trihydroxy-2,4-octadien-1-yl methyl maleate **78a**



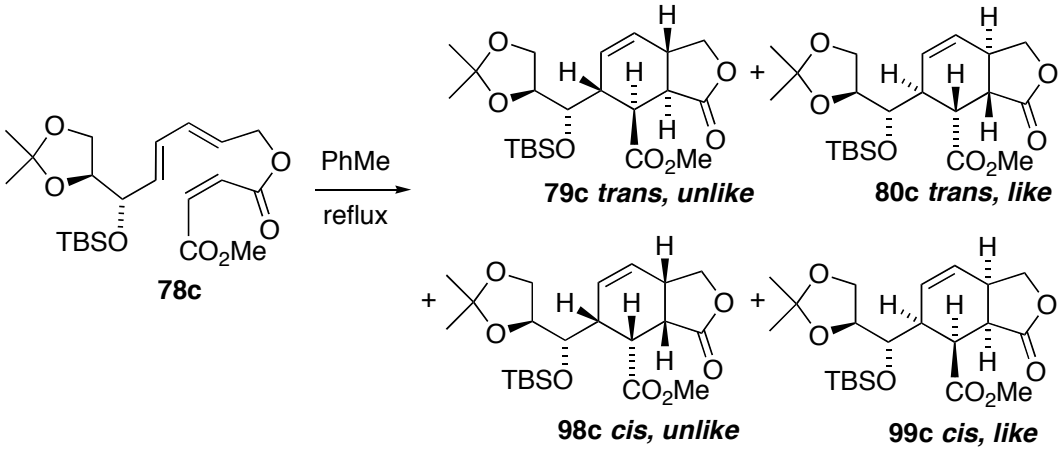
To a stirred solution of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6,7,8-trihydroxy-2,4-octadien-1-yl methyl maleate **78a** (522 mg, 1.60 mmol, 1.0 equiv) in toluene (320 mL) at rt under argon was added BHT (71 mg, 0.32 mmol, 0.2 equiv). The solution was warmed to reflux and heating was continued for 5h. Chromatography of the crude residue (hexane:ethyl acetate 1:1) gave a mixture of the 4 IMDA adducts (**79a, 80a, 98a and 99a)** (448 mg, 1.37 mmol, 86%, **79a:80a:98a:99a** (56:32:8:4)).

IMDA reaction of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((trimethyl-silyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78b**



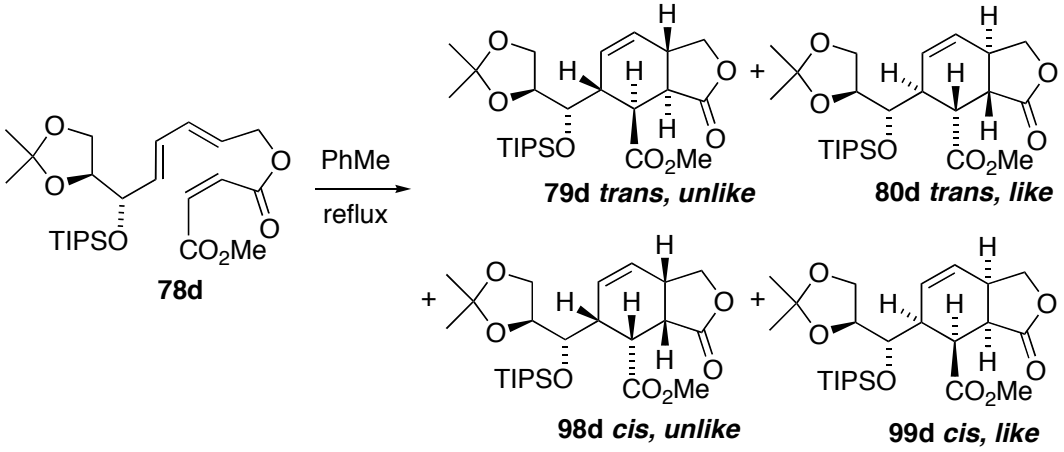
To a stirred solution of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((trimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78b** (45 mg, 0.11 mmol, 1.0 equiv) in toluene (28 mL) at rt under argon was added BHT (6 mg, 0.03 mmol, 0.2 equiv). The solution was warmed to reflux and heating was continued for 12h. Chromatography (hexane:ethyl acetate 4:1) gave the IMDA adducts (**79b, 80b, 98b and 99b**) (30 mg, 0.08 mmol, 67%, **79b:80b:98b:99b** (80:14:4:2)).

IMDA reaction of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78c**



To a stirred solution of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78c** (115 mg, 2.6 mmol, 1.0 equiv) in toluene (52 mL) at rt under argon was added BHT (12 mg, 0.05 mmol, 0.2 equiv). The solution was warmed to reflux and heating was continued for 15h. Chromatography (hexane:ethyl acetate 4:1) gave the IMDA adducts (**79c, 80c, 98c and 99c**) (92 mg, 0.21 mmol, 80%, **79c:80c:98c:99c** (86:9:4:1)). ^{1}H NMR data for these compounds were consistent with that previously reported.[216,217]

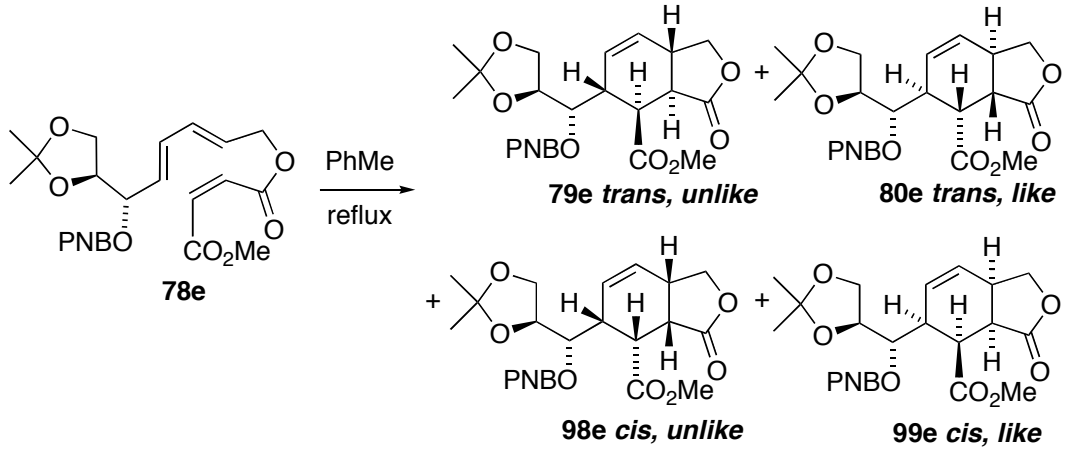
IMDA reaction of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((triiso-propylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78d**



To a stirred solution of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((triisopropylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78d** (37 mg, 0.08 mmol, 1.0 equiv) in toluene (15 mL) at rt under argon was added BHT (3 mg, 0.02 mmol, 0.2 equiv). The solution was warmed to reflux and heating was continued for 18h. Evaporation of the solvent gave the crude product. Chromatography (hexane:ethyl acetate 4:1) gave the

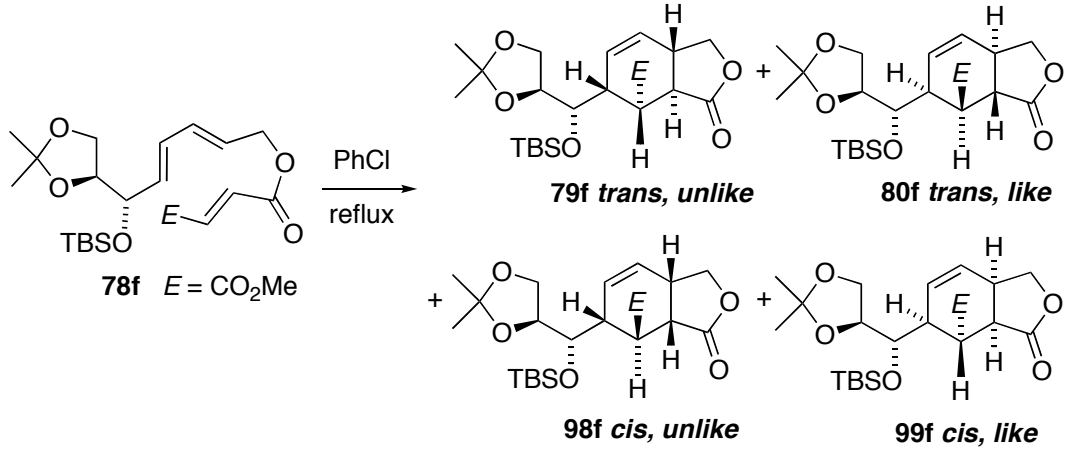
IMDA adducts (**79d, 80d, 98d and 99d**) (25.1mg, 0.052mmol, 68%, **79d:80d:98d:99d** (92:7:1:0)).

IMDA reaction (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-Isopropylidene-6-(4-nitrobenzoyloxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **78e**



To a stirred solution of **78e** (37 mg, 0.078 mmol, 1.0 equiv) in toluene (8 mL) was added BHT (3 mg, 0.015 mmol, 0.2 equiv), The solution was warmed to reflux and heating was continued for 12 h. Evaporation of the solvent gave the crude product as a yellow oil. Chromatographhy (hexane:ethyl acetate 1:1) gave the IMDA adducts (**79e, 80e, 98e and 99e**) (25 mg, 0.052 mmol, 68%, **79e:80e:98e:99e** (49:39:6:6).

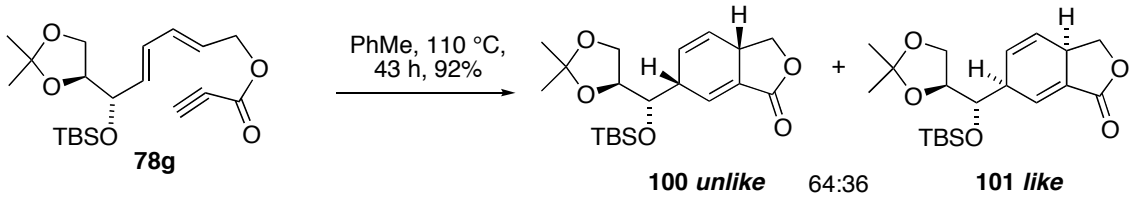
IMDA reaction of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl fumarate **78f**



To a stirred solution of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl fumarate **78f** (187 mg, 0.42 mmol, 1.0 equiv) in chlorobenzene (85 mL) was added BHT (3 mg, 0.04 mmol, 0.1 equiv). The solution was warmed to reflux and heating was continued for 53 h before the reaction mixture was concentrated *in vacuo*. Column chromatography on

silica (hexane/ethyl acetate 78:22) gave a mixture of the 4 IMDA adducts (**79f, 80f, 98f and 99f)** (116 mg, 0.26 mmol, 62%, **79f:80f:98f:99f** (12:3:82:3).

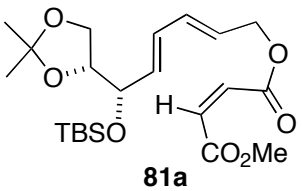
IMDA reaction of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl propiolate **78g**



To a stirred solution of (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl propiolate **78g** (13 mg, 0.03 mmol) in toluene (3 mL) at rt under argon was added BHT (1 mg, 0.003 mmol, 0.1 equiv). The solution was warmed to reflux and heating was continued for 43h. Evaporation of the solvent gave the crude product as a yellow oil. Chromatography (hexane:ethyl acetate 80:20) gave the IMDA adducts (**100** and **101**) (12 mg, 0.03 mmol, 92% , **100:101** (64:36)). ^{1}H NMR data for these compounds were consistent with that previously reported.[216,217]

7.2.3 Isoascorbate and Malate series

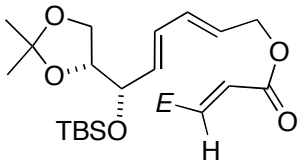
(2*E*,4*E*,6*S*,7*R*)-7,8-*O*-Isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **81a**



To a stirred solution of (2*R*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-((*tert*-butyldimethylsilyl)oxy)-4,6-octadien-1,2,8-triol **89** (234 mg, 0.71 mmol, 1.0 equiv) in dichloromethane (5 mL) at 0 °C was added triethylamine (159 μL, 1.14 mmol, 1.6 equiv), maleic anhydride (181 mg, 1.85 mmol, 2.6 equiv) and DMAP (10 mg, 0.08 mmol, 0.12 equiv). The reaction was stirred at this temperature for 15 min before being diluted with diethyl ether (50 mL), washed with 2M HCl (25 ml), water (25 mL), dried and concencetrated *in vacuo*. Chromatography of the crude product on silica (hexane/ethyl acetate/ acetic acid 49:50:1) gave (2*E*,4*E*,6*S*,7*R*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl hydrogen maleate (302

mg, 0.71 mmol, 100 %) as a colourless oil. To a stirred solution of (2*E*,4*E*,6*S*,7*R*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl hydrogen maleate (215 mg, 0.50 mmol) in dichloromethane (5 mL) at – 78 °C was added an ethereal solution of diazomethane. After 15 min the reaction mixture was concentrated *in vacuo*. After column chromatography on silica (hexane/ethyl acetate 5:1) (2*E*,4*E*,6*S*,7*R*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **81a** (165 mg, 0.39 mmol, 74%) was obtained as a colourless oil. $[\alpha]_D^{25} = -5.88$ (c= 0.26, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.26 (2H, s), 6.26 (2H, m), 5.74 (2H, m), 4.71 (2H, d, *J* = 6.7 Hz), 4.15 (1H, t, *J* = 5.7 Hz), 3.99 – 3.84 (3H, m), 3.77 (3H, s), 1.40, 1.32 (6H, 2 x s), 0.88 (9H, s), 0.07, 0.02 (6H, 2 x s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 165.7, 165.0, 135.3, 134.3, 130.1, 129.9, 129.7, 126.0, 109.5, 79.1, 73.3, 66.2, 65.5, 52.3, 26.8, 25.9, 25.4, 18.2, -4.1, -4.7 ppm . IR (thin film): ν = 2931, 2858, 1734, 1647 cm^{-1}. EIMS (70 eV) *m/z* (%): 425 (30), 409 (10), 101 (100); HRMS: calcd for $C_{21}H_{33}O_7$ [M-CH_3]: 425.1996; found: 425.1992.

(2*E*,4*E*,6*S*,7*R*)-7,8-*O*-Isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl fumarate **81b**

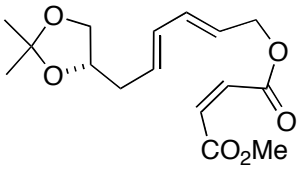


81b *E* = CO_2Me

To a stirred solution of (2*R*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-((*tert*-butyldimethylsilyl)oxy)-4,6-octadien-1,2,8-triol **89** (239 mg, 0.73 mmol, 1.0 equiv) in diethyl ether (15 mL) at room temperature under nitrogen was added monomethyl fumarate (171 mg, 1.31 mmol, 1.8 equiv), DCC (300 mg, 1.45 mmol, 2.0 equiv) and DMAP (13 mg, 0.10 mmol, 0.15 equiv). Stirring was continued for 3 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. Chromatography of the crude product on silica (hexanes/ethyl acetate 89:11) gave (2*E*,4*E*,6*S*,7*R*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl fumarate **81b** (200 mg, 0.45 mmol, 62%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84 (2H, s), 6.25 (2H, m), 5.80-5.67 (2H, m), 4.69 (1H, d, *J* = 5.2 Hz), 4.13 (1H, t, *J* = 5.2 Hz), 3.97-3.79 (3H, m), 3.77 (3H, s), 1.37, 1.29 (6H, 2 x s), 0.86 (9H, s), 0.04, 0.00 (6H, 2 x s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 165.3, 164.6, 135.3, 134.1,

133.6, 133.5, 129.9, 125.9, 109.4, 78.9, 73.2, 66.1, 65.4, 52.3, 26.7, 25.8, 25.4, 18.4, -4.2, -4.7 ppm . IR (thin film): ν = 2954, 2858, 1727 cm^{-1}. EIMS (70 eV) *m/z* (%): 425 (35), 383 (55), 101 (100); HRMS: calcd for $C_{21}H_{33}O_7Si$ [M-CH_3]: 425.1996; found: 425.1991.

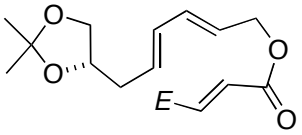
(2*E*,4*E*,7*S*)-7,8-*O*-Isopropylidene-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **82x**



82x

The title compound was synthesised form (2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-4,6-octdadiene-1,2,8-triol **92** (258 mg, 1.3 mmol, 1.0 equiv) according to the procedure of Lilly to give (2*E*,4*E*,7*S*)-7,8-*O*-isopropylidene-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **82x** (226 mg, 0.73 mmol, 56%) as a colourless oil. ^{1}H NMR data for this compound was consistent with that previously reported.[216,217]

(2*E*,4*E*,7*S*)-7,8-*O*-Isopropylidene-7,8-dihydroxy-2,4-octadien-1-yl methyl fumarate **82y**



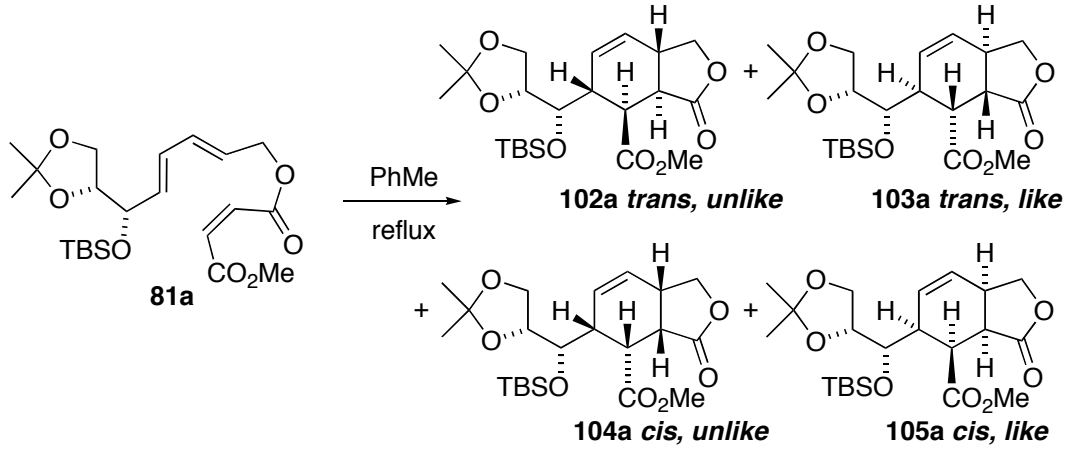
82y *E* = CO_2Me

To a stirred solution of (2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-4,6-octdadiene-1,2,8-triol **92** (210 mg, 1.06 mmol, 1.0 equiv) in diethyl ether (15 mL) was added monomethyl fumarate (248 mg, 1.91 mmol, 1.8 equiv), DCC (437 mg, 2.11 mmol, 2.0 equiv) and DMAP (19.4 mg, 0.16 mmol, 0.15 equiv). The reaction mixture was stirred for 16 h before being filtered. The filtrate was concentrated *in vacuo*. Chromatography of the crude product on silica (hexanes/ethyl acetate 75:25) gave (2*E*,4*E*,7*S*)-7,8-*O*-isopropylidene-7,8-dihydroxy-2,4-octadien-1-yl methyl fumarate **82y** (243 mg, 0.78 mmol, 74%) as a colourless oil. $[\alpha]_D^{25}$ = +2.97 (c= 1.62, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 (2H, m), 6.25 (1H, dd, *J* =15.0, 10.3 Hz), 6.10 (1H, dd, *J* =15.0, 10.3 Hz), 5.69 (1H, m), 5.68 (1H, m), 4.68 (2H, d, *J* = 6.9 Hz), 4.12 (1H, dq, *J* = 6.3 6.3 Hz), 4.01 (1H, dd, *J* = 8.1, 6.1 Hz), 3.78 (3H, s), 3.53 (1H, dd, *J* = 8.2, 7.0 Hz), 2.39 (1H, m), 2.32 (1H, m), 1.39 (3H, s), 1.32 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 164.6, 134.9, 133.6, 133.5, 131.7, 131.2, 124.5, 109.1, 75.2, 68.8, 65.6, 52.4, 36.9, 26.9, 25.6 ppm. IR (thin film): ν = 2987, 2952, 2877, 1725, 1645 cm^{-1}. EIMS (70

eV) *m/z* (%): 310 (2), 295 (30), 221 (10), 113 (40), 101 (100); HRMS: calcd for $C_{16}H_{22}O_6$ [M]: 310.1416; found: 310.1419

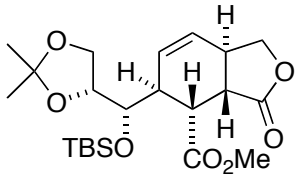
*7.2.3.1 IMDA Reactions of **81** and **82***

IMDA reaction of (2*E*,4*E*,6*S*,7*R*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **81a**



A solution of **81a** (165 mg, 0.37 mmol, 1.0 equiv) and BHT (0.1 equiv) in toluene (37 mL) was heated at reflux for 9.5 h. The solution was then cooled to room temperature and concentrated *in vacuo*. After column chromatography on silica (hexanes/ethyl acetate 85:15) a mixture of 4 products **102a:103a:104a:105a** (141 mg, 0.32 mmol, 86%) in a ratio of 78:16:4:2 was obtained. Normal phase HPLC (hexanes/ethyl acetate 85:15) yielded compounds **102a** and **103a**.

Methyl (3a*S*, 4*R*, 5*S*, 7a*R*)-5-((1*S*,2*R*)-2,3-*O*-isopropylidene-1-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydroxypropyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate **103a**

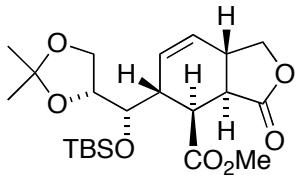


103a *trans, like*

$[\alpha]_D^{25}$ = +60.34 (c= 0.29, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.04 (1H, dt, *J* = 10.3, 2.4 Hz), 5.81 (1H, dt, *J* = 9.8, 2.9 Hz), 4.55 (1H, t, *J* = 7.6 Hz), 4.08-4.00 (2H, m), 3.85 (1H, dd, *J* = 11.7, 8.3 Hz), 3.82-3.76 (2H, m), 3.72 (3H, s), 3.38 (1H, dd, *J* = 4.4, 1.5 Hz), 3.27 (1H, m), 2.95 (1H, m), 2.61 (1H, dd, *J* = 13.4, 4.4 Hz), 1.39, 1.30 (6H, 2 x s), 0.87 (9H, s), 0.11, 0.07 (6H, 2 x s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ*

174.8, 173.3, 130.1, 126.7, 109.6, 76.6, 76.4, 70.5, 67.9, 52.2, 43.9, 43.0, 37.0, 36.2, 26.8, 25.8, 25.5, 18.0, -3.5, -4.6 ppm. IR (thin film): ν = 2955, 2931, 2893, 2858, 1788, 1736 cm^{-1}. EIMS (70 eV) *m/z* (%): 425 (10), 383 (15), 339 (10), 325 (20), 310 (55), 265 (100), 101 (40); HRMS: calcd for $C_{21}H_{33}O_7Si$ [M^+-CH_3]: 425.1996; found: 425.1996.

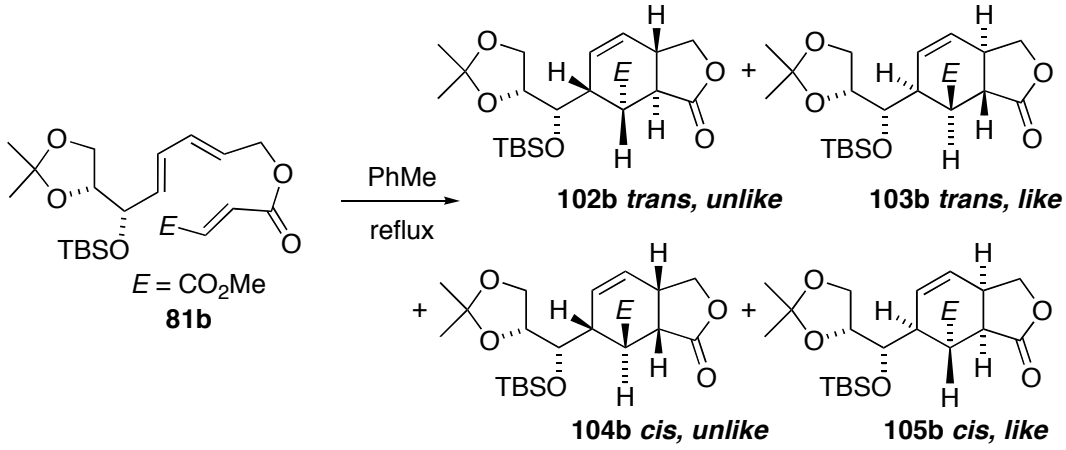
Methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((1*S*,2*R*)-2,3-*O*-isopropylidene-1-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydroxypropyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate **102a**



102a *trans, unlike*

$[\alpha]_D^{25}$ = −23.44 (c= 0.32, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (1H, dm, *J* = 9.3 Hz), 5.76 (1H, dt, *J* = 9.8, 2.6 Hz), 4.53 (1H, dd, *J* = 7.4, 7.4 Hz), 4.06-3.99 (2H, m), 3.87-3.80 (2H, m), 3.70 (3H, s), 3.32 (1H, d, *J* = 4.5 Hz), 3.20 (1H, m), 3.02 (1H, m), 2.57 (1H, dd, *J* = 13.5, 4.7 Hz), 1.37, 1.29 (6H, s), 0.87 (9H, s), 0.11, 0.10 (6H, 2 x s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.7, 172.9, 129.9, 124.6, 109.3, 76.6, 75.6, 70.6, 67.4, 52.2, 43.9, 42.8, 37.5, 36.5, 27.5, 26.7, 25.8, 18.1, -3.9, -4.3 ppm. IR (thin film): ν = 2986, 2892, 2858, 1788, 1735 cm^{-1}. EIMS (70 eV) *m/z* (%): 425 (20), 383 (50), 339 (10), 310 (55), 187 (60), 101 (50), 73 (100); HRMS: calcd for $C_{21}H_{33}O_7Si$ [M^+-CH_3]: 425.1996; found:425.1991

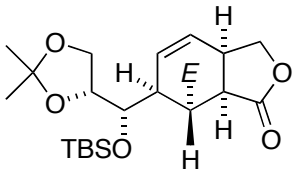
IMDA reaction of (2*E*,4*E*,6*S*,7*R*)-7,8-*O*-isopropylidene-6-((*tert*-butyldimethylsilyl)oxy)-7,8-dihydroxy-2,4-octadien-1-yl methyl fumarate **81b**



A solution of **2b** (330 mg, 0.75 mmol, 1.0 equiv) and BHT (0.1 equiv) in chlorobenzene (75 ml) was heated at reflux for 72 h. The reaction mixture was cooled to rt and

concentrated *in vacuo*. After column chromatography on silica (hexanes/ethyl acetate 80:20) a mixture of 4 products (295 mg, 0.67 mmol, 89%) was obtained. Normal phase HPLC (hexanes/ethyl acetate 85:15) yielded compounds **102b**, **103b**, **104b** and **105b** in a ratio of 9:6:66:19.

Methyl (3a*R*, 4*R*, 5*S*, 7a*R*)-5-((1*S*,2*R*)-2,3-*O*-isopropylidene-1-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydroxypropyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate **105b**

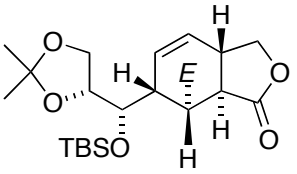


105b *cis, like*

E = CO_2Me

$[\alpha]_D^{25}$ = −149.59 (c= 0.903, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.90 (2H, s), 4.44 (1H, dd, *J* = 8.2, 7.0 Hz), 4.09 (1H, q, *J* = 5.8 Hz), 4.03 (1H, dd, *J* = 7.0, 5.8 Hz), 3.88 (1H, dd, *J* = 11.5, 7.9 hz), 3.77 (3H, s), 3.77 (1H, dd, *J* = 8.3, 5.2 Hz), 3.72 (1H, dd, *J* = 5.9, 2.2 Hz), 3.09 (1H, m), 3.01 (2H, m), 2.78 (1H, m), 1.38 (3H, s), 1.31 (3H, s), 0.86 (9H, s), 0.13, 0.09 (6H, 2 x s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 174.2, 171.5, 130.5, 123.7, 109.4, 77.8, 74.3, 70.4, 67.3, 51.9, 43.5, 41.5, 41.5, 40.5, 26.7, 26.1, 25.1, 18.6, -3.5, -4.2 ppm. IR (thin film): *ν* = 2954, 2931, 2896, 2857, 1790, 1742 cm^{-1}. EIMS (70 eV) *m/z* (%): 425 (15), 383 (100), 339 (85), 325 (50), 73 (95); HRMS: calcd for $C_{21}H_{33}O_7Si$ [M-CH_3]: 425.1996; found: 425.1997

Methyl (3a*R*, 4*R*, 5*R*, 7a*S*)-5-((1*S*,2*R*)-2,3-*O*-isopropylidene-1-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydroxypropyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate **102b**



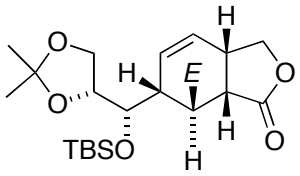
102b *trans, unlike*

E = CO_2Me

$[\alpha]_D^{25}$ = +75.73 (c= 0.780, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.04 (1H, dt, *J* = 10.8, 2.0 Hz), 5.76 (1H, dt, *J* = 9.9, 3.2 Hz), 4.49 (1H, dd, *J* = 8.3, 8.3 Hz), 4.02-3.96 (2H, m), 3.93 (1H, dd, *J* = 8.3, 8.3 Hz), 3.75 (3H, s), 3.75 (1H, dd, *J* = 12.6, 7.1 Hz), 3.70 (1H, dd, *J* = 6.5, 3.6 Hz), 3.18 (1H, m), 3.12 (1H, dd, *J* = 10.8 Hz), 2.86 (1H, dd, *J*

= 10.8, 7.4 Hz), 2.78 (1H, m), 1.35, 1.30 (6H, 2 x s), 0.88 (9H, s), 0.10, 0.08 (6H, 2 x s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 174.1, 128.7, 123.6, 109.5, 76.0, 73.1, 71.8, 67.8, 52.2, 43.5, 41.3, 39.0, 36.2, 29.8, 26.4, 25.8, 18.0, -4.3, -4.7 ppm. IR (thin film): ν = 2954, 2930, 2858, 1782, 1736 cm^{-1}. EIMS (70 eV) *m/z* (%): 425 (10), 383 (15), 339 (40), 325 (40), 105 (100); HRMS: calcd for $C_{21}H_{33}O_7Si$ [M-CH_3]: 425.1996; found: 425.1997.

Methyl (3a*S*, 4*S*, 5*R*, 7a*S*)-5-((1*S*,2*R*)-2,3-*O*-isopropylidene-1-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydroxypropyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate **104b**

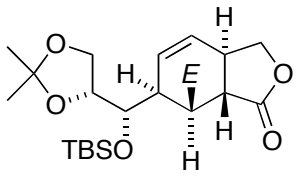


104b *cis, unlike*

E = CO_2Me

$[\alpha]_D^{25}$ = –49.06 (c= 1.27, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.96 (1H, dt, *J* = 11.0, 2.0 Hz), 5.66 (1H, ddd, *J* = 10.4, 3.8, 2.1 Hz), 4.48 (1H, dd, *J* = 8.8, 7.8 Hz), 4.14 (1H, q, *J* = 5.9 Hz), 4.05 (1H, dd, *J* = 8.0, 6.2 Hz), 3.91 (1H, dd, *J* = 8.5, 8.5 Hz), 3.84 (1H, dd, *J* = 8.2, 6.3 Hz), 3.75 (3H, s), 3.69 (1H, dd, *J* = 6.0, 2.1 Hz), 3.18 (1H, m), 3.07 (1H, m), 2.83 (2H, m), 1.38, 1.32 (6H, 2 x s), 0.85 (9H, s), 0.07, 0.06 (6H, 2 xs) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.8, 173.6, 129.6, 123.2, 109.3, 76.9, 73.6, 71.7, 66.9, 52.3, 40.6, 40.5, 40.3, 34.9, 26.7, 26.0, 25.3, 18.3, -4.0, -4.2 ppm. IR (thin film): ν = 2954, 2931, 2897, 2858, 1780, 1741 cm^{-1}. EIMS (70 eV) *m/z* (%):425 (10), 409 (5), 383 (15), 339 (85), 73 (100); HRMS: calcd for $C_{21}H_{33}O_7Si$ [M-CH_3]: 425.1996; found: 425.1996.

Methyl (3a*S*, 4*S*, 5*S*, 7a*R*)-5-((1*S*,2*R*)-2,3-*O*-isopropylidene-1-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydroxypropyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate **103b**

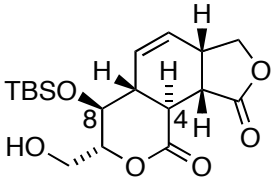


103b ***trans, like***

E = CO_2Me

$[\alpha]_D^{25}$ = +157.09 (c= 1.24, chloroform). ^{1}H NMR (500 MHz, C_6D_6): δ 5.64 (1H, dt, *J* = 10.0, 3.1 Hz), 5.12 (1H, dt, *J* = 10.3, 2.0 Hz), 4.30 (1H, ddd, *J* = 8.3, 6.3, 2.5 Hz), 4.00 (1H, t, *J* = 3.0 Hz), 3.85 (1H, m), 3.81 (1H, m), 3.56 (1H, dd, *J* = 8.3, 6.9 Hz), 3.46 (3H, s), 2.95 (1H, dd, *J* = 12.0, 8.5 Hz), 2.75 (1H, m), 2.71 (1H, dd, *J* = 12.0, 9.4 Hz), 2.37 (1H, dd, *J* = 13.2, 12.2 Hz), 1.88 (1H, m), 1.42, 1.35 (6H, 2 x s), 0.93 (9H, s), 0.14, 0.09 (6H, 2 xs) ppm. ^{13}C NMR (125 MHz, C_6D_6): *δ* 173.1, 170.8, 129.0, 125.1, 107.8, 77.5, 73.3, 69.4, 65.0, 51.6, 43.3, 42.1, 41.9, 40.5, 26.9, 26.1, 26.0, 18.3, -4.3, -4.9 ppm. IR (thin film): *ν* = 2986, 2954, 2929, 2857, 1790, 1743 cm^{-1}. EIMS (70 eV) *m/z* (%):425 (5), 383 (10), 325 (25), 310 (15), 105 (100); HRMS: calcd for $C_{21}H_{33}O_7Si$ [M-CH_3]: 425.1996; found: 425.1991.

(3a*S*,5a*R*,6*S*,7*R*,9a*S*,9b*S*)-3,3a,6,7-Tetrahydro-6-[(*tert*-butyldimethyllsilyl)oxy]-7-(hydroxymethyl)-5a*H*-furo[3,4-*h*]isochromene-1,9(9a*H*,9b*H*)-dione **106**

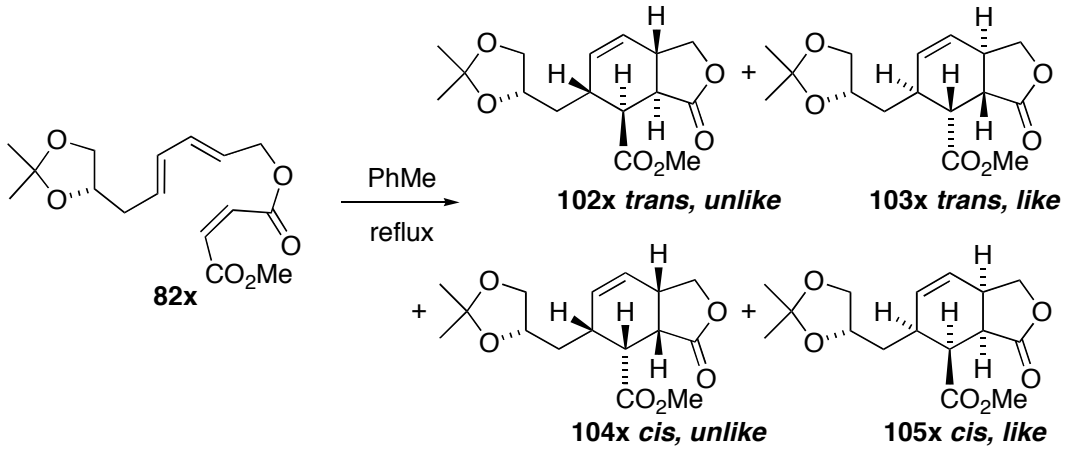


106

To a stirred solution of **104b** (22 mg, 0.05 mmol, 1.0 equiv) in dichloromethane (500 μL) was added trifluoroacteic acid (195 μL, 2.50 mmol, 50 equiv). Stirring was continued for 4 h 40 min. Evaporation of the solvent gave the crude product as a colourless oil. Chromatography of this material on silica (hexane/ethyl acetate 70:30) gave **106** (10 mg, 0.03 mmol, 56%) as a colourless solid. $[\alpha]_D^{25}$ = + 4.18 (c= 0.335, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.12 (1H, dt, *J* = 9.9, 2.4 Hz), 5.85 (1H, dt, *J* = 9.7, 2.7 Hz), 4.49 (dd, *J* = 9.3, 7.0 Hz), 4.28 (1H, ddd, *J* = 9.8, 6.4, 3.2 Hz), 4.25 (1H, dd, *J* = 9.2, 3.1 Hz), 4.05 (1H, dd, *J* = 10.4, 6.5 Hz), 3.95 (1H, dd, *J* = 12.3, 2.4 Hz), 3.80 (1H, dd, *J* = 12.6, 3.5 Hz), 3.57 (1H, dd, *J* = 8.3, 7.3 Hz), 3.07 (1H, m), 2.61

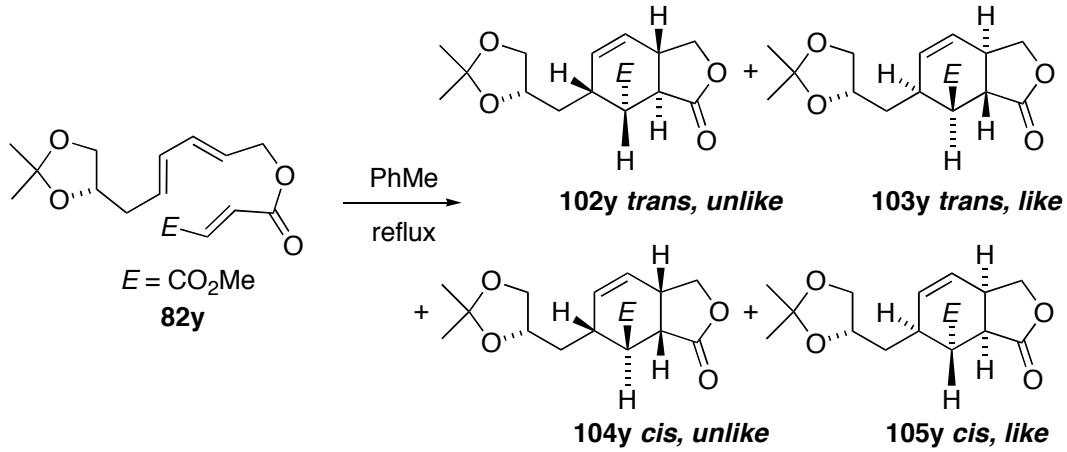
(1H, dd, J = 12.8, 7.4 Hz), 2.38 (1H, ddd, J = 10.1, 2.3, 2.3 Hz), 1.63 (1H, bs), 0.92 (9H, s), 0.17 (3H, s), 0.15 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 171.5, 130.8, 129.6, 86.3, 71.8, 69.7, 62.3, 39.4, 39.3, 38.8, 35.4, 25.8, 18.1, -3.9, -3.9 ppm. IR (thin film): ν = 3468, 2957, 2918, 2851, 1769, 1647 cm^{-1}. EIMS (70 eV) *m/z* (%): 368 (30), 311 (30), 293 (35), 219 (45), 75 (100); HRMS: calcd for $C_{18}H_{28}O_6Si$ [M]: 368.1655; found: 368.1656.

IMDA reaction of (2*E*,4*E*,7*S*)-7,8-*O*-isopropylidene-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **82x**



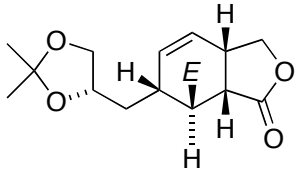
To a stirred solution of (2*E*,4*E*,7*S*)-7,8-*O*-isopropylidene-7,8-dihydroxy-2,4-octadien-1-yl methyl maleate **82x** (200 mg, 0.64 mmol, 1.0 equiv) in toluene (65 mL) at rt under argon was added BHT (5 mg, 0.13 mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 18h. Evaporation of the solvent gave the crude product as a yellow oil. Chromatography (hexane:ethyl acetate 2:1) gave the IMDA adducts (**102x**, **103x, 104x** and **105x**, 41:39:11:9) (86 mg, 0.28 mmol, 43%).

IMDA reaction of (2*E*,4*E*,7*S*)-7,8-*O*-isopropylidene-7,8-dihydroxy-2,4-octadien-1-yl methyl fumarate **82y**



To a stirred solution of **82y** (179 mg, 0.58 mmol, 1.0 equiv) in toluene (65mL) at rt under argon was added BHT (2 mg, 0.06 mmol, 0.1eq). The solution was warmed to reflux and heating was continued for 43h. Evaporation of the solvent gave the crude product as a yellow oil. Chromatography of this material on silica with hexane:ethyl acetate (60:40) gave the ETDA adducts (**102y, 103y, 104y, 105y**) (160 mg, 0.52 mmol, 89%, **102y:103y:104y:105y** (32:33:18:17)) as a mixture.

Methyl (3a*S*, 4*S*, 5*R*, 7a*S*)-5-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate **104y**

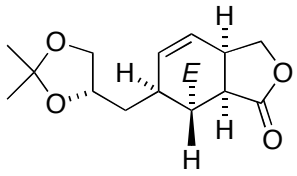


104y *cis, unlike*

E = CO_2Me

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.94 (1H, ddd, *J* = 10.1, 3.9, 1.8 Hz), 5.62 (1H, dt, *J* = 10.1, 2.6 Hz), 4.45 (1H, dd, *J* = 9.0, 7.2 Hz), 4.24 (1H, dq, *J* = 7.2, 5.3 Hz), 4.07 (2H, m), 3.76 (3H, s), 3.50 (1H, t, *J* = 7.9 Hz), 3.22 (1H, m), 3.19 (1H, dd, *J* = 8.3, 4.3 Hz), 3.08 (1H, t, *J* = 4.3 Hz), 2.79 (1H, m), 1.61 (2H, m), 1.40 (3H, s), 1.35 (3H, s) ppm. ^{13}C NMR (125 MHz, C_6D_6): *δ* 176.8, 173.9, 132.6, 124.5, 109.2, 74.5, 71.1, 69.8, 51.9, 41.1, 39.3, 38.8, 33.9, 33.8, 27.3, 26.0 ppm. IR (thin film): *ν* = 2925, 1769, 1734 cm^{-1}. EIMS (70 eV) *m/z* (%): 295 (80), 279 (5), 105 (100); HRMS: calcd for $C_{15}H_{19}O_6$ [M-CH_3]: 295.1182; found: 295.1182.

Methyl (3a*R*, 4*R*, 5*S*, 7a*R*)-5-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancar-boxylate **105y**

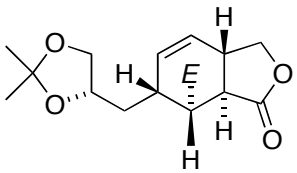


105y *cis, like*

E = CO_2Me

$[\alpha]_D^{25}$ = -48.75 (c = 0.08, chloroform). ^1H NMR (500 MHz, $CDCl_3$): δ 5.97 (1H, ddd, *J* = 10.4, 4.2, 1.7 Hz), 5.67 (1H, dt, *J* = 10.4, 2.2 Hz), 4.45 (1H, dd, *J* = 9.0, 6.9 Hz), 4.19 (1H, m), 4.08 (1H, dd, *J* = 9.0, 3.0 Hz), 4.04 (1H, dd, *J* = 8.0, 5.7 Hz), 3.75 (3H, s), 3.52 (1H, t, *J* = 6.7 Hz), 3.22 (2H, m), 3.01 (1H, t, *J* = 4.1 Hz), 2.87 (1H, m), 1.79 (1H, m), 1.54 (1H, m), 1.42 (3H, s), 1.35 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 177.4, 173.9, 131.3, 124.9, 109.2, 73.5, 71.7, 69.6, 52.5, 42.6, 39.4, 39.2, 33.9, 32.6, 27.1, 25.9 ppm. IR (thin film): *ν* = 2923, 1772, 1734 cm^{-1}. EIMS (70 eV) *m/z* (%):310 (1), 295 (100); HRMS: calcd for $C_{16}H_{22}O_6$ [M]: 310.1416; found: 310.1414.

Methyl (3a*R*, 4*R*, 5*R*, 7a*S*)-5-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancar-boxylate **102y**

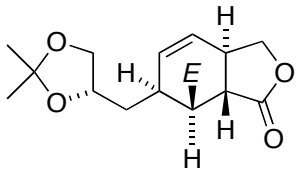


102y *trans, unlike*

E = CO_2Me

$[\alpha]_D^{25}$ = + 130.37 (c= 0.135, chloroform). ^1H NMR (500 MHz, $CDCl_3$): δ 5.86 (2H, m), 4.46 (1H, dd, *J* = 8.2, 6.8 Hz), 4.02 (2H, m), 3.94 (1H, dd, *J* = 11.9, 8.7 Hz), 3.77 (3H, s), 3.45 (1H, m), 2.99 (1H, dd, *J* = 12.4, 7.3 Hz), 2.81 (2H, m), 2.56 (1H, dd, *J* = 14.2, 11.6 Hz), 1.64 (2H, m), 1.39 (3H, s), 1.34 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 174.1, 171.7, 134.1, 123.0, 109.3, 74.7, 70.3, 69.6, 52.0, 43.2, 41.7, 41.1, 36.1, 35.9, 27.1, 25.9 ppm. IR (thin film): *ν* = 2925, 1785, 1735 cm^{-1}. EIMS (70 eV) *m/z* (%): 310 (1), 295 (95), 43 (100); HRMS: calcd for $C_{16}H_{22}O_6$ [M]: 310.1416; found: 310.1414.

Methyl (3a*S*, 4*S*, 5*S*, 7a*R*)-5-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate **103y**



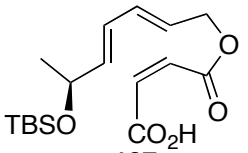
103y *trans, like*

E = CO_2Me

$[\alpha]_D^{25}$ = + 78.4 (c = 0.31, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.96 (1H, dt, *J* = 10.1, 3.3 Hz), 5.87 (1H, d, *J* = 9.8 Hz), 4.46 (1H, dd, *J* = 8.0, 6.6 Hz), 4.18 (1H, m), 4.04 (1H, dd, *J* = 8.0, 6.0 Hz), 3.93 (1H, dd, *J* = 11.2, 8.0 Hz), 3.79 (3H, s), 3.51 (1H, dd, *J* = 7.8, 6.3 Hz), 3.01 (2H, m), 2.84 (1H, m), 2.56 (1H, dd, *J* = 13.4, 11.3 Hz), 1.51 (2H, m), 1.39 (3H, s), 1.34 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 174.1, 171.5, 132.5, 123.7, 109.4, 73.1, 70.3, 69.9, 52.0, 43.5, 41.5, 41.3, 36.6, 34.4, 27.2, 25.6 ppm. IR (thin film): *ν* = 2925, 1785, 1734 cm^{-1}. EIMS (70 eV) *m/z* (%): 295 (80), 279 (15), 105 (100); HRMS: calcd for $C_{15}H_{19}O_6$ [M-CH_3]: 295.1182; found:295.1178.

7.2.4 Lactate series

(2*Z*)-4-[[(2*E*,4*E*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)hepta-2,4-dienyl]oxy]-4- oxobut-2-enoic acid **107**

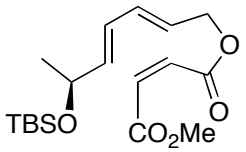


107

To a stirred solution of **94** (1.11 g, 4.58 mmol, 1.0 equiv) in dichloromethane (30 mL) at 0 ˚C under argon was added triethylamine (1.02 mL, 7.33 mmol, 1.6 equiv), maleic anhydride (1.26 g, 12.82 mmol, 2.8 equiv) and DMAP (61 mg, 0.5 mmol, 0.1 equiv). The reaction mixture was stirred at this temperature for 15 min before being diluted with diethyl ether (110 mL), washed with 2M HCl (55 mL), water (55 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography of the crude product on silica (hexane/ethyl acetate/methanol/acetic acid 20:20:1:1) gave **107** (1.16 g, 3.4 mmol, 75%). [α] = +4.54 (c = 0.573, dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 6.47-6.28 (3H, m), 6.17 (1H, ddd, *J* = 15.0, 10.6, 1.5 Hz), 5.80 (1H, dd, *J* = 15.0, 5.5 Hz), 5.73 (1H, dt, *J* = 15.0, 6.6 Hz), 4.78 (2H, d, *J* = 7.0 Hz), 4.35 (1H, dq, *J* = 11.7, 5.5 Hz), 1.22 (3H, d, *J* = 6.6 Hz), 0.89 (9H, s), 0.06, 0.05 (6H, 2 x s). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 167.3, 165.2, 141.2, 136.2, 135.8, 129.5, 126.5, 123.6, 68.6, 67.3, 25.9, 24.3, 18.3, -4.6, -4.7 ppm. IR (thin film): ν = 2955, 2929, 2886, 2857 (C-H), 1769, 1738, 1732, 1713, 1682, 1651, 1633 cm^{-1}. ESIMS (positive ion) *m/z* (%): 341 (100). HRMS: calcd for $C_{17}H_{29}SiO_5$ $[M + H]^+$: 341.1786; found 341.1782

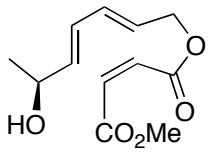
(2*E*,4*E*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)hepta-2,4-dienyl methyl-(2*Z*)-but-2-enedioate **83c**



83c

To a stirred solution of dienol **94** (307 mg, 1.26 mmol, 1.0 equiv) in dichloromethane (8.5 mL) at 0 ˚C was added triethylamine (281 μL, 2.02 mmol, 1.6 equiv), maleic anhydride (347 mg, 3.54 mmol, 2.8 equiv) and DMAP (15 mg, 0.12 mmol, 0.1 equiv). The reaction mixture was stirred at this temperature for 20 min. The mixture was diluted with diethyl ether (30 mL) and washed with 2M HCl (15 mL), water (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in dichloromethane (15 mL) and an ethereal solution of diazomethane was added dropwise at –78 ˚C. The reaction mixture was concentrated *in vacuo.* After column chromatography on silica (hexane/ethyl acetate 88:12) the triene **83c** (384 mg, 1.10 mmol, 87%) was obtained as a colourless oil. $[\alpha]$ = +2.21 (c = 1.27, dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (1H, dd, *J* = 14.9, 10.8 Hz), 6.25 (2H, m), 6.16 (1H, ddd, *J* = 15.2, 10.8, 1.2 Hz), 5.76 (1H, dd, *J* = 15.2, 5.4 Hz), 5.73 (1H, dt, *J* = 14.9, 6.6 Hz), 4.70 (2H, dd, *J* = 6.6, 1.0 Hz), 4.34 (1H, dq, *J* = 12.2, 5.6 Hz), 3.77 (3H, s), 1.20 (3H, d, *J* = 6.4 Hz), 0.89 (9H, s), 0.05, 0.04 (6H, 2 x s) ppm . ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 165.0, 140.3, 134.9, 129.9, 129.7, 126.8, 125.0, 68.7, 65.7, 52.3, 25.9, 24.4, 18.3, -4.6, -4.7 ppm. IR (thin film): ν =2954, 2886, 2856 (C-H), 1732 (C=O), 1644 cm^{-1} (C=C). ESIMS (positive ion) *m/z* (%): 377 (100) HRMS: calcd for $C_{18}H_{30}O_5SiNa$ $[M + Na]^+$: 377.1755; found 377.1756

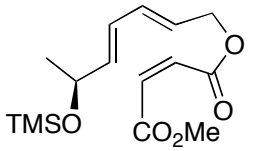
(2*E*,4*E*,6*S*)-6-Hydroxyhepta-2,4-dienyl methyl (2*Z*)-but-2-enedioate **83a**



83a

To a stirred solution of **107** (54 mg, 0.16 mmol, 1.0 equiv) in tetrahydrofuran (2 mL) under argon at 0 ˚C was added tetrabutyl ammonium fluoride (0.50 mL, 0.50 mmol, 3.1 equiv) The reaction mixture was warmed to rt and stirring was continued for 23 h. The reaction mixture was diluted with diethyl ether (20 mL) and partitioned against sat. NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then diluted in dichloromethane (3 mL) and an ethereal solution of diazomethane was added dropwise at –78 ^{o}C. The mixture was then concentrated *in vacuo.* Chromatography of the crude product on silica (hexane/ethyl acetate 60:40) gave **83a** (17 mg, 0.07 mmol, 44%) as a colourless oil. $[\alpha]$ = +5.82 (c = 0.75, dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.31 (1H, dd, J = 15.2, 10.5 Hz), 6.27 (2H, m), 6.22 (1H, dd, J = 14.9, 10.5 Hz), 5.81 (1H, dd, J = 13.7, 6.6 Hz), 5.79 (1H, dt, J = 14.0, 6.6 Hz), 4.72 (2H, d, J = 6.6 Hz), 4.37 (1H, dq, J = 12.7, 6.6 Hz), 3.79 (3H, d, J = 0.5 Hz), 1.80 (1H, s), 1.29 (3H, d, J = 6.36 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 164.9, 139.2, 134.3, 130.0, 129.7, 128.1, 126.0, 68.3, 65.5, 52.3, 23.3 ppm. IR (thin film): ν =. 3437 (OH), 2971, 2875 (C-C), 1738, 1731, 1720 (C=O), 1660, 1651, 1633 (C=C). ESIMS (positive ion) *m/z* (%): 263 (100). HRMS: calcd for $C_{15}H_{16}O_5Na$ $[M + Na]^+$: 263.0896; found 263.0899

(2*E*,4*E*,6*S*)-6-((Trimethylsilyl)oxy)hepta-2,4-dienyl methyl-(2*Z*)-but-2-enedioate **83b**

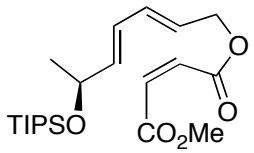


83b

To a stirred solution of **83a** (24.8 mg, 0.10 mmol, 1.0 equiv) in dichloromethane (2 mL) at 0 °C under argon was added 2,6-lutidine (36 μL, 0.31 mmol, 3.0 equiv) and trimethylsilyl triflouromethanesulphonate (35 μL, 0.18 mmol, 1.8 equiv). On completion of addition the solution was warmed to rt and stirred for 15 min. The reaction mixture was diluted with diethyl ether (10 mL) and partitioned against sat. $NaHCO_3$ (10 mL). The aqueous layer was extracted with diethyl ether (2 x 5 mL). The

combined organic layers were washed with NaCl (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. After column chromatography on silica (hexane/ethyl acetate 90:10) **83b** (27.5 mg, 0.09 mmol, 88%) was obtained as a colouless oil. [α] = +8.24 (c = 0.17, dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (1H, dd, J = 15.2, 10.8 Hz), 6.25 (2H, m), 6.14 (1H, ddd, J = 15.2, 10.8, 1.0 Hz), 5.75 (2H, dt, J = 15.2, 5.9 Hz), 4.70 (2H, d, J = 6.4 Hz), 4.33 (1H, dq, J = 12.2, 5.9 Hz), 3.77 (3H, s), 1.23 (3H, d, J = 6.4 Hz), 0.11 (9H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 165.0, 140.0, 134.7, 130.0, 129.7, 127.7, 127.2, 125.3, 120.0, 68.6, 65.6, 52.3, 24.3, 0.2 ppm. IR (thin film) ν = 2955 (C-H), 1732, 1644. ESIMS (positive ion) *m/z* (%): 647 (14), 335 (100), 263 (24). HRMS: calcd for $C_{14}H_{21}O_5Si$ [M-CH_3]: 297.1158; found 297.1166.

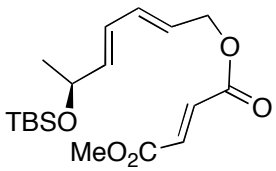
(2*E*,4*E*,6*S*)-6-((Trimethylsilyl)oxy)hepta-2,4-dienyl methyl-(2*Z*)-but-2-enedioate **83d**



83d

To a stirred solution of **83a** (41 mg, 0.17 mmol, 1.0 equiv) in dichloromethane (5 mL) at 0 °C under argon was added 2,6-lutidine (56 μL, 0.51 mmol, 3.0 equiv) and triisopropylsilyl trifluoromethanesulphonate (83 μL, 0.31 mmol, 1.8 equiv). On completion of addition the solution was warmed to rt and the stirring was continued for 1.5 h. The reaction mixture was diluted with diethyl ether (20 mL) and partioned against sat. $NaHCO_3$ (20 mL). The aqueous layer was extracted with diethyl ether (2 x 10 mL) and the combined extracts were washed with NaCl (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. After column chromatography on silica (hexanes/ethyl acetate 85:15) **83d** (53 mg, 0.13 mmol, 78%) was obtained as a colourless oil. [α] = +5.96 (c = 0.94, dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (1H, dd, J = 14.9, 10.3 Hz), 6.26 (2H, m), 6.18 (1H, dd, J = 15.2, 10.8 Hz), 5.79 (1H, dd, J = 14.9, 5.6 Hz), 5.73 (1H, dt, J = 15.2, 6.6 Hz), 4.71 (2H, d, J = 6.6 Hz), 4.44 (1H, dq, J = 6.2, 6.2 Hz), 3.77 (3H, s), 1.24 (3H, d, J = 6.2 Hz), 1.12-0.99 (21H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 165.0, 140.8, 135.0, 139.9, 129.8, 126.7, 124.9, 68.8, 65.8, 52.3, 24.9, 18.1, 12.4 ppm. IR (thin film) ν = 2944, 2866, 1732, 1645, 1463, 1437, 1396, 1368 cm^{-1}. ESIMS (positive ion) *m/z* (%): 419 (100), 815 (10). HRMS: calcd for $C_{21}H_{36}NaSiO_5$ $[M + Na]^+$: 419.2230; found 419.2228.

(2*E*,4*E*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)hepta-2,4-dienyl methyl-(2*E*)-but-2-enedioate **83e**

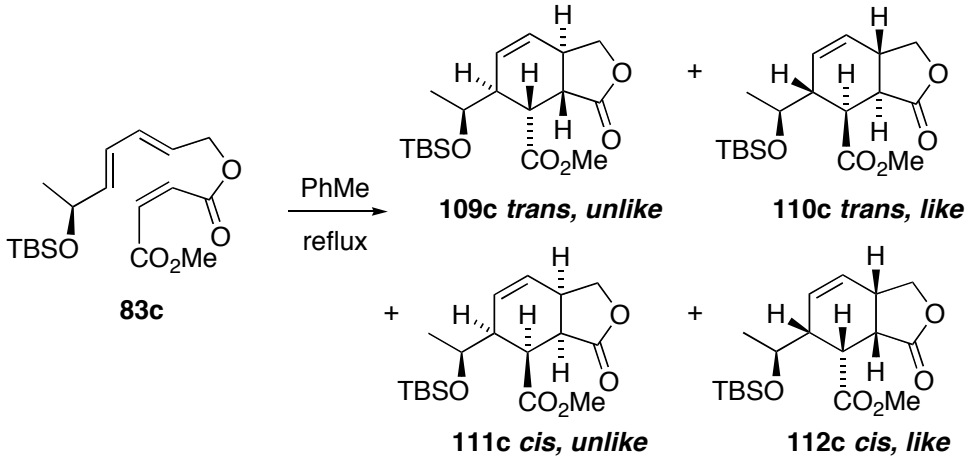


83e

To a stirred solution of **94** (162 mg, 0.60 mmol, 1.0 equiv) in diethyl ether (5 mL) at room temperature under nitrogen was added monomethyl fumarate (140.4 mg, 1.08 mmol, 1.8 eqiuv), DCC (247 mg, 1.20 mmol, 2.0 equiv) and DMAP (11 mg, 0.09 mmol, 0.15 equiv). Stirring was continued for 3 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. Chromatography of the crude product on silica (hexanes/ethyl acetate 97:3) gave (2*E*,4*E*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hepta-2,4-dienyl methyl-(2*E*)-but-2-enedioate **83e** (182.2 mg, 0.53 mmol, 89%) as a colourless oil. $[\alpha]_D^{25}$ = +21.47 (c= 0.340, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 (2H, s), 6.28 (1H, dd, *J* = 15.5, 10.4 Hz), 6.14 (1H, ddd, *J* = 14.8, 10.5, 1.4 Hz), 5.75 (1H, dd, *J* = 15.0, 5.1 Hz), 5.70 (1H, dd, *J* = 14.9, 6.6 Hz), 4.09 (2H, d, *J* = 7.0 Hz), 4.33 (1H, dq, *J* = 11.3, 6.0 Hz), 3.79 (3H, s), 1.19 (3H, d, *J* = 7.4 Hz), 0.88 (9H, s), 0.04, 0.03 (6H, 2 x s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 164.7, 140.3, 134.8, 133.7, 133.5, 126.7, 124.9, 68.6, 65.6, 52.3, 25.9, 24.3, 18.3, -4.7, -4.8 ppm . IR (thin film): ν = 2955, 2930, 2887, 2857, 1727, 1662 cm^{-1}. EIMS (70 eV) *m/z* (%): 339 (2), 297 (30), 224 (35), 187 (100), 113 (50), 75 (65); HRMS: calcd for $C_{17}H_{27}O_5Si$ [M^+-CH_3-]:339.1628; found: 339.1624.

7.2.4.1 IMDA reactions of ***83***

Thermal IMDA reaction of (2*E*,4*E*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hepta-2,4-dienyl methyl-(2*Z*)-but-2-enedioate **83c**



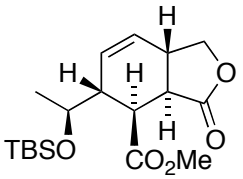
83c

109c *trans, unlike* **110c *trans, like***

111c *cis, unlike* **112c *cis, like***

A solution of **83c** (238 mg, 0.67 mmol, 1.0 equiv) and BHT (15 mg, 0.07 mmol, 0.1 equiv) in toluene (85 mL) was heated at reflux for 7 h and 25 min. The reaction mixture was concentrated *in vacuo*. After column chromatography on silica (hexanes/ethyl acetate 80:20) a mixture of 4 products (229 mg, 0.65 mmol, 96%) was obtained. Normal phase HPLC (hexanes/ethyl acetate 85:15) yielded compounds **111c** as a white solid and **112c** as a colourless oil, as well as a mixture of compounds **109c** and **110c**. Reverse phase HPLC (methanol/water 80:20) of this mixture yielded compound **109c** as a white solid and **110**c as a colourless oil.

Methyl (3a*R*,4*S*,5*R*,7a*S*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyl)oxyethyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **110c**

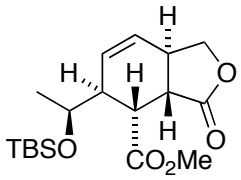


110c *trans, like*

[α] = +53.90 (c = 0.590, dichloromethane). ^{1}H NMR (400 MHz, MeOD): δ 6.01 (1H, ddd, J = 10.0, 2.2, 2.2 Hz), 5.74 (1H, ddd, J = 10.0, 3.2, 3.2 Hz), 4.56 (1H, dd, J = 8.1, 7.1 Hz), 4.04 (1H, dq, J = 6.1, 3.9 Hz), 3.84 (1H, dd, J = 11.5, 8.1 Hz), 3.69 (3H, s), 3.35 (1H, d, J = 3.7 Hz), 3.2 (1H, m), 2.67 (1H, dd, J = 13.5, 3.9 Hz), 2.63 (1H, m), 1.28 (3H, d, J = 6.1 Hz), 0.89 (9H, s), 0.10, 0.07 (6H, 2 x s) ppm. ^{13}C NMR (100 MHz, MeOD): δ 177.6, 174.6, 132.6, 127.0, 72.3, 72.3, 52.5, 48.0, 44.0, 37.5, 37.2, 26.3, 22.2, 18.8, -4.3, -4.5 ppm. IR (thin film): ν =2953 (C-H), 1790, 1731 (C=O) cm^{-1}. EIMS (70

eV) *m/z* (%): 339 (7), 323 (15), 310 (55), 297 (100), 159 (85), 73 (85) HRMS: calcd for $C_{17}H_{27}O_5Si$ $[M - CH_3]^+$: 339.1628; found 339.1629.

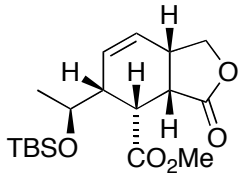
Methyl (3a*S*,4*R*,5*S*,7a*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyl)oxyethyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **109c**



109c *trans, unlike*

m.p. 54-56 °C. [α] = +84.0 (c = 0.300, dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 (1H, ddd, *J* = 10.0, 2.2, 2.2 Hz,), 5.74 (1H, ddd, *J* = 10.0, 3.0, 3.0 Hz), 4.52 (1H, dd, *J* = 7.8, 7.8 Hz), 4.00 (1H, dq, *J* = 6.4, 4.7 Hz), 3.83 (1H, dd, *J* = 11.5, 7.8 Hz), 3.68 (3H, s), 3.31 (1H, d, *J* = 3.9 Hz), 3.24 (1H, m), 2.78 (1H, m), 2.50 (1H, dd, *J* = 13.5, 4.2 Hz), 1.16 (3H, d, *J* = 6.4), 0.87 (9H, s), 0.07, 0.06 (6H, 2 x s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 173.2, 129.4, 125.9, 71.3, 70.6, 52.1, 46.1, 43.1, 38.0, 36.4, 25.8, 20.9, 18.1, -4.4, -4.9 ppm. IR (KBr disc): ν =2950, 2929, 2857, 2350 (C-H), 1780, 1731 (C=O) cm^{-1}. EIMS (70 eV) *m/z* (%): 339 (30), 310 (30), 297 (100), 159 (65), 73 (70). HRMS: calcd for $C_{17}H_{27}O_5Si$ $[M - CH_3]^+$: 339.1628; found 339.1626.

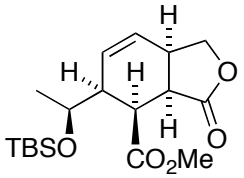
Methyl (3a*S*,4*R*,5*R*,7a*S*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyl)oxyethyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **112c**



112c *cis, like*

[α] = +23.53 (c = 0.136, dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 (1H, ddd, *J* = 10.0, 2.5, 2.5 Hz), 5.68 (1H, ddd, *J* = 10.0, 2.7, 2.7 Hz), 4.53 (1H, dd, *J*= 9.5, 8.3 Hz), 4.09 (1H, dd, *J* = 9.8, 8.1 Hz), 3.84 (1H, dq, *J* = 9.8, 5.9 Hz), 3.64 (3H, s), 3.36 (1H, dd, *J* = 5.6, 4.2 Hz), 3.21 (1H, m, C7a-H), 2.95 (1H, dd, *J* = 11.3, 6.1 Hz), 2.24 (1H, m), 1.29 (3H, d, *J* = 5.9 Hz), 0.89 (9H, s), 0.09, 0.08 (6H, 2 x s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 172.3, 129.1, 125.0, 72.0, 69.4, 51.9, 46.7, 41.3, 40.5, 34.0, 25.9, 22.1, 18.2, -3.8, -4.6 ppm. IR (thin film): ν =2958, 2856, 2358 (C-H), 1770, 1731 (C=O) cm^{-1}. EIMS (70 eV) *m/z* (%): 355 (5), 339 (35), 297 (100), 159 (30), 73 (80). HRMS: calcd for $C_{17}H_{27}O_5Si$ $[M - CH_3]^+$: 339.1628; found 339.1629.

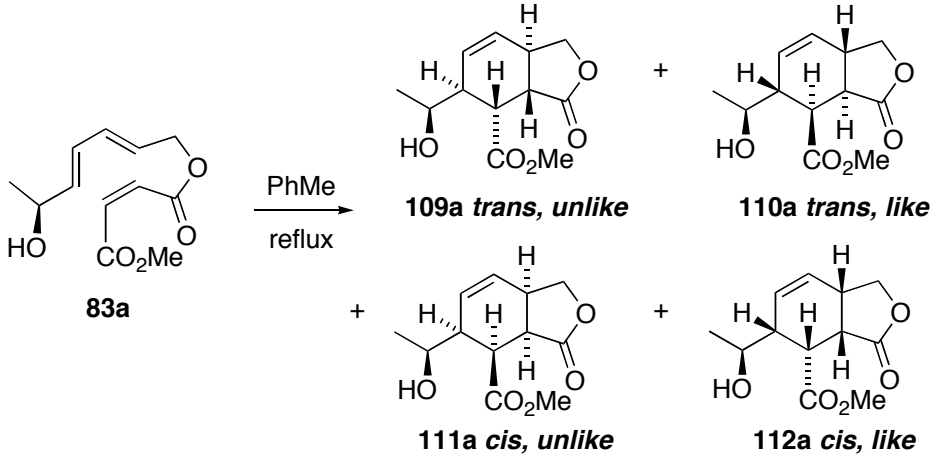
Methyl (3a*R*,4*S*,5*S*,7a*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyl)oxyethyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **111c**



111c *cis, unlike*

m.p. 95-98 °C [α] = -20.44 (c = 0.450, dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.67 (2H, m), 4.50 (1H, dd, *J* = 9.5, 8.1 Hz), 4.06 (1H, dq, *J* = 9.3, 6.1 Hz), 4.00 (1H, dd, *J* = 10.3, 8.3 Hz), 3.62 (3H, s), 3.60 (1H, dd, *J* = 6.1, 3.9 Hz), 3.20 (1H, m), 2.95 (1H, dd, *J* = 10.8, 6.4), 2.24 (1H, m), 1.24 (3H, d, *J* = 5.9 Hz), 0.87 (9H, s), 0.07, 0.03 (6H, 2 x s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 172.3, 128.2, 125.7, 71.6, 68.6, 51.6, 47.0, 41.6, 39.5, 34.6, 26.0, 22.3, 18.1, -3.9, -4.9 ppm. IR (KBr disc): ν = 2931, 2857 (C-H), 1760, 1737 (C=O) cm^{-1}. EIMS (70 eV) *m/z* (%): 339 (40), 297 (100), 159 (30), 89 (80), 73 (85). HRMS calcd for $C_{17}H_{27}O_5Si$ $[M - CH_3]^+$: 339.1628; found 339.1627.

Thermal IMDA reaction of (2*E*,4*E*,6*S*)-6-hydroxyhepta-2,4-dienyl methyl (2*Z*)-but-2-enedioate **83a**



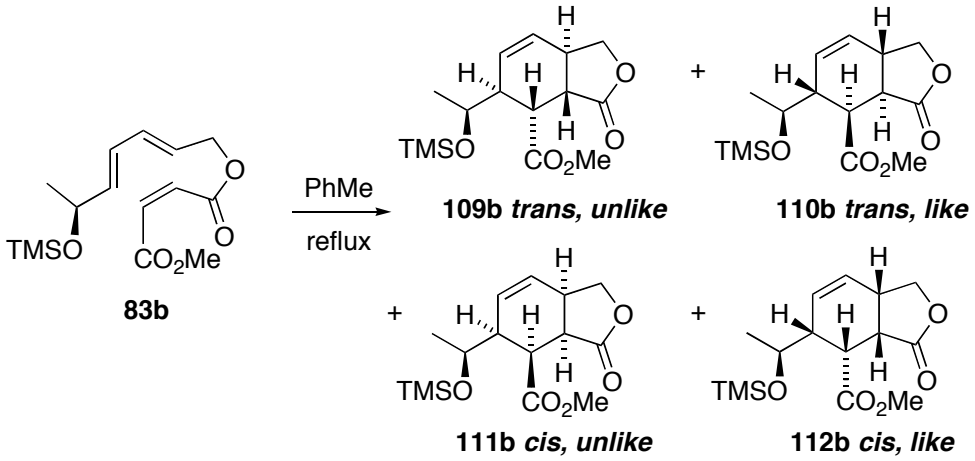
83a

109a *trans, unlike* **110a *trans, like***

111a *cis, unlike* **112a *cis, like***

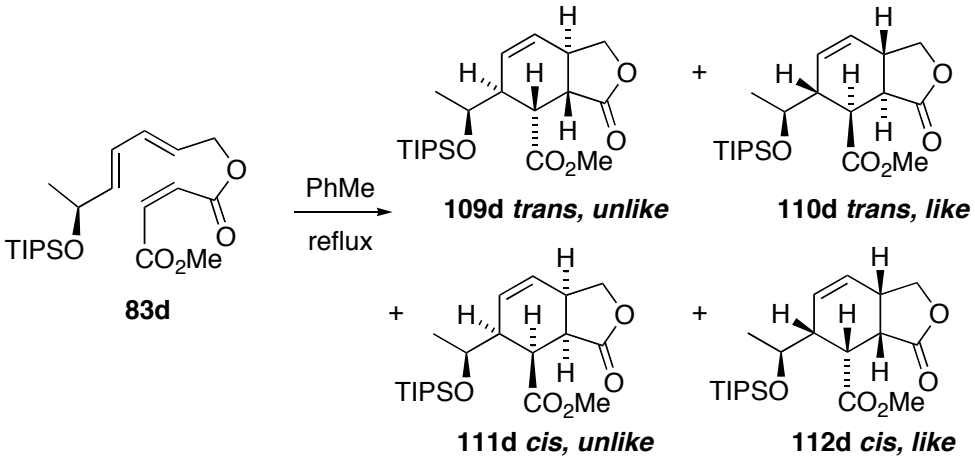
A solution of **83a** (35 mg, 0.15 mmol, 1.0 equiv) and BHT (4 mg, 0.02 mmol, 0.1 equiv) in toluene (15 mL) was heated at reflux for 4.5 h. The reaction mixture was concentrated *in vacuo.* After column chromatography on silica (hexanes/ethyl acetate 40:60) a mixture of 4 products **109a:110a:111a:112a** (31 mg, 0.13 mmol, 88%) was obtained.

Thermal IMDA reaction of (2*E*,4*E*,6*S*)-6-((trimethylsilyl)oxy)hepta-2,4-dienyl methyl-(2*Z*)-but-2-enedioate **83b**



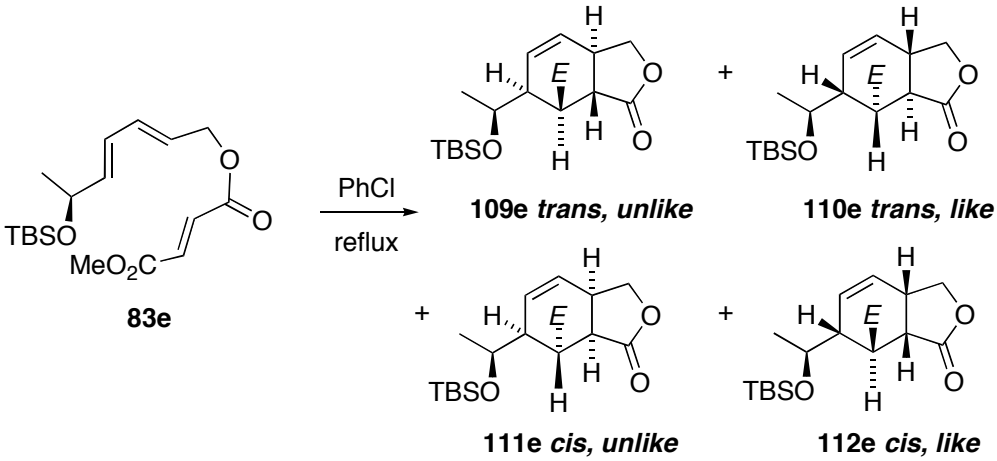
A solution of **83b** (99 mg, 0.32 mmol, 1.0 equiv) and BHT (7 mg, 0.03 mmol, 0.1 equiv) in toluene (32 mL) was heated at reflux for 6.5 h. The reaction mixture was concentrated *in vacuo.* After column chromatography on silica (hexanes/ethyl acetate 60:40) a mixture of 4 products **109b, 110b, 111b,** and **112b** (82 mg, 0.27 mmol, 83%) was obtained.

Thermal IMDA reaction of (2*E*,4*E*,6*S*)-6-((trimethylsilyl)oxy)hepta-2,4-dienyl methyl-(2*Z*)-but-2-enedioate **83d**



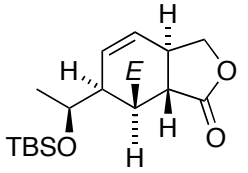
A solution of **83d** (53 mg, 0.13 mmol, 1.0 equiv) and BHT (3 mg, 0.01 mmol, 0.1 equiv) in toluene (13 mL) was heated at reflux for 8.25 h. The reaction mixture was concentrated *in vacuo.* After column chromatography on silica (hexanes/ethyl acetate 85:15) a mixture of 4 products **109d, 110d, 111d** and **112d** (45 mg, 0.11 mmol, 85%) was obtained.

IMDA reaction of (2*E*,4*E*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hepta-2,4-dienyl methyl-(2*E*)-but-2-enedioate **83e**



A solution of **83e** (173 mg, 0.51 mmol, 1.0 equiv) and BHT (0.05 equiv) in chlorobenzene (102 mL) was heated at reflux for 43 h. The solution was cooled to room temperature and concentrated *in vacuo*. After column chromatography on silica (hexanes/ethyl acetate 80:20) a mixture of 4 products (130 mg, 0.38 mmol, 75%) was obtained. Normal phase HPLC of the mixture yielded compounds **109e**, **110e**, **111e** and **112e** in a ratio of 8:28:40:24.

Methyl (3a*S*,4*S*,5*S*,7a*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyl)oxyethyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **109e**

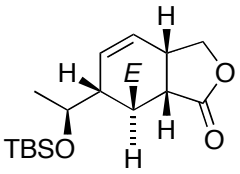


109e *trans, unlike*

E = CO_2Me

$[\alpha]_D^{25}$ = −164.52 (c= 0.420, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.00 (2H, m), 4.46 (1H, t, *J* = 7.4 Hz), 3.95 (1H, dd, *J* = 11.5, 8.4 Hz), 3.77 (3H, s), 3.68 (1H, m), 3.03 (1H, dd, *J* = 12.3, 9.0 Hz), 2.93 (1H, m), 2.57 (1H,t, *J* = 12.7 Hz), 1.10 (3H, d, *J* = 6.4 Hz), 0.86 (9H, s), 0.04, 0.04 (6H, 2 x s). ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 174.2, 171.3, 129.9, 124.5, 70.5, 68.9, 51.8, 44.7, 41.7, 41.5, 41.2, 25.8, 20.7, 18.1, -4.7, -5.0 ppm. IR (thin film): ν = 3032, 2954, 2930, 1788, 1735 cm^{-1}. EIMS (70 eV) *m/z* (%): 339 (4), 310 (20), 297 (90), 159 (55), 73 (100); HRMS: calcd for $C_{17}H_{27}O_5Si$ [M^+-CH_3-]:339.1628; found: 339.1625.

Methyl (3a*S*,4*S*,5*R*,7a*S*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyl)oxyethyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **112e**

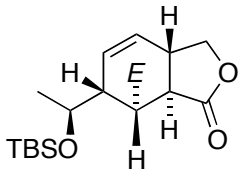


112e *cis, like*

E = CO_2Me

$[\alpha]_D^{25}$ = +191.98 (c= 0.424, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.94 (1H, ddd, *J* = 10.3, 1.9, 1.9 Hz), 5.87 (1H, ddd, *J* = 9.9, 3.3, 3.3 Hz), 4.43 (1H, dd, *J* = 8.0, 6.7 Hz), 3.90 (1H, dq, *J* = 6.6, 2.7 Hz), 3.88 (1H, dd, *J* = 11.3, 7.8 Hz), 3.77 (3H, s), 3.14 (1H, dd, *J* = 14.4, 12.0 Hz), 2.95 (1H, dd, *J* = 11.1, 7.4 Hz), 2.78 (1H, m), 2.64 (1H, m), 1.24 (3H, d, *J* = 6.4 Hz), 0.90 (9H, s), 0.07, 0.04 (6H, 2 x s). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 174.3, 171.5, 129.5, 124.5, 70.3, 69.4, 51.8, 45.4, 43.8, 41.6, 41.3, 26.0, 23.0, 18.2, -3.7, -4.8 ppm. IR (thin film): *ν* = 3015, 2951, 2929, 2904, 2882, 1783, 1748 cm^{-1}. EIMS (70 eV) *m/z* (%):310 (15), 297 (100), 159 (35), 75 (65); HRMS: calcd for $C_{14}H_{21}O_5Si$ [M^+-C_4H_9]:297.1158; found: 297.1157.

Methyl (3a*R*,4*R*,5*R*,7a*S*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyl)oxyethyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **110e**

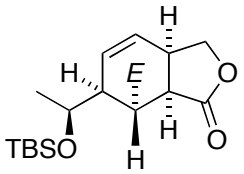


110e *trans, like*

E = CO_2Me

$[\alpha]_D^{25}$ = −44.88 (c= 0.205, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.94 (1H, ddd, *J* = 10.4, 2.3, 2.3 Hz), 5.70 (1H, ddd, *J* = 10.4, 2.9, 2.9 Hz), 4.45 (1H, dd, *J* = 8.9, 7.5 Hz), 3.98 (1H, dd, *J* = 8.8, 6.0 Hz), 3.75 (1H, dq, *J* = 12.3, 6.3 Hz), 3.75 (3H, s), 3.20 (1H, m), 3.10 (1H, dd, *J* = 7.7, 7.7 Hz), 2.99 (1H, dd, *J* = 6.6, 6.6 Hz), 2.58 (1H, m), 1.09 (3H, d, *J* = 6.5 Hz), 0.90 (9H, s), 0.10, 0.06 (6H, 2 x s). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 177.0, 174.4, 129.3, 125.0, 71.7, 69.0, 52.4, 44.6, 39.9, 39.0, 34.7, 25.9, 20.2, 18.1, -4.3, -4.8 ppm. IR (thin film): *ν* = 2930, 2847, 1778, 1735 cm^{-1}. EIMS (70 eV) *m/z* (%):339 (5), 297 (100), 159 (55), 73 (75); HRMS: calcd for $C_{14}H_{21}O_5Si$ [M^+-C_4H_9-]:297.1158; found: 297.1158.

Methyl (3a*R*,4*R*,5*S*,7a*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyl)oxyethyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **111e**

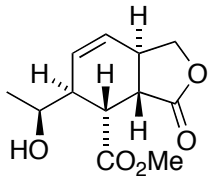


111e *cis, unlike*

E = CO_2Me

$[\alpha]_D^{25}$ = +92.86 (c= 0.868,). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.96 (1H, ddd, *J* = 10.5, 3.2, 2.1 Hz), 5.66 (1H, ddd, *J* = 10.4, 3.3, 2.6 Hz), 4.45 (1H, dd, *J* = 8.9, 7.5 Hz), 3.97, (1H, dd, *J* = 9.3, 6.5 Hz), 3.76 (1H, dq, *J* = 11.9, 6.0 Hz), 3.73 (3H, s), 3.20 (1H, m), 3.07 (1H, dd, *J* = 8.0, 8.0 Hz), 2.93 (1H, dd, *J* = 7.5, 6.1 Hz), 2.52 (1H, m), 1.25 (3H, d, *J* = 6.4 Hz), 0.87 (9H, s), 0.02, 0.00 (6H, 2 x s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 177.3, 174.3, 130.3, 123.9, 71.9, 69.8, 52.3, 44.4, 40.0, 39.3, 34.6, 25.9, 21.6, 18.1, -4.2, -5.1 ppm. IR (thin film): *ν* = 2929, 2856, 1788, 1735 cm^{-1}. EIMS (70 eV) *m/z* (%): 339 (4), 310 (15), 297 (100), 159 (50), 73 (70); HRMS: calcd for $C_{17}H_{27}O_5Si$ [M^+-CH_3]: 339.1628; found: 339.1629.

Methyl (3a*S*,4*R*,5*S*,7a*R*)-5-[(1*S*)-1-hydroxyethyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **109a**

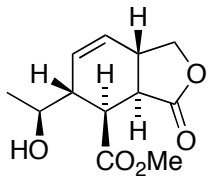


109a *trans, unlike*

To a stirred solution of **109c** (40 mg, 0.11 mmol, 1.0 equiv) in $CDCl_3$ (500 μL) was added trifluoroacetic acid (348 μL, 4.5 mmol, 40 equiv). After 2.5 h the mixture was concentrated *in vacuo*. Chromatography of the crude product on silica (hexane/ethyl acetate 50:50) gave **109a** (26 mg, 0.11 mmol, 95%) as a colourless oil. $[\alpha]_D^{25}$ = +3.20 (c= 0.625, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.06 (1H, dt, *J* = 10.0, 2.1 Hz), 5.82 (1H, dt, *J* = 10.1, 3.1 Hz), 4.55 (1H, t, *J* = 8.3 Hz), 4.05 (1H, dq, *J* = 6.5, 4.2 Hz), 3.89 (1H, dd, *J* = 11.5, 8.2 Hz), 3.73 (3H, s), 3.31 (1H, d, *J* = 4.3 Hz), 3.24 (1H, m), 2.80 (1H, m), 2.64 (1H, dd, *J* = 13.6, 4.3 Hz), 1.97 (1H, bs), 1.30 (3H, d, *J* = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 174.8, 172.9, 128.0, 127.1, 71.4, 70.6, 52.3, 45.4, 42.8, 39.4, 36.4, 21.2 ppm. IR (thin film): *ν* = 3462, 2962, 2902, 1781, 1730

cm^{-1}. EIMS (70 eV) *m/z* (%): 209 (15), 196 (35), 136 (70), 119 (75), 91 (100) ; HRMS: calcd for $C_{11}H_{13}O_4$ [M-OMe]: 209.0814; found: 209.0815.

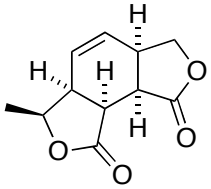
Methyl (3a*R*,4*S*,5*R*,7a*S*)-5-[(1*S*)-1-hydroxyethyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **110a**



110a *trans, like*

To a stirred solution of **110c** (15 mg, 0.04 mmol, 1.0 equiv) in $CDCl_3$ (300 μL) was added trifluoroacetic acid (132 μL, 1.8 mmol, 40 equiv). After 5 h the mixture was concentrated *in vacuo*. Chromatography of the crude product on silica (hexane/ethyl acetate 50:50) gave **110a** (10 mg, 0.04 mmol, 98%) as colourless crystals. $[\alpha]_D^{25}$ = -20.57 (c = 0.125, chloroform). m.p 128 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.03 (1H, dt, *J* = 10.0, 1.8 Hz), 5.72 (1H, dt, *J* = 9.8, 3.1 Hz), 4.55 (1H, t, *J* = 7.9 Hz), 3.94 (1H, dq, *J* = 6.4, 4.8 Hz), 3.87 (1H, dd, *J* = 11.4, 8.1 Hz), 3.71 (3H, s), 3.49 (1H, d, *J* = 4.3 Hz), 3.28 (1H, m), 2.67 (1H, m), 2.49 (1H, dd, *J* = 13.6, 4.1 Hz), 1.56 (1H, bs), 1.35 (3H, d, *J* = 6.2 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 174.8, 173.0, 130.9, 126.8, 70.6, 70.2, 52.4, 46.5, 42.8, 36.3, 36.2, 21.5 ppm. IR (thin film): *ν* = 3469, 2917, 1780, 1730 cm^{-1}. EIMS (70 eV) *m/z* (%): 209 (20), 196 (35), 150 (45), 136 (70), 119 (70), 91 (100); HRMS: calcd for $C_{11}H_{13}O_4$ [M-OMe]: 209.0814; found: 209.0814.

(3*S*,3a*R*,5a*S*,8a*S*,8b*R*)-3-Methyl-3,3a,5a,6,8a,8b-hexahydrofuro[3,4-e][2]benzo-furan-1,8-dione **113**

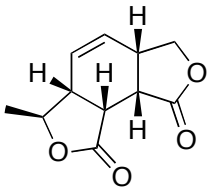


113

To a stirred solution of **111c** (31 mg, 0.09 mmol, 1.0 equiv) in $CDCl_3$ (300 μL) was added trifluoroacetic acid (250 μL, 3.20 mmol, 36 equiv). The mixture was stirred at room temperature for 2.25 h before being concentrated *in vacuo*. After column chromatography on silica (hexane/ethyl acetate 15:85) **113** (13 mg, 0.06 mmol, 66%) was obtained as a colourless crystalline solid. m.p 90 °C ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.89 (1H, ddd, *J* = 10.3, 3.4, 2.0 Hz), 5.80 (1H, ddd, *J* = 10.3, 2.0, 2.0 Hz), 4.37 (1H,

dd, J = 9.3, 6.4 Hz), 4.24 (1H, dq, J = 8.3, 6.4 Hz), 4.13 (1H, dd, J = 9.3, 2.9 Hz), 3.24 (1H, dd, J = 6.9, 6.9 Hz), 3.19-3.11 (2H, m), 2.68 (1H, m), 1.47 (3H, d, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 175.7, 127.9, 126.9, 80.4, 71.4, 41.7, 37.4, 37.2, 35.6, 19.4 ppm . IR (KBr disc): ν 2989, 2878, 2359, 2339, 1764 cm^{-1} . EIMS (70 eV) *m/z* (%): 209 (30), 164 (47), 149 (20), 136 (70), 92 (100). HRMS: calcd for $C_{11}H_{13}O_4$ $[M+H]^+$: 209.0814; found 209.0813.

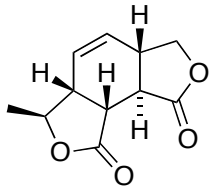
(3*S*,3a*S*,5a*R*,8a*R*,8b*S*)-3-Methyl-3,3a,5a,6,8a,8b-hexahydrofuro[3,4-e][2]benzo-furan-1,8-dione **114.**



114

To a stirred solution of **112c** (10 mg, 0.03 mmol, 1.0 equiv) in $CDCl_3$ (300 µL) at room temperature was added trifluoroacteic acid (89 µL, 1.15 mmol, 40 equiv). The mixture was stirred at room temperature for 3 h before being concentrated *in vacuo*. Recrystalisation from TBME gave (3*S*,3a*S*,5a*R*,8a*R*,8b*S*)-3-methyl-3,3a,5a,6,8a,8b-hexahydrofuro[3,4-e][2]benzo-furan-1,8-dione **114** (5mg, 0.02 mmol, 85%) as a colourless crystalline solid. $[\alpha]_D^{25}$ = -1.19 (c = 0.23, chloroform). m.p 139 ^oC ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 (2H, m), 4.71 (1H, dq, J = 6.4, 5.3 Hz) 4.51 (1H, t, J = 8.6 Hz), 3.90 (1H, dd, J = 10.2, 8.5 Hz), 3.39 (1H, t, J = 6.6 Hz), 3.20 (1H, m), 3.06 (1H, m), 2.97 (1H, dd, J = 9.5, 6.8 Hz), 1.46 (3H, d, J = 6.4 Hz) ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.8, 175.3, 147.8, 127.8, 124.0, 71.6, 39.9, 39.3, 35.9, 34.6, 29.8, 16.0 ppm. IR (thin film): ν = 3749, 2916, 1768 cm^{-1} . EIMS (70 eV) *m/z* (%): 208 (10), 164 (40), 149 (15), 136 (75), 91 (100). HRMS: calcd for $C_{11}H_{12}O_4$ $[M]^+$: 208.0736; found 208.0730.

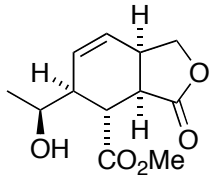
(3*S*,3a*S*,5a*R*,8a*S*,8b*S*)-3-Methyl-3,3a,5a,6,8a,8b-hexahydrofuro[3,4-e][2]benzo-furan-1,8-dione **115**



115

To a stirred solution of **110e** (6 mg, 0.02 mmol, 1.0 equiv) in $CDCl_3$ (300 μL) at room temperature was added trifluoroacteic acid (55 μL). The mixture was stirred at room temperature for 3 h before being concentrated *in vacuo*. Recrystalisation from TBME gave **115** (3mg, 0.01 mmol, 81%) as a colourless crystalline solid. $[\alpha]_D^{25}$ = -59.13 (c = 0.12, chloroform). m.p 170 ^oC ^1H NMR (500 MHz, $CDCl_3$): δ 6.05 (1H, dt, *J* = 9.8, 2.1 Hz), 5.80 (1H, dt, *J* = 9.8, 3.3 Hz), 4.55 (1H, dd, *J* = 8.4, 7.1 Hz), 4.34 (1H, dq, *J* = 8.6, 6.1 Hz), 4.00 (1H, dd, *J* = 10.5, 7.7 Hz), 3.13 (1H, dd, *J* = 12.2, 8.8 Hz), 2.99-2.79 (2H, m), 2.43 (1H, t, *J* = 13.2 Hz), 1.51 (3H, d, *J* = 6.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 173.5, 172.4, 127.7, 126.6, 79.9, 70.0, 45.2, 40.7, 40.4, 39.7, 20.0 ppm. IR (thin film): *ν* = 3749, 2973, 2917, 2851, 1788 cm^{-1}. EIMS (70 eV) *m/z* (%): 208 (10), 164 (35), 149 (20), 136 (80), 91 (100). HRMS: calcd for $C_{11}H_{12}O_4$ $[M]^+$: 208.0736; found 208.0730.

Methyl (3a*R*,4*R*,5*S*,7a*R*)-5-[(1*S*)-1-hydroxyethyl]-3-oxo-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **116**



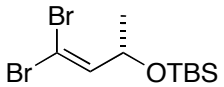
116

To a stirred solution of **111e** (21 mg, 0.09 mmol, 1.0 equiv) in dichloromethane (1 mL) was added trifluoroacetic acid (183 μL, 3.75 mmol, 40 equiv). After 5 h the mixture was concentrated *in vacuo*. Chromatography of the crude product on silica (hexane/ethyl acetate 50:50) gave **116** (12 mg, 0.06 mmol, 85%) as colourless crystals. $[\alpha]_D^{25}$ = + 83.85 (c= 0.390, chloroform). m.p 90 ^oC ^1H NMR (500 MHz, $CDCl_3$): δ 5.99 (1H, ddd, *J* = 10.2, 3.1, 1.9 Hz), 5.78 (1H, dt, *J* = 10.2, 2.8 Hz), 4.50 (1H, dd, *J* = 8.7, 7.5 Hz), 4.08 (1H, dd, *J* = 8.7, 5.0 Hz), 3.90 (1H, dq, *J* = 11.8, 6.0 Hz), 3.77 (3H, s), 3.24 (1H, m), 3.18 (1H, t, *J* = 6.4 Hz), 3.04 (1H, t, *J* = 6.0 Hz), 2.62 (1H, m), 1.66 (1H, bs), 1.33 (3H, d, *J* = 6.3 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 177.7, 174.3, 128.2,

126.1, 71.8, 69.8, 52.6, 43.4, 40.2, 39.7, 34.3, 21.1 ppm. IR (thin film): ν = 3503, 2956, 2917, 1770, 1733 cm^{-1}. EIMS (70 eV) *m/z* (%): 209 (4), 196 (80), 164 (35), 136 (65), 105 (40), 92 (100); HRMS: calcd for $C_{11}H_{13}O_4$ [M-OMe]: 209.0814; found: 209.0817.

7.3 Chapter 3

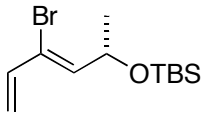
1,1-Dibromo[(3*S*)-(*tert*-butyldimethylsilyl)oxy]-1-butene **139**



139

This compound was prepared according to modified literature procedures.[91,219,220] To a stirred solution of triphenyl phospine (56.9 g, 217 mmol, 4.0 equiv) in dichloromethane (200 mL) at 0 ^oC under argon, was added a solution of carbon tetrabromide (35.98 g, 108 mmol, 2 equiv) in dichloromethane (80 mL) over 45 min, *via* cannula. The reaction mixture was stirred at rt for 30 min before being cooled to 0 ^oC. A solution of aldehyde **93**[91,219,220] (10.22 g, 54 mmol, 1.0 equiv) in dichloromethane (40 mL) was added dropwise. The reaction mixture was warmed to rt and stirring continued for a further 30 min. To the reaction mixture was added hexanes and the resulting precipitate was filtered. The filtrate was then concentrated under reduced pressure. After column chromatography (hexanes) **139** (14.15 g, 41 mmol, 76%) was obtained as a colourless oil. ^1H NMR data was consistent with that reported in the literature.[91,219,220]

(2*S*, 3*Z*)-4-Bromo[(*tert*-butyldimethylsilyl)oxy]-hexa-3,5-diene **140**

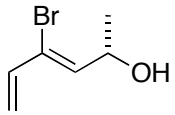


140

This compound was prepared according to modified literature procedures.[85] To a stirred solution of **139** (1.0 g, 2.9 mmol, 1.0 equiv) and tributyl(vinyl)tin (970 mg, 3.05 mmol, 1.05 equiv) in tetrahydrofuran (16 mL) was added triphenyl arsine (89 mg, 0.29 mmol, 0.10 equiv) and tris(dibenzylideneacetone)dipalladium (0) (33 mg, 0.04 mmol, 0.013 equiv). The mixture was freeze/thaw degassed (x 2) then heated to 50 ^oC and stirred for 20 h. The mixture was diluted with diethyl ether (80 mL) and filtered through a short pad of silica. The filtrate was washed with aq. ammonia solution (20 mL x 3), dried and concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 98:2) gave **140**

(638 mg, 2.2 mmol, 76%). ^{1}H NMR data was consistent with that reported in the literature.[85]

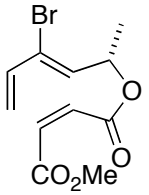
(2*S*, 3*Z*)-4-Bromohexa-3,5-dien-2-ol **138**



138

To a stirred solution of **140** (230 mg, 0.78 mmol, 1.0 equiv) in tetrahydrofuran (10 mL) at 0 ^{o}C was added tetrabutyl ammonium fluoride (1.0 M sol, 1.58 mL, 1.58 mmol, 2.0 equiv). The mixture was warmed to rt and stirring was continued for 4 h. The reaction mixture was diluted with diethyl ether (20 mL) and partitioned against sat. NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 90:10) gave **138** (88 mg, 0.50 mmol, 64%) as a colourless oil. ^{1}H NMR data was consistent with that reported in the literature.[85]

Methyl (1*S*,2*E*)-3-Bromo-1-methylpenta-2,4-dien-1-yl Maleate **43*Z***

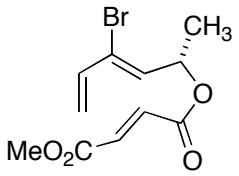


43*Z*

Triethylamine (52 μL, 0.37 mmol, 1.6 equiv), maleic anhydride (64 mg, 0.65 mmol, 2.8 equiv) and DMAP (3 mg, 0.03 mmol, 0.12 equiv) were added to a stirred solution of alcohol **141** (41 mg, 0.23 mmol, 1.0 equiv) in dichloromethane (2 mL) at 0 ^{o}C. The mixture was stirred at this temperature for 2.5 h. The solution was allowed to warm to rt before being diluted with diethyl ether (20 mL). The mixture was washed with 2M HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was diluted with tetrahydrofuran (5 mL) and cooled to -78 ^{o}C with stirring. An ethereal solution of diazomethane was added dropwise until tlc confirmed the reaction had gone to completion. Excess diazomethane was removed by bubbling N_2 gas through the solution. The solution was concentrated *in vacuo* and subjected to column chromatography on silica (hexanes/ethyl acetate 90:10) to give maleate **43*Z*** (27 mg, 0.09 mmol, 40 %) as a colourless oil. $[\alpha] = +37.4$ (c = 0.42, chloroform). ^{1}H NMR (300 MHz, C_6D_6): δ 6.03 (1H, dq, J = 7.7, 6.3 Hz), 5.90 (1H,

ddd, J = 16.3, 10.3, 0.8 Hz), 5.79 (1H, dd, J = 7.7, 0.7 Hz), 5.68 (2H, d, J = 3.2 Hz), 5.58 (1H, dt, J = 16.3, 0.7 Hz), 4.94 (1H, d, J = 10.5 Hz), 3.31 (3H, s), 1.23 (3H, d, J = 6.5 Hz) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ 164.9, 163.7, 134.9, 133.4, 129.9, 129.0, 126.2, 119.5, 71.4, 51.1, 18.8 ppm . IR (thin film): ν 2918, 1788, 1731 cm^{-1}. EIMS (70 eV) *m/z* (%): 290 (2), 288 (2), 175 (15), 113 (100). HRMS: calcd for $C_{11}H_{13}O_4{}^{79}Br$ $[M]^+$: 287.9997; found: 288.0003.

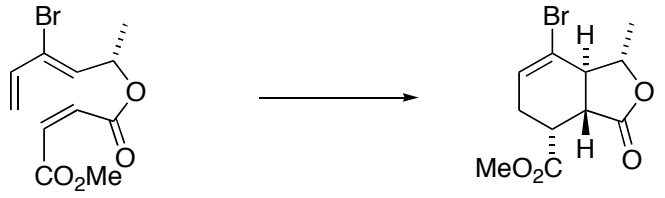
Methyl (1*S*,2*E*)-3-bromo-1-methylpenta-2,4-dien-1-yl Fumarate **43*E***



43*E*

To a stirred solution of alcohol **141** (54 mg, 0.31 mmol, 1.0 equiv) in diethyl ether (1.5 mL) at room temperature was added (*E*)-3-methoxycarbonylacrylic acid (72 mg, 0.5 mmol, 1.8 equiv), DCC (127 mg, 0.61 mmol, 2.0 equiv) and DMAP (6 mg, 0.05 mmol, 0.15 equiv). Stirring was continued for 3 h. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude residue was subjected to column chromatography on silica (hexanes/ethyl acetate 9:1) to give fumarate **43*E*** (56 mg, 0.19 mmol, 63%) as a colourless oil. $[\alpha]$ = + 94.0 (c = 0.92, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (2H, s), 6.29 (1H, dd, J = 16.3, 10.4 Hz), 6.03 (1H, d, J = 7.9 Hz), 5.88 (1H, dq, J = 6.6, 6.3 Hz), 5.68 (1H, d, J = 16.3 Hz), 5.32 (1H, d, J = 10.5 Hz), 3.80 (3H, s), 1.42 (3H, d, J = 6.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 164.0, 134.9, 133.8, 133.6, 132.6, 126.8, 120.6, 72.0, 52.4, 19.5 ppm . IR (thin film): ν 2953, 2849, 1723, 1645 cm^{-1} . EIMS (70 eV) *m/z* (%): 290 (18), 288 (20), 209 (25), 159 (50), 113 (95), 85 (80), 79 (90), 59 (75), 53 (100). HRMS: calcd for $C_{11}H_{13}O_4{}^{79}Br$ $[M]^+$: 287.9997; found: 288.0003.

IMDA Reaction of Maleate **43*Z*** in Toluene at 110 °C



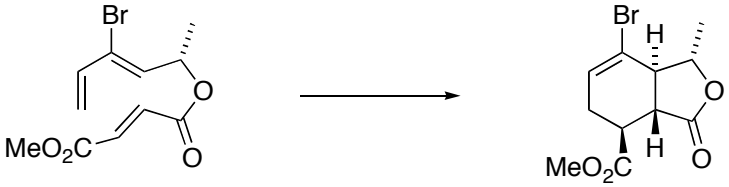
43*Z* ***trans,lk*-142*Z***

A solution of maleate **43*Z*** (12 mg, 42 μmol, 1.0 equiv) and BHT (1 mg, 4.5 μmol, 0.1 equiv) in toluene (4.2 mL) was stirred at 110 °C for 40 min. The reaction mixture was concentrated *in vacuo*. After column chromatography cycloadduct **142*Z*** (10 mg, 35 μmol, 83%) was obtained as a single isomer.

Methyl (3*S*,3a*R*,7*R*,7a*S*)-4-bromo-3-methyl-1-oxo-3,3a,6,7,7a-hexahydro-7-isobenzofurancarboxylate **142*Z***

White crystalline solid after recrystallistaion from hexane/dichloromethane. m.p. 86-88 °C $[\alpha] = -42.0$ (c = 0.82, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.05 (1H, m), 4.36 (1H, dq, J = 9.7, 5.9 Hz), 3.74 (3H, s), 3.35 (1H, dd, J = 8.3, 3.8 Hz), 3.11 (1H, m), 2.77 (1H, m), 2.71 (1H, dd, J = 13.2, 3.5 Hz), 2.58 (1H, ddt, J = 19.1, 8.0, 3.7 Hz), 1.69 (1H, d, J = 6.1 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 172.0, 130.0, 116.4, 79.8, 52.6, 47.3, 47.3, 35.0, 31.2, 19.9 ppm . IR (thin film): ν 2920, 1787, 1732 cm^{-1} . EIMS (70 eV) *m/z* (%): 290 (2), 244 (30), 228 (15), 105 (100), 77 (95). HRMS: calcd for $C_{11}H_{14}O_4{}^{81}Br$ $[M+H]^+$: 289.0075; found: 289.0082.

IMDA Reaction of Fumarate **43*E*** in Toluene at 110 °C



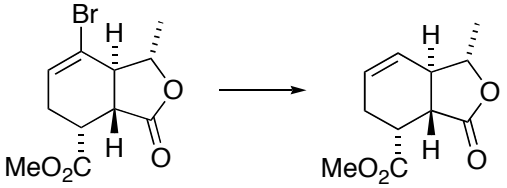
43*E* ***trans,lk*-142*E***

A solution of fumarate **43*E*** (15 mg, 50 μmol, 1.0 equiv) and BHT (1 mg, 4.5 μmol, 0.1 equiv) in toluene (5 mL) was stirred at 110 °C for 9 h 50 min. The reaction mixture was concentrated *in vacuo*. After column chromatography cycloadduct **142*E*** (10 mg, 36 μmol, 71%) was obtained as a single isomer.

Methyl (3*S*,3a*R*,7*S*,7a*S*)-4-bromo-3-methyl-1-oxo-3,3a,6,7,7a-hexahydro-7-isobenzofurancarboxylate **142*E***

White crystalline solid after recrystallisation from hepatane/dichloromethane. m.p. 181-182 °C. [α] = + 88.7 (c = 0.94, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.09 (1H, q, *J* = 3.4 Hz), 4.41 (1H, dq, *J* = 10.0, 6.2 Hz), 3.78 (3H,s), 3.00 (1H, dd, *J* = 12.5, 11.7 Hz), 2.77 (1H, ddd, *J* = 11.7, 10.3, 7.0 Hz), 2.66 (1H, m), 2.53 (1H, dddd, *J* = 18.4, 6.8, 4.5, 2.7 Hz) 2.44 (1H, ddt, *J* = 18.4, 10.1, 3.7 Hz), 1.66 (3H, d, *J* = 6.2 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 172.0, 130.3, 115.6, 79.7, 52.5, 50.8, 47.6, 39.0, 32.7, 19.8 ppm . IR (thin film): ν 2990, 2937, 1779, 1743 cm^{-1} . EIMS (70 eV) *m/z* (%): 288 (20), 230 (25), 213 (60), 105 (98), 77 (100). HRMS: calcd for $C_{11}H_{14}O_4{}^{81}Br$ $[M+H]^+$: 289.0075; found: 289.0081.

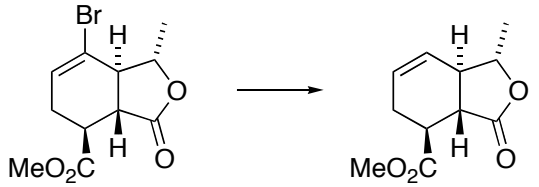
Reductive debromination of methyl (3*S*,3a*R*,7*R*,7a*S*)-4-bromo-3-methyl-1-oxo-3,3a,6,7,7a-hexahydro-7-isobenzofurancarboxylate **142*Z***



trans,lk*-142*Z ***trans,lk*-39*Z***

To a solution of cycloadduct **142*Z*** (10 mg, 30 μmol, 1.0 equiv) in toluene (500 μL) at room temperature was added tributyltin hydride (27 μL, 0.10 mmol, 2.9 equiv) and AIBN (1.0 mg, 6 μmol, 0.2 equiv) before warming to 80 °C for 3 h 50 min. The reaction mixture was then concentrated *in vacuo*. The crude product was passed through a short pad of silica (dichloromethane) to give **39*Z*** (4 mg, 18 mmol, 59%), spectroscopically identical to the major product obtained upon IMDA reaction of **38*Z*.** ^{1}H NMR data was consistent with that reported in the literature.[112]

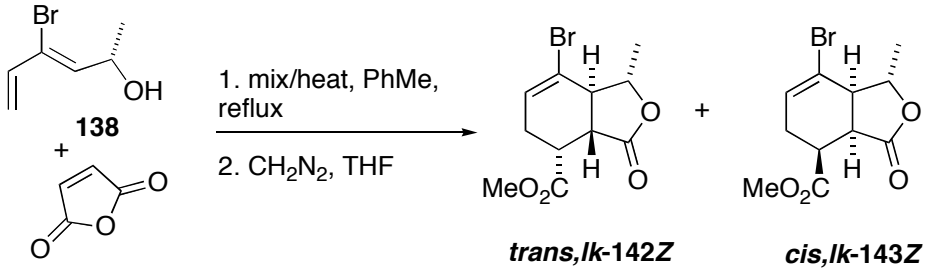
Reductive debromination of methyl (3*S*,3a*R*,7*S*,7a*S*)-4-bromo-3-methyl-1-oxo-3,3a,6,7,7a-hexahydro-7-isobenzofurancarboxylate **142*E***



trans,lk*-142*E ***trans,lk*-39*E***

To a solution of cycloadduct **142*E*** (10 mg, 30 µmol, 1.0 equiv) in toluene (500 µL) at rt was added tributyltin hydride (27 µL, 0.10 mmol, 2.9 equiv) and AIBN (1 mg, 6 µmol, 0.2 equiv) before warming to 80 °C for 2 h 40 min. The reaction mixture was then concentrated *in vacuo*. The crude product was passed through a short pad of silica (dichloromethane) to give **39*E*** (4 mg, 18 µmol, 59%), spectroscopically identical to the major product obtained upon IMDA reaction of **38*E***

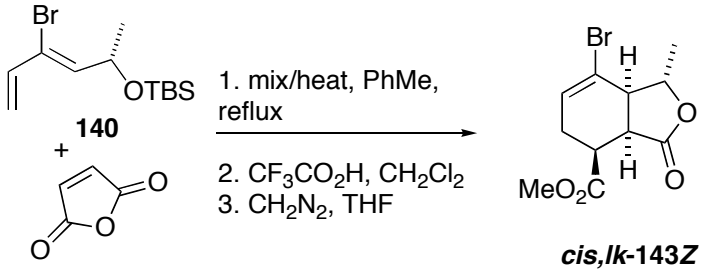
"Mix and Heat" Procedure for (*S*,*Z*)-4-bromohexa-3,5-dien-2-ol **138**



trans,lk*-142*Z ***cis,lk*-143*Z***

To a solution of **138** (22 mg, 0.13 mmol, 1.0 equiv) in toluene (1mL) was added maleic anhydride (18 mg, 0.18 mmol, 1.5 equiv). The mixture was heated at reflux for 5 h 30 min then concentrated *in vacuo*. The crude material was diluted with tetrahydrofuran (5 mL) and cooled to -78 ^{o}C with stirring. An ethereal solution of diazomethane was added dropwise until tlc confirmed the reaction had gone to completion. Excess diazomethane was removed by bubbling N_2 gas through the solution. The solution was concentrated *in vacuo* and subjected to column chromatography on silica (hexanes/ethyl acetate 88:12) to give a mixture of **142Z** and **143*Z*** 13:87 (21 mg, 0.08 mmol, 58%).

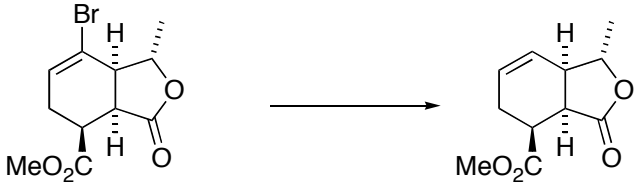
"Mix and Heat" Procedure for ((*S*,*Z*)-4-bromohexa-3,5-dien-2-yloxy)(*tert*-butyl)dimethylsilane **140**



cis,lk*-143*Z

To a solution of **140** (30 mg, 0.10 mmol, 1.0 equiv) in toluene (1 mL) was added maleic anhydride (11 mg, 0.11 mmol, 1.1 equiv). The mixture was heated at reflux for 74 h then concentrated *in vacuo*. The crude material was dissolved in dichloromethane (2 mL) and trifluoroacetic acid (250 µL) was added the reaction mixture was stirred at rt for 18h then concentrated *in vacuo.* The crude material was diluted with tetrahydrofuran (5 mL) and cooled to -78 ^{o}C with stirring. An ethereal solution of diazomethane was added dropwise until tlc confirmed the reaction had gone to completion. Excess diazomethane was removed by bubbling N_2 gas through the solution. The solution was concentrated *in vacuo* and subjected to column chromatography on silica (hexanes/ethyl acetate 88:12) to give **143*Z*** (17 mg, 0.06 mmol, 58%). $[\alpha] = +64.6$ (c = 1.4, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.25 (1H, m), 4.84 (1H, q, J = 6.8 Hz), 3.80 (3H,s), 3.74 (1H, ddd, J = 8.3, 4.4, 1.0 Hz), 3.07 (1H, dd, J = 8.3, 1.5 Hz), 2.83 (1H, m), 2.50-2.35 (3H, m), 1.48 (3H, d, J = 6.8 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.7, 171.9, 131.2, 121.7, 79.6, 52.5, 49.6, 41.3, 36.3, 25.5, 20.6 ppm . IR (thin film): ν 2929, 1771, 1735 cm^{-1} . ESIMS (positive ion) *m/z* (%): 313 (90), 311 (95), 289 (100). HRMS: calcd for $C_{11}H_{13}O_4Br$ Na $[M+Na]^+$: 310.9895; found: 310.9897.

Reductive debromination of methyl (3*S*,3a*R*,7*S*,7a*R*)- 4-bromo-3-methyl-1-oxo-3,3a,6,7,7a-hexahydro-7-isobenzofurancarboxylate **143*Z***



cis,lk*-143*Z ***cis,lk*-40*Z***

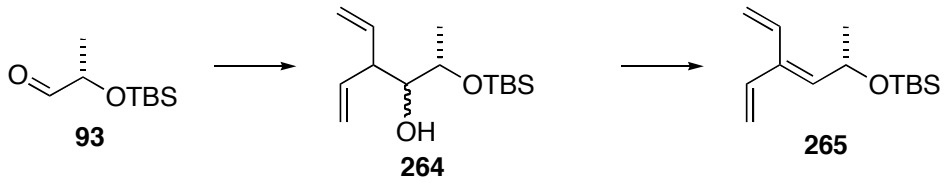
To a solution of cycloadduct **143*Z*** (6 mg, 19 µmol, 1.0 equiv) in toluene (500 µL) at rt was added tributyltin hydride (15 µL, 0.06 mmol, 2.9 equiv) and AIBN (1 mg, 6 µmol, 0.32 equiv) before warming to 80 °C for 3h. The reaction mixture was then

concentrated *in vacuo*. The crude product was passed through a short pad of silica (dichloromethane) to give **40*Z*** (3 mg, 14 μmol, 72%). ^{1}H NMR data was consistent with that reported in the literature.[112]

7.4 Chapter 4

7.4.1 Substituted Chiral Dendralenes

(2*S*)-2-(*tert*-Butyldimethylsilyl)oxy-4-vinylhexa-3,5-diene **265** by indium-mediated coupling



To a stirred solution of aldehyde **93** (500 mg, 2.7 mmol, 1.0 equiv) and (*E*)-1-bromobuta-1,3-diene (463 mg, 3.2, mmol, 1.2 equiv) in dry DMF (1.5 mL) was added indium metal (336 mg, 2.9 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with sat. NH_4Cl solution (5 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with brine (20 mL), dried and concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 96:4) gave **264** (366 mg, 1.4 mmol, 54%) as a 1:1 mixture of diastereomers.

To a stirred solution of **264** (143 mg, 0.56 mmol, 1.0 equiv) in tetrahydrofuran (3 mL) was added triphenyl phosphine (293 mg, 1.12 mmol, 2.0 equiv) and DEAD (176 μL, 1.12 mmol, 2.0 equiv). The mixture was heated at 60 ºC for 3.25 h before being concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 99:1) gave **265** (61 mg, 0.26 mmol, 46%) as a colourless oil. $[\alpha] = -24.3$ (c = 0.77, dichloromethane). ^{1}H NMR (400 MHz, C_6D_6): δ 6.36 (1H, dd, J = 17.6, 11.3 Hz), 6.30 (1H, dd, J = 17.1, 10.8 Hz), 5.67 (1H, d, J = 8.8 Hz), 5.29 (1H, dd, J = 17.6, 2.0 Hz), 5.17 (1H, dd, J = 17.2, 2.0 Hz,), 5.13 (1H, dd, J = 10.3, 2.0 Hz), 4.97 (1H, dd, J = 10.3, 1.5 Hz), 4.73 (1H, dq, J = 8.8, 6.4 Hz), 1.22 (3H, d, J = 6.4 Hz), 0.96 (9H, s), 0.06 (3H, s), 0.05 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 136.8, 135.1, 131.9, 118.4, 115.1, 65.7, 26.0, 24.7, 18.3, -4.3, -4.6 ppm . IR (thin film): ν 2956, 2928, 2894, 2857cm^{-1} . EIMS (70 eV) *m/z* (%): 181 (40), 75 (100). HRMS: calcd for $C_{10}H_{17}OSi$ $[M-C_4H_9]^+$: 181.1049; found 181.1048

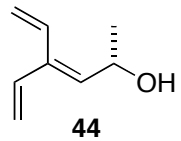
(2*S*)-2-(*tert*-Butyldimethylsilyl)oxy-4-vinylhexa-3,5-diene **265** by Stille coupling

To a stirred solution of dibromoalkene **139**[91,219,220] (1.0 g, 2.9 mmol, 1.0 equiv) and tributyl(vinyl)tin (2.54 g, 7.3 mmol, 2.5 equiv) in acetonitrile (10 mL) under argon was added palladium (II) acetate (33 mg, 5 mol%) and triphenyl phosphine (76 mg, 10 mol%). The mixture was stirred at 60 ºC for 20 h before the addition of a further amount of palladium (II) acetate (15 mg, 2.5 mol%) and triphenyl phosphine (40 mg, 5 mol%). The reaction mixture was stirred at 60 ºC for a further 5 h. The mixture was diluted with diethyl ether (100 mL) and partitioned against aqueous ammonia solution (30 %v/v, 2 x 80 mL). The organic layer was washed with brine (100 mL), dried and concentrated *in vacuo*. After column chromatography on silica (hexanes) **265** (419 mg, 1.76 mmol, 61%) was obtained as a colourless oil.

(2*S*)-2-(*tert*-Butyldimethylsilyl)oxy-4-vinylhexa-3,5-diene **265** by Negishi coupling

To a stirred solution of vinyl magnesium bromide (1.0 M sol. in THF, 14.5 mL, 14.5 mmol, 3.33 equiv) in tetrahyrdofuran (5 mL) at 0 ^{o}C was added zinc bromide (3.4 g, 15 mmol, 3.47 equiv). After 5 min a solution of **139** (1.5 g, 4.4 mmol, 1.0 equiv) and tetrakis(triphenylphosphine)palladium(0) (161 mg, 0.1 mmol, 0.032 equiv) in tetrahyrdofuran (8 mL) was added dropwise *via* canula. Stirring was continued for 2 h before the mixture was diluted with hexane and filtered. The filtrate was concentrated *in vacuo*. After column chromatography (hexanes) **265** (693 mg, 2.9 mmol, 67%) was obtained as a colourless oil.

(2*S*)-4-Vinylhexa-3,5-dien-2-ol **44**

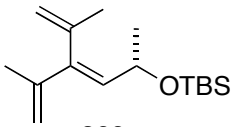


44

To a stirred solution of **265** (863 mg, 3.62 mmol, 1.0 equiv) in tetrahydrofuran at 0 ºC under argon, was added TBAF (1M solution in tetrahydrofuran, 7.25 mL, 7.25 mmol, 2.0 equiv). Stirring was continued at this temperature for 10 min before being warmed to rt. After 2.5 h the reaction mixture was diluted in diethyl ether (50 mL) and partitioned against sat. NH_4Cl (25 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried and concentrated *in vacuo*. After column chromatography on silica (hexanes/ethyl acetate 85:15) the title compound **44** (389 mg, 3.13 mmol, 86%) was obtained as a colourless oil. $[\alpha] = -31.2$

(c = 1.65, dichloromethane) ^{1}H NMR (400 MHz, C_6D_6): δ 6.34 (1H, dd, J = 17.7, 11.4 Hz), 6.31 (1H, dd, J = 10.9, 17.2 Hz), 5.54 (1H, d, J = 8.8 Hz), 5.30 (1H, dd, J = 17.1, 1.5 Hz), 5.20 (1H, dd, J = 17.6, 1.5 Hz), 5.11 (1H, dd, J = 10.8, 1.5 Hz), 4.99 (1H, dd, J = 10.8, 1.5 Hz), 4.55 (1H, dq, J = 8.8, 6.4 Hz), 1.76 (1H, s), 1.14 (3H, d, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ 138.0, 137.3, 136.2, 132.1, 118.6, 115.5, 64.4, 23.7 ppm. IR (thin film): ν 3329 (OH), 3088, 2972, 1603, 1452, 1424, 1368, 1293 cm^{-1} . EIMS (70 eV) *m/z* (%): 124 (10), 109 (20), 43 (100). HRMS: calcd for $C_8H_{12}O$ $[M]^+$: 124.0888; found 124.0892.

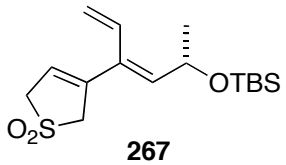
(2*S*)-2-(*tert*-Butyldimethylsilyl)oxy-5-methyl-4-(prop-1-en-2-yl)hexa-3,5-diene **266**



266

To a stirred solution of zinc bromide (360 mg, 1.60 mmol, 5.5 equiv) in tetrahydrofuran (2 mL) was added a solution of isopropenyl magnesium bromide (3.8 mL of a 0.38 M solution in tetrahydrofuran, 1.45 mmol, 5.0 equiv). After 30 min the solution was cooled to -78 ^{o}C and a solution of **139** (100 mg, 0.29 mmol, 1.0 equiv) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol, 0.05 equiv) in tetrahydrofuran (2 mL) was added dropwise *via* canula. Stirring was continued at rt for 18 h before the mixture was diluted with hexane and filtered. The filtrate was concentrated *in vacuo*. After column chromatography (hexanes) **266** (64 mg, 0.24 mmol, 83%) was obtained as a colourless oil. $[\alpha]_D^{25}$ = - 70.5 (c = 2.46, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.49 (1H, d, J = 8.4 Hz), 5.13 (1H, bs), 4.99 (2H, m), 4.69 (1H, bs), 4.53 (1H, dq, J = 8.4, 6.3 Hz), 1.89 (3H, bs), 1.82 (3H, bs), 1.21 (3H, d, J = 6.2 Hz), 0.87 (9H, s), 0.03 (3H, s), 0.02 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7, 142.1, 141.8, 131.5, 115.6, 114.7, 67.2, 26.0, 25.5, 23.5, 20.6, 18.2, -4.2, -4.5 ppm. IR (thin film): ν = 3080, 2956, 2929, 2894, 2857 cm^{-1}. EIMS (70 eV) *m/z* (%): 245 (35), 209 (50), 171 (20), 135 (22), 75 (100); HRMS: calcd for $C_{12}H_{21}OSi$ [M-C_4H_9]: 209.1362; found: 209.1362.

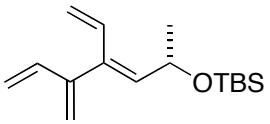
(2*S*, 3*Z*)-2-(*tert*-Butyldimethylsilyl)oxy-4-(1,1-dioxo-2,5-dihydrothiene-3-yl)hexa-3,5-diene **267**



267

To a stirred solution of **140** (172 mg, 0.59 mmol, 1.0 equiv) and 3-(tributylstannyl)-3-sulfolene (289 mg, 0.71 mmol, 1.02 equiv) in acetonitrile (5 mL) under argon was added palladium (II) acetate (4 mg, 0.02 mmol, 5 mol%) and triphenyl phosphine (9 mg, 0.03 mmol, 10 mol%). The reaction mixture was stirred at 60 °C for 48 h. The mixture was diluted in diethyl ether (50 mL) and partitioned against aqueous ammonia solution (30 %v/v, 2 x 40 mL). The organic layer was washed with brine (40 mL), dried and concentrated *in vacuo*. After column chromatography on silica (hexanes/ethyl acetate 90:10) **267** (174 mg, 0.53 mmol, 90%) was obtained as a colourless oil. $[\alpha]_D^{25} = -45.1$ (c = 3.4, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.31 (1H, dd, *J* = 18.0, 11.3 Hz), 5.94 (1H, m), 5.46 (1H, ddd, *J* = 11.2, 1.7, 0.7 Hz), 5.44 (1H, d, *J* = 8.3 Hz), 5.21 (1H, dd, *J* = 17.7, 1.6 Hz), 4.65 (1H, dq, *J* = 8.3, 6.2 Hz), 3.93-3.84 (4H, m), 1.23 (3H, d, *J* = 6.5 Hz), 0.86 (9H, s), 0.02 (3H, s), 0.00 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 137.7, 136.9, 132.2, 130.7, 121.3, 120.0, 65.8, 57.5, 56.3, 25.9, 24.6, 18.2, -4.4, -4.6 ppm. IR (thin film): ν = 2955, 2928, 2856 cm^{-1}. EIMS (70 eV) *m/z* (%): 271 (20), 207 (100), 133 (70), 75 (95); HRMS: calcd for $C_{12}H_{19}O_3SiS$ [M-C_4H_9]: 271.0824; found: 271.0824.

(2*S*, 3*E*)-2-(*tert*-Butyldimethylsilyl)oxy-5-methylene-4-vinylhepta-3,6-diene **268**

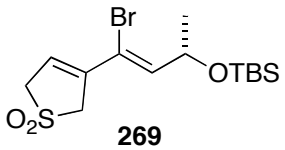


268

A solution of (2*S*, 3*Z*)-4-bromo-2-(*tert*-butyldimethylsilyl)oxy-hexa-3,5-diene **267** (34 mg, 0.10 mmol, 1.0 equiv) in chlorobenzene (10 mL) was heated at reflux for 1.5 h before being concentrated *in vacuo*. After column chromatography (hexanes/ethyl acetate 98:2) **268** (19 mg, 0.07 mmol, 69%) was obtained as a colourless oil. $[\alpha]_D^{25} = +14.3$ (c = 0.86, chloroform). ^{1}H NMR (500 MHz, C_6D_6): δ 6.60 (1H, dd, *J* = 17.5, 11.2 Hz), 6.34 (1H, dd, *J* = 17.3, 10.3 Hz), 5.63 (1H, d, *J* = 8.4 Hz), 5.30 (2H, ddd, *J* = 17.4, 11.9, 1.7 Hz), 5.11-5.02 (4H, m), 4.80 (1H, dq, *J* = 8.3, 6.4 Hz), 1.24 (3H, d, *J* = 6.4 Hz), 0.98 (9H, s), 0.10 (3H, s), 0.09 (3H, s) ppm. ^{13}C NMR (125 MHz, C_6D_6):

δ 147.9, 138.8, 137.5, 136.2, 131.7, 118.1, 118.0, 116.6, 65.3, 26.1, 25.0, 18.3, -4.2, -4.5 ppm. IR (thin film): ν = 2957, 2929, 2857 cm^{-1}. EIMS (70 eV) *m/z* (%): 264 (2), 207 (60), 159 (15), 75 (100); HRMS: calcd for $C_{16}H_{28}OSi$ [M]: 264.1909; found: 264.1905.

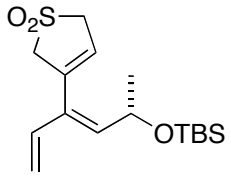
(2*S*, 3*Z*)-4-Bromo-2-(*tert*-butyldimethylsilyl)oxy-4-(1,1-dioxo-2,5-dihydrothiene-3-yl)but-3-ene **269**



269

To a stirred solution of **139** (1.50 g, 4.36 mmol, 1.0 equiv) and 3-(tributylstannyl)-3-sulfolene (1.80 g, 4.40 mmol, 1.0 equiv) in toluene (40 mL) was added tris(dibenzylideneacetone)dipalladium (0) (99 mg, 0.11 mmol, 2.5 mol%) and tri(2-furyl)phosphine (151 mg, 0.65 mmol, 15 mol%). The reaction mixture was heated at 55 ^{o}C for 16 h before cooling to rt and diluting with diethyl ether (50 mL). The organic layer was treated with ammonia solution (2 x 50 mL), washed with brine (50 mL) and concentrated *in vacuo*. After column chromatography (hexanes/ethyl acetate 90:10) **269** (895 mg, 2.34 mmol, 54%) was obtained as a yellow oil. $[\alpha]_D^{25}$ = +1.28 (c= 1.8, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.39 (1H, m), 5.92 (1H, d, *J* = 6.9 Hz), 4.76 (1H, dq, *J* = 6.6, 6.6 Hz), 4.02-3.94 (4H, m), 1.26 (3H, d, *J* = 6.4 Hz), 0.88 (9H, s), 0.08 (3H, s), 0.05 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.9, 133.9, 123.6, 117.2, 69.4, 57.6, 56.4, 25.9, 23.0, 18.2, -4.5, -4.7 ppm. IR (thin film): ν = 2955, 2929, 2887, 2857 cm^{-1}. EIMS (70 eV) *m/z* (%): 325 (5), 323 (6), 281 (55), 279 (53), 261 (60), 259 (65), 181 (100); HRMS: calcd for $C_{10}H_{16}O_3SiS^{81}Br$ [M-C_4H_9]: 324.9752; found: 324.9736.

(2*S*, 3*E*)-2-(*tert*-Butyldimethylsilyl)oxy-4-(1,1-dioxo-2,5-dihydrothiene-3-yl)hexa-3,5-diene **270**

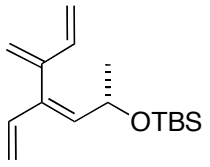


270

A solution of **269** (78 mg, 0.2 mmol, 1.0 equiv) and tributyl(vinyl)tin (107 mg, 0.41 mmol, 2.0 equiv) in acetonitrile (2 mL) was degassed by the freeze/thaw method (x 2). To the resulting solution was added palladium (II) acetate (2 mg, 0.01 mmol, 5 mol%) and triphenyl phosphine (5 mg, 0.02 mmol, 10 mol%). The solution was then heated at

60 °C for 4 h before cooling to RT and dilution with diethyl ether (50 mL). The organic layer was treated with ammonia solution (2 x 50 mL), washed with brine (50 mL) and concentrated *in vacuo*. After column chromatography (hexanes/ethyl acetate 90:10) **270** (62 mg, 0.19 mmol, 92%) was obtained as a colourless oil. $[\alpha]_D^{25} = -10.7$ (c = 2.9, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.27 (1H, dd, *J* = 17.7, 10.7 Hz), 5.82 (1H, m), 5.66 (1H, d, *J* = 8.8 Hz), 5.14 (1H, d, *J* = 10.8, 5.1 Hz), 5.10 (1H, d, *J* = 17.4 Hz), 4.45 (1H, dq, *J* = 8.6, 6.3 Hz), 3.93 (2H, m), 3.77 (2H, dq, *J* = 16.6, 1.6 Hz), 1.22 (3H, d, *J* = 6.3 Hz), 0.86 (9H, s), 0.03 (3H, s), 0.01 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 139.6, 136.9, 134.3, 133.0, 122.9, 116.2, 66.1, 57.5, 56.6, 25.8, 25.2, 18.2, -4.3, -4.4 ppm. IR (thin film): ν = 2956, 2929, 2857 cm^{-1}. EIMS (70 eV) *m/z* (%): 271 (70), 208 (40), 207 (100), 133 (50); HRMS: calcd for $C_{12}H_{19}O_3SiS$ [M-C_4H_9]: 271.0824; found: 271.0818.

(2*S*, 3*Z*)-2-(*tert*-Butyldimethylsilyl)oxy-5-methylene-4-vinylhepta-3,6-diene **271**

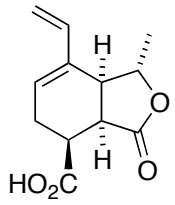


271

A solution of **270** (29 mg, 0.088 mmol, 1.0 equiv) in chlorobenzene (10 mL) was heated at reflux for 1.5 h before being concentrated *in vacuo*. After column chromatography (hexanes/ethyl acetate 98:2) **271** (21 mg, 0.079 mmol, 90%) was obtained as a colourless oil. $[\alpha]_D^{25} = -10.7$ (c = 0.97, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.30 (1H, ddd, *J* = 17.1, 10.4, 0.6 Hz), 6.27 (1H, dd, *J* = 16.6, 10.4 Hz), 5.72 (1H, d, *J* = 8.3 Hz), 5.22 (1H, ddd, *J* = 5.1, 1.5, 0.5 Hz), 5.18 (1H, ddd, *J* = 5.4, 1.5, 0.7 Hz), 5.16 (1H, m), 4.99 (1H, dm, *J* = 10.5 Hz), 4.96 (1H, ddd, *J* = 10.5, 1.5, 0.7 Hz), 4.92 (1H, m), 4.50 (1H, dq, *J* = 8.4, 6.3 Hz), 1.23 (3H, d, *J* = 6.4 Hz), 0.99 (9H, s), 0.08 (3H, s), 0.06 (3H, s) ppm. ^{13}C NMR (125 MHz, C_6D_6): *δ* 144.3, 139.0, 138.3, 137.5, 137.1, 119.2, 117.2, 115.4, 67.0, 26.1, 25.1, 18.3, -4.0, -4.3 ppm. IR (thin film): ν = 2958, 2857 cm^{-1}. EIMS (70 eV) *m/z* (%): 221 (20), 207 (35), 159 (34), 75 (100); HRMS: calcd for $C_{12}H_{19}OSi$ [M-C_4H_9]: 207.1205; found: 207.1203.

7.4.2 DTDA reactions

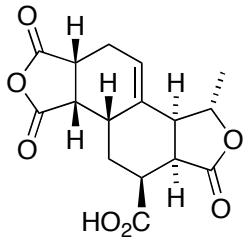
(1*S*,3a*R*,4*S*,7a*S*)-1-Methyl-3-oxo-7-vinyl-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylic acid **279**



279

To a solution of [3] dendralene **44** (45 mg, 0.36 mmol, 1.0 equiv) in d_6-benzene (1.2 mL) was added maleic anhydride (35 mg, 0.36 mmol, 1.0 equiv). The mixture was left at rt for 48 h. The product was filtered to give **279** (67 mg, 0.30 mmol, 83%) as a white solid. m.p. 163 – 165 °C. $[\alpha] = +150$ (c = 0.88, methanol). ^{1}H NMR (400 MHz, d_6-acetone): δ 6.35 (1H, dd, *J* = 18.1, 11.3 Hz), 5.97 (1H, dd, *J* = 6.4, 2.5 Hz), 5.08 (1H, d, *J* = 11.3 Hz), 5.02 (1H, d, *J* = 18.1 Hz), 4.50 (1H, q, *J* = 6.4 Hz), 3.87 (1H, ddd, *J* = 8.3, 3.9, 1.0 Hz), 3.29 (1H, dm, *J* = 8.3 Hz), 2.72 (1H, ddd, *J* = 11.7, 5.4, 3.9 Hz), 2.49-2.30 (2H, m), 1.49 (3H, d, *J* = 6.9 Hz) ppm. ^{13}C NMR (100 MHz, d_6- acetone): δ 176.3, 173.4, 138.4, 136.4, 131.4, 115.2, 80.5, 42.4, 39.7, 37.3, 24.3, 20.5 ppm. IR (KBr disc): ν 2993, 1770, 1700, 1644, 1452, 1419 cm^{-1}. ESIMS (positive ion) *m/z* (%): 467 (100), 246 (87), 224 (55). HRMS: calcd for $C_{12}H_{14}O_4$ $[M]^+$: 222.0892; found 222.0891.

Tetracycle **280**

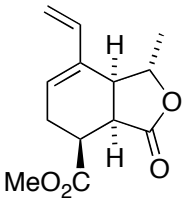


280

To a solution of **44** (27 mg, 0.22 mmol, 1.0 equiv) in deuterated acetonitrile (1 mL) was added maleic anhydride (43 mg, 0.44 mmol, 2.0 equiv). The mixture was left at rt for 60 h before being concentrated *in vacuo* to give **280** (70 mg, 0.22 mmol, 100%) as a colourless solid of approximately 90 % purity. $[\alpha]_D^{25} = -4.34$ (c= 1.66, chloroform). ^{1}H NMR (500 MHz, CD_3CN): δ 5.88 (1H, m), 4.49 (1H, dq, *J* = 6.4, 6.2 Hz), 3.55-3.48 (2H, m), 3.26 (1H, m), 3.15 (1H, dd, *J* = 12.2, 6.4 Hz), 2.98 (1H, m), 2.66 (1H, dd, *J* = 15.1, 7.0 Hz), 2.49 (1H, m), 2.38 (1H, ddd, *J* = 14.1, 11.2, 3.4 Hz), 2.29-2.15 (2H, m), 1.49 (3H, d, *J* = 6.4 Hz) ppm. ^{13}C NMR (125 MHz, CD_3CN): δ 178.1, 175.8, 174.7,

174.1, 132.7, 123.0, 83.2, 45.4, 43.1, 41.9, 41.8, 39.9, 32.8, 26.3, 25.36, 22.5 ppm. IR (thin film): ν = 2926, 2855, 1846, 1773, 1712, 1630 cm^{-1}. EIMS (70 eV) *m/z* (%): 320 (10), 230 (100); HRMS: calcd for $C_{16}H_{16}O_7$ $[M]^+$: 320.0896; found: 320.0895.

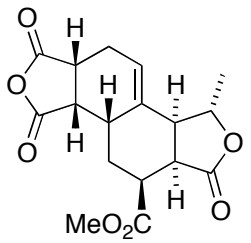
Methyl (1*S*,3a*R*,4*S*,7a*S*)-1-methyl-3-oxo-7-vinyl-1,3,3a,4,5,7a-hexahydro-2-benzofuran-4-carboxylate **281**



281

To a stirred solution of **279** (29 mg, 0.13 mmol, 1.0 equiv) in tetrahydrofuran (3 mL) at –78 °C was added a solution of diazomethane. After 15 min the reaction mixture was concentrated *in vacuo*. Purification by column chromatography on silica (hexanes/ethyl acetate 85:15) gave **281** (21 mg, 0.09 mmol, 70%) was obtained as a colourless solid. m.p. 74-75 °C. [α] = +120.0 (c = 0.20, dichloromethane) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (1H, dd, *J* = 17.9, 11.0 Hz), 5.94 (1H, dd, *J* = 5.9, 2.9 Hz), 5.06 (1H, d, *J* = 11.0 Hz), 4.91 (1H, d, *J* = 17.9 Hz), 4.56 (1H, q, *J* = 6.6 Hz), 3.79 (3H, s), 3.17 (1H, d, *J* = 8.4 Hz), 2.66 (1H, ddd, *J* = 11.0, 5.9, 4.0 Hz), 2.49-2.37 (2H, m), 1.49 (3H, d, *J* = 6.6 Hz) ppm. . ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 172.6, 137.4, 134.9, 130.7, 112.0, 80.1, 52.2, 41.6, 39.2, 37.1, 23.4, 20.6 ppm. IR (KBr disc): ν 2359, 1772, 1726, 1644, 1432 cm^{-1} . EIMS (70 eV) *m/z* (%): 236 (45), 176 (70), 131 (50), 117 (80), 105 (100), 91 (35), 77 (40). HRMS: calcd for $C_{13}H_{16}O_4$ $[M]^+$: 236.1049; found 236.1048.

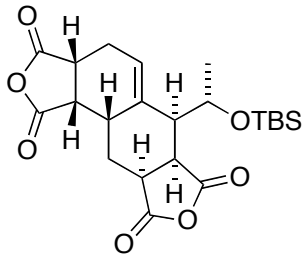
Tetracycle **282**



282

To a solution of **281** (18 mg, 0.07 mmol, 1.0 equiv) in deuterated benzene (1 mL) was added maleic anhydride (7 mg, 0.07mmol, 1.0 equiv). The mixture was heated at reflux for 3.5 h before additional maleic anhydride (4 mg, 0.04 mmol 0.5 equiv) was added. The mixture was heated at reflux for a further 14 h. The mixture was cooled to rt and the product was filtered to give **282** (17 mg, 0.05 mmol, 67%) as a white solid. The product was recrystallised from heptane/dichloromethane to give coulourless crystals. m.p.176-179 ^{o}C. $[\alpha] = -11.72$ (c = 0.51, methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86-5.81 (1H, m), 4.55 (1H, q, J = 6.4 Hz), 3.69 (3H, s), 3.48-3.44 (2H, m), 3.11 (1H, dd, J = 12.2, 6.4 Hz), 2.99-2.90 (1H, m), 2.80 (1H, ddd, J = 15.7, 7.3, 1.5 Hz), 2.50 (1H, ddd, J = 13.2, 10.8, 3.4), 2.41-2.32 (1H, m), 2.32-2.16 (2H, m), 1.54 (3H, d, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 173.5, 173.1, 172.0, 139.6, 122.4, 82.5, 52.4, 44.6, 42.6, 41.1, 40.8, 39.3, 32.4, 25.9, 24.9, 22.6 ppm. IR (KBr disc): ν 2988, 2360, 2339, 1772, 1717 cm^{-1} . EIMS (70 eV) *m/z* (%): 334 (20), 302 (40), 230 (95), 157 (70), 129 (100). HRMS: calcd for $C_{17}H_{18}O_7$ $[M]^+$: 334.1052; found 334.1055.

Tetracycle **284**

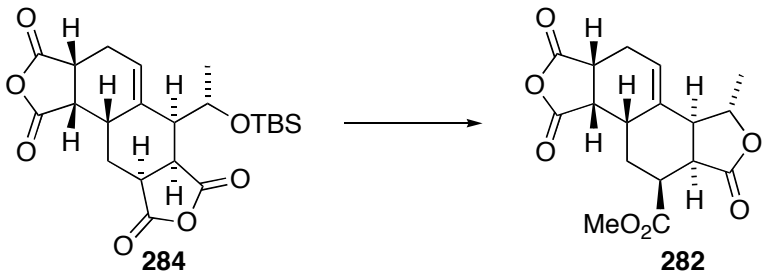


284

To a solution of **265** (44 mg, 0.18 mmol, 1.0 equiv) in deuterated benzene (1 mL) at rt was added maleic anhydride (39 mg, 0.37 mmol, 1.0 equiv). After 115 h the reaction mixture was concentrated *in vacuo* to give **284** (78 mg, 0.18 mmol, 97%) as a colourless solid. m.p. 80-83 ^{o}C. $[\alpha]_D^{25} = +21.9$ (c = 0.77, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72 (1H, m), 4.36 (1H, dq, J = 9.9, 5.5 Hz), 4.01 (1H, dd, J = 10.6, 4.8 Hz),

3.58 (1H, ddd, J = 11.0, 6.4, 2.2 Hz), 3.43 (1H, ddd, J = 9.5, 7.4, 1.7 Hz), 3.38 (1H, dd, J = 9.6, 5.4 Hz), 2.84 (1H, dd, J = 15.7, 7.7 Hz), 2.73 (1H, ddd, J = 13.8, 13.8, 6.1 Hz), 2.43 (1H, m), 2.33 (1H, ddd, J = 14.4, 4.6, 1.9 Hz), 2.18 (2H, m), 1.23 (3H, d, J = 5.8 Hz), 0.88 (9 H, s), 0.15 (3H, s), 0.11 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 173.3, 171.3, 171.0, 138.2, 123.4, 65.4, 46.5, 44.0, 40.4, 40.0, 34.1, 26.0, 25.0, 23.8, 23.5, 18.1, -4.0, -4.9 ppm. IR (thin film): ν = 2930, 1850, 1777 cm^{-1}. EIMS (70 eV) *m/z* (%): 419 (10), 377 (100), 75 (80); HRMS: calcd for $C_{18}H_{21}O_7Si$ [M-C_4H_7]: 377.1057; found: 377.1056. Anal. Calcd for $C_{22}H_{30}O_7Si$: C, 60.81; H, 6.96. Found: C, 60.98; H, 7.09.

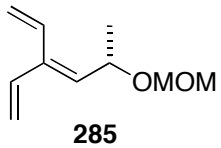
Conversion of tetracycle **284** to tetracycle **282**



284 **282**

To a stirred solution of **284** (47 mg, 0.11 mmol, 1.0 equiv) in dichloromethane (2 mL) was added trifluoroacetic acid (250 μL, 3.20 mmol, 30 equiv). Stirring was continued for 16 h before the reaction mixture was concentrated *in vacuo*. The crude residue was dissolved in tetrahydrofuran (5 mL) and cooled to -78 ^{o}C with stirring. An ethereal solution of diazomethane was added dropwise until tlc confirmed the reaction had gone to completion. Excess diazomethane was removed by bubbling N_2 gas through the solution. The solution was concentrated *in vacuo*. Recrystallisation from heptane/dichloromethane gave **282** (30 mg, 0.09 mmol, 81%) as colourless crystals.

(*S)*-5-(Methoxymethoxy)-3-vinylhexa-1,3-diene **285**

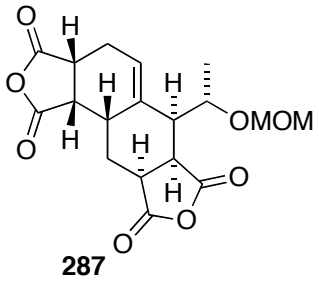


285

To a stirred solution of **44** (25 mg, 0.20 mmol, 1.0 equiv) in dichloromethane (2 mL) was added *i*Pr_2NEt (346 μL, 1.98 mmol, 10.0 equiv) and MOM-Cl (79 μL, 0.99 mmol, 5.0 equiv). Stirring was continued for 18 h before the reaction was quenched with sat. $NaHCO_3$ (5 mL). Ethyl acetate (10 mL) was added and the organic layer was washed with 2 M HCl (5 mL), $NaHCO_3$ (5 mL) and brine (5 mL) before being dried and

concentrated *in vacuo*. Column chromatography of the crude material (hexane/ethyl acetate 96:4) yielded **285** (20 mg, 0.11 mmol, 55%) as a colourless oil. $[\alpha]_D^{25}$ = −166.8 (c = 0.61, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.49 (1H, dd, *J* = 17.8, 11.6 Hz), 6.39 (1H, ddd, *J* = 17.3, 10.7, 0.9 Hz), 5.48 (1H, d, *J* = 9.7 Hz), 5.36 (1H, m), 5.33-5.24 (2H, m), 5.12 (1H, dd, *J* = 10.8, 1.9 Hz), 4.67 (1H, dq, *J* = 9.2, 6.4 Hz), 4.63 (1H, d, *J* = 6.5 Hz), 4.53 (1H, d, *J* = 6.5 Hz), 3.36 (3H, s), 1.29 (3H, d, *J* = 6.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 139.0, 137.3, 132.6, 131.6, 118.9, 115.9, 93.8, 67.8, 55.3, 21.5 ppm. IR (thin film): *ν* = 2919, 2850, 1996 cm^{-1}. EIMS (70 eV) *m/z* (%): 167.0 (28), 149 (100), 57 (92); HRMS: calcd for $C_{10}H_{16}O_2$ $[M]^+$: 168.1150; found: 168.1143.

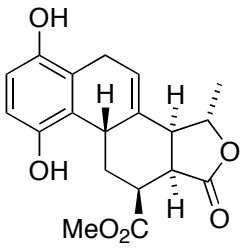
Tetracycle **287**



287

To a stirred solution of **285** (12 mg, 0.07 mmol, 1.0 equiv) in deutereated benzene (1 mL) was added maleic anhydride (14 mg, 0.14 mmol, 2.0 equiv). The reaction mixture was allowed to stand at rt for 48 h before being concentrated *in vacuo*. Recrystalisation from benzene/dichloromethane yielded **287** (26 mg, 0.07 mmol, 100%) as colourless crystals. m.p. 194-195 ^{o}C. $[\alpha]_D^{25}$ = -48.1 (c = 0.185, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (1H, m), 4.87 (1H, d, *J* = 6.7 Hz), 4.74 (1 H, d, *J* = 6.7 Hz), 4.13 (1H, dq, *J* = 6.0, 4.2 Hz), 4.05 (1H, dd, *J* = 10.8, 5.0 Hz), 3.58 (1H, ddd, *J* = 10.7, 6.3, 2.3 Hz), 3.45 (1H, ddd, *J* = 9.4, 7.4, 1.5 Hz), 3.40 (3H, s), 3.38 (1H, dd, *J* = 9.7, 5.3 Hz), 2.86 (1H, dd, *J* = 15.9, 7.7 Hz), 2.72 (1H, dt, *J* = 13.9, 6.5 Hz), 2.53 (1H, m), 2.35 (1H, ddd, *J* = 14.4, 4.6, 2.6 Hz), 2.24-2.14 (2H, m), 1.30 (3H, d, *J* = 6.0 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 174.2, 173.2, 171.4, 171.3, 137.9, 123.6, 96.9, 71.2, 56.0, 45.1, 44.1, 40.4, 40.2, 39.9, 34.0, 25.0, 23.7, 20.9 ppm. IR (thin film): *ν* = 2956, 1845, 1774 cm^{-1}. EIMS (70 eV) *m/z* (%): 364 (1), 333 (10), 319 (15), 302 (20), 45 (100); HRMS: calcd for $C_{18}H_{20}O_8$ $[M]^+$: 364.1158; found: 364.1154.

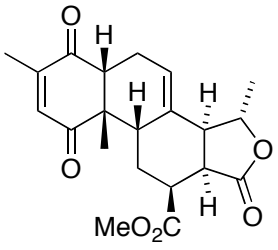
Tetracycle **289**



289

To a solution of **281** (51 mg, 0.22 mmol, 1.0 equiv) in deuterated benzene (1mL) was added benzoquinone (23 mg, 0.22 mmol, 1.0 equiv). The mixture was heated at reflux for 48 h before being cooled to RT and concentrated *in vacuo*. After column chromatography on silica gel (hexanes/ethyl acetate 60:40) **289** (52 mg, 0.15 mmol, 70%) was obtained as an off white solid. m.p. 127 – 130 °C. $[\alpha] = +62.3$ (c = 0.26, methanol). ^{1}H NMR (400 MHz, acetone): δ 7.77 (1H, s), 7.62 (1H, s), 6.56 (2H, dd, J = 8.3, 2.0 Hz), 5.85 (1H, m), 4.68 (1H, dq, J = 7.8, 6.4 Hz), 3.67 (3H, s), 3.57-3.47 (1H, m), 3.30-3.24 (2H, m), 3.24-3.16 (2H, m), 3.00 (1H, dd, J = 9.8, 7.8 Hz), 2.91-2.84 (1H, m), 1.58 (1H, ddd, J = 13.2, 11.3, 5.9 Hz), 1.39 (3H, d, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, acetone): δ 177.6, 174.7, 148.5, 148.2, 125.4, 122.0, 121.7, 113.4, 113.2, 79.6, 52.1, 51.7, 42.4, 41.0, 35.1, 28.4, 25.9, 19.9 ppm. IR (KBr disc): ν 3200, 2973, 1743, 1490 cm^{-1} . EIMS (70 eV) *m/z* 344 (100), 312 (90), 284 (55), 239 (50), 211 (90); HRMS: calcd for $C_{19}H_{20}O_6$ $[M]^+$: 344.1260; found: 344.1262.

Tetracycle **45**

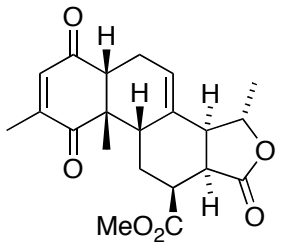


45

To a stirred solution of **281** (30 mg, 0.13 mmol, 1.0 equiv) in deutereated toluene (1 mL) was added 2,5-dimethyl benzoquinone (21 mg, 0.15 mmol, 1.2 equiv). The mixture was heated to reflux for 125 h before being cooled to RT and concentrated *in vacuo*. HPLC of the crude material (hexane/ethyl acetate, 55:45) yielded **45** (37 mg, 0.10 mmol, 78%) as a yellow oil. $[\alpha]_D^{25} = +78.4$ (c = 0.37, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.54 (1H, m), 5.65 (1H, m), 4.49 (1H, dq, J = 8.1, 6.0 Hz), 3.71 (3H, s), 3.16 (1H, dt, J = 7.6, 6.0 Hz), 3.08 (1H, dd, J = 10.6, 7.6 Hz), 2.90 (1H, dd, J = 6.6, 3.3 Hz), 2.81-2.73 (2H, m), 2.15 (1H, ddt, J = 18.5, 6.8, 2.5 Hz), 2.07 (1H, m), 2.02

(3H, d, J = 1.5 Hz), 1.89 (1H, dt, J = 13.8, 5.4 Hz), 1.55 (1H, ddd, J = 13.8, 11.6, 5.9 Hz), 1.39 (3H, d, J = 6.3 Hz), 1.38 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 199.7, 176.9, 173.3, 150.1, 137.2, 132.6, 122.1, 79.5, 52.5, 51.0, 50.8, 50.6, 41.7, 40.2, 39.2, 30.1, 24.2, 21.1, 19.8, 16.3 ppm. IR (thin film): ν = 2931, 1766, 1735, 1676, 1625 cm^{-1}. EIMS (70 eV) *m/z* (%): 372 (30), 341 (10), 312 (10), 32 (100); HRMS: calcd for $C_{21}H_{24}O_6$ $[M]^+$: 372.1573; found: 372.1573.

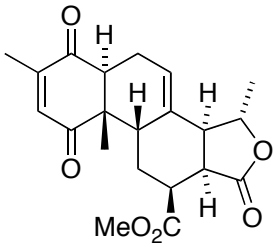
Tetracycle **290**



290

To a stirred solution of **281** (47 mg, 0.20 mmol, 1.0 equiv) in deuterated toluene (1 mL) was added 2,6-dimethylbenzoquinone (33 mg, 0.23 mmol, 1.2 equiv). The reaction mixture was heated to reflux for 109 h before being cooled to rt and concentrated *in vacuo*. After column chromatography (hexane/ethyl acetate, 55:45) **290** (56 mg, 0.15 mmol, 76%) was obtained as a yellow oil. $[\alpha]_D^{25}$ = +72.0 (c = 0.35, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.59 (1H, dd, J = 3.0, 1.5 Hz), 5.62 (1H, m), 4.45 (1H, dq, J = 7.8, 6.3 Hz), 3.71 (3H, s), 3.17 (1H, dt, J = 6.9, 5.9 Hz), 3.10 (1H, dd, J = 10.3, 7.3 Hz), 2.88 (1H, dd, J = 6.6, 4.2 Hz), 2.79 (1H, dd, J = 10.1, 7.9 Hz), 2.72 (1H, ddt, J = 18.5, 4.8, 1.8 Hz), 2.15 (1H, m), 2.08 (1H, m), 2.01 (3H, d, J = 1.4 Hz), 1.78(1H, dt, J = 13.6, 5.6 Hz), 1.69 (1H, ddd, J = 13.6, 11.0, 5.6 Hz), 1.40 (3H, s), 1.38 (3H, d, J = 6.3 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.3, 198.8, 176.8, 173.2, 149.9, 136.6, 132.8, 122.2, 79.7, 52.5, 51.6, 50.6, 50.4, 41.7, 40.1, 39.4, 29.5, 24.3, 22.5, 19.9, 16.6 ppm. IR (thin film): ν = 2930, 1769, 1735, 1678 cm^{-1}. EIMS (70 eV) *m/z* (%): 372 (100), 340 (40), 312 (45); HRMS: calcd for $C_{21}H_{24}O_6$ $[M]^+$: 372.1573; found: 372.1570.

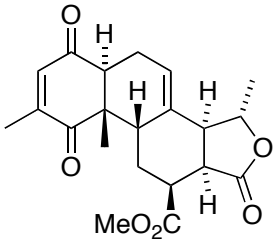
Tetracycle **292**



292

To a stirred solution of **45** (10 mg, 0.03 mmol, 1.0 equiv) in chloroform (4 ml) was added dry silica (2.5 g). Stirring was continued for 8 h before the reaction mixture was filtered. The silica was rinsed with ethyl acetate (2 x 10 mL) and the filtrate concentrated *in vacuo* to give **292** (10 mg, 0.03 mmol, 100%). Recrystallisation (heptane/dichloromethane/chloroform) gave colourless needles. m.p. 110-112 ^{o}C. $[\alpha]_D^{25}$ = +132.4 (c = 0.18, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.48 (1H, q, *J* = 1.4 Hz), 5.66 (1H, d, *J* = 4.9 Hz), 4.43 (1H, dq, *J* = 6.4, 3.8 Hz), 3.77 (3H, s), 3.48 (1H, dd, *J* = 10.4, 5.0 Hz), 2.89 (1H, dd, *J* = 8.3, 5.3 Hz), 2.87 (1H, dd, *J* = 6.1, 3.3 Hz), 2.74 (1H, dd, *J* = 7.4, 4.8 Hz), 2.73 (1H, dd, *J* = 7.4, 5.2 Hz), 2.50 (1H, m), 2.47-2.38 (2H, m), 2.33 (1H, ddt, *J* = 18.5, 11.0, 1.9 Hz), 2.01 (3H, d, *J* = 1.5 Hz), 1.41 (3H, d, *J* = 6.4 Hz), 1.37 (1H, m), 1.08 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 201.0, 200.3, 176.3, 173.1, 150.3, 136.2, 135.8, 121.7, 79.9, 52.4, 51.0, 50.5, 45.7, 41.2, 38.8, 37.1, 29.0, 22.1, 21.7, 21.5, 16.2 ppm. IR (thin film): ν = 2927, 1766, 1736, 1674 cm^{-1}. EIMS (70 eV) *m/z* (%): 372 (50), 312 (60), 69 (100); HRMS: calcd for $C_{21}H_{24}O_6$ $[M]^+$: 372.1573; found: 372.1577

Tetracycle **291**

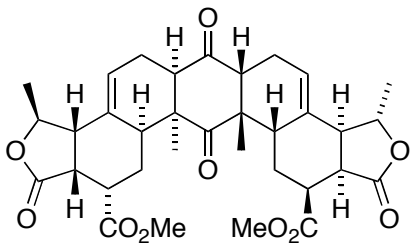


291

To a stirred solution of **290** (8 mg, 0.02 mmol, 1.0 equiv) in chloroform (4 mL) was added dry silica (2 g). Stirring was continued for 4 h before the reaction mixture was filtered. The silica was rinsed with ethyl acetate (15 mL x 2) to give **291** (8 mg, 0.02 mmol, 100%). Recrystalisation (heptane/ethyl acetate) gave colourless needles. m.p. 180-182 ^{o}C. $[\alpha]_D^{25}$ = +214.0 (c = 0.83, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.64 (1H, ddd, *J* = 2.8, 1.5, 1.5 Hz), 5.68 (1H, dd, *J* = 5.0, 1.7 Hz), 4.44 (1H, dq, *J* = 6.4, 3.5 Hz), 3.79 (3H, s), 3.51 (1H, dd, *J* = 10.3, 4.6 Hz), 2.92 (1H, m), 2.88 (1H, m), 2.74 (1H, ddd, *J* = 9.8, 7.3, 4.8 Hz), 2.61-2.40 (2H, m), 2.30 (1H, ddt, *J* = 2.0,m 11.0, 19 Hz), 2.01 (3H, d, *J* = 1.5 Hz), 1.43 (3H, d, *J* = 6.4 Hz), 1.36 (1H, m), 1.10 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 199.3, 176.2, 173.0, 148.4, 137.1, 135.9, 121.7, 79.9, 52.4, 50.7, 50.5, 45.7, 41.1, 38.7, 37.0, 28.9, 22.1, 21.8, 21.5, 16.5 ppm. IR (thin film): ν = 2933, 1764, 1737, 1680, 1628 cm^{-1}. EIMS (70 eV) *m/z* (%): 372 (100), 341 (25), 312 (80); HRMS: calcd for: $C_{21}H_{24}O_6$ $[M]^+$: 372.1573; found: 372.1576.

Heptacycle **293**



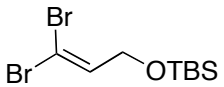
293

To a solution of **281** (160 mg, 0.68 mmol, 1.0 equiv) in dichloromethane (3 mL) was added 2,6-dimethylbenzoquinone (46 mg, 0.34 mmol, 0.5 equiv). The reaction mixture was compressed at 19 kbar for 72 h then concentrated *in vacuo*. After column chromatography **293** (176 mg, 0.29, 85%) was obtained. Recrystallisation (heptane/dichloromethane) gave colourless needles. m.p. 132-135 ^{o}C. $[\alpha]_D^{25}$ = +4.24 (c = 0.66, chloroform). ^{1}H NMR (500 MHz, C_6D_6): δ 5.17 (2H, m), 4.47 (2H, dq, *J* = 8.8, 6.2 Hz), 3.31 (6 H, s), 2.97 (2H, m), 2.88 (2H, dd, *J* = 17.6, 6.1 Hz), 2.50 (2H, dd, *J* = 10.7, 7.8 Hz), 2.24 (2H, d, *J* = 5.9 Hz), 2.19 (2H, t, *J* = 9.6 Hz), 2.00 (2H, d, *J* = 12.2 Hz), 1.84 (2H, dt, *J* = 12.5, 4.1 Hz), 1.68 (2H, dd, *J* = 17.3, 6.6 Hz), 1.11 (6H, s), 1.04 (6H, d, *J* = 6.2 Hz), 1.06-0.09 (2H, m) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ 215.8, 208.0, 175.8, 173.1, 133.9, 122.4, 79.2, 52.1, 49.8, 49.6, 49.0, 41.7, 41.1, 40.17, 31.9, 26.3, 22.5, 19.7 ppm. IR (thin film): ν = 2974, 2892, 1768, 1734, 1701 cm^{-1}. EIMS (70 eV) *m/z* (%): 608 (100), 576 (50), 372 (40), 277 (45), 243 (70), 171 (95); HRMS: calcd for: $C_{34}H_{40}O_{10}$ $[M]^+$: 608.2621; found: 608.2624.

7.5 Chapter 5

7.5.1 Syntheses of Substituted Dendralenes

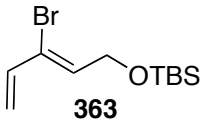
3,3-Dibromo-1-[(*tert*-butyldimethylsilyl)oxy]-prop-2-ene **362**



362

The title compound was prepared according to modified literature procedures.[85] To a stirred solution of triphenyl phoshpine (11.0 g, 40 mmol, 4.0 equiv) in dichloromethane (35 mL) at 0 ^{o}C under argon, was added a solution of carbon tetrabromide (7.0 g, 20 mmol, 2.0 equiv) in dichloromethane (15 mL) over 45 min, *via* cannula. The reaction mixture was stirred at rt for 30 min, NEt_3 (1.46 mL, 10 mmol, 1.0 equiv) was added before the mixture was cooled to 0 ^{o}C. A solution of [(*tert*-butyldimethylsilyl)oxy]acetaldehyde[91,169] (1.83 g, 10 mmol, 1.0 equiv) in dichloromethane (5 mL) was added dropwise. The reaction mixture was warmed to rt and stirring continued for a further 30 min. To the reaction mixture was added hexanes and the resulting precipitate was filtered. The filtrate was then concentrated under reduced pressure. After column chromatography (hexanes/diethyl ether 97:3) **362** (1.98 g, 6 mmol, 57 %) was obtained as a colourless oil. ^{1}H NMR data was consistent with that reported in the literature.[85]

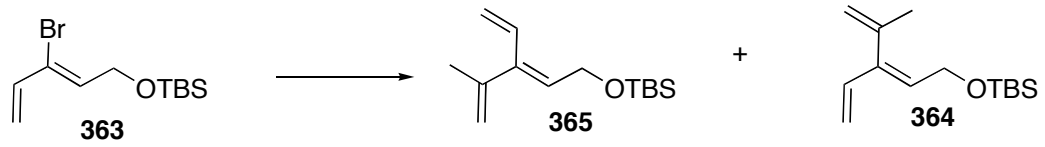
(2*Z*)-3-Bromo-1-[(*tert*-butyldimethylsilyl)oxy]-penta-2,4-diene **363**



363

The title compound was prepared according to modified literature procedures.[85] To a stirred solution of **362** (750 mg, 2.27 mmol, 1.0 equiv) and tributyl(vinyl)tin (756 mg, 2.38 mmol, 1.05 equiv) in tetrahydrofuran (12 mL) was added tris(dibenzylideneacetone)dipalladium (0) (26 mg, 0.03 mmol, 0.0125 equiv) and triphenyl arsine (70 mg, 0.23 mmol, 0.1 equiv). The mixture was freeze thaw degassed (x 2). The mixture was heated to 55 ^{o}C and stirring was continued for 18 h. The mixture was cooled and diluted with diethyl ether (50 mL), washed with aq NH_3 (20 mL x 2). The aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were washed with brine, dried and concentrated *in vacuo*. Column chromatography gave **363** (436 mg, 1.49 mmol, 66%) as a colourless oil. ^{1}H NMR data was consistent with that reported in the literature.[85]

Stille reaction of (2*Z*)-3-bromo-1-[(*tert*-butyldimethylsilyl)oxy]-penta-2,4-diene **363** with tributyl(prop-1-en-2-yl)stannane.



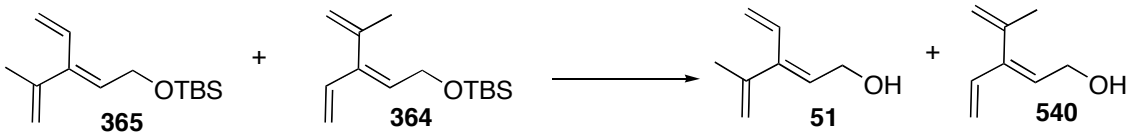
Method A

To a stirred solution of **363** (200 mg, 0.69 mmol, 1.0 equiv) and tributyl(prop-1-en-2-yl)stannane (250 mg, 0.76 mmol, 1.1 equiv) in acetonitrile (4 mL) was added palladium acetate (8 mg, 0.03 mmol, 0.05 equiv) and triphenyl phosphine (18 mg, 0.06 mmol, 0.1 equiv). The mixture was freeze/thaw degassed (x 2) then heated to 60 ^{o}C for 18 h. The mixture was diluted with diethyl ether (20 mL) and washed with aq. NH_3 (2 x 20 mL). The aqueous layer was extracted with diethyl ether (2 x 20 ml). The combined organic layers were washed with brine, dried and concentrated *in vacuo*. Column chromatography gave **364** and **365** as an inseprable mixture (1:1, 70 mg, 0.29 mmol, 42%).

Method B

To a stirred solution of **363** (51 mg, 0.18 mmol, 1.0 equiv) and tributyl(prop-1-en-2-yl)stannane (122 mg, 0.37 mmol, 2.0 equiv) in DMF (200 µL) was added CsF (56 mg, 0.37 mmol, 2.0 equiv). The mixture was freeze/thaw degassed (x 2). CuI (4 mg, 0.02 mmol, 0.12 equiv), palladium chloride (2 mg, 0.01 mmol, 0.06 equiv) and P*t*Bu$_3$ (6 mg, 0.02 mmol, 0.12 equiv) were added and the mixture was heated to 45 ^{o}C for 18 h. The mixture was filtered through a pad of celite with dichloromethane (50 mL). The filtrate was washed with brine, dried and concentrated *in vacuo*. Column chromatography (hexanes/dichloromethane 90:10) gave **364** and **365** as an inseparable mixture (1:1, 22 mg, 0.09 mmol, 44%).

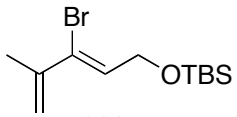
Deprotection of **364** and **365**



To a stirred solution of **364** and **365** (1:1, 70 mg, 0.29 mmol, 1.0 equiv) in tetrahydrofuran (4 mL) was added TBAF (1.0 M sol, 590 µL, 0.59 mmol, 2.0 equiv). Stirring was continued for 30 min before the mixture was diluted with diethyl ether (20 mL). The mixture was washed with sat. aqueous NH_4Cl (20 mL), brine (20 mL), dried

and concentrated *in vacuo*. Column chromatography gave **540** and **51** as an inseparable mixture (1:1, 16 mg, 0.12 mmol, 43%).

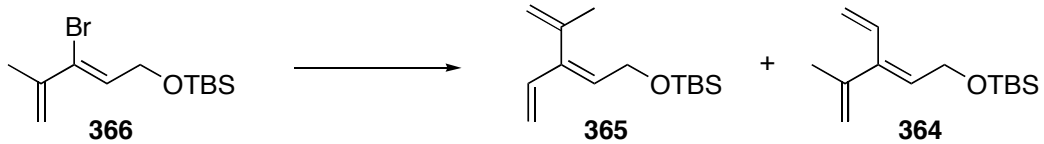
(2*Z*)-3-Bromo-1-[(*tert*-butyldimethylsilyl)oxy]-4-methylpenta-2,4-diene **366**



366

To a stirred solution of zinc bromide (1.12 g, 5.0 mmol, 1.1 equiv) in tetrahydrofuran (5 mL) at 0 ^{o}C was added a solution of isopropenyl magnesium bromide (0.26 M solution in tetrahydrofuran, 17.5 mL, 4.5 mmol, equiv). The resulting mixture was warmed to rt before the dropwise addition of a solution of **362** (1.5 g, 4.5 mmol, 1.0 equiv) and tetrakis(triphenylphosphine)palladium(0) (263 mg, 0.23 mmol, 0.05 equiv) in tetrahydrofuran (15 mL). The reaction mixture was stirred at rt for 45 min before being diluted with hexane (100 mL) and filtered. The filtrate was concentraed *in vacuo* and after column chromatography (hexane/ethyl acetate 99:1) **366** (1.03 g, 3.5 mmol, 78%) was obtained as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.16 (1H, t, J = 5.1 Hz), 5.49 (1H, m), 5.13 (1H, m), 4.43 (2H, d, J = 5.1 Hz), 2.00 (3H, m), 0.92 (9H, s), 0.10 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 131.8, 125.3, 118.4, 64.6, 26.0, 20.8, 18.4, -5.1 ppm . IR (thin film): ν = 2955, 2930, 2886, 2858, 1609 cm^{-1}. EIMS (70 eV) *m/z* (%): 290 (20), 249 (30), 235 (28), 115 (50), 75 (100); HRMS: calcd for $C_8H_{14}OSiBr$ [M]: 232.9997; found: 232.9994.

Stille reaction of (2*Z*)-3-bromo-1-[(*tert*-butyldimethylsilyl)oxy]-4-methylpenta-2,4-diene **366** and tributyl(vinyl)tin



366 **365** **364**

Method A

To a stirred solution of **366** (84 mg, 0.29 mmol, 1.0 equiv) and tributyl(vinyl)tin (110 mg, 0.34 mmol, 1.2 equiv) in DMF (500 μL) was added CsF (87 mg, 0.58 mmol, 2.0 equiv). The mixture was freeze/thaw degassed (x 2). CuI (4 mg, 0.02 mmol, 0.08 equiv), palladium chloride (2 mg, 0.01 mmol, 0.04 equiv) and P*t*Bu$_3$ (5 mg, 0.02 mmol, 0.08 equiv) were added and the mixture was heated to 45 ^{o}C for 18 h. The mixture was filtered through a pad of celite with dichloromethane (50 mL). The filtrate was washed

with brine, dried and concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 99:1) gave **366, 364** and **365** (50% conversion, 28 mg of **366** and 34 mg of **364** and **365** (91:9), 69% based on recovered s.m). Column chromatography of this mixture (hexanes/dichloromethane 90:10) gave **364** and **365** (91:9).

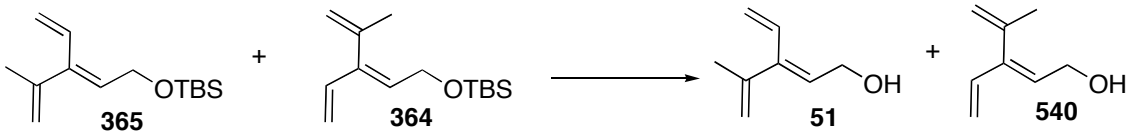
(2*Z*)- 1-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-3-vinylpenta-2,4-diene **365**

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.31 (1H, dd, *J* = 17.4, 10.5 Hz), 5.55 (1H, t, *J* = 6.4 Hz), 5.16 (1H, bs), 5.15 (1H, d, *J* = 17.4 Hz), 5.07 (1H, d, *J* = 10.5 Hz), 4.72 (1H, bs), 4.26 (2H, d, *J* = 6.4 Hz), 1.85 (3H, s), 0.91 (9H, s), 0.08 (6H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 143.4, 141.1, 138.0, 130.3, 115.7, 114.9, 60.9, 26.1, 23.0, 18.5, -5.0 ppm. IR (thin film): ν = 2957, 2929, 2857 cm^{-1}. EIMS (70 eV) *m/z* (%): 238 (2), 223 (2), 181 (55), 75 (100); HRMS: calcd for $C_{10}H_{17}OSi$ [M-C_4H_9]: 181.1049; found: 181.1050.

Method B

A solution of **366** (300 mg, 1.03 mmol, 1.0 equiv) and tributyl(vinyl)tin (448 mg, 2.06 mmol, 2.0 equiv) in acetonitrile (4 mL) was freeze/thaw degassed (x 2). Triphenyl phosphine (24 mg, 0.10 mmol, 0.10 equiv) and palladium acetate (14 mg, 0.05 mmol, 0.05 equiv) were added and the mixture was heated to 60 ^{o}C for 18 h. The mixture was diluted with diethyl ether (20 mL) and washed with aq. NH_3 (2 x 20 mL). The aqueous layer was extracted with diethyl ether (2 x 20 ml). The combined organic layers were washed with brine, dried and concentrated *in vacuo*. Column chromatography gave **364** and **365** as an inseprable mixture (72:28, 113 mg, 0.47 mmol, 46%).

Deprotection of **364** and **365**



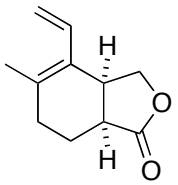
To a stirred solution of **364** and **365** (91:9, 10 mg, 0.04 mmol, 1.0 equiv) in tetrahydrofuran (2 mL) was added tetrabutyl ammonium fluoride (1.0 M sol, 140 μL, 0.14 mmol, 3.3 equiv). Stirring was continued for 2 h before the mixture was diluted with diethyl ether (20 mL). The mixture was washed with sat. NH_4Cl sol (20 mL), brine (20 mL), dried and concentrated *in vacuo*. Column chromatography (dichloromethane) gave **540** and **51** as an inseparable mixture (91:9, 4 mg, 0.03 mmol, 77%).

(2*Z*)-4-Methyl-3-vinylpenta-2,4-dien-1-ol **540**

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.30 (1H, dd, *J* = 17.4, 10.5 Hz), 5.60 (1H, t, *J* = 6.7 Hz), 5.24-5.08 (3H, m), 4.74 (1H, bs), 4.22 (2H, d, *J* = 6.7 Hz), 1.86 (3H, s), 1.54 (1H, bs, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 141.1, 137.7, 128.7, 115.9, 60.2, 31.0, 23.4 ppm. IR (thin film): ν = 3361, 2921, 2851 cm^{-1}. EIMS (70 eV) *m/z* (%):124 (5), 123 (7), 95 (100); HRMS: calcd for $C_8H_{11}O$ [M-H]: 123.0810; found:123.0810.

7.5.2 Synthesis of the Bicyclic Intermediate

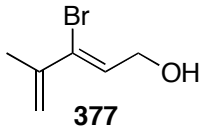
(±)-(3a*S*,7a*S*)-3,3a,7,7a-Tetrahydro-5-methyl-4-vinylisobenzofuran-1(6*H*)-one **49**



49

To a stirred solution of **365** and **364** (72:28, 113 mg, 0.47 mmol, 1.0 equiv) in tetrahydrofuran (5 mL) was added tetrabutyl ammonium fluoride (1.0 M sol, 2.5 mL, 2.5 mmol, 5.2 equiv). Stirring was continued for 2 h before the mixture was diluted with diethyl ether (20 mL). The mixture was washed with sat NH_4Cl sol (20 mL), brine (20 mL), dried and concentrated *in vacuo*. Column chromatography (dichloromethane) gave **51** and **540** as an inseparable mixture (72:28). Toluene (2 mL) and methyl acrylate (2 mL) were added and the mixture was heated in a sealed tube for 18 h. Concentration *in vacuo* followed by column chromatography (hexanes/ethyl acetate 75:25) gave **49** (18 mg, 0.10 mmol, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 91H, dd, *J* = 17.7, 11.3 Hz), 5.04 (1H, d, *J* = 11.3 Hz), 4.95 (1H, d, *J* = 17.8 Hz), 4.52 (1H, dd, *J* = 9.0, 7.5 Hz), 4.06 (1H, dd, *J* = 9.0, 4.9 Hz), 3.42 (1H, m), 2.86 (1H, m), 2.23-1.90 (3H, m), 1.81 (3H, s), 1.77 (1H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.3, 136.8, 133.2, 126.5, 111.8, 72.5, 38.3, 34.8, 29.6, 20.5, 19.9 ppm . IR (thin film): ν = 3087, 2919, 1772 cm^{-1}. EIMS (70 eV) *m/z* (%): 178 (65), 163 (15), 134 (28), 105 (100); HRMS: calcd for $C_{11}H_{14}O_2$: 178.0994; found: 178.0999.

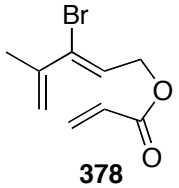
(2*Z*)-3-Bromo-4-methylpenta-2,4-dien-1-ol **377**



377

To a stirred solution of **366** (174 mg, 0.59 mmol, 1.0 equiv) in tetrahydrofuran (4 mL) at 0 ^{o}C was added tetrabutyl ammonium fluoride (1M in tetrahydrofuran, 1.19 mL, 1.19 mmol, 2.0 equiv). The resulting solution was warmed to rt and stirred for 30 min before being quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with diethyl ether (2 x 20 mL), and the combined organic layers were washed with brine, dried and concentrated *in vacuo*. After column chromatography **377** (94 mg, 0.52 mmol, 88%) was obtained as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.22 (1H, t, J = 5.7 Hz), 5.52 (1H, m), 5.16 (1H, m), 4.41 (2H, d, J = 5.7 H), 2.19 (1H, s), 2.00 (3H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 129.9, 127.7, 119.2, 63.3, 20.7 ppm . IR (thin film): ν = 3325, 2952, 2925, 1608 cm^{-1}. EIMS (70 eV) *m/z* (%): 178 (5), 149 (20), 97 (70), 41 (100); HRMS: calcd for $C_6H_9O^{81}Br$: 177.9811; found: 177.9816.

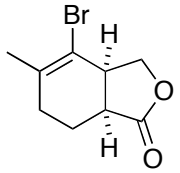
(2*Z*)-3-Bromo-4-methylpenta-2,4-dienyl acrylate **378**



378

To a stirred solution of **377** (91 mg, 0.51 mmol, 1.0 equiv) in dichloromethane (5 mL) at 0 ^{o}C was added triethylamine (150 μL, 1.08 mmol, 2.1 equiv) and acryloyl chloride (63 μL, 0.77 mmol, 1.5 equiv). Stirring was continued at this temperature for 1.5 h before warming to rt and quenching with sat. $NaHCO_3$ (15 mL). The aqueous layer was extracted with diethyl ether (3 x 15 mL) and the combined organic layers were dried and concentrated *in vacuo*. After column chromatography (hexanes/ethyl acetate 85:15) **378** (81 mg, 0.35 mmol, 69%) was obtained as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.40 (1H, dd, J = 17.3, 1.5 Hz), 6.17 (1H, t, J = 5.7 Hz), 6.13 (1H, dd, J = 17.2, 10.3 Hz), 5.85 (1H, dd, J = 10.3, 1.5 Hz), 5.55 (1H, m), 5.18 (1H, m), 4.91 (2H, d, J = 5.7 Hz), 1.99 (3H, dd, J = 1.4, 0.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 140.0, 131.4, 129.5, 128.0, 125.0, 119.7, 64.9, 20.6 ppm . IR (thin film): ν = 2954, 2927, 1728, 1634, 1611 cm^{-1}. EIMS (70 eV) *m/z* (%): 232.0 (2), 230.0 (2), 151 (12), 79 (20), 55 (100); HRMS: calcd for $C_9H_{11}O_2{}^{79}Br$ [M]: 229.9942; found: 229.9931.

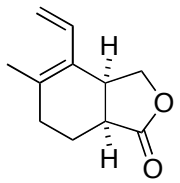
(±)-(3a*R*,7a*S*)-4-Bromo-3,3a,7,7a-tetrahydro-5-methylisobenzofuran-1(6*H*)-one **379**



379

A solution of **378** (284 mg, 1.23 mmol, 1.0 equiv) and BHT (14 mg, 0.06 mmol, 0.05 equiv) in dichlorobenzene (90 mL) was heated at reflux for 72 h. The solvent was distilled under reduced pressure. The crude residue was dissolved in dichloromethane (15 mL) and DBU (202 μL, 1.35 mmol, 1.1 equiv) was added. The mixture was heated to reflux for 2.5 h then cooled to rt. The mixture was diluted with ether (50 mL), washed with 1 M HCl (20 ml), water (20 mL) and brine (20 mL). The organic layer was dried and concentrated *in vacuo*. After column chromatography (hexanes/ethyl acetate 85:15) **379** (113 mg, 0.53 mmol, 40%) was obtained as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.41 (1H, dd, *J* = 9.4, 2.9 Hz), 4.35 (1H, ddd, *J* = 9.4, 6.5, 0.8 Hz), 3.36 (1H, bs), 2.91 (1H, m), 2.23-2.04 (3H, m), 1.86 (1H, m), 1.84 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 177.7, 137.0, 117.3, 71.8, 44.3, 40.5, 29.3, 24.0, 20.3 ppm . IR (thin film): ν = 2918, 1773 cm^{-1}. EIMS (70 eV) *m/z* (%): 232 (28), 230 (30), 187 (48), 185 (50), 172 (20), 93 (100); HRMS: calcd for $C_9H_{11}O_2{}^{79}Br$ [M]: 229.9942; found: 229.9935.

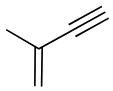
(±)-(3a*S*,7a*S*)-3,3a,7,7a-Tetrahydro-5-methyl-4-vinylisobenzofuran-1(6*H*)-one **49**



49

A solution of **378** (29 mg, 0.13 mmol, 1.0 equiv) and tributyl(vinyl)tin (80 mg, 0.25 mmol, 2.0 equiv) in DMF (1 mL) was freeze/thaw degassed (x 2). bis(acetonitrile)palladium dichloride (3.2 mg, 0.01 mmol, 0.10 equiv) was added and the mixture heated to 100 ^{o}C for 6 d. Concentration *in vacuo* followed by column chromatography (hexanes/ethyl acetate 85:15) gave **49** (8 mg, 0.05 mmol, 36%).

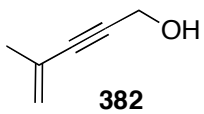
2-Methylbut-1-en-3-yne **381**



381

2-Methylbut-1-en-3-yne **381** was prepared following a modified procedure of Brandsma.[212] A mixture of acetic anhydride (50 mL, 530 mmol, 1.5 equiv) and *p*-toluenesulphonic acid (3.5 g, 20 mmol, 0.06 equiv) were placed in a two-necked flask fitted to a distillation apparatus. The mixture was cooled to 0 ^{o}C and 2-methylbut-3-yn-2-ol (33 mL, 350 mmol, 1.0 equiv) was added. The mixture was gradually heated in a oil bath and the product was distilled. The crude product was washed with cold KOH solution and dried ($MgSO_4$). Distillation through a short column afforded 2-methylbut-1-en-3-yne **381** (11.5 g, 170 mmol, 50%).

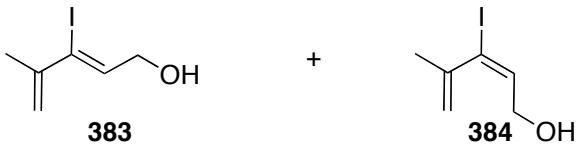
4-Methylpent-4-en-2-yn-1-ol **382**



382

The title compound was prepared according to modified literature procedures.[173] To a solution of ethyl magnesium bromide (1.25 M in tetrahydrofuran, 140 mL, 170 mmol, 1.0 equiv) at 0 ^{o}C was added 2-methylbut-1-en-3-yne **381**(11.5 g, 170 mmol, 1.0 equiv) and paraformaldehyde (10 g). The mixture was stirred at rt for 1 h then heated to reflux for 6 h. The reaction was cooled to rt and aq. NH_4Cl (100 mL) was added. The mixture was extacted with ether (200 mL), dried and concentrated *in vacuo*. Distillation afforded **382** (9.25 g, 96 mmol, 55%).

(2*Z*)-3-Iodo-4-methylpenta-2,4-dien-1-ol **383** and (2*E*)-3-Iodo-4-methylpenta-2,4-dien-1-ol **384**

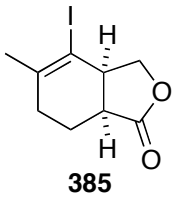


383 **384**

The title compounds were prepared according to modified literature procedures.[174] To a suspension of lithium aluminium hydride (1.81g, 48 mmol, 1.2 equiv) in diethyl ether (40 mL) at 0 ^{o}C was added a solution of **382** (3.82 g, 40 mmol, 1.0 equiv) in diethyl ether (8 mL). The mixture was stirred at rt for 1 h then cooled to 0 ^{o}C. Ethyl acetate (4.7 mL, 48 mmol, 1.2 equiv) was added dropwise and stirring was continued at this temperature for 1 h. The mixture was cooled to -78 ^{o}C and solid I_2 (20 g, 79 mmol, 2.0

equiv) was added in portions. The reaction was stirred at -78 °C for 1 h, 0 °C for 1 h then warmed to rt. Sodium thiosulphate solution (50 mL) was added and the mixture was filtered. The mixture was extracted with ether (2 x 100 mL). The combined organic layers were washed with sodium thiosulphate solution (50 mL), brine (50 mL) and dried. Concentration *in vacuo* followed by column chromatography (hexanes/ethyl acetate 85:15) gave **383** and **384** (3.79 g, 17 mmol, 42%) as a 2.75:1 ratio of *E/Z* isomers.

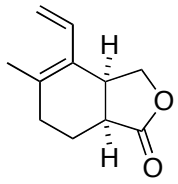
(±)-(3a*R*,7a*S*)-3,3a,7,7a-Tetrahydro-4-iodo-5-methylisobenzofuran-1(6*H*)-one **385**



385

A solution of **383** and **384** (2.75:1 mixture of *E/Z* isomers, 3.79 g, 17 mmol, 1.0 equiv) in methyl acrylate (15 mL) and toluene (10 mL) was heated at 100 °C for 18 h. The mixture was concentrated *in vacuo* and the crude residue was dissolved in CH_2Cl_2 (15 mL). Imidazole (1.73 g, 25 mmol, 1.5 equiv), *tert*-butyldimethylsilyl chloride (2.55 g, 17 mmol, 1.0 equiv) and DMAP (378 mg, 3.4 mmol, 0.2 equiv) were added. Stirring was continued for 4 h. Water (20 mL) was added and the mixture was extracted with ether (100 mL). The organic layer was washed with brine, dried and concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 85:15) gave **385** (2.10 g, 7.6 mmol, 61%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.38 (1H, ddd, J = 9.4, 6.5, 1.4 Hz), 4.32 (1H, ddd, J = 9.4, 3.7, 1.2 Hz), 3.47 (1H, bs), 2.81 (1H, dd, J = 12.4, 5.4 Hz), 2.27-2.06 (3H, m), 1.90 (3H, s), 1.90 (1H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 142.7, 97.0, 73.5, 47.6, 40.7, 30.0, 29.3, 26.9, 20.7 ppm . IR (thin film): ν = 2917, 1769, 1646 cm^{-1}. EIMS (70 eV) *m/z* (%): 278 (95), 233 (30), 220 (28), 151 (12), 93 (100); HRMS: calcd for $C_9H_{11}O_2{}^{127}I$: 277.9804; found: 277.9803.

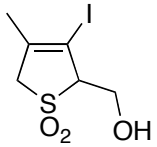
(±)-(3a*S*,7a*S*)-3,3a,7,7a-Tetrahydro-5-methyl-4-vinylisobenzofuran-1(6*H*)-one **49**



49

A solution of **385** (500 mg, 1.79 mmol, 1.0 equiv) and tributyl(vinyl)tin (1.14 g, 3.60 mmol, 2.0 equiv) in toluene (10 mL) was freeze/thaw degassed (x 2). tris(dibenzylideneacetone)dipalladium (0) (41 mg, 0.04 mmol, 2.5 mol%) and tri-2-furylphosphine (63 mg, 0.27 mmol, 15 mol%) were added and the mixture was heated to 60 ^{o}C for 24 h. The mixture was diluted with diethyl ether (20 mL) and washed with aq. ammonia solution (50 mL). The aqueous layer was extracted with diethyl ether (20 mL). The combined organic layers were washed with brine, dried and concentrated *in vacuo*. Column chromatography (hexanes to hexanes/ethyl acetate 85:15) gave **49** (277 mg, 1.55 mmol, 86%).

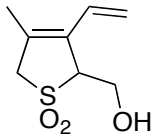
3-Iodo-2-methanol-4-methyl(2,5-dihydrothiphene-1,1-dioxide) **386**



386

To a solution of **383/384** (1:1 mixture of *E/Z* isomers, 3.24 g, 14 mmol, 1.0 equiv) in methanol/ether (1:1, 8 mL) in a sealable tube was added quinol (5 mg). The mixture was cooled to -78 ^{o}C and liquid SO_2 (20 mL) was added and the tube was sealed. The mixture was stirred at rt for 4 d. Concentration *in vacuo* followed by column chromatography (hexanes/ethyl acetate 60:40) gave **386** (2.13 g, 7.4 mmol, 51%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.20 (1H, ddd, J = 12.7, 2.4, 0.7 Hz), 4.02 (1H, dd, J = 12.7, 5.7 Hz), 3.86 (1H, m), 3.83 (1H, d, J = 17.4 Hz), 3.73 (1H, d, J = 15.7 Hz), 1.99 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 87.5, 74.6, 60.0, 59.9, 22.7 ppm . IR (thin film): ν = 3503, 2923, 1307, 1126 cm^{-1}. EIMS (70 eV) *m/z* (%): 289 (76), 258 (95), 41 (100); HRMS: calcd for $C_6H_9O_3S^{127}I$ [M]: 287.9317; found: 287.9312.

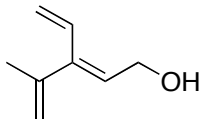
2-Methanol-4-methyl-3-vinyl(2,5-dihydrothiphene-1,1-dioxide) **387**



387

To a solution of **386** (200 mg, 0.69 mmol, 1.0 equiv) in DMF (1 mL) was added tributyl(vinyl)tin (440 mg, 1.39 mmol, 2.0 equiv) and bis(acetonitrile)palladium dichloride (18 mg, 0.07 mmol, 10 mol%). The mixture was freeze/thaw degassed (x 2) and heated to 100 ^{o}C for 22 h. The solvent was removed under reduced pressure. Column chromatography (hexanes/ethyl acetate 60:40) gave **387** (98 mg, 0.52 mmol, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (1H, dd, *J* = 18.0, 11.5 Hz), 5.37 (1H, d, *J* = 11.5 Hz), 5.26 (1H, d, *J* = 18.0 Hz), 4.10 (1H, dd, *J* = 12.7, 3.1 Hz), 4.05 (1H, d, *J* = 7.9 Hz), 3.96 (1H, d, *J* = 16.9 Hz), 3.94 (1H, dd, *J* = 12.5, 7.1 Hz), 3.72 (1H, d, *J* = 16.9 Hz), 1.97 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 131.1, 129.6, 128.1, 117.7, 67.1, 60.3, 60.1, 15.2 ppm . IR (thin film): ν = 3503, 2922, 1298, 1109 cm^{-1}. EIMS (70 eV) *m/z* (%): 188 (25), 158 (75), 123 (30), 95 (100); HRMS: calcd for $C_8H_{12}O_3S$: 188.0507; found: 188.0506.

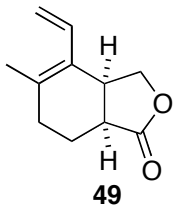
(2*E*)-3-(Prop-1-en-2-yl)penta-2,4-dien-1-ol **51**



51

387 (61 mg, 0.32 mmol, 1.0 equiv) was heated to 240 ^{o}C under reduced pressure (85 mm). The distillate was purified by column chromatography (dichloromethane) to give **51** (4 mg, 0.03 mmol, 10%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.40 (1H, dd, *J* = 17.5, 10.9 Hz), 5.74 (1H, t, *J* = 6.7 Hz), 5.36 (1H, ddd, *J* = 10.9, 2.1, 0.8 Hz), 5.15 (1H, dd, *J* = 17.5, 2.1 Hz), 5.03 (1H, bs), 5.01 (1H, bs), 4.35 (2H, d, *J* = 6.7 Hz), 1.92 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 143.4, 142.6, 132.5, 127.2, 119.5, 115.2, 60.1, 21.5 ppm. IR (thin film): ν = 3395, 2918, 2849 cm^{-1}. EIMS (70 eV) *m/z* (%): 124 (7), 123 (10), 43 (100); HRMS: calcd for $C_8H_{11}O$ [M-H]: 123.0810; found: 123.0810.

(±)-(3a*S*,7a*S*)-3,3a,7,7a-Tetrahydro-5-methyl-4-vinylisobenzofuran-1(6*H*)-one **49**

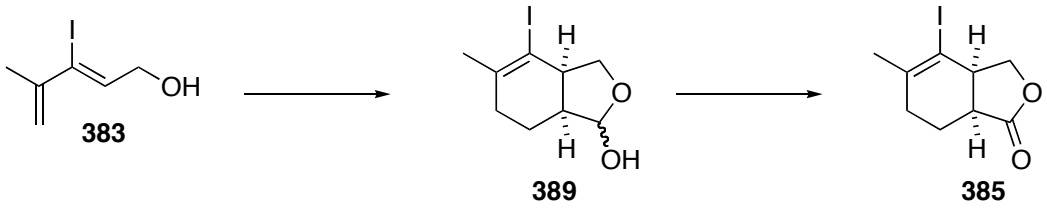


49

To a stirred solution of **51** (12 mg, 0.096 mmol, 1.0 equiv) in methanol/water (95:5, 100 μL) was added acrolein (65 μL, 0.96 mmol, 10.0 equiv). Stirring was continued for 18 h. Concentration *in vacuo* and column chromatography (hexanes/ethyl acetate 85:15) gave **351** (5.1 mg, 0.028 mmol, 29%).

To a stirred solution of **351** (9.1 mg, 0.05 mmol, 1.0 equiv) in dichloromethane (1 mL) was added celite (20 mg), PCC (22 mg, 0.10 mmol, 2.0 equiv), NaOAc (7 mg, 0.05 mmol, 1.0 equiv) and $NaHCO_3$ (4 mg, 0.05 mmol, 1.0 equiv). Stirring was continued for 18 h. The mixture was dilted with diethyl ether (20 mL), filtered and concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 85:15) gave **49** (8.4 mg, 0.05 mmol, 93%).

(±)-(3a*R*,7a*S*)-3,3a,7,7a-Tetrahydro-4-iodo-5-methylisobenzofuran-1(6*H*)-one **385**



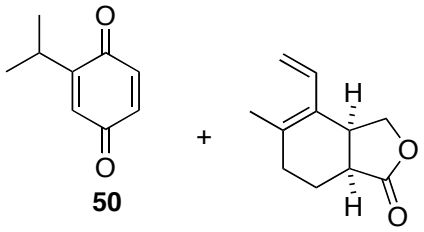
383 **389** **385**

To a stirred solution of **383** and **384** (1:1, 100 mg, 0.36 mmol, 1.0 equiv) in methanol/water (95:5, 360 μL) was added acrolein (240 μL, 3.6 mmol, 10.0 equiv). The mixture was stirred at rt for 6 d. Concentration *in vacuo* and column chromatography (hexanes/ethyl acetate 80:20) gave **389** (41 mg, 0.15 mmol, 83%).

To a stirred solution of **389** (41 mg, 0.15 mmol, 1.0 equiv) in dichloromethane (5 mL) was added celite (100 mg), PCC (63 mg, 0.30 mmol, 2.0 equiv), NaOAc (20 mg, 0.15 mmol, 1.0 equiv) and $NaHCO_3$ (12 mg, 0.15 mmol, 1.0 equiv). The mixture was stirred at rt for 18 h before being diluted with diethyl ether (20 mL). The mixture was filtered and concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 85:15) gave **385** (34 mg, 0.12 mmol, 82%).

7.5.3 Completion of the Synthesis

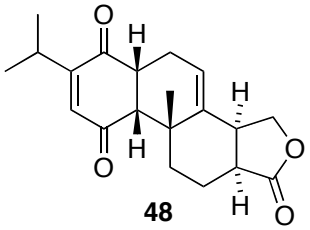
Diels-Alder reaction between diene **49** and quinone **50**



50 + **49**

A solution of **49** (890 mg, 4.99 mmol, 1.0 equiv) and quinone **50**[177] (1.10 g, 7.32 mmol, 1.5 equiv) in dichloromethane (3 mL) was compressed at 19 kbar for 7 days. The mixture was concentrated *in vacuo*. After column chromatography **48** (819 mg, 2.49 mmol, 50%) was obtained. Further elution gave **394** as a minor product.

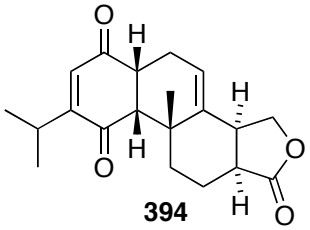
(±)-(3a*S*,5a*R*,9a*R*,9b*R*,11a*S*)-3,3a,5,5a,9b,10,11,11a-Octahydro-7-isopropyl-9b-methylphenanthro[2,1-*c*]furan-1,6,9(9a*H*)-trione **48**



48

Recrystalisation from heptane/dichloromethane gave colourless crystals. m.p. 167-170 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.42 (1H, s), 5.42 (1H, t, *J* = 3.7 Hz), 4.30 (1H, t, *J* = 9.2 Hz), 4.09 (1H, dd, *J* = 11.2, 9.2 Hz), 3.54 (1H, ddd, *J* = 10.5, 7.2, 4.9 Hz), 3.29 (1H, dd, *J* = 19.0, 8.8 Hz), 3.03 (1H, d, *J* = 4.8 Hz), 2.92 (1H, dsept. *J* = 6.8, 1.0), 2.77 (1H, ddd, *J* = 12.4, 8.1, 6.1 Hz), 2.63 (1H, dt, *J* = 13.3, 3.5 Hz), 2.36 (1H, ddd, *J* = 19.0, 7.2, 3.9 Hz), 2.09 (1H, ddd, *J* = 19.0, 10.5, 3.5 Hz), 2.05 (1H, m), 1.81 (1H, ddd, *J* = 26.6, 13.3, 3.5 Hz), 1.29 (1H, dt, *J* = 13.3, 3.7 Hz), 1.26 (3H, s), 1.10 (3H, d, *J* = 6.8 Hz), 1.06 (3H, d, *J* = 6.8 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 200.1, 199.3, 179.3, 155.1, 136.7, 135.5, 123.2, 71.6, 58.1, 45.6, 41.8, 40.2, 35.0, 31.2, 28.3, 26.6, 21.3, 20.9, 20.0 ppm. IR (thin film): ν = 2962, 1768, 1673 cm^{-1}. EIMS (70 eV) *m/z* (%): 328 (80), 285 (19), 177 (24), 152 (100); HRMS: calcd for $C_{20}H_{24}O_4$: 328.1675; found:328.1682.

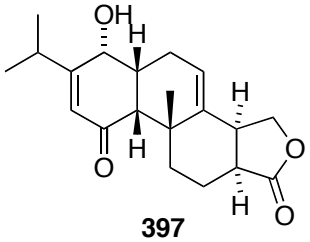
(±)-(3a*S*,5a*R*,9a*R*,9b*R*,11a*S*)-3,3a,5,5a,9b,10,11,11a-Octahydro-8-isopropyl-9b-methylphenanthro[2,1-*c*]furan-1,6,9(9a*H*)-trione **394**



394

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.21 (1H, s), 5.38 (1H, t, *J* = 4.1 Hz), 4.28 (1H, t, *J* = 9.2 Hz), 4.07 (1H, dd, *J* = 11.1, 9.2 Hz), 3.46 (1H, dddd, *J* = 12.1, 6.7, 5.1, 1.3 Hz), 3.30 (1H, dd, *J* = 19.3, 8.9 Hz), 3.04 (1H, d, *J* = 4.8 Hz), 2.91 (1H, dsept. *J* = 6.9, 1.0), 2.74 (1H, ddd, *J* = 12.6, 8.3, 6.2 Hz), 2.47 (1H, dt, *J* = 13.0, 3.4 Hz), 2.37 (1H, ddd, *J* = 19.2, 7.1, 3.6 Hz), 2.08-1.92 (2H, m), 1.80 (1H, ddd, *J* = 26.6, 13.4, 3.6 Hz), 1.27 (1H, m), 1.22 (3H, s), 1.09 (3H, d, *J* = 6.9 Hz), 1.02 (3H, d, *J* = 6.9 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 200.6, 199.9, 179.2, 162.3, 136.2, 129.8, 122.9, 71.6, 59.2, 45.1, 41.7, 40.2, 34.6, 31.0, 28.2, 26.7, 21.3, 20.5, 19.9 ppm. IR (thin film): ν = 2969, 2928, 1776, 1796, 1674 cm^{-1}. EIMS (70 eV) *m/z* (%): 328 (70), 285 (10), 177 (5), 152 (40), 84 (100); HRMS: calcd for $C_{20}H_{24}O_4$: 328.1675; found:328.1676.

(±)- (3a*S*,5a*R*,6*R*,9a*R*,9b*R*,11a*S*)-3,3a,5a,6,9b,10,11,11a-Octahydro-6-hydroxy-7-isopropyl-9b-methylphenanthro[2,1-*c*]furan-1,9(5*H*,9a*H*)-dione **397**

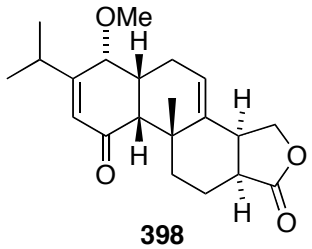


397

To a stirred solution of **48** (270 mg, 0.83 mmol, 1.0 equiv) in tetrahydrofuran (14 mL) at 0 ^{o}C was added a solution of $NaBH_4$ (25 mg, 0.66 mmol, 0.8 equiv) in water (2 mL). Stirring was continued for 30 min before the reaction was quenched by the addition of sat NH_4Cl. (20 mL). The mixture was extracted with ethyl acetate (20 mL x 2). The combined organics were dried and concentrated *in vacuo* to give **397** (270 mg, 0.83 mmol, 100%). Recrystalisation gave **397** as colourless crystals. m.p. 176-178 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.70 (1H, bs), 5.36 (1H, t, *J* = 3.2 Hz), 4.88 (1H, d, *J* = 3.2 Hz), 4.28 (1H, t, *J* = 9.2 Hz), 4.06 (1H, dd, *J* = 11.1, 9.2 Hz), 3.25 (1H, q, *J* = 8.8 Hz), 3.19 (1H, m), 2.98 (1H, dt, *J* = 13.7, 3.9 Hz), 2.78 (1H, sept., *J* = 6.9 Hz), 2.75 (1H, ddd, *J* = 12.6, 8.0, 5.9 Hz), 2.41 (1H, d, *J* = 3.9 Hz), 2.18 (1H, ddd, *J* = 19.2, 6.3, 4.7

Hz), 2.01-1.97 (2H, m), 1.78 (1H, dq, *J* = 13.4, 3.6 Hz), 1.28-1.23 (1H, m), 1.26 (3H, s), 1.14 (3H, d, *J* = 6.9 Hz), 1.09 (3H, d, *J* = 6.9 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.5, 180.0, 165.7, 136.6, 124.3, 123.9, 71.9, 71.6, 56.9, 41.8, 40.3, 38.5, 35.8, 31.3, 29.1, 29.0, 23.1, 22.0, 20.4, 20.0 ppm . IR (thin film): ν = 3469, 2965, 2872, 1762, 1668 cm^{-1}. EIMS (70 eV) *m/z* (%): 330 (12), 178 (54), 150 (50), 111 (100); HRMS: calcd for $C_{20}H_{26}O_4$: 330.1831; found: 330.1834.

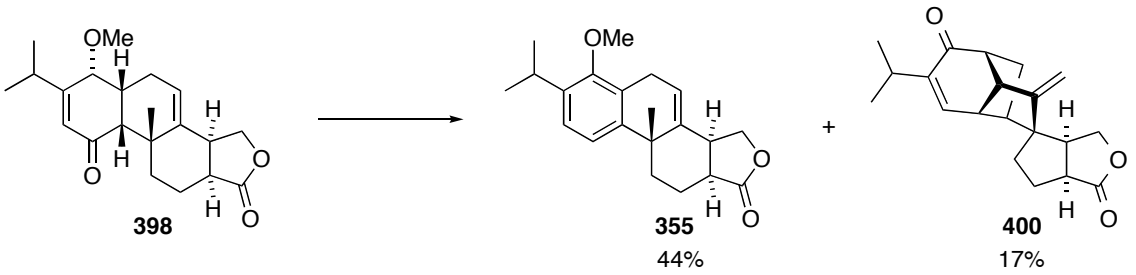
(±)- (3a*S*,5a*R*,6*R*,9a*R*,9b*R*,11a*S*)-3,3a,5a,6,9b,10,11,11a-Octahydro-7-isopropyl-6-methoxy-9b-methylphenanthro[2,1-*c*]furan-1,9(5*H*,9a*H*)-dione **398**



398

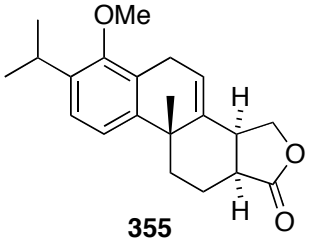
A solution of **397** (40 mg, 0.12 mmol, 1.0 equiv) and Ag_2O (280 mg, 1.21 mmol, 10 equiv) in methyl iodide (5 mL) was heated to reflux for 18 h. The solution was diluted with dichloromethane (20 mL), filtered through celite and concentrated *in vacuo*. After column chromatography (hexanes/ethyl acetate 70:30) gave **398** (41 mg, 0.12 mmol, 99%). Recrysatalisation (heptane/dichloromethane) gave colourless needles. m.p. 88-90 ^{o}C ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.68 (1H, bs), 5.36 (1H, t, *J* = 3.7 Hz), 4.30 (1H, dd, *J* = 4.7, 2.1 Hz), 4.27 (1H, t, *J* = 9.1 Hz), 4.06 (1H, dd, *J* = 11.2, 9.1 Hz), 3.49 (3H, s), 3.37 (1H, m), 3.25 (1H, q, *J* = 8.7 Hz), 3.00 (1H, dt, *J* = 13.0, 3.6 Hz), 2.79-2.72 (2H, m), 2.34 (1 H, d, *J* = 3.8 Hz), 2.09 – 1.95 (3H, m), 1.79 (1H, dq, *J* = 13.3, 3.8 Hz), 1.29 (3H, s), 1.27 (1H, dt, *J* = 13.3, 3.8 Hz), 1.07 (3H, d, *J* = 6.7 Hz), 1.05 (3H, d, *J* = 6.7 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.4, 179.8, 165.0, 136.6, 124.5, 123.9, 80.3, 71.8, 57.1, 56.3, 41.9, 40.3, 36.0, 33.6, 31.4, 29.1, 29.0, 23.0, 21.8, 20.3, 20.1 ppm . IR (thin film): ν = 2925, 1778, 1672 cm^{-1}. EIMS (70 eV) *m/z* (%): 344 (9), 312 (25), 178 (45), 125 (100); HRMS: calcd for $C_{21}H_{28}O_4$: 344.1988; found: 344.1996. Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.12; H, 7.97.

Reaction of (±)- (3a*S*,5a*R*,6*R*,9a*R*,9b*R*,11a*S*)-3,3a,5a,6,9b,10,11,11a-octahydro-7-isopropyl-6-methoxy-9b-methylphenanthro[2,1-*c*]furan-1,9(5*H*,9a*H*)-dione **398** with triflic anhydride



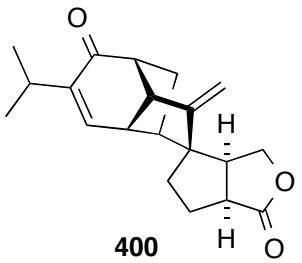
To a stirred solution of **398** (133 mg, 0.39 mmol, 1.0 equiv) in dichloromethane (2 mL) at -78 ^{o}C was added 2,6-di*tert*butyl-4-methyl pyridine (95 mg, 0.46 mmol, 1.2 equiv) and triflic anhydride (71 μL, 0.42 mmol, 1.1 equiv). The mixture was gradually warmed to rt and stirring was continued for 72 h. The mixture was diluted with dichloromethane (20 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with dichloromethane (10 mL). The combined organic layers were washed with brine (10 mL), dried and concentrated *in vacuo*. Column chromatography (heaxanes/diethyl ether 60:40) gave **355** (55 mg, 0.17 mmol, 43%) and **400** (21 mg, 0.07 mmol, 17%).

(±)- (3a*S*,9b*S*,11a*S*)-3,3a,9b,10,11,11a-Hexahydro-7-isopropyl-6-methoxy-9b-methylphenanthro[2,1-*c*]furan-1(5*H*)-one **355**



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (1H, d, *J* = 8.4 Hz), 7.10 (1H, d, *J* = 8.4 Hz), 5.95 (1H, dd, *J* = 6.4, 2.3 Hz), 4.43 (1H, t, *J* = 9.3 Hz), 4.27 (1H, dd, *J* = 11.7, 9.3 Hz), 3.75 (3H, s), 3.64 (1H, dd, *J* = 21.6, 6.1 Hz), 3.45 (1H, q, *J* = 9.2 Hz), 3.32 (1H, sept., *J* = 6.8 Hz), 3.14 (1H, d, *J* = 21.1 Hz), 2.57 (1H, m), 2.35 (1H, ddd, *J* = 13.4, 4.2, 3.1 Hz), 2.13 (1H, m), 1.88 (1H, ddd, *J* = 26.3, 13.4, 2.7 Hz), 1.75 (1H, dt, *J* = 13.3, 2.7 Hz), 1.30 (3H, s), 1.26 (3H, d, *J* = 6.8 Hz), 1.20 (3H, d, *J* = 6.8 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 179.5, 154.2, 144.4, 138.8, 136.2, 127.6, 126.2, 124.8, 119.8, 72.0, 61.1, 42.3, 40.2, 37.5, 34.9, 29.1, 26.3, 24.5, 24.2, 23.7, 20.5 ppm. IR (thin film): *ν* = 2961, 2868, 2823, 1777 cm^{-1}. EIMS (70 eV) *m/z* (%): 326 (35), 311 (55), 269 (100); HRMS: calcd for $C_{21}H_{26}O_3$: 326.1882; found: 326.1883.

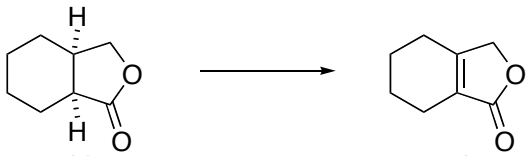
Rearranged product **400**



400

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.56 (1H, dd, *J* = 6.7, 1.0 Hz), 5.09 (1H, s), 4.57 (1H, s), 4.38 (1H, dd, *J* = 9.6, 7.7 Hz), 4.30 (1H, dd, *J* = 9.6, 2.1 Hz), 3.20 (1H, ddd, *J* = 10.0, 8.4, 6.2 Hz), 3.02-2.97 (2H, m), 2.84 (1H, d, *J* = 6.4 Hz), 2.74 (1H, sept., *J* = 6.8 Hz), 2.56 (1H, d, *J* = 7.4 Hz), 2.09-2.03 (3H, m), 1.93 (1H, ddd, *J* = 13.1, 14.9, 7.6 Hz), 1.75 (1H, ddd, *J* = 19.8, 13.4, 6.7 Hz), 1.61 (1H, dd, *J* = 14.0, 7.9 Hz), 1.49 (1H, ddd, *J* = 14.0, 5.0, 1.7 Hz), 1.01 (3H, d, *J* = 6.8 Hz), 0.96 (3H, d, *J* = 6.8 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 201.6, 180.2, 154.2, 144.5, 139.4, 108.1, 69.8, 62.3, 60.3, 51.8, 50.8, 46.0, 46.0, 42.0, 27.3, 27.0, 26.1, 21.6, 21.6 ppm . IR (thin film): ν = 2959, 1771, 1675 cm^{-1}. EIMS (70 eV) *m/z* (%): 312 (100), 297 (39), 269 (44); HRMS: calcd for $C_{20}H_{24}O_3$: 312.1725; found: 312.1719.

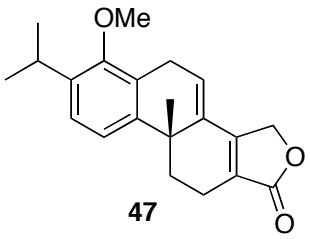
4,5,6,7-Tetrahydroisobenzofuran-1(3*H*)-one **410**



408 **410**

To a stirred solution of **408** (36.6 mg, 0.26 mmol, 1.0 equiv) in dichloromethane (2 mL) at 0 ^{o}C was added triethylamine (110 μL, 0.79 mmol, 3.0 equiv) and triispropysilyl triflouromethansulphonate (142 μL, 0.53 mmol, 2.0 equiv). Stirring was continued for 30 min before the addition of PhSeCl (151 mg, 0.79 mmol, 3.0 equiv). Stirring was continued for 30 min before the mixture was diluted with dichloromethane (10 mL). The mixture was washed with sat aq. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo*. The crude residue was dissolved in dichloromethane (5 mL) and cooled to 0 ^{o}C. 30% H_2O_2 (1 mL) was added and the mixture stirred for 1.5 h. The mixture was diluted with dichloromethane (10 mL) and washed with water (10 mL) and brine (10 mL), dried and concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 80:20) gave **410** (24 mg, 0.17 mmol, 66%). Data for this compound was constistant with that reported in the literature.[221]

(±)- (9b*S*)-10,11-Dihydro-7-isopropyl-6-methoxy-9b-methylphenanthro[2,1-*c*]furan-1(3*H*,5*H*,9b*H*)-one **47**



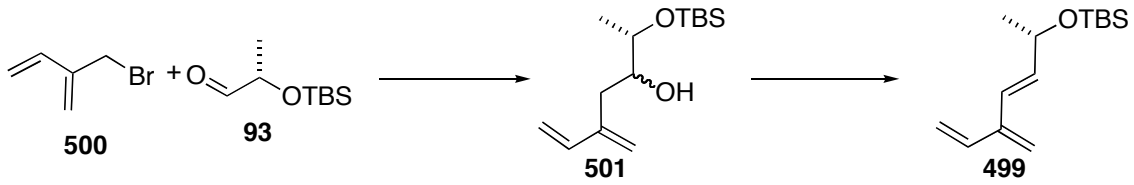
47

To a solution of **355** (7.5 mg, 0.02 mmol, 1.0 equiv) in CD_2Cl_2 (500 μL) at 0 °C was added triethylamine (13 μL, 0.08 mmol, 4.0 equiv) and triispropysilyl triflouromethansulphonate (19 μL, 0.06 mmol, 3.0 equiv). After 15 min triethylamine (13 μL, 0.08 mmol, 4.0 equiv) and triispropysilyl triflouromethansulphonate (19 μL, 0.06 mmol, 3.0 equiv) were added again. After 30 min PhSeCl (70 mg, 0.16 mmol, 8.0 equiv) was added. After 30 min the solution was diluted with dichloromethane (10 mL) and washed with sat. aq. $NaHCO_3$ (5 mL). The solution was dired and concentrated *in vacuo*. The crude residue was dissolved in dichloromethane (10 mL) and cooled to 0 °C. H_2O_2 (30% solution, 2 mL) was added and the mixture stirred for 2 h. The organic layer was collected, dried and concentrated *in vacuo*. NMR of the crude mixture showed 50% conversion of **355** to **47**. Column chromatography (hexanes/dethyl ether 60:40) gave **47**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (2H, s), 6.17 (1H, dd, *J* = 5.6, 2.3 Hz), 5.02 (1H, dt, *J* = 16.0, 2.6 Hz), 4.93 (1H, dd, *J* = 16.0, 3.1 Hz), 3.81 (1H, dd, *J* = 23.0, 5.5 Hz), 3.77 (3H, s), 3.39 (1H, d, *J* = 23.0 Hz), 3.32 (1H, sept., *J* = 7.1 Hz), 2.64-2.44 (2H, m), 1.80 (1H, m), 1.27 (3H, d, *J* = 7.1 Hz), 1.21 (3H, d, *J* = 7.1 Hz), 1.19 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 174.2, 154.9, 154.5, 142.4, 139.2, 135.3, 126.3, 125.9, 125.2, 123.8, 120.6, 69.2, 61.1, 37.0, 32.9, 27.3, 26.3, 25.0, 24.2, 23.7, 18.0 ppm . IR (thin film): ν = 2962, 2869, 1755 cm^{-1}. EIMS (70 eV) *m/z* (%): 324 (40), 309 (35), 281 (20), 267 (65), 43 (100); HRMS: calcd for $C_{21}H_{24}O_3$: 324.1725; found: 324.1728. All data was consistent with that reported in the literature.[160] The ^{1}H NMR data in the literature is incomplete.

7.6 Chapter 6

7.6.1 Synthesis of a Terminally-Substituted [3]Dendralene

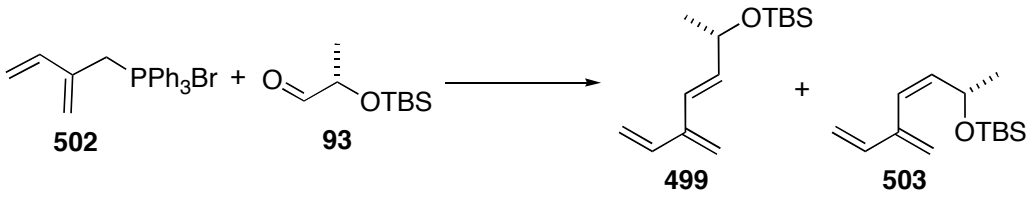
((2*S*, 3*E*)-5-Methylenehepta-3,6-dien-2-yloxy)(*tert*-butyl)dimethylsilane *via* indium mediated coupling



To a stirred solution of **500**[207,222] (279 mg, 1.91 mmol, 1.1 equiv) and **93** (327 mg, 1.74 mmol, 1.0 equiv) in DMF (1 mL) was added indium metal (219 mg, 1.91 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 16 h. The reaction was quenched with sat. NH_4Cl solution (5 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with brine (20 mL), dried and concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 96:4) gave **501** (259 mg, 1.01 mmol, 58 %) as a 1:1 mixture of diastereomers.

To a stirred solution of **501** (130 mg, 0.51 mmol, 1.0 equiv) in tetrahydrofuran (5 mL) was added triphenyl phosphine (266 mg, 1.01 mmol, 2.0 equiv) and DEAD (160 µL, 1.01 mmol, 2.0 equiv). The mixture was heated at 63 ºC for 5 h before being concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 95:5) gave **499** (31 mg, 0.13 mmol, 26%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.44 (1H, dd, *J* = 17.4, 11.0 Hz), 6.26 (1H, d, *J* = 15.9 Hz), 5.88 (1H, dd, *J* = 15.9, 5.5 Hz), 5.38 (1H, d, *J* = 17.4 Hz), 5.13 (1H, d, *J* = 11.0 Hz), 5.11 (1H, s), 5.10 (1H, s), 4.38 (1H, dq, *J* = 6.2, 6.2 Hz), 1.25 (3H, d, *J* = 6.2 Hz), 0.91 (9H, s), 0.08 (3H, s), 0.07 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 136.6, 136.4, 126.6, 115.5, 115.0, 69.2, 26.0, 24.6, 18.4, -4.5, -4.7ppm. IR (thin film): ν = 2956, 2929, 2857cm^{-1}. EIMS (70 eV) *m/z* (%): 181 (20), 159 (10), 75 (100); HRMS: calcd for $C_{10}H_{17}OSi$ [M-C_4H_9]: 181.1049; found: 181.1048.

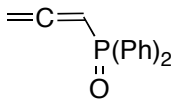
((2*S*, 3*E*)-5-Methylenehepta-3,6-dien-2-yloxy)(*tert*-butyl)dimethylsilane **499** *via* Wittig reaction



502 **93** **499** **503**

To a stirred solution of **502** (391 mg, 0.96 mmol, 1.2 equiv) in tetrahydrofuran (5 mL) at -78 °C was added *n*-butyllithium (1.56 M in hexanes, 511 μL, 0.80 mmol, 1.0 equiv). The mixture was warmed to -40 °C and stirring was continued for 45 min. A solution of **93** (150 mg, 0.80 mmol, 1.0 equiv) in tetrahydrofuran (2 mL) was added dropwise *via* cannula. The mixture was stirred at this temperature for 45 min before being warmed to rt. Stirring was continued for 1.5 h. The mixture was diluted with diethyl ether (20 mL) and washed with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with diethyl ether (10 mL)). The combined organic extracts were washed with brine (10 mL), dried and concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 197:3) gave **499/503** (*E*/*Z* 70:30, 71 mg, 0.30 mmol, 37%) as a colourless oil.

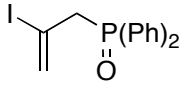
Allenyldiphenylphosphine oxide **510**



510

The title compound was prepared according to a modified literature procedure.[172] To a stirred solution of propargyl alcohol (17.46 mL, 0.30 mol, 1.0 equiv) and triethylamine (46 mL, 0.33 mol, 1.1 equiv) in dichloromethane (300 mL) at -80 °C was added a solution of Ph_2PCl (27 mL, 0.15 mol, 0.5 mmol) in dichloromethane (225 mL) at such a rate to maintain the temperature. The mixture was warmed to -10 °C then poured into a solution of HCl (7.5 mL) in water (300 mL). The aqueous layer was extracted with dichloromethane (100 mL x 2). The combined organic layers were washed with water (200 mL x 2), dried and concentrated *in vacuo* to give allenyldiphenylphosphine oxide **510** (33 g, 0.14 mmol, 92%).

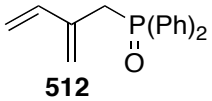
2-Iodo-2-propenyl diphenyl phosphine oxide **511**



511

The title compound was prepared according to a modified literature procedure.[213] To a stirred solution of allenyldiphenylphosphine oxide **510** (8.87 g, 34 mmol, 1.0 equiv) in acetic acid (40 mL) was added $LiI.H_2O$ (6.26 g, 41 mmol, 1.2 equiv). The mixture was heated at 100 ^oC for 18h. After cooling to rt water (50 mL) was added and the mixture was extracted with ethyl acetate (5 x 50 mL). The combined organic layers were washed with 5% aq $Na_2S_2O_3$ (100 mL) and sat. aq. NH_4Cl (100 mL), dried then concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 20:80) gave 2-iodo-2-propenyl diphenyl phosphine oxide **511** (10.1 g, 27 mmol, 81%).

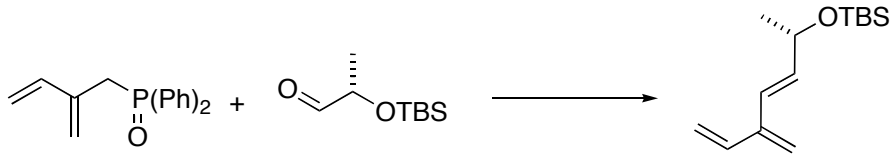
2-Propenyl-2-vinyldiphenyl phosphine oxide **512**



512

A solution of 2-iodo-2-propenyl diphenyl phosphine oxide **511** (500 mg, 1.36 mmol, 1.0 equiv) and tributyl(vinyl)tin (517 mg, 1.63 mmol, 1.2 equiv) in dry DMF (8 mL) was freeze/thaw degassed (x2). To this solution was added bis(acetonitrile)palladium dichloride (18 mg, 0.07 mmol, 5 mol%). The reaction mixture was stirred at rt for 3 h before being diluted with diethyl ether (50 mL) and washed with aqueous ammonia solution (2 x 50 mL). The organic layer was washed with brine (50 mL), dried and concentrated *in vacuo*. Column chromatography (hexanes/ethyl acetate 20:80) gave phosphine oxide **512** (262 mg, 0.98 mmol, 72%) as a white soild. ^1H NMR (300 MHz, $CDCl_3$): δ 7.80-7.70 (4H, m), 7.53-7.40 (6H, m), 6.32 (1H, dd, J = 18.0, 11.6 Hz), 5.24 (1H, s), 5.18 (1H, s), 5.14 (1H, dd, J = 17.5, 3.9 Hz), 5.03 (1H, d, J = 10.7 Hz), 3.26 (2H, dd, J = 13.9, 0.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5 (J = 0.54 ppm), 136.4 (J = 0.11 ppm), 132.8 (J = 1.32 ppm), 131.8 (J = 0.4 ppm), 131.1 (J = 0.12 ppm), 128.5 (J = 0.16 ppm), 120.8 (J = 0.11 ppm), 114.9, 32.7 (J = 0.90 ppm). IR (thin film): ν = 3055, 2916, 1437, 1189, 1119cm^{-1}. EIMS (70 eV) *m/z* (%):268 (75), 201 (100); HRMS: calcd for $C_{17}H_{17}OP$: 268.1017; found: 268.1011.

((2*S*, 3*E*)-5-Methylenehepta-3,6-dien-2-yloxy)(*tert*-butyl)dimethylsilane *via* Horner-Emmons type reaction

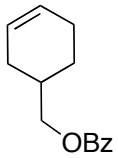


512 **93** **499**

To a stirred solution of phosphine oxide **512** (121 mg, 0.45 mmol, 1.2 equiv) in tetrahydrofuran (2 mL) and HMPA (157 μL, 0.90 mmol, 2.4 equiv) at -78 °C was added *n*-butyllithium (1.60 M in hexanes, 280 μL, 1.2 equiv). The reaction mixtrure was stirred at this temperature for 15 min before the dropwise addition of a solution of aldehyde **93** (71 mg, 0.38 mmol, 1.0 equiv) in tetrahydrofuran (2 mL). The mixture was stirred at -78 °C for 30 min, 0 °C for 1 h and finally at rt for 2 h. The reaction mixture was quenched with ice cold 1M aqueous HCl (20 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL) dried and concentrated. Column chromatography (hexanes/diethyl ether 98:2) gave dendralene **499** (49 mg, 0.20 mmol, 55%) as a colourless oil.

7.6.2 Formation of the Tetracyclic Framework

(Cyclohex-3-enyl)methyl benzoate **498**



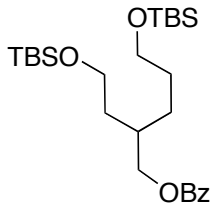
498

To a stirred solution of lithium aluminium hydride (3.34 g, 88 mmol, 1.0 equiv) in diethyl ether (200 mL) at 0 ^{o}C was added a solution of **520** (9.7 g, 88 mmol, 1.0 equiv) in diethyl ether (20 mL). Stirring was continued at rt for 30 min. 30% sodium sulfate solution (40 mL) was added dropwise at 0 ^{o}C. The mixture was stirred for 30 min, filtered, dried and concentrated *in vacuo* to give **541** (9.88 g, 88 mmol, 100%) as a colourless oil.

To a stirred solution of alcohol **541** (8.0 g, 71 mmol, 1.0 equiv) in dichloromethane (500 mL) at 0 ^{o}C was added triethylamine (11.93 mL, 86 mmol, 1.2 equiv) and benzoyl chloride (9.93 mL, 86 mmol, 1.2 equiv). Stirring was continued for 18 h. The mixture was washed with 1M HCl (200 mL), sat. $NaHCO_3$ (200 mL) and brine (200 mL). The organic layer was dried and concentrated *in vacuo*. Distillation 128-132 ^{o}C at 1.5

mm/Hg) gave **498** (13.0 g, 60 mmol, 84%) as a colourless oil. Data was consistant with that reported in the literature.

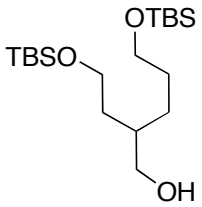
3-(Benzyloxy)methyl-1,6-di[(*tert*-butyldimethylsilyl)oxy]hexane **513**



513

Ozone was bubbled through a stirred solution of **498** (1.27 g, 5.9 mmol, 1.0 equiv) in dichloromethane (25 mL) and methanol (5 mL) at -78 ^{o}C. After the mixture turned blue nitrogen was bubbled through the mixture for 30 min. $NaBH_4$ (222 mg, 5.9 mmol, 1.0 equiv) was added and the reaction was warmed to rt. A second portion of $NaBH_4$ (222 mg, 5.9 mmol, 1.0 equiv) was added and the mixture was stirred for 18 h. A solution of NH_4Cl (20 ml) was added. The mixture was extracted with ethyl acetate (50 mL x 5). The combined organic layers were washed with brine (100 mL), dried and concentrated *in vacuo*. The crude product was dissolved in DMF (8 mL) and cooled to 0 ^{o}C. Imidazole (1.17 g, 17.2 mmol, 2.9 equiv) and *tert*-butyldimethylsilyl chloride (2.16 g, 14.3 mmol, 2.4 equiv) were added. The mixture was warmed to rt and stirring was continued for 1.5 h. The mixture was diluted with diethyl ether (20 mL) and washed with water (20 mL). The aqueous layer was extracted with diethyl ether (20 mL x 2). The combined organic layers were washed with brine, dried and concentrated *in vacuo*. After column chromatography (hexanes/diethyl ether 96.5:3.5) **513** (2.27 g, 4.72 mmol, 80%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (2H, dd, J = 8.1, 1.5 Hz), 7.55 (1H, dt, J = 7.4, 1.4 Hz), 7.43 (2H, t, J = 7.9 Hz), 4.27 (4H, d, J = 5.5 Hz), 3.72 (2H, t, J = 6.6 Hz), 3.62 (2H, t, J = 6.6 Hz), 1.98 (1H, sept. 6.2 Hz), 1.72-1.44 (7H, m), 0.89 (9H, s), 0.88 (9H, s), 0.05 (6H, s), 0.04 (6H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.7, 132.9, 130.5, 129.6, 128.4, 67.5, 63.3, 61.0, 34.7, 34.4, 30.1, 27.8, 26.0 (2 coincident peaks), 18.4, 18.4, -5.2 (2 coincident peaks) ppm . IR (thin film): ν = 2953, 2929, 2894, 2857, 1722 cm^{-1}. EIMS (70 eV) *m/z* (%): 423 (72), 179 (98), 95 (100); HRMS: calcd for $C_{22}H_{39}O_4Si_2$ [M-C_4H_9]: 423.2387; found: 423.2385.

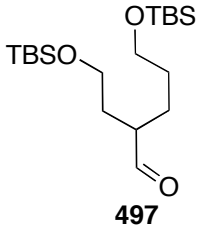
1,6-Di[(*tert*-butyldimethylsilyl)oxy]-3-methanolhexane **521**



521

To **513** (2.5 g, 5.2 mmol, 1.0 equiv) was added a methanolic solution of NaOH (196 mL of a 0.18 M solution). The mixture was stirred for 8 h then concentrated *in vacuo*. Water (100 mL) and diethyl ether (100 mL) were added. The organic layer was washed with brine (50 mL), dried and concentrated *in vacuo*. After column chromatography **521** (1.51 g, 4.0 mmol, 77%) was obtained as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (1H, ddd, J = 10.5, 6.2, 4.0 Hz), 3.70-3.54 (4H, m), 3.45 (1H, dd, J = 11.1, 6.5 Hz), 1.73-1.46 (5H, m), 1.42-1.23 (2H, m), 0.89 (9H, s), 0.85 (9H, s), 0.07 (6H, s), 0.04 (6H, s)ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.1, 63.4, 61.9, 39.5, 35.7, 30.4, 27.9, 26.0, 25.9, 18.4 (2 coincident peaks), -5.2, -5.4 ppm . IR (thin film): ν = 3339, 2929, 2885, 2858 cm^{-1}. EIMS (70 eV) *m/z* (%): 319 (40), 115 (50), 57 (100); HRMS: calcd for $C_{15}H_{35}O_3Si_2$ [M-C_4H_9]: 319.2125; found: 319.2130.

1,6-Di[(*tert*-butyldimethylsilyl)oxy]-3-formylhexane **497**

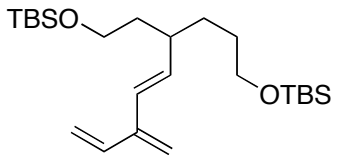


497

To a solution of oxalyl chloride (419 μL, 4.8 mmol, 1.2 equiv) in dichloromethane (50 mL) at -78 ^{o}C was added dimethyl sulfoxide (568 μL, 8.0 mmol, 2.0 equiv). After 10 min a solution of **521** (1.51 g, 4.0 mmol, 1.0 equiv) in dichloromethane (25 mL) was added. Stirring was continued for 1.5 h before the addition of triethylamine (2.23 mL, 16 mmol, 4.0 equiv). The mixture was gradually allowed to warm to rt. The mixture was washed with water (50 mL). The aqueous layer was extracted with diethyl ether (20 mL x 2). The combined organic layers were washed with brine, dried and concentrated *in vacuo*. Column chromatography (hexanes/diethyl ether 95:5) gave **497** (1.14 g, 3.0 mmol, 76%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.59 (1H, d, J = 2.62 Hz), 3.67-3.55 (4H, m), 2.44-2.32 (1H, m), 1.96-1.46 (6H, m), 0.87 (9H, s), 0.86 (9H, s), 0.03 (6H, s), 0.01 (6H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.0, 62.8, 60.6,

48.9, 32.3, 30.1, 26.0, 25.9, 24.9, 18.4, 18.3, -5.3, -5.4 ppm. IR (thin film): ν = 2929, 2886, 1728, 1708 cm^{-1}. EIMS (70 eV) *m/z* (%): 317 (25), 259 (5), 75 (100); HRMS: calcd for $C_{15}H_{33}O_3Si_2$ [M-C_4H_9]: 317.1968; found: 317.1964.

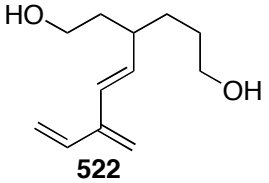
(5*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-[(*tert*-butyldimethylsilyl)oxyethyl]-7-methylenenona-5,8-diene **514**



514

To a stirred solution of phosphine oxide **512** (478 mg, 1.78 mmol, 1.2 equiv) in tetrahydrofuran (20 mL) at -78 °C was added *n*-butyllithium (1.6 M sol. in hexanes, 1.02 mL, 1.1 equiv). After 15 min a solution of aldehyde **497** (556 mg, 1.48 mmol, 1.0 equiv) in tetrahydrofuran (10 mL) was added. The mixture was stirred at -78 °C for 1 h, 0 °C for 1 h and rt for 2.5 h. The mixture was washed with 1M HCl solution (10 mL). The aqueous layer was extracted with diethyl ether (20 mL x 3). The combined organic layers were washed with water (20 mL) and brine (20 mL) then dried and concentrated *in vacuo*. Column chromatography (hexanes/diethyl ether 96:4) gave **514** (545 mg, 1.28 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.43 (1H, dd, *J* = 17.4, 10.8 Hz), 6.07 (1H, d, *J* = 15.5 Hz), 5.58 (1H, dd, *J* = 15.5, 9.1 Hz), 5.37 (1H, dd, *J* = 17.5, 1.4 Hz), 5.12 (1H, d, *J* = 10.6 Hz), 5.04 (2H, s), 3.65-3.53 (4H, m), 2.20 (1H, m), 1.70-1.41 (5H, m), 1.35-1.27 (1H, m), 0.9 (18 H, s), 0.04 (6H, s), 0.03 (6H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.4, 136.8, 136.5, 129.0, 115.4, 114.0, 63.3, 61.2, 39.5, 38.4, 31.6, 30.6, 26.1, 26.1, 18.5, 18.4, -5.2 (2 coincident peaks) ppm. IR (thin film): ν = 2954, 2929, 2896, 2857 cm^{-1}. EIMS (70 eV) *m/z* (%): 367 (55), 292 (20), 235 (100); HRMS: calcd for $C_{20}H_{39}O_2Si_2$ [M-C_4H_9]: 367.2489; found: 367.2484.

3-((*E*)-3-Methylenepenta-1,4-dienyl)hexane-1,6-diol **522**

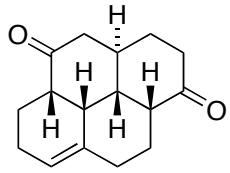


522

To a stirred solution of **514** (525 mg, 1.24 mmol, 1.0 equiv) in tetrahydrofuran (33 mL) at 0 °C was added tetrabutyl ammonium fluoride (1.0 M sol in tetrahydrofuran, 3.71 mL, 3.71 mmol, 3.0 equiv). Stirring was continued at rt for 2.5 h before the addition of a

solution of NH_4Cl (10 mL). The mixture was extracted with diethyl ether (10 mL) and ethyl acetate (10 mL x 2). The combined organic layers were washed with brine (20 mL), dried and concentrated *in vacuo*. Column chromatography (hexane/ethyl acetate 10:90) gave **522** (185 mg, 0.94 mmol, 76%). ^{1}H NMR (500 MHz, C_6D_6): δ 6.46 (1H, dd, *J* = 17.6, 10.8 Hz), 6.16 (1H, d, *J* = 15.7 Hz), 5.63 (1H, dd, *J* = 15.7, 9.1 Hz), 5.40 (1H, dd, *J* = 17.3, 1.4 Hz), 5.16 (1H, d, *J* = 10.8 Hz), 5.10 (2H, s), 3.74-3.57 (4H, m), 2.29 (1H, m), 1.80-1.27 (6H, m) ppm. ^{13}C NMR (125 MHz, C_6D_6): *δ* 144.9, 137.1, 136.9, 129.7, 115.7, 114.5, 62.4, 60.6, 39.8, 38.5, 31.7, 30.7ppm . IR (thin film): ν = 3306, 2953, 2923, 2854 cm^{-1}. EIMS (70 eV) *m/z* (%): 196 (1), 91 (100), 79 (70); HRMS: calcd for $C_{12}H_{20}O_2$: 196.1463; found: 196.1472.

Tetracycle **524**



524

To a solution of oxalyl chloride (102 μL, 1.17 mmol, 2.4 equiv) in dichloromethane (20 mL) at -78 ^{o}C was added dimethyl sulfoxide (139 μL, 1.96 mmol, 4.0 equiv). After 10 min a solution of **522** (96 mg, 0.049 mmol, 1.0 equiv) in dichloromethane (10 mL) was added. Stirring was continued for 1.5 h before the addition of triethylamine (545 μL, 3.91 mmol, 8.0 equiv). The mixture was gradually allowed to warm to rt. The mixture was washed with water (50 mL). The aqueous layer was extracted with diethyl ether (20 mL x 2). The combined organic layers were washed with brine, dried and concentrated *in vacuo*. The crude reside was dissolved in tetrahydrofuran (15 mL) and cooled to 0 ^{o}C. Vinyl magnesium bromide (1.0 M sol. in tetrahydrofuran, 2.5 mL, 2.5 mmol, 5.1 equiv) was added and the mixture stirred for 1 h. Sat. NH_4Cl (10 mL) was added and the mixture extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried and concentrated *in vacuo*. The crude diol **523** was dissolved in dichloromethane (10 mL).

To a solution of oxalyl chloride (102 μL, 1.17 mmol, 2.4 equiv) in dichloromethane (20 mL) at -78 ^{o}C was added dimethyl sulfoxide (139 μL, 1.96 mmol, 4.0 equiv). After 10 min a solution of crude diol **523** in dichloromethane (10 mL) was added. Stirring was continued for 1.5 h before the addition of triethylamine (545 μL, 3.91 mmol, 8.0 equiv). The mixture was gradually allowed to warm to rt. The mixture was washed with water

(50 mL). The aqueous layer was extracted with diethyl ether (20 mL x 2). The combined organic layers were washed with brine, dried and concentrated *in vacuo*. The residue was dissolved in $CDCl_3$ (1.5 mL) and TFA (70 μL) was added. The mixture was stood at rt for 48 h before being concentrated *in vacuo*. HPLC gave **524** (4 mg, 1.6 μm, 3%).

^{1}H NMR (800 MHz, $CDCl_3$): δ 5.51 (1H, dd, *J* = 3.5, 2.5 Hz), 2.85 (1H, m), 2.64 (1H, ddd, *J* = 13.1, 3.7, 1.4 Hz), 2.56 (1H, dt, *J* = 14.4, 6.6 Hz), 2.53 (1H, m), 2.48 (1H, dd, *J* = 14.4, 3.7 Hz), 2.35 (1H, ddd, *J* = 14.6, 4.4, 2.2 Hz), 2.31-2.14 (5H, m), 2.11 (1H, t, *J* = 13.7 Hz), 2.06-2.00 (2H, m), 1.84 (1H, d, *J* = 18.1 Hz), 1.78 (1H, dq, *J* = 13.2, 4.4 Hz), 1.66 (1H, m), 1.46 (1H, m), 1.32 (1H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 213.7, 209.8, 133.1, 124.4, 53.0, 47.8, 45.9, 44.9, 42.2, 36.8, 33.8, 33.6, 30.8, 26.0, 22.2, 21.5 ppm. EIMS (70 eV) *m/z* (%): 244 (100); HRMS: calcd for $C_{16}H_{20}O_2$: 244.1463; found: 244.1463.

Appendix

X-Ray crystallography reports for compounds **110a**, **113**, **114**, **115**, **116**, **282**, **287**, **291**, **292**, **293**, **48**, **397**, **398**, **355**, **400** and **524** are provided on the CD on the inside back cover of this thesis. Single crystal X-Ray analyses were performed by Dr Anthony Willis, Dr Alison Edwards and Dr Peter Turner.

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