Investigations Into The Stereochemical Outcome Of Intramolecular Diels-Alder Reactions

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Into

The Stereochemical Outcome

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Abstract

The Diels-Alder (DA) reaction is an important tool in synthetic organic chemistry, since it allows the simultaneous formation of two carbon-carbon (or carbon-heteroatom) bonds. The stereoselectivity of intramolecular versions of this reaction is, however, difficult to predict. A systematic study of the intramolecular Diels-Alder (IMDA) reaction has been carried out which provides new insights into factors affecting stereocontrol. Ester tethered substrates were chosen for this investigation because there are relatively few literature examples of this type and esterification provides a versatile way of attaching the diene to the dienophile.

Two chiral dienols were prepared and these were used to synthesize a range of precursors for investigating asymmetric induction in ester tethered DA (ETDA) reactions. When a stereogenic centre was incorporated into precursors at the allylic position to the diene terminus, high levels of π-facial stereoselectivity were observed. The amount of stereocontrol was dependent on the size of the stereocontrolling element that was used, but diastereoisomer ratios of up to 96:4:0:0 were achieved. This method of stereocontrol represents a powerful new method for achieving asymmetric induction in IMDA reactions. Conversely, no diastereofacial selectivity was observed when the ETDA precursor lacked a stereocentre at the allylic position.

The *endo:exo* and π-facial stereoselectivity of maleate and fumarate derivatives of the chiral dienols (and achiral examples prepared from (2*E*,4*E*)-2,4-hexadien-1-ol) were compared and an explanation of the observed stereoselectivity is proposed. For maleates there was a clear preference for *trans*-fused *exo* adducts, whether the dienophile was terminated with a carboxylic acid or a methyl ester group. In contrast to this, *cis*-fused *endo* adducts were favoured for chiral fumarate precursors, regardless of the type of functional group that the dienophile was terminated with. In each case the π-facial stereoselectivity was slightly greater for the ester than the corresponding carboxylic acid. These observations undermine previous literature reports which claim that the geometry of the dienophile is not a dominant factor in the *endo:exo* stereoselectivity of ETDA reactions. It is also counter to the view that carboxylic acids promote the formation of *endo* adducts, and esters promote *exo* adducts respectively.

Determination of the stereochemistry of the ETDA adducts was accomplished by taking into account the absolute stereochemistry of existing stereogenic centres in the precursors, COSY and NOESY spectra of the adducts, the coupling constants arising at the ring junction, and conformational analysis using molecular models. A tricyclic derivative was prepared from one of the ETDA adducts and nOe difference experiments were carried out on it, which confirmed the stereochemical assignments that were made. Preparation of this derivative serves as a model system for the syntheses of himbacine

(which is a lead compound in the treatment of Alzheimer's disease) and velutinal (a powerful antifeedant for the opossum), both of which possess a similar carbocyclic backbone to the tricycle that was formed.

The assertion that carboxylic acids form *endo* adducts in ETDA reactions has gone unchallenged for over twenty years. The most frequently cited evidence for this behaviour involves DA reactions of citraconate derivatives of (2*E*,4*E*)-2,4-hexadien-1-ol. Since the results obtained for a range of maleate half esters conflicted with the published results for citraconate half esters, a thorough reinvestigation of the literature examples was carried out. Each of the possible *exo* and *endo* DA adducts for the two regioisomeric (2*E*,4*E*)-2,4-hexadien-1-yl hydrogen citraconate precursors was prepared and characterized independently, to enable the products formed in the DA reactions to be identified by proton NMR analysis. It was demonstrated that (2*E*,4*E*)-2,4-hexadien-1-yl citraconate half esters are thermally labile and break down when heated in refluxing solvent to form citraconic anhydride and (2*E*,4*E*)-2,4-hexadien-1-ol. This impacts upon the commonly held belief that (2*E*,4*E*)-2,4-hexadien-1-yl citraconate half esters undergo *ETDA* reactions to form predominantly *endo* adducts. In fact, the experiments described herein demonstrate that the *endo* adducts form by way of *bimolecular* DA reactions between citraconate anhydride and (2*E*,4*E*)-2,4-hexadien-1-ol, which occur subsequent to cleavage of the ester tether. In reactions of other citraconate half esters (involving alcohols which are less volatile than (2*E*,4*E*)-2,4-hexadien-1-ol) it was possible to isolate the respective alcohols in yields of 54-63%.

Steroids are attractive synthetic targets, since rare examples of steroidal natural products with potent biological activity are regularly discovered. Practical synthesis of steroids *via* transannular Diels-Alder (TDA) reactions is an attractive strategy, since it should be accomplished by simply heating the starting material in an appropriate solvent (which can be subsequently recycled). A more ambitious approach involves the stereocontrolled tandem TDA reaction of a macrocycle containing a *bis*-diene (in the form of a conjugated tetraene) and a *bis*-dienophile. Such a reaction would involve the simultaneous formation of four carbon-carbon bonds and eight new stereogenic centres in a single step. A chiral tetraenol and a monoprotected dienedioic acid containing a *bis*-dienophile moiety have been prepared. Esterification of these materials and selective manipulation of the protecting groups was carried out, but macrocyclisation has yet to be achieved. Progress in this area has set the scene for tandem TDA reactions to be attempted.

Adele,

Mum and Jim,

Dad,

Philip and Greg,

Nanna Morris, Nanna Lilly and Grandy.

It gives me great pleasure to thank the following people for their help!

Mick Sherburn for offering me support of every kind throughout this project and for the unshakable conviction that the transformations eventually would work.

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Tony Burrell for carrying out an X-Ray crystallographic experiment for me and for being an all around good guy.

All of the Sherburnites (past and present) who made this process much more fun than it otherwise might have been.

Cheers,

Mike.

"What have you lost Mulla?"

"My key," said Nasrudin.

"Where did you drop it?"

"At home."

"Then why, for heaven's sake, are you looking for it here?"

"There is more light here."

A Sufi Parable.

Contents

Abbreviations

%	percentage yield
Δ	heat
Ac	$-O_2CCH_3$
AIBN	2,2'-azo-*bis*-isobutyronitrile
APT	attached proton test
BDA	bimolecular Diels-Alder
BHT	2,6-di-*tert*-butyl-4-methylphenol
BMS	borane methyl sulphide complex
Bn	benzyl
°C	degree Celsius
ca	circa (approximately)
CA	citraconic anhydride
CI	chemical ionization
COSY	correlated spectroscopy
d	day/s or doublet/s
DA	Diels-Alder
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimde
DEPT	distortionless enhancement by polarization transfer
DMAP	N,N-diemthylaminopyridine
DMES	dimethylethylsilyl
DMF	dimethylformamide
DMP	dimethoxypropane
DIBALH	diisobutylaluminium hydride
DMSO	dimethylsulphoxide
EDG	electron donating group
EI	electron impact
endo	tether carbonyl distant from diene in the transition state
eq	molar equivalents
Et	ethyl
ETDA	ester tethered Diels-Alder
EWG	electron withdrawing group
eV	electron Volts
exo	tether carbonyl close to diene in transition state
h	hour/s
HETCOR	heteronuclear COSY

HMQC	heteronuclear multiple quantum correlation
HOMO	highest occupied molecular orbital
HSQC	heteronuclear single quantum correlation
IMDA	intramolecular Diels-Alder
imid.	imidazole
internal	carbon atom/bond close to tether
iPr	isopropyl
LUMO	lowest unoccupied molecular orbital
MA	maleic anhydride
Me	methyl
min	minute
MOM	methoxymethyl
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
peripheral	carbon atom/bond distant from tether
Ph	phenyl
$PhCH_3$	toluene
PhH	benzene
Pip	piperonyl
PMB	*para*-methoxybenzyl
ppm	parts per million
pyr.	pyridine
q	quartet
ROESY	rotating frame Overhauser enhancement spectroscopy
RT	room temperature
s	singulet
t	time or triplet
T	temperature
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TDA	transannular Diels-Alder
TFA	trifluoroacetic acid
TfO	trifluoromethanesulphonate
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
TIMDA	tandem intramolecular Diels-Alder
TIPS	triisopropylsilyl

TLC	thin layer chromatography
TMS	trimethylsilyl
xyl	xylene
$\chi\rho$	chiral group

1 Background

1.1 Introduction

Since its inception in 1928[1] the Diels-Alder (DA) reaction has become one of the mainstays of synthetic organic chemistry. The significance of this reaction was recognized in 1950 when Otto Diels (1876-1954) and Kurt Alder (1902-1958) were awarded the Nobel Prize for Chemistry for its discovery (although there is some controversy concerning the first time that this most ubiquitous of chemical transformations was actually observed.[2])

The DA reaction is a thermally allowed pericyclic process in which a conjugated diene and a dienophile add together to form a cyclohexene (**Figure 1.1**). There are several aspects of this [4+2] cycloaddition reaction which render it a powerful synthetic tool. The most important of these is that two carbon-carbon bonds can be formed in a single step, rapidly advancing any stepwise synthesis. It is also an important method of forming six membered carbocycles, often involving no more than the judicious application of heat to the starting materials in an appropriate solvent. When the diene or dienophile has appropriate functionality up to four new stereogenic centres can be produced simultaneously, allowing structurally complex molecules to be built up very quickly. In addition, aromatic, acetylenic and heteroatomic moieties may be incorporated into the diene or dienophile greatly augmenting the structural diversity which can be achieved.[3-6]

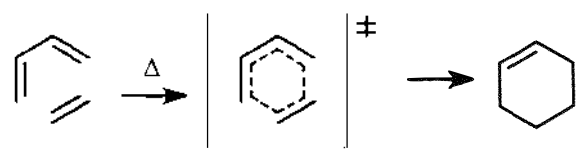


Figure 1.1

The DA reaction is very flexible but there are some criteria which must be considered in order to ensure that the reaction is successful. The diene must be conjugated and it must be able to adopt an *s-cis* conformation in order for the two ends of the molecule to be close enough together to react with the dienophile. Electron withdrawing groups (EWG) are normally attached to the dienophile and electron donating groups (EDG) to the diene. This lowers the energy of the lowest unoccupied molecular orbital (LUMO) of the dienophile and raises the energy of the highest occupied molecular orbital (HOMO) of the diene, which increases the overlap between these orbitals and reduces the amount of thermal energy required.[7] Inverse electron demand DA reactions

(in which EDG are attached to the dienophile or EWG to the diene) have also been reported.[8]

The first intramolecular Diels-Alder (IMDA) reactions (**Section 1.2**) were reported in 1963,[9-11] although the idea was proffered by Alder ten years earlier.[12] Despite the entropic, regiochemical and stereochemical advantages that these reactions have over their bimolecular Diels-Alder (BDA) counterparts, they have not achieved the synthetic prominence that might have been expected. IMDA reactions are often employed late in a synthetic regime and the precursors often incorporate complex functionality which poses a very real risk to the completion of a synthesis, because reactivity and stereoselectivity can be difficult to predict. Despite these problems several reviews on IMDA reactions are available[13-20] and there are many recent asymmetric total syntheses which demonstrate that it is a versatile synthetic tool.[21-27] Due to this versatility one reviewer[15] has quipped that "if it's worth synthesizing, an IMDA reaction is worth considering".

The first transannular Diels-Alder (TDA) reaction (**Section 1.3**) was reported in 1962.[28] The potential pitfalls and rewards associated with IMDA reactions are even further accentuated with TDA reactions, with the result that literature accounts of them are rare. However, one review in the area has been published[29] and several natural product directed syntheses incorporating TDA reactions have been reported.[30-35] The stereochemical characteristics of these reactions are now becoming better understood.

1.2 The intramolecular Diels-Alder (IMDA) reaction

The most frequently reported IMDA reactions are those in which the tether connecting the diene and dienophile is made up entirely of carbon atoms. This includes examples which have unsaturated carbons in the tether arising from olefinic, aromatic or carbonyl groups. (Carbonyl groups are often used to activate the starting material in carbocyclic systems by placing them in conjugation with the dienophile.) IMDA reactions where the tether contains one or more heteroatoms (particularly nitrogen or oxygen) have also been investigated. A range of functional groups have been used to connect the diene to the dienophile, including amines, amides, ethers and esters. In addition the tether can be substituted with further branching groups, which often have a marked effect on the stereochemical outcome of the reaction.

Figure 1.2 shows six different arrangements which can lead to IMDA reactions. Arrangements **1-4**, in which the tether is attached to the first carbon of the diene, are referred to as **Type 1** reactions, whereas **5** and **6** are referred to as **Type 2** reactions.

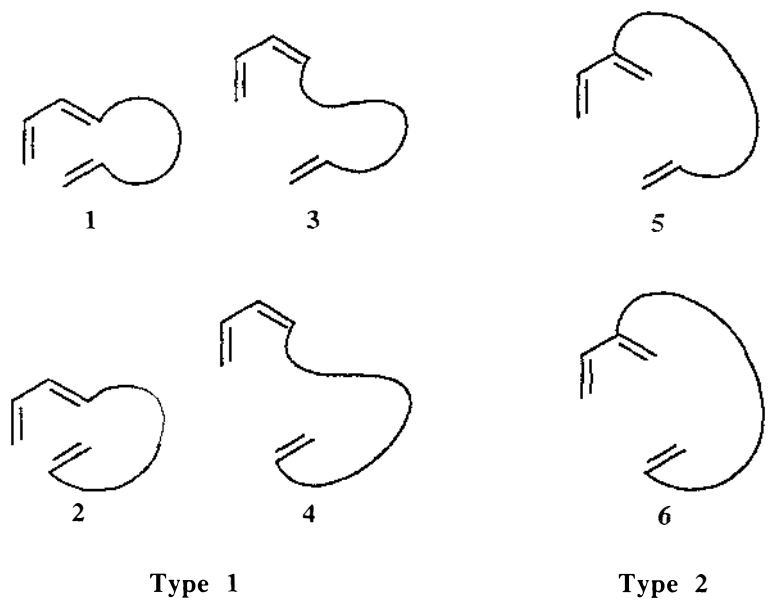


Figure 1.2

The number of atoms in the diene-dienophile tether has a dramatic effect on the regioselectivity and stereoselectivity of the IMDA reaction which ensues. For *E*-dienes,[†] arrangements **1** and **2** are both possible, leading to fused and bridged products respectively (**Figure 1.3**). No reaction occurs if the chain contains less than three atoms because the transition states which lead to either product are highly strained.[11] With three to five atoms arrangement **1** is highly preferred and fused adducts are produced exclusively. There are few **Type 1** examples in the literature in which six to nine atoms have been incorporated in the tether,[36-38] highlighting the entropic problems associated with forming eight to eleven membered rings.

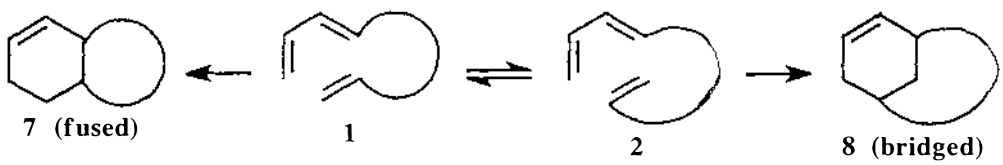
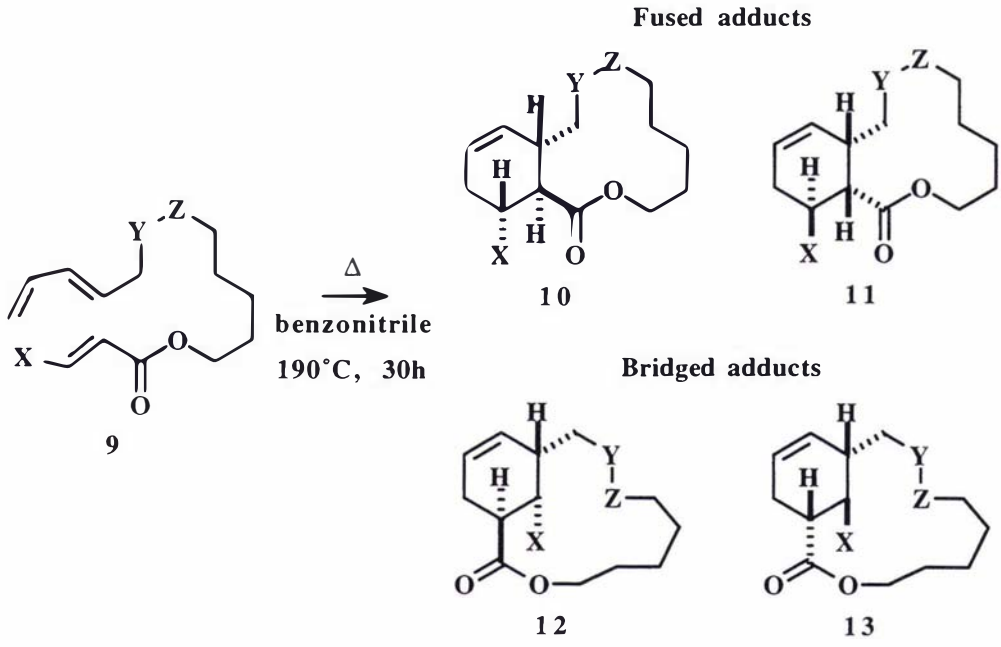


Figure 1.3

[†] *E*- or *Z*-diene refers to the internal alkene geometry in arrangements **1-4**

In rare cases where **Type 1** reactions have been carried out on substrates with ten to twelve atom tethers the regiochemical and stereochemical outcome is similar to the BDA case.[39-42] Two ester tethered examples involving substrates with ten atom tethers (**9a** and **b**) are shown in **Figure 1.4**.[39] It is evident from the product distribution that there is little regiocheimcal or stereochemical preference in the ETDA reaction of diester **9a**, although triester **9b** exhibits some regioselectivity for bridged adducts **12b** and **13b**.



9	X	Y	Z	10:11:12:13	%
a	H	O	CO	49:44:0:7	80
b*	CO_2Me	CH_2	CH_2	47:20:6:27	77

*** The stereochemistry of fused adducts 10b and 11b were not proven.**

Figure 1.4

The situation for arrangements **3-6** (**Figure 1.2**) is quite different. For *Z*-dienes with arrangements **3** and **4**, shorter tethers can be accommodated than for *E*-dienes and arrangement **4** is more frequently encountered.[14] Arrangements **5** and **6** both produce bridged adducts (**Figure 1.5**). *Meta*-bridged adducts (**14**) are favoured with tethers of up to five atoms but small amounts of *para*-bridged regioisomers (**15**) may be produced when six or more atoms are used.[43]

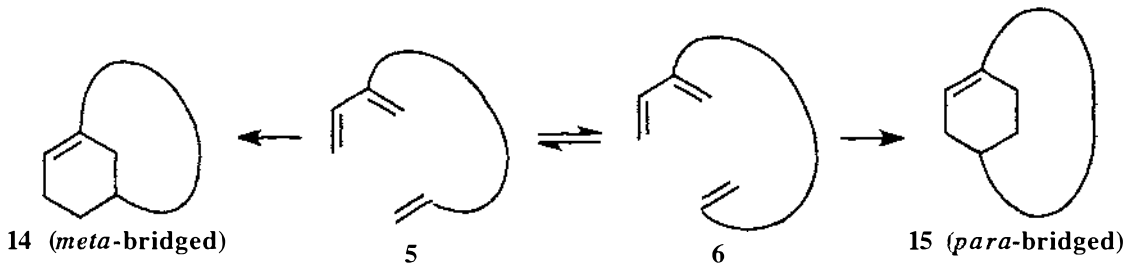


Figure 1.5

For each of the six arrangements depicted in **Figure 1.2** four modes of cycloaddition are possible: two of these are *syn* and two are *anti*. Cycloaddition is classified as *syn* or *anti* depending on the way in which the tether carbon of the dienophile is orientated with respect to the diene, as illustrated for arrangement **1** in **Figure 1.6**. For arrangement **1**, *anti* addition leads to the formation of *trans* adducts **16** and **17**, whereas *syn* addition leads to *cis* fused adducts **18** and **19**. If the dienophile approaches from below the plane of the diene then *anti* addition leads to adduct **16**, whereas approach from above leads to adduct **17**. Conversely, *syn* addition leads to adducts **18** and **19** when the dienophile approaches from below or above the plane of the diene respectively.

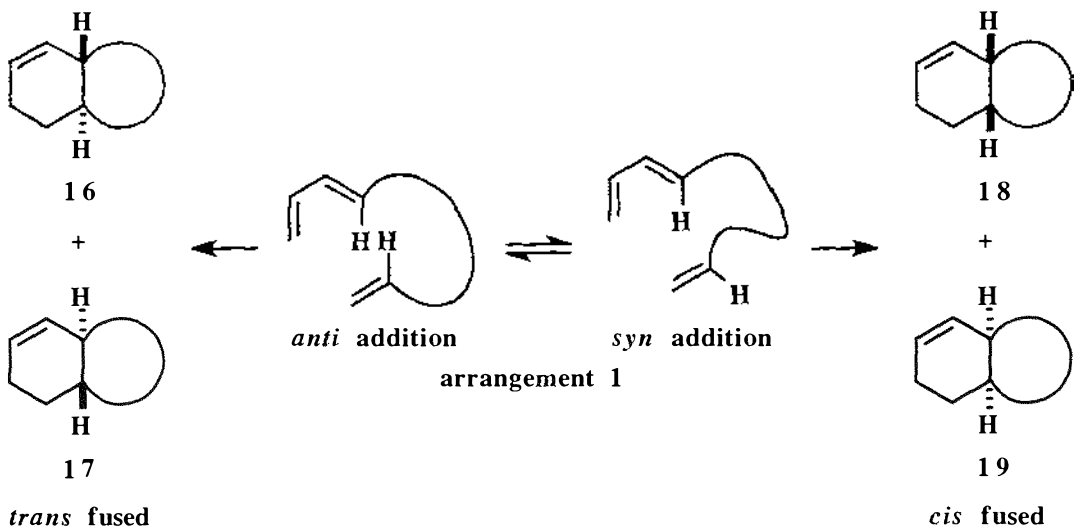
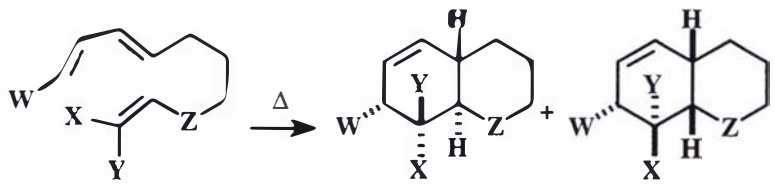


Figure 1.6

The preference for transition states which determine the stereoselectivity of the cycloaddition are difficult to predict. However, with the exception of furan dienes,[44] IMDA reactions are normally irreversible and therefore kinetically controlled,[11] so a knowledge of the relative energy of each transition state is useful in terms of explaining the final product distribution. Some examples which highlight the *syn:anti* stereoselectivity of IMDA reactions are discussed below.

For 1,3,9-decatrienes (**Figure 1.7**) a strong preference for the *cis* adduct is observed if the dienophile is conjugated to a carbonyl in the tether as in the case of trienone **20f**.[45] However, the *exo:endo* ratio tends towards unity when the system is unactivated (**20a**)[46] or activation is provided by a terminal ester group in conjugation with the dienophile (**20b-e**).[47, 48]

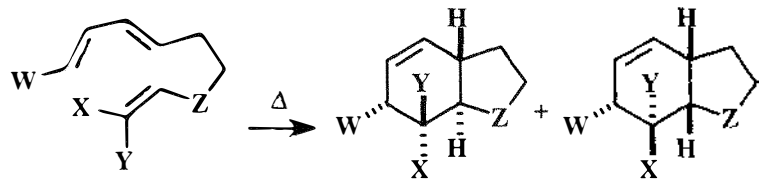


20 21 22

20	W	X	Y	Z	Solvent	T/°C	t/°C	21:22	%
a	H	H	H	CH_2	cyclohexane	250	1.5	48:52	95
b	H	H	CO_2Me	CH_2	toluene	155	45	51:49	90
c	H	CO_2Me	H	CH_2	toluene	155	45	51:49	94
d	iPr	H	CO_2Me	CH_2	toluene	180	3	55:45	71
e	iPr	CO_2Me	H	CH_2	toluene	160	48	50:50	69
f	H	H	H	CO	chloroform	22	4	5:95	100

Figure 1.7

For 1,3,8-nonatrienes (**Figure 1.8**) *cis* fused adducts are favoured when the starting material is unactivated (**23a**)[46] or has a tether carbonyl in conjugation with the dienophile (**23f**).[49] However, when the dienophile is in conjugation with a terminal ester functionality there is a marked preference for the *trans* adduct, particularly when the terminus of the diene is also substituted (**23b-e**).[50]



23 24 25

23	W	X	Y	Z	Solvent	T/°C	t/h	24:25	%
a	H	H	H	CH_2	cyclohexane	250	1.5	27:73	95
b	H	H	CO_2Me	CH_2	toluene	180	5	65:35	75
c	H	CO_2Me	H	CH_2	toluene	150	24	60:40	65
d	iPr	H	CO_2Me	CH_2	toluene	180	5	67:33	75
e	iPr	CO_2Me	H	CH_2	toluene	150	40	72:28	72
f	H	H	H	CO	o-dichlorobenzene	180	1.5	13:87	51

Figure 1.8

For BDA reactions the *anti:syn* stereoselectivity can often be explained by invoking the Alder *endo* rule.[51] This explanation relies on the effect of secondary orbital overlap[52] between the π-system of the diene and unsaturated substituents on the dienophile. The dienophile approaches the diene so that there is maximum overlap of the π-orbitals in the transition state and this affects the *anti:syn* product ratio.

The preceding discussion shows that for IMDA reactions the Alder *endo* rule is generally not observed (**Figure 1.7** and **1.8**). This is further illustrated in **Figure 1.9** for compounds **23b** and **23c**. Compound **23b** may cyclise *via* an *anti* or a *syn* transition state to form *trans* adduct **24b** or *cis* adduct **25b** respectively. (Only one of the possible *anti* and *syn* transition states are shown.) Compound **25b** is termed the *endo* adduct because the carbonyl of the ester group in **23b** is proximal to the diene in transition state **27**, whereas compound **24b** is called the *exo* adduct. The situation is quite different for compound **23c**, because it has an *E*-dienophile instead of a *Z*-dienophile. Here the *trans* adduct is formed *via* an *endo* transition state and the *cis* adduct *via* an *exo* transition state. If secondary orbital overlap were the dominant factor affecting *syn:anti* stereoselectivity then *endo* compounds **25b** and **24c** would be favoured in the IMDA reactions, however, a modest stereoselectivity for *exo* adduct **24b** is observed for *Z*-dienophile compound **23b** (**Figure 1.8**) and with the *E*-dienophile substrate **23c**, the selectivity for the *exo* product is very modest.

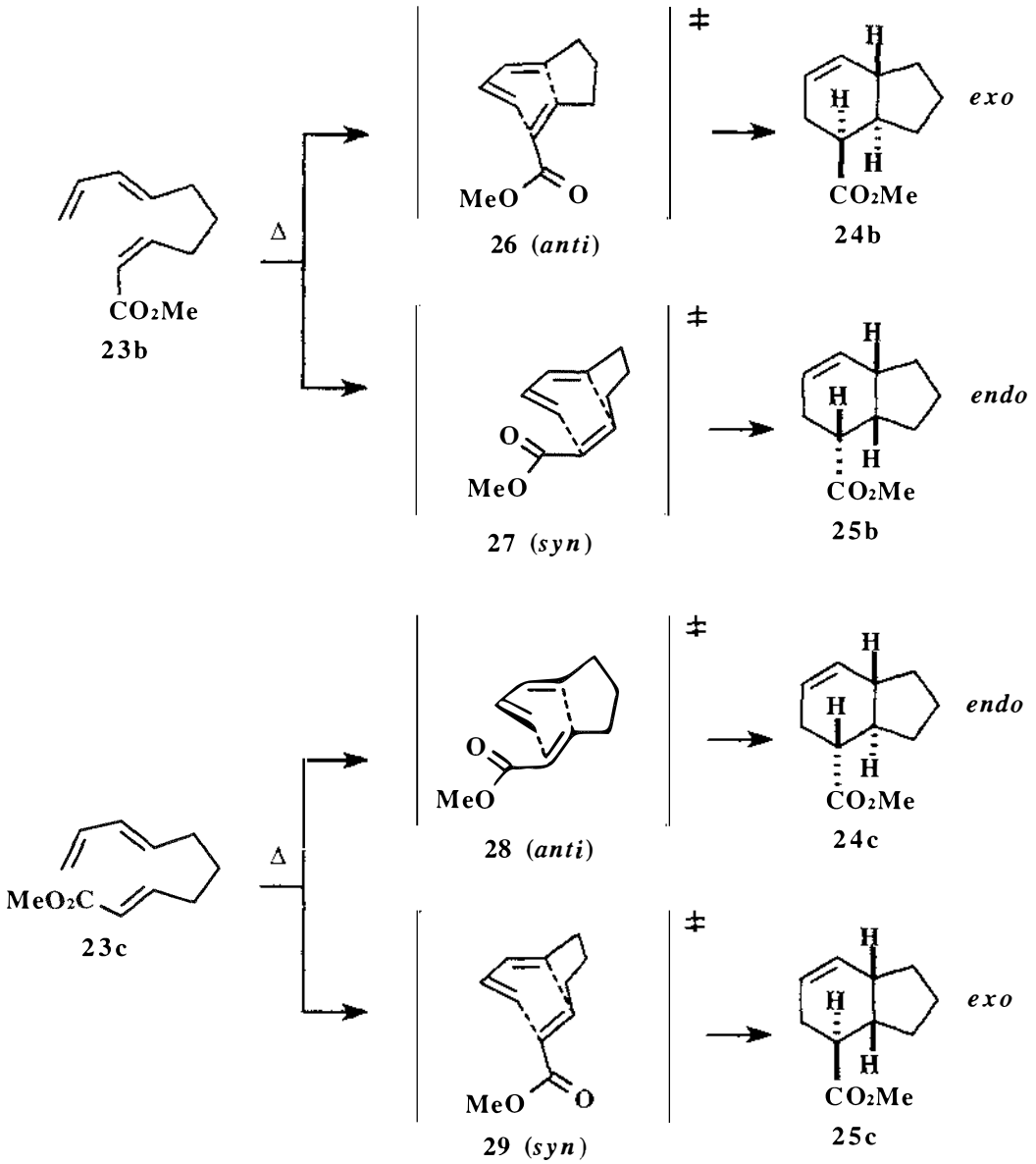
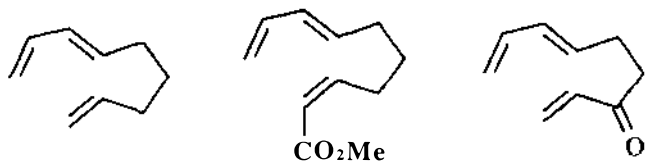


Figure 1.9

Instead, the observed stereoselectivity in IMDA reactions can be explained by invoking concerted but asynchronous transition states.[53-55] This explanation assumes that the two new σ-bonds *begin* to form (and finish forming) simultaneously, but the *progress* in the formation of one of the bonds is greater. The extent of the asynchronicity depends on the coefficients of the HOMO of the diene and the LUMO of the dienophile and the geometrical constraints imposed on the transition state by the tether. These factors play a much greater role in the cycloaddition of 1,3,8-nonatrienes than 1,3,9-decatrienes, hence the stereoselectivity of the former are affected to a greater extent by the position of the substituents.



23a **23b** **23f**

Figure 1.10

Consider compounds **23a**, **23b** and **23f** (**Figure 1.10**). In **23a** the LUMO coefficients for the two carbon atoms of the dienophile are approximately the same. However, in **23b** the LUMO coefficient of the internal carbon atom of the dienophile† is larger than the peripheral one, whereas in **23f** the peripheral carbon atom has the largest LUMO coefficient.[7] This implies that activation by an internal carbonyl, such as the ketone in compound **23f**, will cause the peripheral σ-bond (**Figure 1.11**) to form more rapidly than the internal one. In this case nine membered ring character is displayed in the transition state, which favours the formation of *cis* fused products.[56, 57, 17]

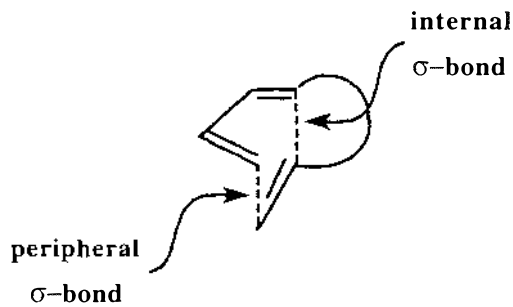


Figure 1.11

Conversely, peripheral dienophile activating groups, such as the carbonyl in methyl ester **23b**, cause the internal σ-bond to form more rapidly. The steric demands of substituents near the newly forming internal σ-bond are the dominant stereocontrolling factors in this case. Two different types of asynchronicity have been identified (**Figure 1.12**):[58] *asymmetric stretch asynchronicity* and *twist asynchronicity*. Asymmetric stretch asynchronicity causes the internal carbon atoms of the diene and dienophile to move together with a concomitant lengthening of the distance between the peripheral carbon atoms. Consequently the transition state has more of the character of the incipient five membered ring. For steric reasons *trans* fused rings are favoured in this case. Twist asynchronicity occurs about the bond which is more fully formed in the transition state. For compounds such as **23b** twisting occurs about the internal σ-bond due to conformational pressure exerted by the incipient five membered ring. This forces the

† The internal carbon atoms of the diene or dienophile are the ones nearest the tether. The peripheral carbon atoms are the ones nearest the diene or dienophile terminus.

dienophile to twist in an *exo* direction (away from the diene, or to the right in **Figure 1.12**). This increases the non-bonded interactions in the *endo* transition state and destabilizes it relative to the *exo* transition state, hence *trans* adduct **24b** becomes more favoured. It is important to stress that whilst these models give insight into the stereoselectivity of IMDA reactions, other factors may come into play which can markedly affect the product distributions which are observed.[17]

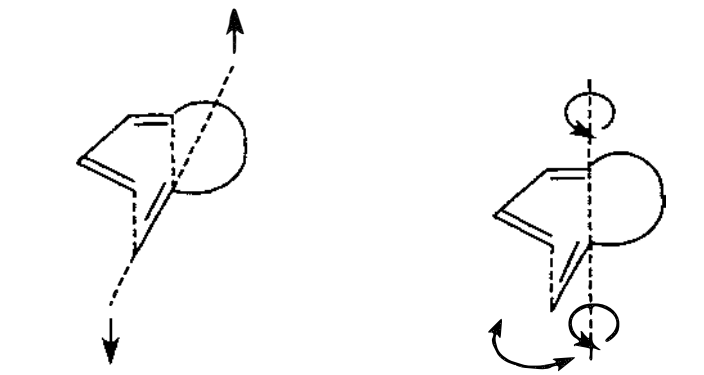
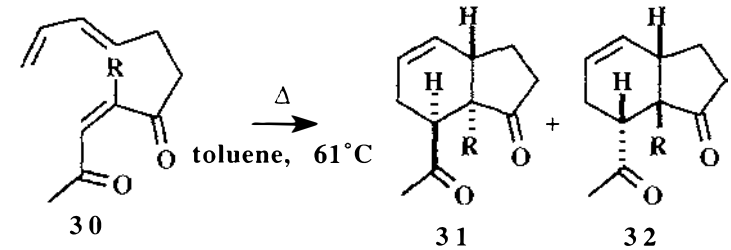


Figure 1.12

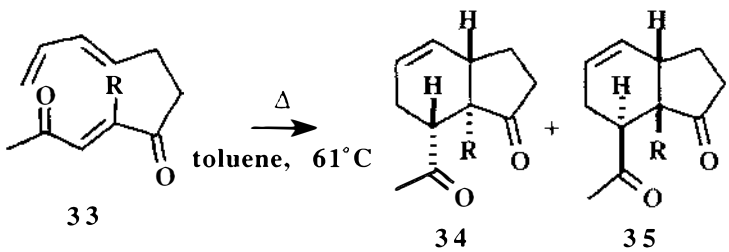
These arguments are difficult to apply when the precursor for the IMDA reaction has both an internal and a peripheral dienophile activating group (**Figure 1.13**).[59] In this case it is not possible to say which of the two σ-bonds will be more fully developed, therefore the stereoselectivity cannot be accurately predicted because it isn't certain whether the transition state will resemble the incipient five or nine membered ring. (This is also the case for the ester tethered IMDA (ETDA) reactions discussed in **Section 1.2.1**.) Experimentally, no stereoselectivity is observed for compounds **30a** and **33b**, but there is a reasonable preference for the *trans* adducts in the IMDA reaction of **30b** and **33a**

A second problem encountered for precursors with both internal and peripheral activating groups is the use of the terms *exo* and *endo* to describe the transition states and the geometry of the resulting adducts. Precursors **33a** and **b** have an *E*-dienophile so a transition state which is *exo* with respect to the peripheral carbonyl is *endo* with respect to the internal carbonyl. To avoid this confusion, the terms *exo* and *endo* will refer to the position of the tether carbonyl from this point on, by definition. (In all cases addition occurs suprafacially with respect to both the diene and the dienophile and the stereochemistry of the starting material is conserved.[7])



30 31 32

30	R	t1/2/h	%	31:32
a	H	0.5	92	50:50
b	Me	9	87	83:17



33 34 35

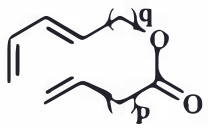
33	R	t1/2/h	%	34:35
a	H	4	82	67:37*
b	Me	>15	67	50:50

* This error is present in the original paper.[59]

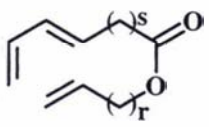
Figure 1.13

1.2.1 Ester tethered DA (ETDA) reactions

Esterification provides a very versatile way of connecting the diene to the dienophile[60] and the ester group can be orientated in several different ways as shown in **Figure 1.14.** Formally, structure **36** arises from a reaction between a dienol and an alkenoic acid, whereas structure **37** is formed from condensation of a dienoic acid with an alkenol. In general, ester tethered substrates have low reactivity[61] and ETDA reactions are favoured only if the tether carbonyl is conjugated to the dienophile (**Section 1.2.1.2**).



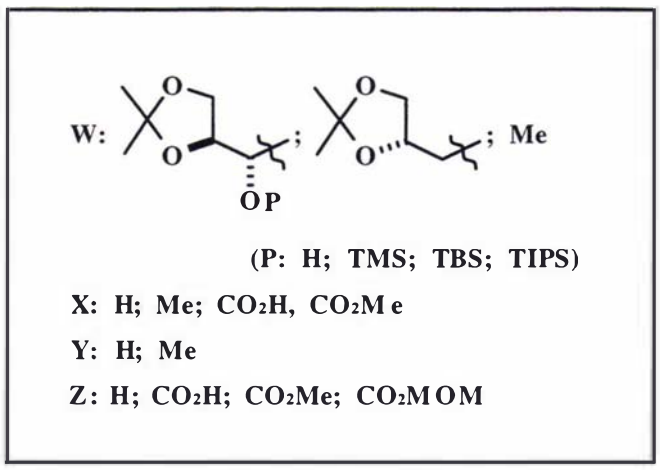
36



37

Figure 1.14

A general summary of the functional groups present in the substrates which have been prepared in this **Thesis** for subsequent ETDA reactions is shown in **Figure 1.15**. (ETDA reactions were also carried out on an acrylate and a propiolate derivative (**Section 3.3.4**). (One hundred and ninety two different precursors could be prepared using the functional groups indicated in **Figure 1.15** but ETDA reactions were actually carried out on a specific subset of these.) The main features of each of the ETDA precursors that were prepared are: they were all **Type 1** (**Figure 1.2**); the tether between the diene and the dienophile contained three atoms; the diene and dienophile were acyclic; maleate, fumarate and citraconate diesters and half esters were used; and the tether carbonyl was in conjugation with the dienophile.



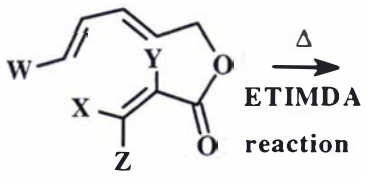
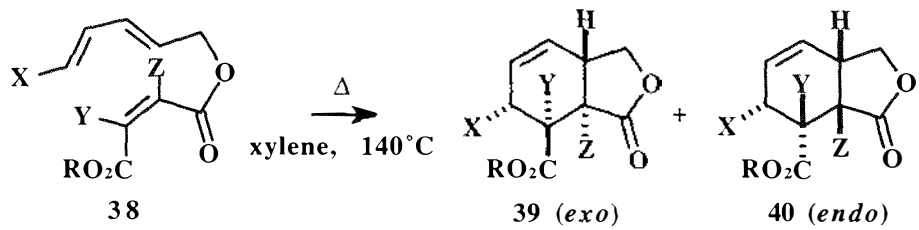


Figure 1.15

Because of the number of literature examples available and the requirement that the discussion of these examples is relevant to the current work, it is necessary to limit the scope of the review that follows. ETDA reactions of precursors with three atom tethers are discussed in detail, excluding examples with: furan dienes;[62-66] other cyclic dienes;[67-72] semicyclic dienes;[73-88] cyclic dienophiles;[89, 90] tether carbonyls which are not conjugated to the dienophile;[91-93] and those which are ambiguous (for example the stereochemistry has not been rigorously demonstrated, the synthetic methodology is unclear or the yields are low).[94-96, 24] However, examples of this type have occasionally been included to illustrate specific points.

1.2.1.1 Doubly activated dienophiles

The first series of examples (**Figure 1.16**) illustrate the *endo:exo* diastereoselectivity of citraconic acid derivatives obtained by White *et al.*[97, 98] Methyl ester **38a** was heated to reflux in xylene yielding the highly strained *trans* fused product **39a**, which arises through an *exo* cycloaddition mode. Likewise, **38b** produced **39b** exclusively. It was reported that *cis* fused lactones **40a** and **40b** were not formed.



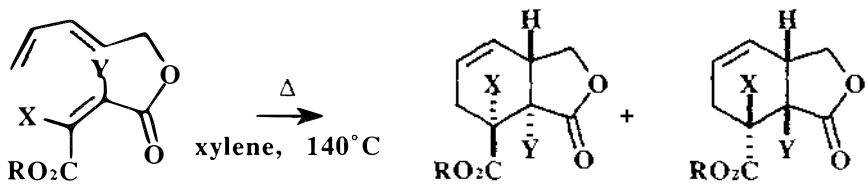
38	R	X	Y	Z	t/h	39:40	%
a	Me	Me	Me	H	24h	100:0	40
b	Me	H	Me	H	24h	100:0	55
c	H	Me	Me	H	15h	0:100	32
d	H	Me	H	Me	15h	-	-
e	H	H	Me	H	15h	0:100	50
f	H	H	H	Me	15h	-	-

Figure 1.16

An unexpected result was obtained for analogous carboxylic acids **38c** and **38d**. These regioisomeric acids were formed in a 1:1 ratio from the reaction of sorbyl alcohol with citraconic anhydride and they were found to be inseparable. A portion of this mixture was heated in refluxing xylene and on cooling **40c** crystallized from the mixture in 32% yield (based on **38c**). No evidence for the formation of the three other adducts (**39c**, **40c** or **40d**) was obtained from the reaction mixture although a substantial amount of polymer had been formed. It was assumed that **38c** had cyclised *via* the *endo* mode and that **38d** had suffered 'autocatalytic polymerization'. A similar result was obtained on heating pentadienol derived acids **38e** and **38f**, with **40e** being produced exclusively in 50% yield.[99]

It appeared from these examples that the group terminating the dienophile was affecting the outcome of the ETDA reaction, causing it to be kinetically controlled for the methyl esters and thermodynamically controlled when the carboxylic acids were used. This phenomenon had not been observed previously. The authors[98] admitted that this effect could not be explained satisfactorily in terms of steric or electronic effects and suggested that protonation of the lactone carbonyl by the carboxylic acid group could catalyze the reverse DA reaction, which would enable the *cis* fused thermodynamic adduct to form. However, they warned that this proposition was tentative since the yield of the reaction was low and most of the material was unaccounted for.

Similar trends in *exo:endo* diastereoselectivity were observed by Mellor *et al.*[100, 101] in systems where the dienophile was substituted with chlorine or bromine (**Figure 1.17**). Esters **41a-e** cyclised primarily *via* the *exo* mode to produce *trans* fused adducts **42a-e** in variable yield. On the other hand, carboxylic acid **41f** produced the *endo* adduct **43f** exclusively, albeit in low yield. Polymeric products were produced when acid **41g** was heated.



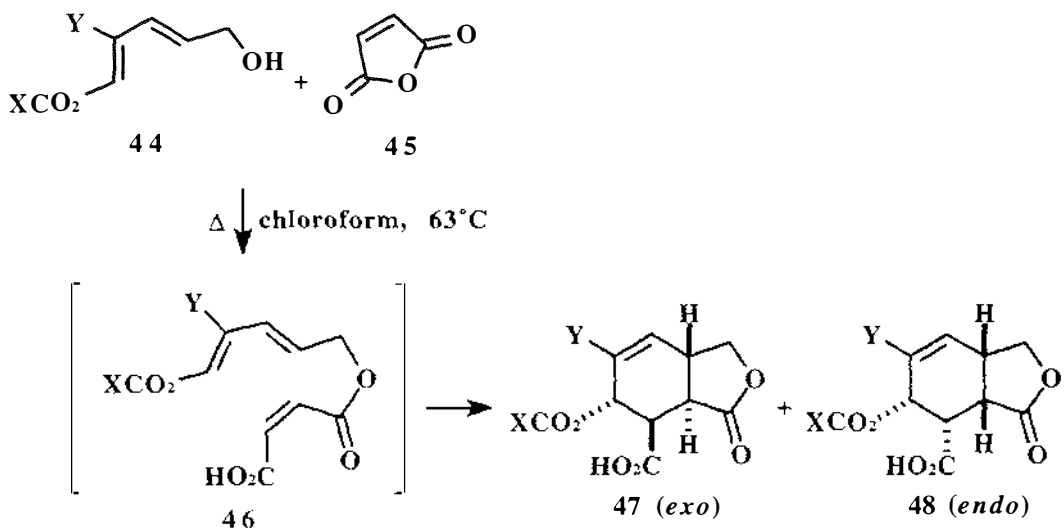
41 42 (*exo*) 43 (*endo*)

41	R	X	Y	t/h	42:43	%
a	Me	Cl	Cl	48	100:0	68
b	Bn	Cl	Cl	24	89:11	57
c	Pip	Cl	Cl	18	100:0	33
d	DMES	Cl	Cl	36	72:28	53
e	Me	Br	H	18	83:17	80
f	H	Cl	Cl	18	0:100	20
g	H	H	Br	-	-	-

Figure 1.17

Mellor did not accept White's view that thermodynamic control was responsible for the formation of *cis* fused adducts when carboxylic acids were cyclised and put forward the hypothesis that acid catalysis might lead to kinetic control.[101] In this scenario the *endo* adducts arise from a *syn* transition state resulting from protonation of the ester carbonyl group in the starting material. In order to test which of these theories was correct, Mellor attempted to prepare **42f** which he then planned to heat in xylene (under the same conditions as used for **41a-g**) to investigate isomerisation to **43f**. However, this compound could not be isolated even though a number of derivatives (**42a-d**) were available.

In a study by Becher *et al.*,[102-104] a series of substituted pentadienols **44a-d** were themolysed in chloroform in the presence of maleic anhydride (**45**) (**Figure 1.18**). In each case, *cis* fused lactones **48a-d** crystallized from the reaction mixture when it was cooled. These results seemed to be in keeping with results obtained by White and Mellor. It was assumed that initial esterification produced half esters **46a-d** with subsequent cycloaddition.



44	X	Y	t/h	47:48	%
a	Ph	H	4	0:100	72
b	PhCHCH	H	12	0:100	80
c	Ph	Me	10	0:100	76
d	EtO	H	12	0:100	77

Figure 1.18

The evidence provided for the initial esterification was that the analogous BDA reaction between protected alcohol **49** and maleic anhydride (**45**) (**Figure 1.19**) only produced *cis* fused adduct **50** when they were heated together in toluene at higher temperatures than those employed for unprotected alcohols **44a-d**. However, since half esters **46a-d** were not isolated, there was no direct evidence for the initial esterification. This has lead to speculation that BDA reactions may have occurred initially with subsequent intramolecular lactonisation, since the *endo* products obtained (**48a-d**) are those expected for the BDA case.[51]

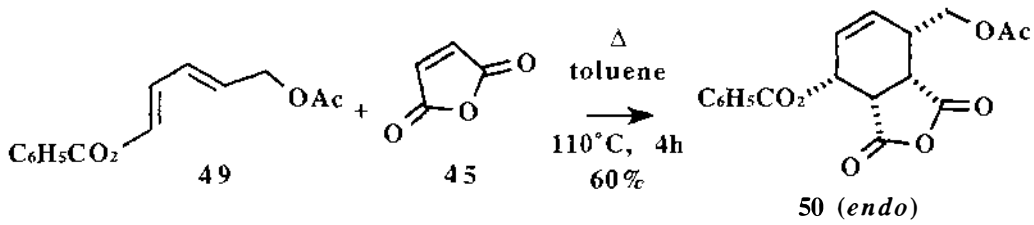
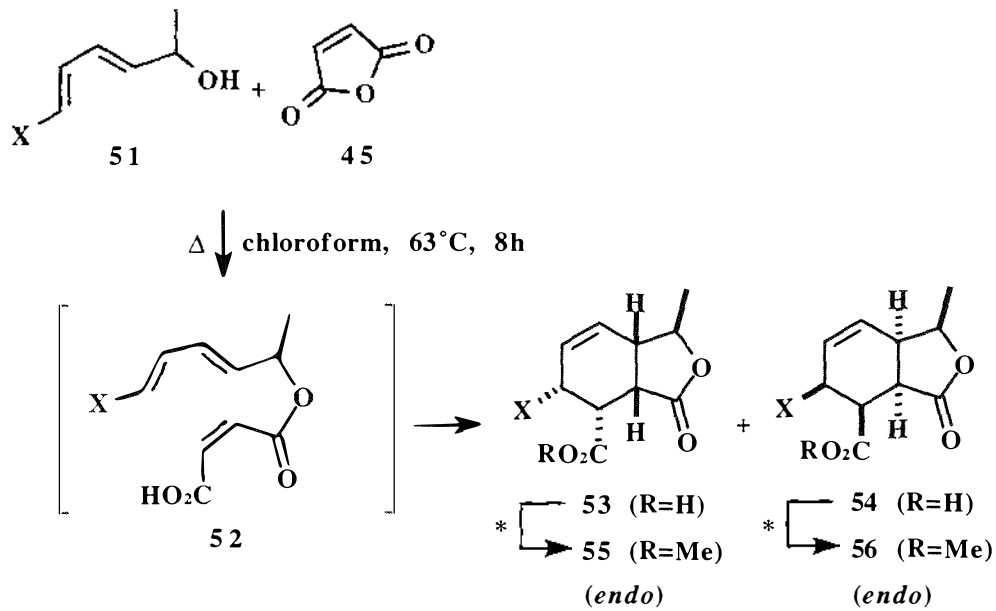


Figure 1.19



51	X	55:56	%
a	Me	50:50	72
b	$CH_2OTBDPS$	70:30	80

*** To facilitate separation of the ETDA adducts the crude mixture of carboxylic acids (53 and 54) was treated with diazomethane prior to chromatography. Structures 53-56 indicate relative stereochemistry only, since the compounds they represent are racemic.**

Figure 1.20

Similar results were obtained by Gree *et al.*[105] when alcohols **51a** and **b** (**Figure 1.20**) were heated with maleic anhydride (**45**) in chloroform and then the cycloadduct mixture was treated with diazomethane. *Endo* adducts **55** and **56** were the only products observed in each case. Again the intermediate half acids (**52a** and **b**) were not isolated and adducts **53** and **54** were assumed to form *via* IMDA reactions. In the case of alcohol **51b** there was evidence of diastereofacial selectivity between the two *endo* modes of cycloaddition, leading to an excess of adduct **55b**. This will be discussed more fully in **Section 1.2.3**.

There are three examples in the literature in which maleate half esters have been isolated prior to carrying out ETDA reactions, with variable results.[106-109] In the first example[108] (**Figure 1.21**) the authors compared the assumed BDA reaction of alcohol **57** and maleic anhydride (**45**) with the ETDA reaction of triene **58**. Both of these reactions gave rise to the same adduct, however, no spectroscopic data was provided for compound **59** and there was no rigorous explanation of the way in which the stereochemistry was determined. It will be shown (**Section 3.1**) that this result is counter to the stereoselectivity obtained for the analogous ETDA reaction of sorbyl maleate, in which the *exo* adduct is favoured under similar conditions. It is possible that the stereochemistry of **59** has been misassinged and the *exo* adduct was produced in both cases. The reaction of **57** and **45** may occur *via* intermolecular esterification with subsequent ETDA reaction, although the authors used the *apparent* production of the *endo* adduct as evidence for an initial BDA reaction followed by intramolecular esterification (in spite of the fact that their own results do not exclude the possibility that the esterification may have occurred first, since the same product was observed in both cases.)

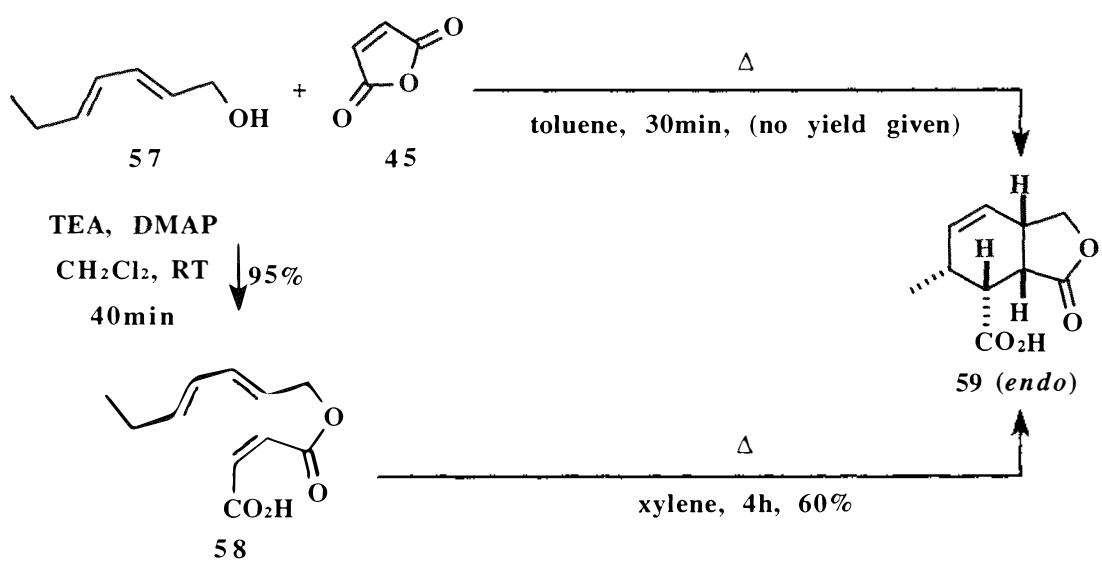
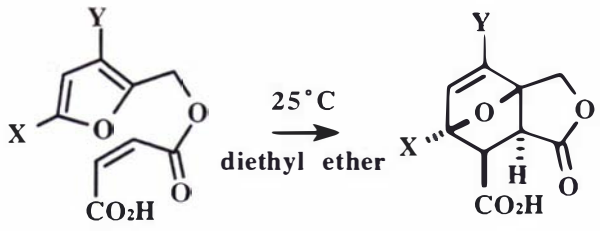


Figure 1.21

Furan derivatives **60a** and **60b**[106, 107] (**Figure 1.22**) were extremely labile and cycloaddition occurred in a few days at 25°C in diethyl ether to give *exo* adducts **61a** and **61b** respectively. Compound **60c** polymerized under these conditions, preventing the isolation of ETDA adducts. (Another example bearing a furan diene has been published,[110] but in this case the ETDA precursor was not isolated prior to cycloaddition.) IMDA reactions involving furan dienes are reversible and therefore thermodynamically controlled,[44] whereas IMDA reactions involving simple dienes are irreversible and therefore kinetically controlled.[11] Hence it is not possible to compare the stereoselectivities of the furan derivatives in **Figure 1.22** with those given earlier (**Figures 1.16-1.18** and **1.20**).



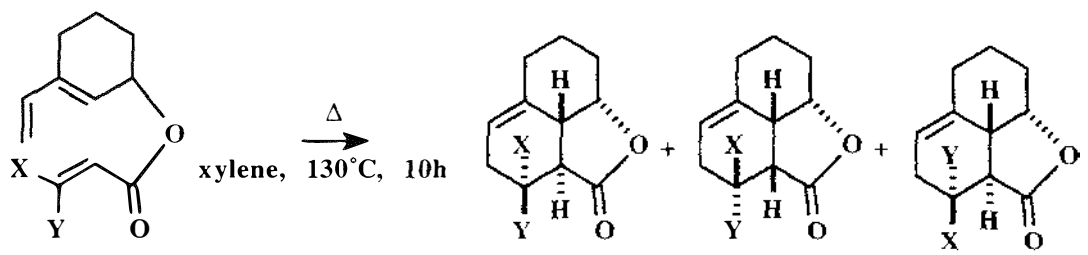
60

61 (*endo*)

60	X	Y	t/d	%
a	H	H	7	40
b	H	Me	2	31
c	Me	H	polymer	

Figure 1.22

In the ETDA reaction of maleate esters **62a** and **62b**[109] (**Scheme 1.23**) containing semicyclic dienes, *exo* adducts (**63a** and **63b**) were favoured over *endo* adducts (**64a** and **64b**) regardless of whether the dienophile was terminated with a methyl ester (**Entry 1**) or a carboxylic acid group (**Entry 2**). A small amount of epimerized material was also produced which brings into question the suitability of this system as a vehicle for investigating stereochemical control in IMDA reactions of this type. (Microwave radiation was also used to effect the IMDA reactions of **62a** (2 x 9min) and **62c** (5 x 9min). It was found that the reaction time was considerably shorter, but the product ratios and yields obtained were nearly identical to those obtained with prolonged heating in xylene.) In these examples the conformational rigidity of the semicyclic diene might override the subtle factors responsible for causing methyl esters and carboxylic acids to give different *exo:endo* stereoselectivity in open chain systems (**Figure 1.16** and **1.17**). The last example (**62c**, **Entry 3**) is a fumarate diester and this also predominantly gave rise to an *exo* adduct (**63c**). The corresponding fumarate half ester was not reported.

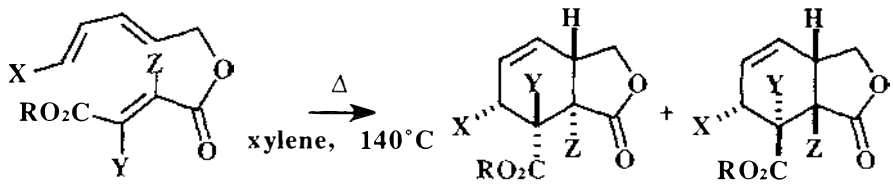


62 63 (*exo*) 64 (*endo*) 65 (epimer of 63)

Entry	62	X	Y	%	63:64:65
1	a	H	CO_2Et	63	91:8:1
2	b	H	CO_2H	51	82:6:12
3	c	CO_2Et	H	76	87:13:0

Figure 1.23

Other triene esters incorporating *E*-dienophiles have also been investigated (**Figure 1.24**). Reactions of citraconate esters **66a** and **b**[97, 98] were very slow but a clear preference for *trans* fused products was observed and good yields were obtained (84% of **67a** and **68a** based on 60% conversion, and 85% of **67b** and **68b** based on 50% conversion). A similar observation was made for fumarate example **66c**.[101] When the diene was activated with an EDG (**66d-f**) *trans* fused isomers (**67d-f**) were obtained exclusively as white solids when the reaction mixtures were cooled,[102, 103] although the yield of **67e** was very low. Unfortunately there have been no literature reports of ETDA reactions on precursors with *E*-dienophiles terminated with carboxylic acids. A study of this type would clearly shed new light on the *endo:exo* preference of ETDA reactions.



66 67 (*exo*) 68 (*endo*)

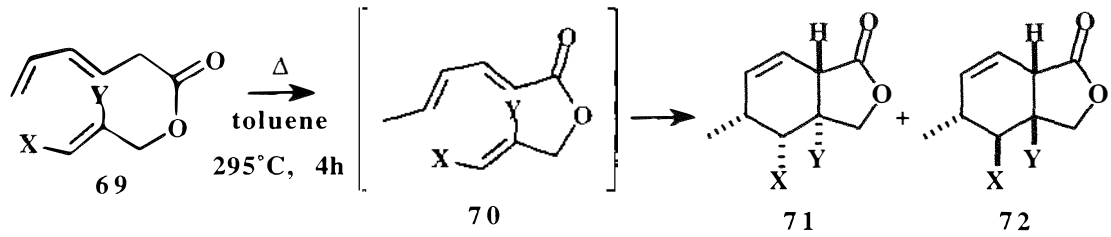
66	R	X	Y	Z	t	67:68	%
a	Me	Me	Me	H	6d	81:19	84
b	Me	Me	H	Me	11d	83:17	85
c	Me	H	H	H	18h	67:33	48
d	Et	$PhCO_2$	H	H	18h	100:0	74
e	Et	$PhCHCHCO_2$	H	H	24h	100:0	13
f	Me	$PhCO_2$	H	H	20h	100:0	88

Figure 1.24

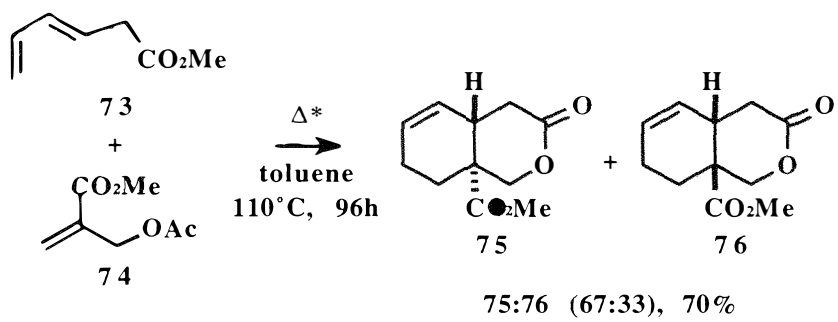
When examples **38a** and **b** (**Figure 1.16**) and **41a-e** (**Figure 1.17**) are taken in conjunction with **62a** and **62c** (**Figure 1.23**) and **66a-f** (**Figure 1.24**) it is clear that the geometry of the dienophile does *not* have a significant impact on the *exo:endo* diastereoselectivity of ETDA reactions *where the dienophile is terminated with a terminal ester group.* Because *trans* fused adducts are produced from starting materials with *Z*-dienophiles it is clear that secondary orbital effects[52] are not the dominant factors involved in the *exo:endo* diastereoselectivity in this case, since neither the terminal EWG or the tether carbonyl are proximal to the diene in the transition state.[47] Instead, the stereoselectivity of ETDA reactions is best explained in terms of concerted but asynchronous transition states (**Section 1.2**).

1.2.1.2 The rate retarding effect of the ester tether

Compound **69a** (**Figure 1.25**) required strong heating in toluene at 295°C for 4h in a sealed tube in order for a reaction to occur.[61] The analogous BDA reaction between **73** and **74** proceeded at 110°C to give **75** and **76** after ring closure, which highlights the rate retarding effect of the ester tether in ETDA reactions.



69	X	Y	71:72	%
a	H	CO_2Me	37:63	15
b	CO_2Et	H	89:11	40

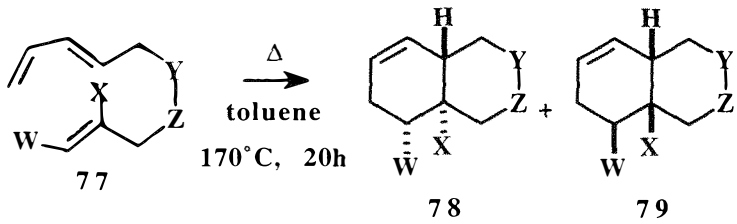


*** After heating in toluene the acetate group was removed by treatment with sodium methoxide in methanol at RT. Lactonisation was effected with hydrochloric acid in methanol at RT.**

Figure 1.25

In addition to the low reactivity, the ETDA adducts obtained from **69a** were not the expected δ-lactones **75** and **76**, but γ-lactones **71a** and **72a.** This indicates that rearrangement of **69a** to **70a** (by an undisclosed mechanism) occurs prior to cycloaddition. Compound **70a** was prepared and heated independently, resulting in a similar yield and ratio of **71a** and **72a** to that obtained for **69a**. Similar results were obtained when **69b** and **70b** were heated under the same conditions. *Trans* fused adducts were favoured in each case, as expected for γ-lactone systems (**Section 1.2.2.1**).

In order to demonstrate that the ester tether itself was the cause of the lack of reactivity, a second series of reactions was carried out (**Figure 1.26**). Ether **77a** underwent cycloaddition under comparatively mild conditions to give **78a** and **79a**. Ether **77b** and ketone **77c** also reacted under similar conditions. No rearranged products were observed in any of these examples.

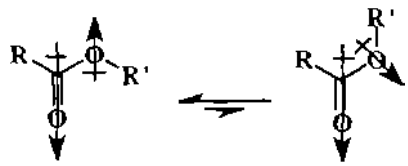


77 78 79

77	W	X	Y	Z	78:79	%
a	H	CO_2Me	CH_2	O	30:70	50
b	CO_2Et	H	CH_2	O	60:40	86
c	H	CO_2Me	CO	CH_2	25:75	50

Figure 1.26

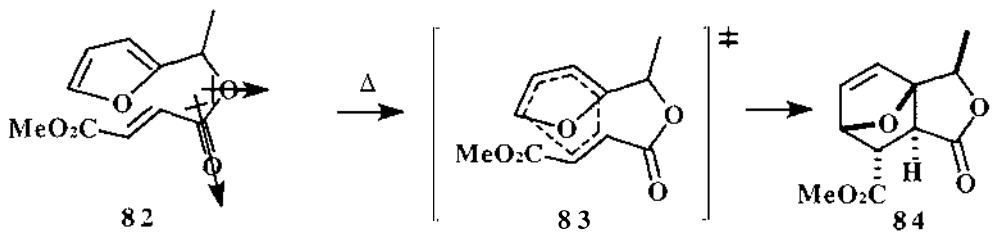
The reason for the low reactivity of IMDA precursors bearing ester tethers can be explained in terms of the transoid effect (**Figure 1.27**).[111] The unfavourable dipole-dipole interactions in the *s-cis* conformation (**80**) cause esters to adopt the *s-trans* conformation (**81**), which does not dispose the molecule towards intramolecular cycloaddition. It has been proposed that the barrier to rotation is not high enough to account for the low reactivity which is observed,[61] however, recent investigations into solvent effects which arise for ETDA reactions (*vide infra*) are counter to this view.



80 81

Figure 1.27

The polarity of **81** (in which the dipoles are additive) is greater than **80** and this has been used to explain why the rate of formation of **84** (**Figure 1.28**) increases as a function of the dielectric constant of the solvent used.[112, 113, 64] Polar solvents favour conformer **82** which promotes the formation of transition state **83**, causing the rate constant k_1 to increase. These results give weight to the theory that the conformational rigidity illustrated in **Figure 1.27** is largely responsible for the lack of reactivity conferred on ETDA precursors by the ester tether. A computational study which augments this experimental investigation has also been reported.[114]



82 83 84

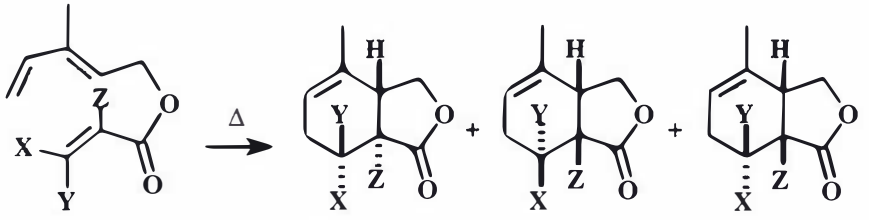
k_1
82 ⇌ 84
k_{-1}

Solvent	Dielectric constant	k_1 (relative)	k_{-1} (relative)
DMSO-d_6	48.9	220	4.8
CD_3CN	37.9	37	1.3
acetone-d_6	20.5	18	1
CD_2Cl_2	8.9	10	1.7
$CDCl_3$	4.7	14	2.6
toluene-d_8	2.38	1	1.6

Compounds 82 and 84 were racemic. Structure 84 indicates relative stereochemistry only.

Figure 1.28

Unfortunately the yield and selectivity of ETDA reactions do not seem to be improved by the addition of Lewis acid catalysts (**Figure 1.29**).[115] In examples where the dienophile was activated only by the carbonyl of the ester group in the tether (**85a-d**) no real advantage was gained by the addition of diethylaluminium chloride and the catalyst had an adverse effect where the dienophile was doubly activated (**85e** and **f**). In addition, the catalyst caused epimerisation of **86c** to **88c** and **86f** to **88f** respectively, since the geometry of the diene in **85c** and **85f** preclude the formation of these compounds in a normal ETDA reaction.[7]



85 86 (*exo*) 87 (*endo*) 88 (an epimer of 86)

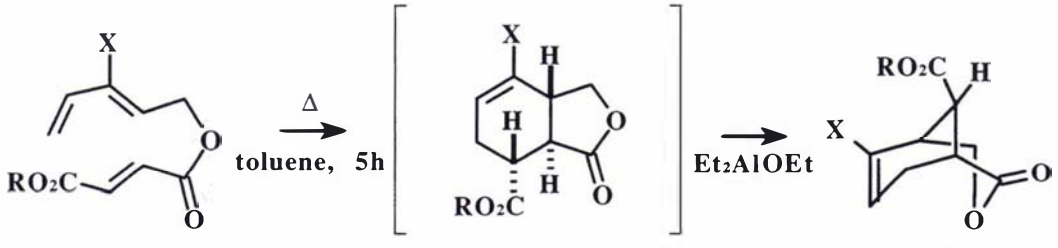
85	X	Y	Z	A, % 86	A, % 87	A, % 88	B, % 86	B, % 87	B, % 88
a	H	H	H	0	0	0	0	10	0
b	H	H	Me	0	0	0	1.8	1.8	0
c	Me	H	H	0	0	0	5	3	3
d	Ph	H	H	8	3	0	4	2	0
e	CO_2Et	H	H	34	11	0	0	10	0
f	H	CO_2Me	H	35	23	0	0	22	45

A: Yield from uncatalysed reactions (toluene, 160°C).

B: Yield from catalyzed reactions (toluene, 160°C, Et_2AlCl (0.2eq)).

Figure 1.29

In a similar reaction catalyzed by diethyl aluminium ethoxide (**Figure 1.30**) a cationic rearrangement of ETDA adducts **90a** or **90b** (mediated by the Lewis acid) results in the formation of ∂-lactones **91a** and **91b** respectively in modest yield.[116]



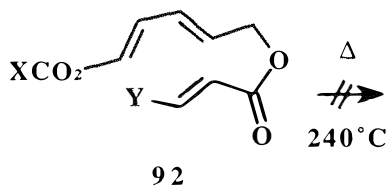
89 90 91

89	X	R	%
a	Br	Et	45
b	Me	Me	49

Figure 1.30

1.2.1.3 Singly activated dienophiles

The rate of ETDA reactions is often lower than expected (**Section 1.2.1.2**) and this is highlighted by the unsuccessful examples compiled in **Figure 1.31.**[103] Even though the diene is activated by an EDG in **92a-g** the dienophile is only activated by a single carbonyl, which forms part of the ester tether. No reaction was observed for any of these cases, even when strong heating was applied. Other unsuccessful examples of this type have also been reported.[117-119]



92

92	X	Y
a	Ph	Ph
b	Ph	4-nitrophenyl
c	Ph	4-chlorophenyl
d	Ph	Piperonyl
e	Ph	2,4-dichlorophenyl
f	$Ph(CH)_2$	Ph
g	$Ph(CH)_2$	4-chlorophenyl

Figure 1.31

In contrast to cinnamate ester **92a**, phenylpropiolate ester **93** (**Figure 1.32**) cyclised readily in xylene over 20h.[103] Instead of expected product **94**, aromatic compound **95** was produced due to *in situ* loss of benzoic acid. Adduct **94** could be produced by heating **93** in chloroform for 12 days and this could be converted into **95** by further heating in refluxing xylene.

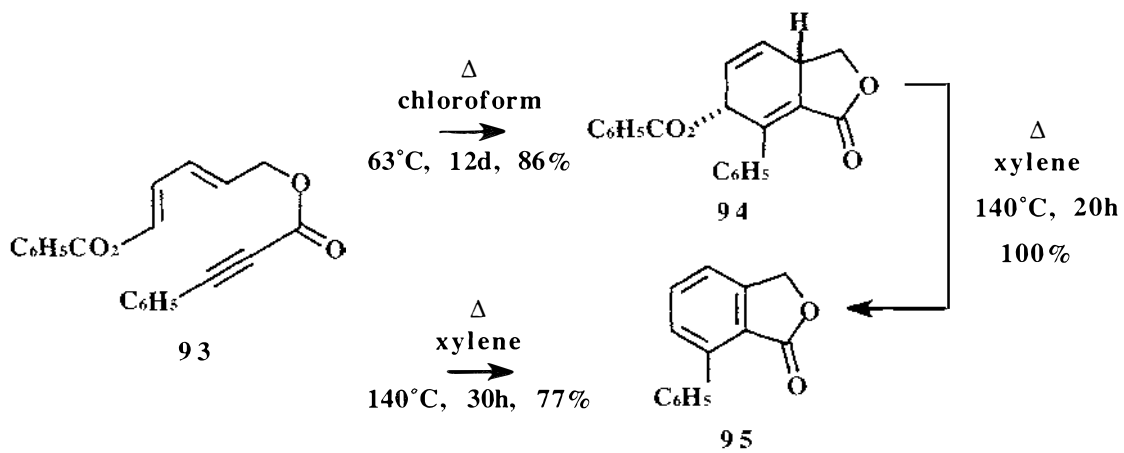
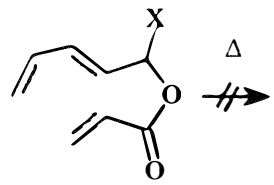


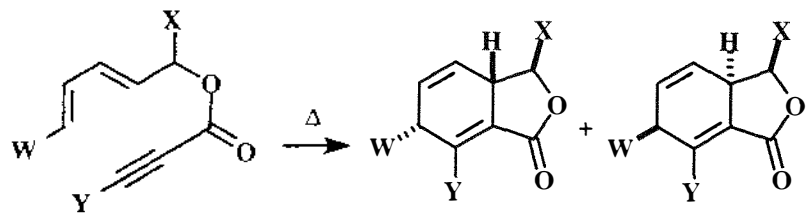
Figure 1.32

Additional examples which highlight the difference in reactivity between acrylate and propiolate derivatives are shown on **Figure 1.33**. Acrylate **96a**[11] was recovered in near quantitative yield after heating in refluxing in xylene, whereas **96b** was found to be prone to polymerization[120] to the extent that an ETDA reaction was not even attempted. In contrast, **97a** reacted readily in toluene[120] yielding predominantly **98a** in which the hydrogen on the ring junction is *cis* to the alkyl group in the lactone ring. A similar observation was made for **97b**. (The influence of tether groups on the diastereofacial selectivity of ETDA reactions will be discussed in **Section 1.2.2.1**) Achiral starting material **97c** gave racemates **98c** and **99c** in high yield.[98]



96

96	X	Solvent	T/°C	t/h
a	Me	xylene	140	18
b	H	-	-	-



97 **98** **99**

97	W	X	Y	Solvent	T/°C	t/h	98:99	%
a	H	Me	H	toluene	110	15	86:14	97
b	H	iPr	H	toluene	80	18	97:3	96
c	Me	H	Me	xylene	140	24	50:50	96

All of the compounds represented in this Figure are racemic. Structures 98 and 99 indicate relative stereochemistry only.

Figure 1.33

Two examples of attempted ETDA reactions in which the carbonyl of the ester was conjugated to the diene are shown in **Figure 1.34**. The lack of reactivity of triene **100** is unsurprising (*vide supra*), but the inertia of **101** demonstrates that even the more reactive actetylenic dienophile requires the additional activation of the tether carbonyl in order for an ETDA reaction to occur.[121]

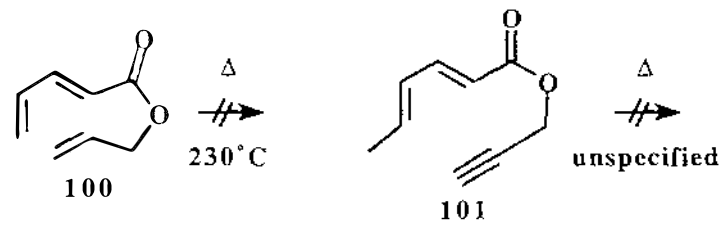


Figure 1.34

In direct conflict with these results, precursor **102**[122] (**Figure 1.35**) has been shown to undergo cycloaddition at 250°C over 5 days with a modest selectivity for *exo* adduct **103**. This brings into question the results illustrated in **Figure 1.34**.

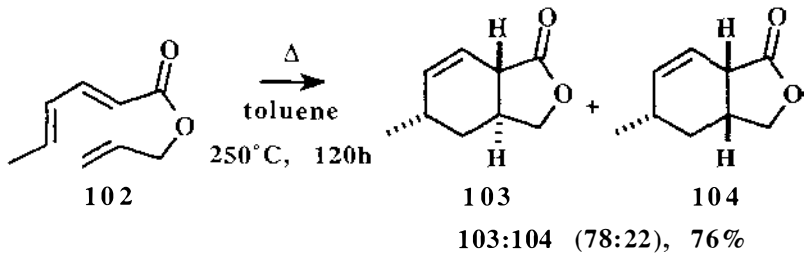


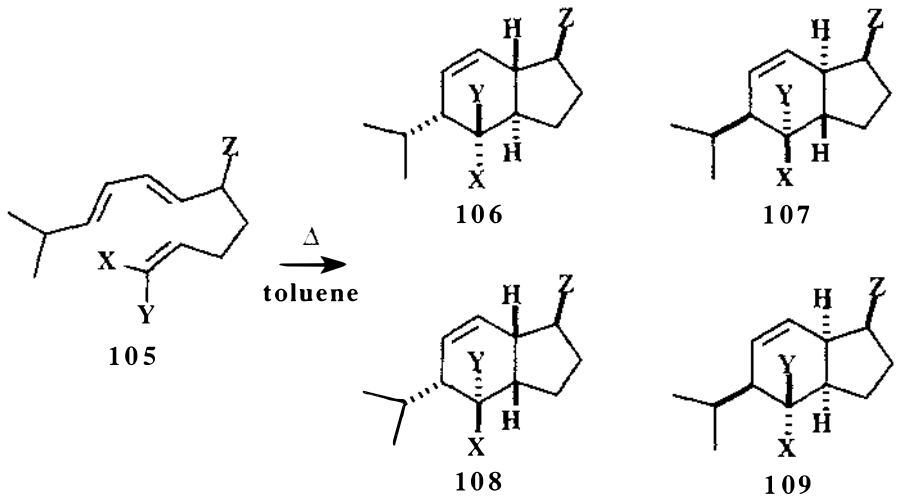
Figure 1.35

1.2.2 Diastereofacial control of IMDA reactions

The examples in **Section 1.2.1** deal mainly with differentiation between the *exo* and *endo* modes of cycloaddition, which is sometimes termed *simple diastereoselection.* What follows is an account of the way in which facial diastereoselection can be superimposed onto these two modes. This has been achieved by placing substituents in the tether between the diene and the dienophile (**Section 1.2.2.1**), incorporation of chiral auxiliaries (**Section 1.2.3.2**) and enantioselective catalysis (**Section 1.2.3.3**). (In examples where the starting materials and reagents are achiral, the *relative stereochemistry* of the racemic products is represented by a single enantiomer only.)

1.2.2.1 Tether control of facial diastereoselectivity

The examples in **Figure 1.36** each have a tether group allylic to the diene.[123] In each case *trans* fused adducts **106** and **107** were favoured over *cis* adducts **108** and **109**, as expected for 1,3,8-nonatrienes with terminally activated dienophiles (**Section 1.2**). In the case of alcohol **105a** there was a modest diastereofacial selectivity for adduct **107a** over **106a**. This increased to a 2:1 preference for silyl derivative **105b.** However, no increase in diastereoselectivity was observed when the benzyl derivative **105c** was heated. Greater diastereofacial selectivity was also observed for silyl derivative **105e** compared to alcohol **105d**, although adduct **106f** was favoured when benzyl derivative **105f** was heated.

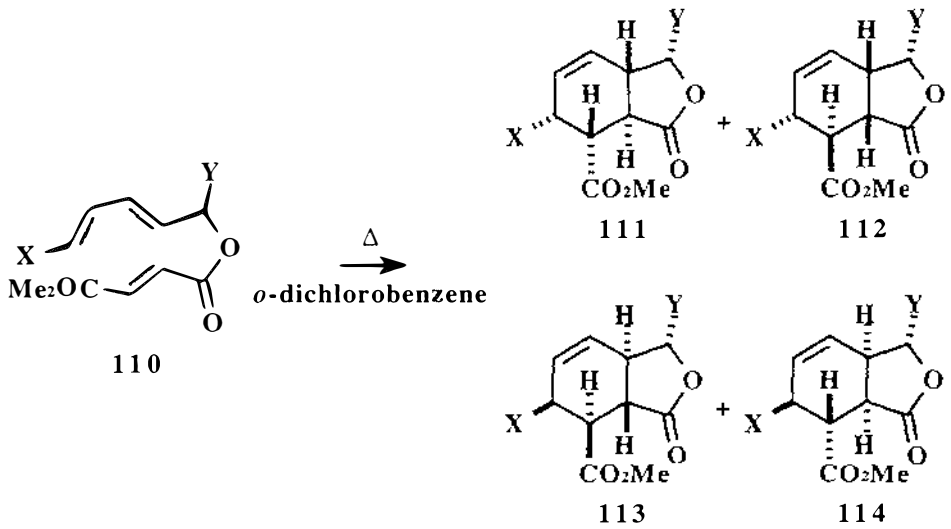


105	X	Y	Z	T/°C	t/h	106:107:108:109	%
a	H	CO_2Me	OH	150	36h	32:45:23:0	60
b	H	CO_2Me	OTMS	150	36h	25:50:25:0	73
c	H	CO_2Me	OBn	115	44h	29:37:34:0	92
d	CO_2Me	H	OH	150	36h	37:33:26:4	71
e	CO_2Me	H	OTMS	150	36h	31:48:17:4	83
f	CO_2Me	H	OBn	115	110h	53:30:13:4	78

All of the compounds represented in this Figure are racemic. Structures 106-109 indicate relative stereochemistry only.

Figure 1.36

Diastereofacial selectivity in IMDA reactions is demonstrated further by the ester tethered examples in **Figure 1.37**.[124] In the first two examples only enantiomeric *exo* adducts with structures **111** and **112** are observed. (In precursors **110a** and **110b** there are no stereogenic centres (because **Y** is a hydrogen atom), hence the two *exo* transition states which lead to structures **111** and **112** are equal in energy and racemic mixtures of these adducts are produced.) The third example has a stereogenic centre in the tether which causes the *exo* transition states to be unequal in energy, hence adduct **112c** is favoured over **111c**. However, starting material **110c** is racemic, hence **111c**, **112c** and **113c** are also racemic. (The structures illustrated indicate the relative stereochemistry of the products only.)

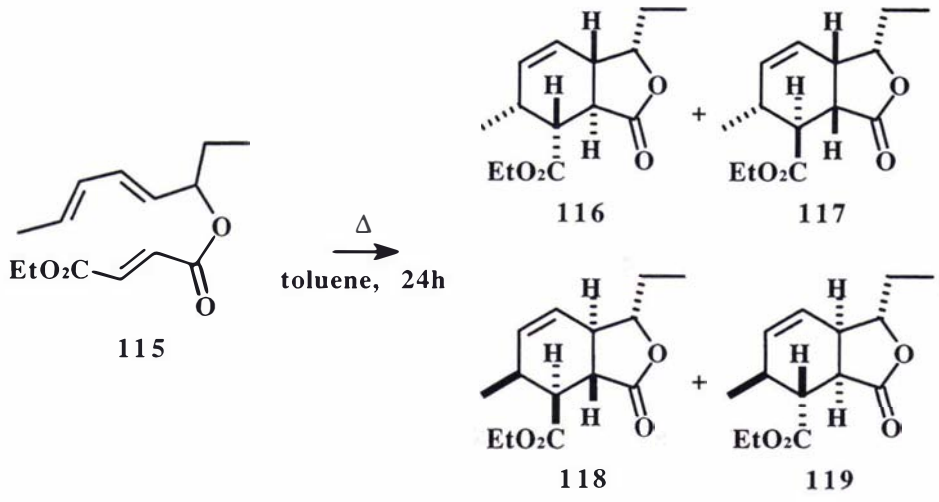


Entry	110	X	Y	T/°C	t/h	%	111:112:113:114
1	a	$PhCO_2$	H	110	3	-	50:50:0:0
2	b	$CH_2CHCH_2CO_2$	H	130	3	85	50:50:0:0
3	c	$CH_2CHCH_2CO_2$	Me	130	5	83	19:76:5:0*

*** The relative stereochemistry of the *endo* adduct was not determined and so the product formed in this case could be either 113c or 114c. All of the compounds represented in this Figure are racemic. Structures 111-114 indicate relative stereochemistry only.**

Figure 1.37

A similar investigation was carried out on precursor **115**[125, 126] (**Figure 1.38**). *Exo* adducts were produced in excess with a significant stereoselectivity for compound **118** (having the same relative stereochemistry as adduct **112c**, illustrated in **Figure 1.37**).



116:117:118:119 (8:83:7:2)

92% (at 92% conversion)

All of the compounds represented in this Figure are racemic. Structures 116-119 indicate relative stereochemistry only.

Figure 1.38

As a synthetic organic chemist it is rewarding to work with enantiopure compounds since these are by far the most commonly encountered targets in natural product synthesis. An example of such a reaction is given in **Figure 1.39**.[127] Adduct **121** was obtained in good yield with high enantiopurity. This compound was later elaborated to compound **122** (the ionophore antibiotic indanomycin).[128] The diastereofacial selectivity was greater for the ethyl moiety than any of the alcohol derivatives in **Figure 1.36**, highlighting the increased steric demand of the alkyl group.

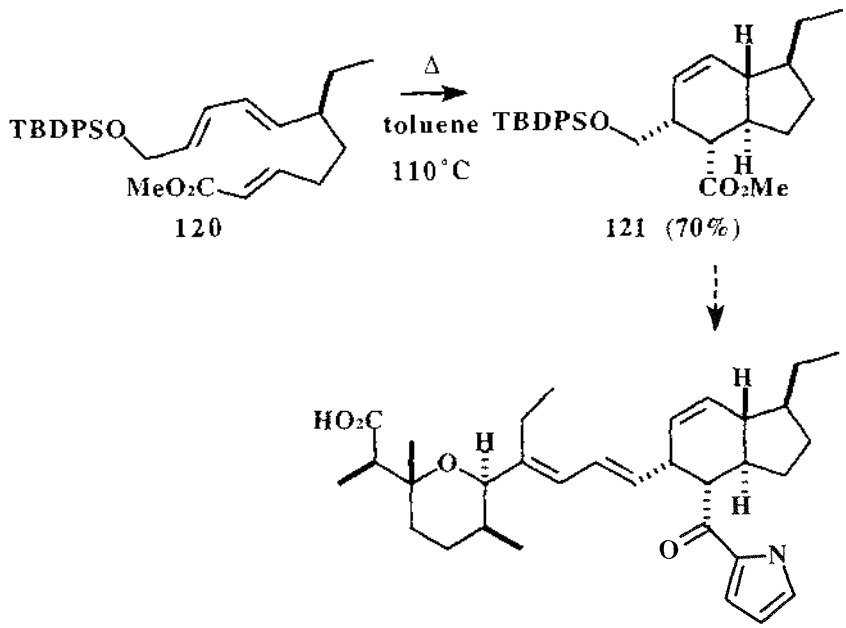


Figure 1.39

A successful ETDA reaction on a conjugated dienoic acid derivative is shown in **Figure 1.40**.[129] Good diastereoselectivity was obtained for compound **125** which arises from epimerization of *trans* fused *exo* ETDA adduct **124**, under the reaction conditions used.

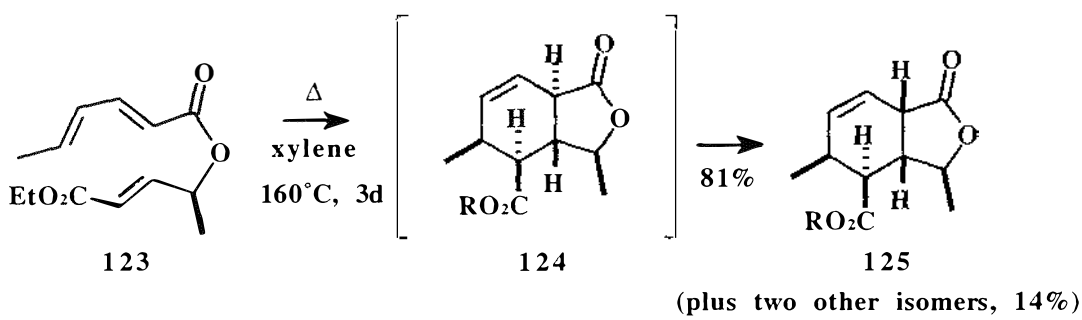


Figure 1.40

As part of a recent synthetic study towards the superstolides an IMDA reaction was carried out on chiral aldehyde **126** (**Figure 1.41**).[130] In this case the two tether groups responsible for the relative diastereoselection work synergistically with each other to produce the major isomer (**130**) with a reasonable yield and diastereofacial selectivity.

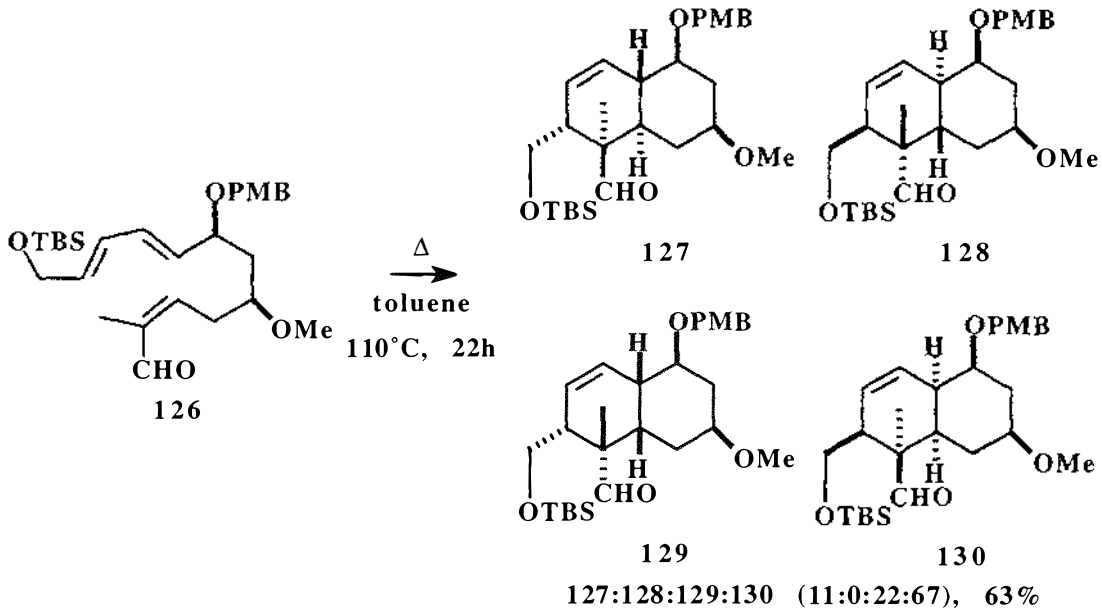


Figure 1.41

The chair-like transition state (**131**) which leads to adduct **130** (**Figure 1.42**) is representative for precursors with saturated four carbon tethers.[19]

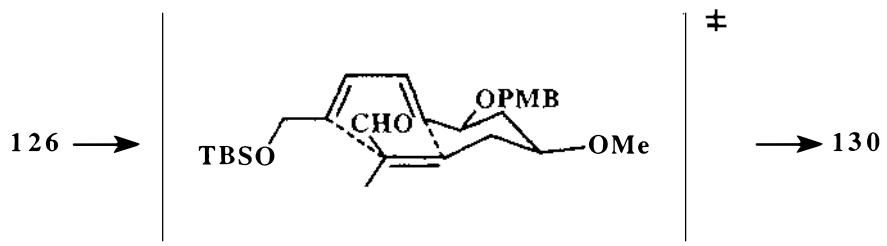
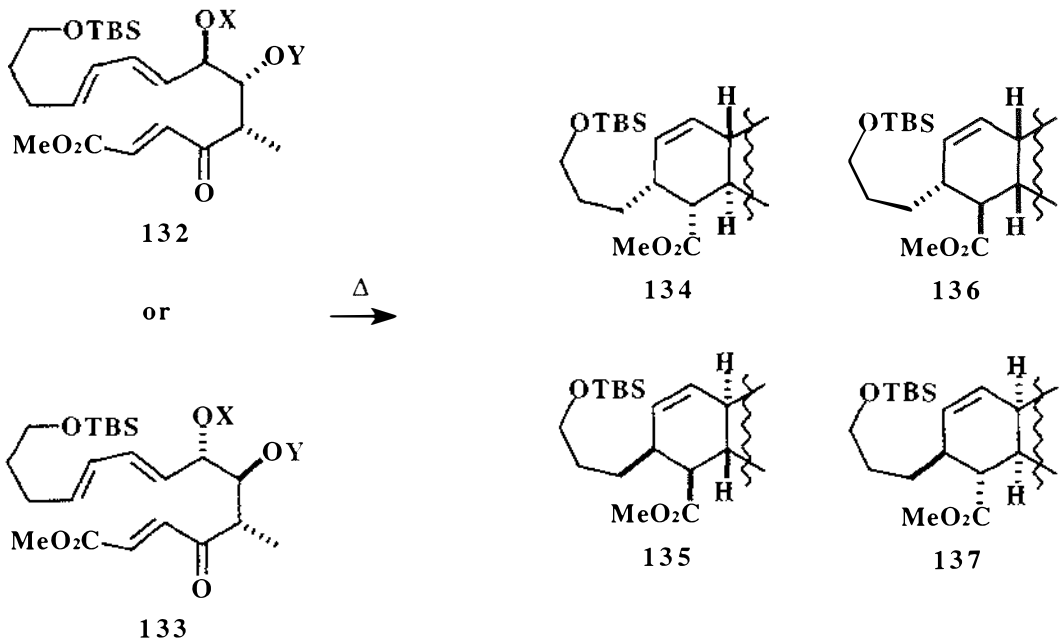


Figure 1.42

For IMDA reactions of precursors with four carbon tethers containing a carbonyl in conjugation with the dienophile it was found that the position and character of the tether substituents had a profound effect on the diastereofacial selectivity of the cycloaddition.[131, 132] Compound **132a** (**Figure 1.43**) cyclised to give *trans* fused ring system **135** predominantly, whereas **132b** (in which the protecting groups at C5 and C6 were replaced with the rigid dioxolane ring) produced *cis* fused variant **136** exclusively. In contrast to **132a**, cycloaddition of **133a** (in which the stereochemistry at C5 and C6 was inverted) favoured *cis* fused ring system **137,** whereas the rigid dioxolane moiety in **133b** instigated a slight preference for *trans* fused structure **135**.



Entry		X	Y	Conditions*	T/°C	t/h	134:135:136:137	%
1	132a	MOM	Bn	CH_2Cl_2	23	2-5	3:78:19:0	80
2	132b	$C(CH_3)_2$		toluene	110	22	0:0:100:0	78
3	133a	MOM	Bn	CH_2Cl_2	23	1	25:22:0:50	75
4	133b	$C(CH_3)_2$		benzene	80	5	0:40:33:27	-

* For Entries 2-4 cyclisation was carried out in the presence of catalytic 2-thiopyridine or iodine to convert unresolved olefins to the Z-geometry.

Figure 1.43

The cycloadducts in **Figure 1.43** arise from the intervention of boat-like transition states. These are generally favoured for precursors with four carbon tethers containing one or more sp^2 centres.[19] A specific example (transition state **138** arising from starting material **132b** leading to *cis* fused ring system **136b**) is given in **Figure 1.44.**

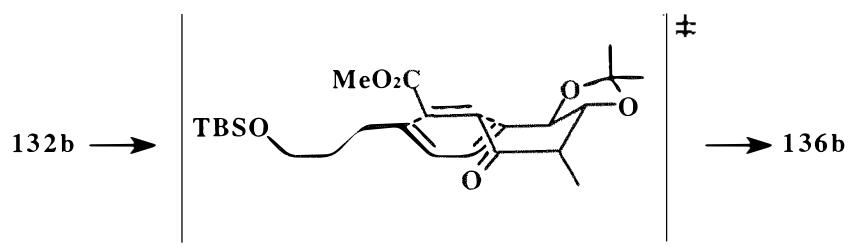
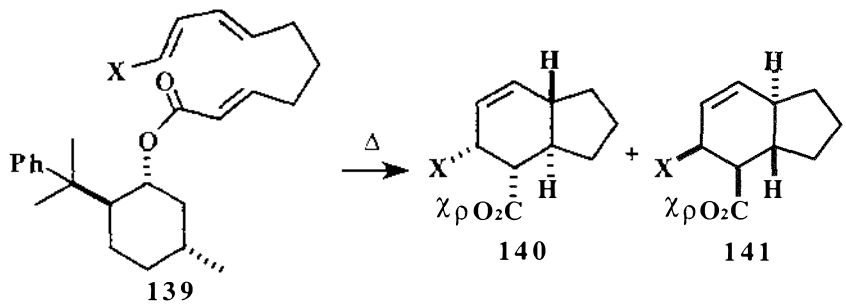


Figure 1.44

1.2.2.2 Chiral auxiliaries at the dienophile terminus

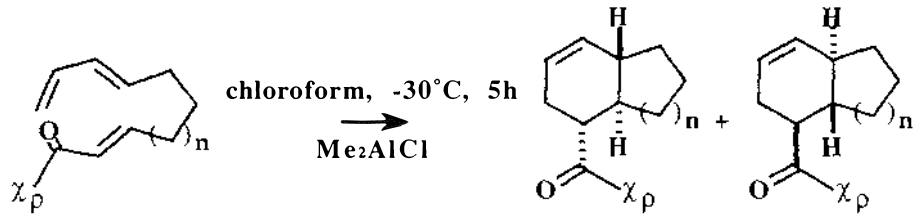
In the first report in which chiral auxiliaries attached to the dienophile terminus were used to control the facial diastereoselectivity of IMDA reactions, (-)-phenylmenthyl esters (**Figure 1.45**) were cyclised in the presence of a range of Lewis acid catalysts at various temperatures (**Entries 1-6**).[50] Only *trans* fused structures **140** and **141** were obtained in each case. The results for **Entries 1-4** show that the choice of catalyst has a dramatic effect on the diastereofacial selectivity and yield of the reaction. The best results (which combined good yields and diastereoselectivities) were obtained when low temperatures and long reaction times were used (**Entries 5** and **6**). However, even then the highest d.e. obtained was only 72% (**Entry 6**). The results were not as good as those obtained in the BDA case, where it was possible to carry out the cycloadditions at much lower temperatures.[133, 134]

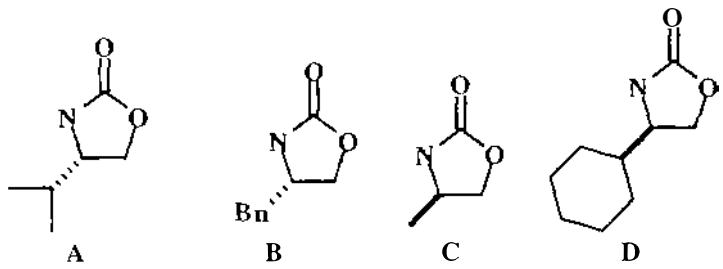


Entry	139	X	Catalyst	T/°C	t	140:141	%
1	a	iPr	$TiCl_4$	23	6h	14:86	8
2	a	iPr	$EtAlCl_2$	23	18h	42:58	21
3	a	iPr	menthyloxy$AlCl_2$	23	84h	33:67	75
4	a	iPr	*l*-bornyloxy$AlCl_2$	23	92h	33:67	61
5	a	iPr	menthyloxy$AlCl_2$	8	10d	32:68	75
6	b	H	*l*-bornyloxy$AlCl_2$	8	14d	14:86	72

Figure 1.45

Much better yields and diastereofacial selectivities were obtained for [4.2.0] and [4.3.0] bicyclic adducts with chiral α,β–unsaturated N-acyloxazoladinone auxiliaries (**Entries 1-4** and **5-8** respectively, **Figure 1.46**).[135-137] In each series, auxiliaries **A** and **B** produced ring system **144** in excess, whereas **C** and **D** produced **143**. The *exo:endo* diastereoselectivity was excellent in each case, particularly for **Entries 1-4**.





Entry	142	χ_p	n	143:144	*trans:cis*	% (maj)
1	a	A	1	17:83	99:1	60
2	b	B	1	5:95	99:1	73
3	c	C	1	85:15	99:1	70
4	d	D	1	97:3	99:1	65
5	e	A	2	8:92	30:1	65
6	f	B	2	3:97	50:1	88
7	g	C	2	91:9	50:1	70
8	h	D	2	94:6	30:1	70

Figure 1.46

The diastereofacial selectivity induced by chiral N-acyl-camphor-sultams has also been investigated[138] and this methodology has been utilized in the synthesis of enantiomerically pure natural product **147** ((-)-pulo'upone).[139] These results are summarized in **Figure 1.47**. Compound **146** was produced with a yield of 71% and 93% d.e., which was increased to 100% d.e. by crystallization. This provided a highly efficient pathway to the target as well as direct confirmation of the absolute stereochemistry. Comparison to the BDA case[140] indicates that chelation of the catalyst not only increases the rate of the reaction but it also enhances the π-facial selectivity observed.

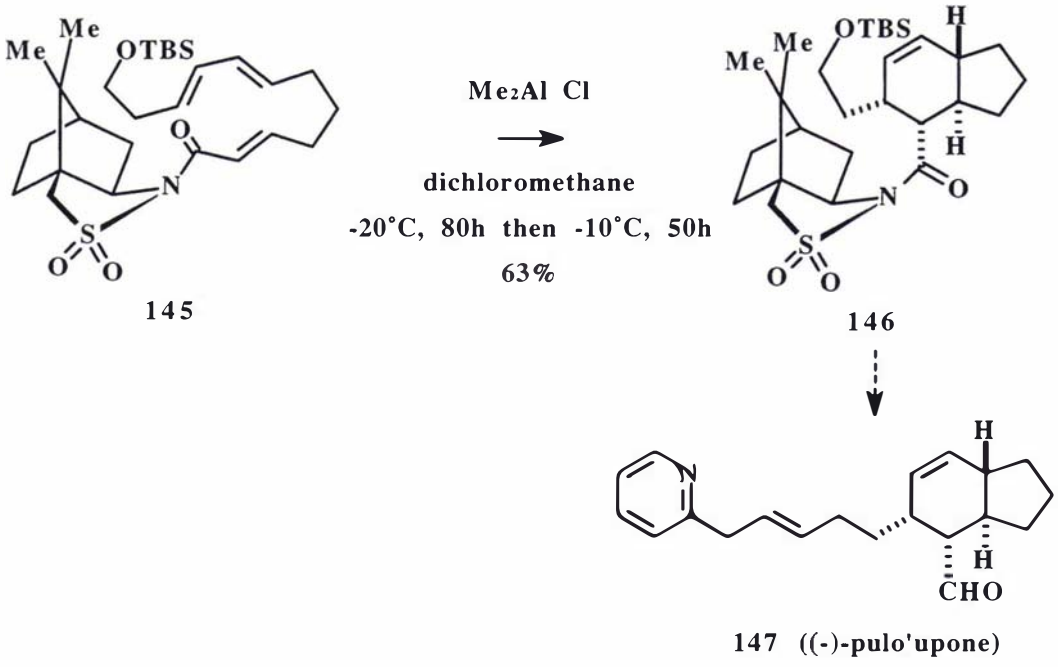
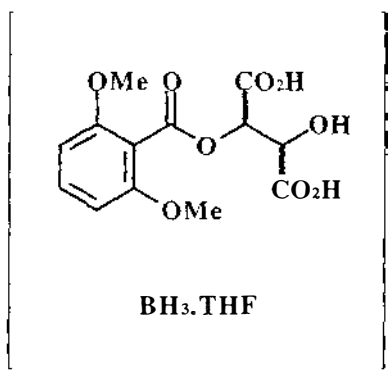


Figure 1.47

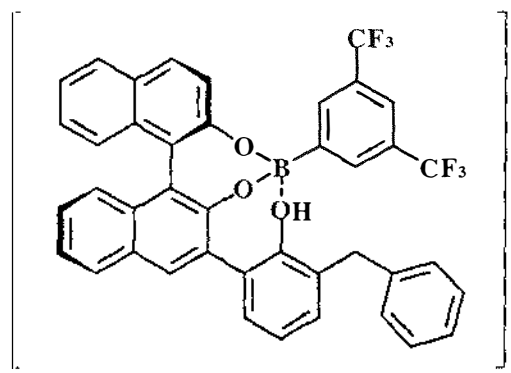
In addition to the diastereofacial selectivity conferred upon the IMDA reaction by the sultam (**Figure 1.47**) it is also easy to remove and recycle. There have also been reports in which the dienophile has been terminated with more permanent chiral moieties responsible for diastereofacial induction.[94, 95]

1.2.2.3 Enantioselective catalysis

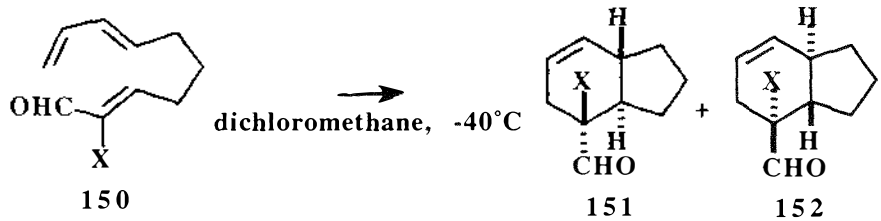
Boron catalysts **148**[141, 142] and **149**[143] (**Figure 1.48**) have been used successfully to control the enantiofacial selectivity of the IMDA reactions of 2,7,9-decatrienals. Chiral (acyloxy) borane (CAB) complex **148** is formed from borane:THF and the (+)-tartaric acid derivative shown. Although the exact nature of the catalyst is not yet known, it produced an excellent yield and enantiofacial selectivity of *trans* fused adduct **152a** over **151a** (**Entry 1**). This was not matched in the case of **152b** (**Entry 2**) which was produced with an e.e. of 46%.[144] It was possible to increase the yield and enantioselectivity of **150b** by using chiral Bronsted Lewis acid (BLA) **149**, however, the opposite enantiomer **151b** was produced (**Entry 3**).[143]



148 (CAB)



149 (BLA)

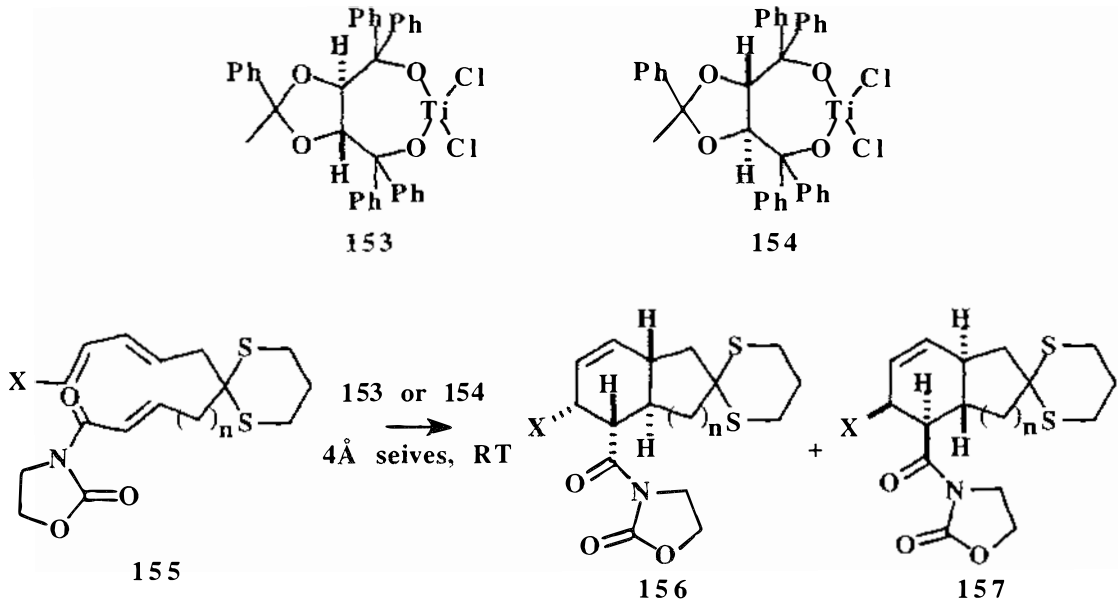


150 151 152

Entry	150	X	Catalyst	151:152	*trans:cis*	%
1	a	Me	148	4:96	1:99	84
2	b	H	148	27:73	1:99	74
3	b	H	149	90:10	100:0	95

Figure 1.48

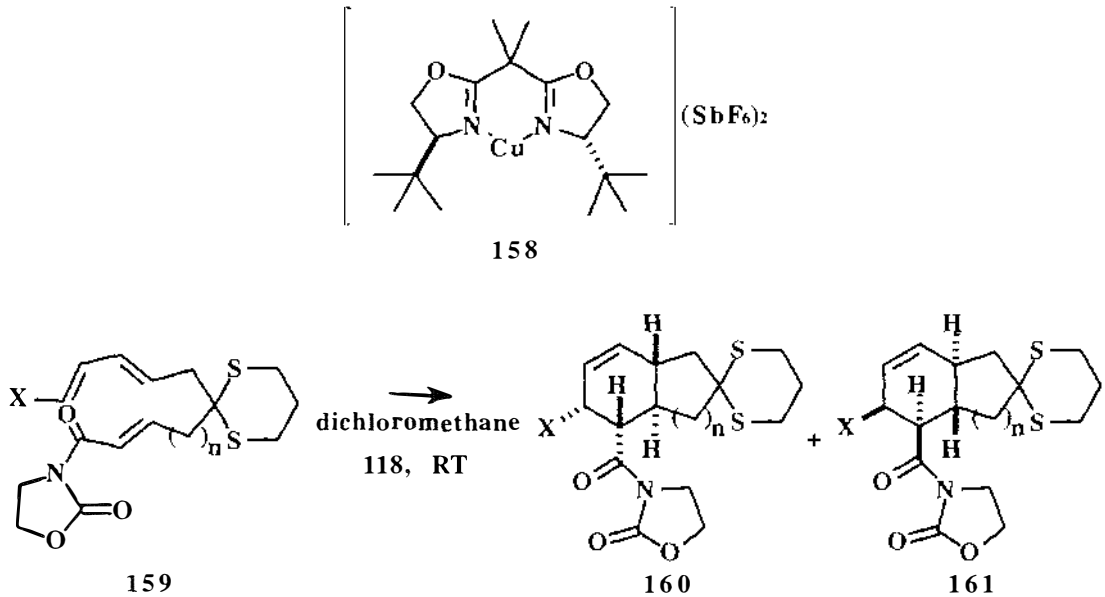
Good results have also been obtained with titanium catalysts **153** and **154** (**Figure 1.49**) derived from (+)- and (-)-tartaric acid respectively.[145] Catalyst **153** produced good yields and enantiofacial selectivity in IMDA reactions of triene starting materials with three or four carbon tethers (**Entries 1-3**). In each case, *trans* fused ring system **156** was favoured.[146] The enantioselectivity of the third reaction was increased by carrying out the reaction with catalyst **154** in toluene/petroleum ether instead of mesitylene (**Entry 4**). As expected, the opposite enantiomer (**157c**) was produced in excess.[147]



Entry	155	X	n	Catalyst	Solvent	156:157	%
1	a	H	1	153 (0.1eq)	mesitylene	98:2	95
2	b	H	2	153 (0.1eq)	mesitylene	93:7	86
3	c	Me	2	153 (0.1eq)	mesitylene	94:6	87
4	c	Me	2	154 (0.3eq)	toluene/pet. ether	2:98	70

Figure 1.49

In a similar study, starting materials **159a-d** were treated with chiral copper catalyst **158** (**Figure 1.50**).[27] Treatment of three of the starting materials (**159a**,**b** and **d**) with the catalyst provided high levels of asymmetric induction and excellent yields, but the fourth (**159c**) failed to cyclise even after extended periods of time. This anomalous behaviour has not yet been rationalized. The high level of enantiofacial control possible for the cycloaddition of **159a** and **b** provided the authors with the methodology for total synthesis of (-)-isopulo'upone.



159	X	n	Catalyst	t/h	160:161	*trans:cis*	%
a	H	1	158 (1.0eq)	24	93:7	99:1	89
b	Ph	1	158 (0.5eq)	5	96:4	95:5	86
c	H	2	158 (1.0eq)	24	99:1	-	<20
d	Ph	2	158 (1.0eq)	14	98:2	84:16	97

Figure 1.50

1.3 The transannular Diels-Alder (TDA) reaction

The TDA reaction is a special subset of IMDA reactions in which the diene and dienophile are connected by two tethers to form a macrocycle. Cycloaddition produces a tricyclic structure which has four new stereogenic centres and an alkene functional group, which provides a convenient access point for elaboration of the product (**Figure 1.51**). Structure **163** (which arises from the TDA reaction of fourteen membered macrocycle **162**) and **165** (from thirteen membered macrocycle **164**) provide potential access to the ABC and BCD rings of the cyclopentano perhydronaphthalene nucleus of steroids (**166**) respectively. From a synthetic viewpoint, consideration of the TDA strategy is eminently worthwhile in the synthesis of rare and biologically active steroids.

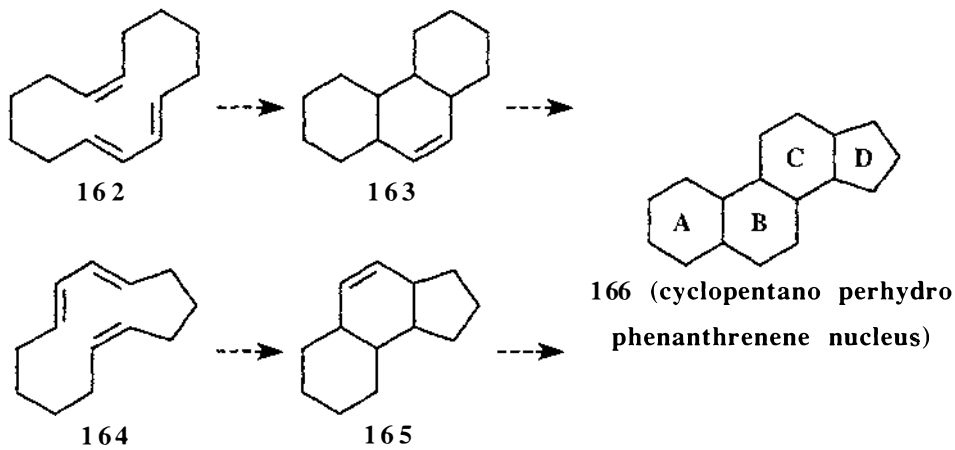


Figure 1.51

In an even more elaborate scenario (**Figure 1.52**) it may be possible that macrocycle **167**, containing a *bis*-diene (in the form of a conjugated tetraene) and a *bis*-dienophile, could undergo a tandem TDA reaction to produce the ABCD ring system of a steroid (**168**) in a single step. A suitable stereocontrolling element (R) could be included to influence the relative stereochemistry of the eight incipient stereogenic centres. The elegance of this strategy cannot be overemphasized. It may be possible that four carbon-carbon bonds could be formed simultaneously in a stereocontrolled manner, simply by heating the starting material in an appropriate solvent. Recycling of the solvent, the only other substance required, would result in a synthesis that was both economically and environmentally sound. The operational simplicity of this reaction being matched only by the remarkable stereochemical complexity of the adduct produced.

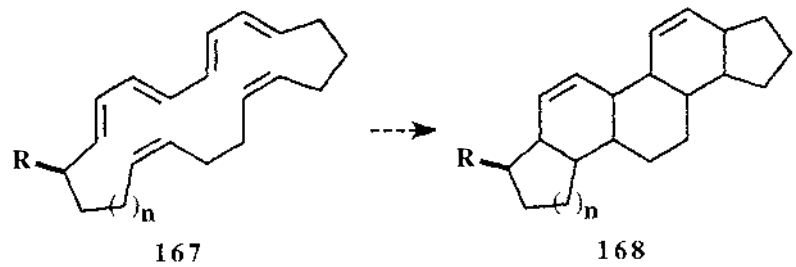


Figure 1.52

1.3.1 TDA of carbocyclic systems

Deslongchamps has been pre-eminent in unlocking the stereochemical factors affecting TDA reactions of thirteen, fourteen and fifteen membered macrocycles.[29] An example of a TDA reaction of a fourteen membered macrocycle is given in **Figure 1.40**. Each of the alkenes in the starting material can be either *cis* or *trans*, giving rise to eight stereoisomers of macrocycle **170**. These in turn can give rise to eight diastereomeric TDA adducts.

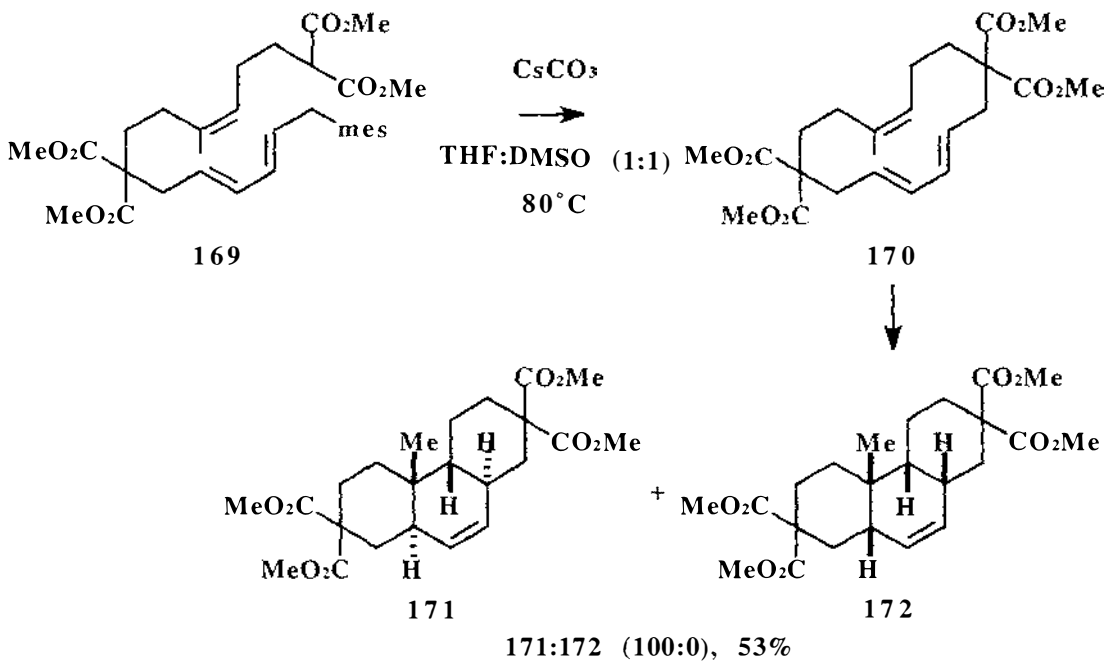


Figure 1.53

Each of the eight triene precursors were prepared,[148] macrocyclised and subjected to conditions intended to promote TDA reactions.[149, 150] Macrocycle **170** was formed under mildly basic conditions from acyclic starting material **169** at 80°C. This *Z,Z,E*-cyclotetradecatriene proved to be very reactive and cyclised to give racemic adduct **171** exclusively under the conditions used for macrocyclisation, albeit with an unimpressive yield. Adduct **172** was not detected.

The reactivity of the starting materials and stereoselectivity of each reaction could be predicted by invoking chair-boat-chair transition states.[151] Two of these transition states are possible for each of the macrocycles and they are illustrated for starting material **170** in **Figure 1.54**. In this case there are unfavourable steric interactions in *syn* transition state **174** which are not found in *anti* transition state **173**, hence adduct **171** was formed exclusively.[150]

In five out of the eight examples this transition state model accurately predicted the adducts which formed. The study also showed that six out of the eight possible diastereomeric products could be produced with remarkable levels of stereocontrol. For the three macrocycles which gave rise to unexpected products it was found that transannular ene reactions, 1,5-sigmatropic hydrogen migrations and thermal isomerisation of the diene or dienophile had occurred. Semiempirical calculations on some of these competing processes have been undertaken and good correlation between the experimental results and theoretical studies were observed.[152]

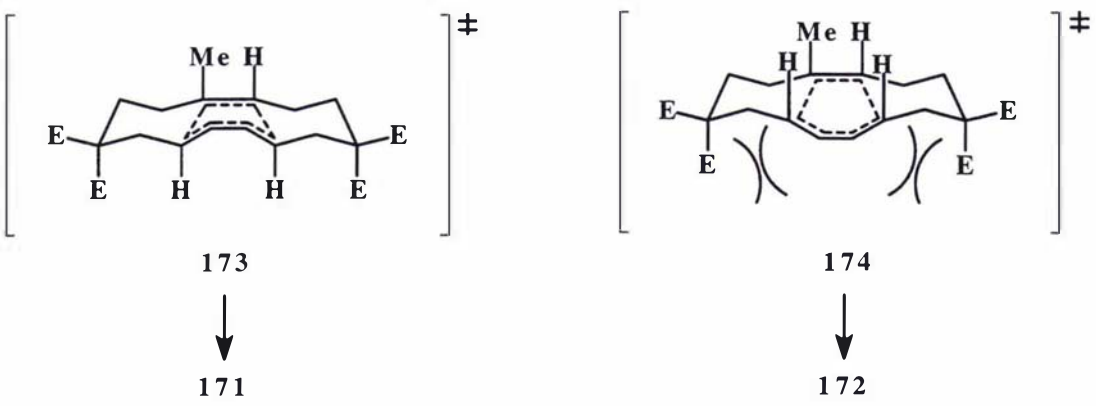


Figure 1.54

This methodology has been utilized in a study directed towards the enantioselective synthesis of quassine (**178**), from the quassinoid family of steroids (**Figure 1.55**).[153] Adducts **176** and **177** both arise from *anti* chair-boat-chair transition states, however, severe steric interactions in the latter result in a high level of diastereofacial selectivity and impressive yield of the major tricycle. Products arising from *syn* transition states were not reported.

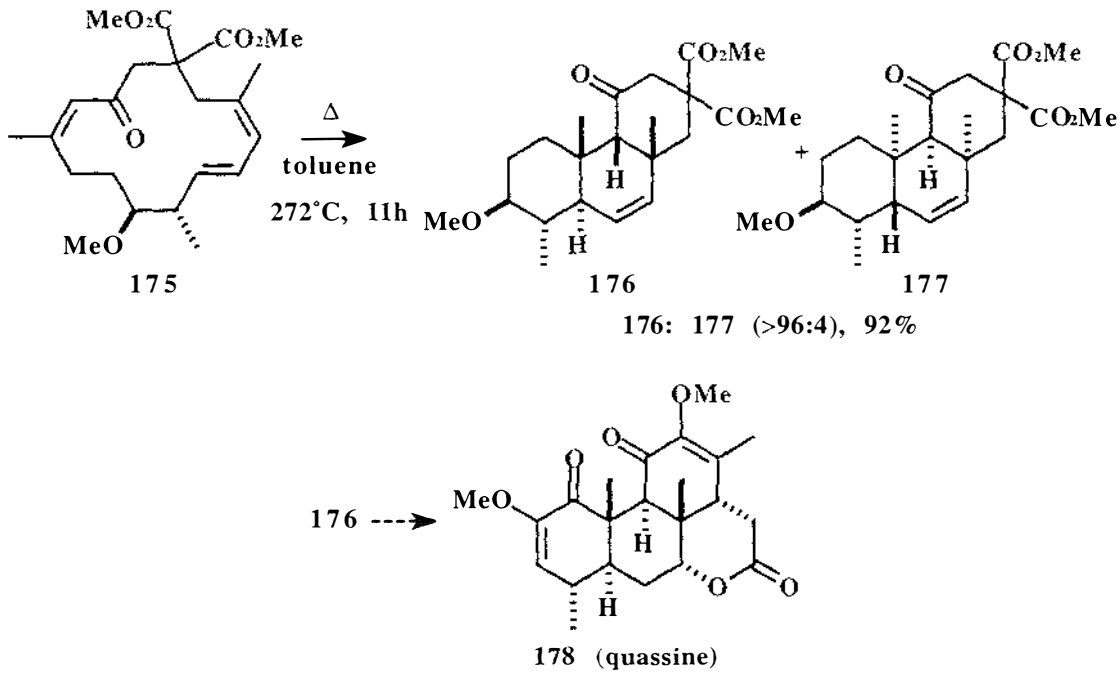


Figure 1.55

1.3.2 TDA of macrocyclic lactones

Three examples of TDA reactions on macrolactones have been reported.[154, 32, 33] In the first example,[154] the intramolecular Horner-Emmons reaction of aldehyde **179** resulted in the formation of *endo* adduct **181** directly, as a single racemic product in 63% yield. The intermediate macrocycle **180** was not detected.

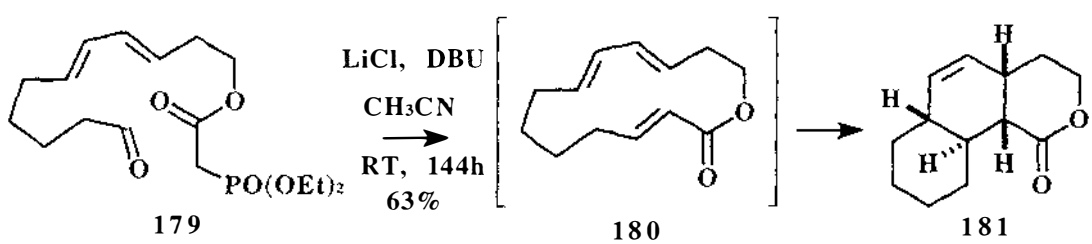


Figure 1.56

Production of *endo* adduct **181** (**Figure 1.56**) *via* TDA reaction of **179** is in sharp contrast to the ETDA reaction of **140** (**Figure 1.57**), which required heating in toluene for 44h at 170°C to cause cycloaddition and produced *exo* adduct **183** in excess (*exo:endo* (4:1)).

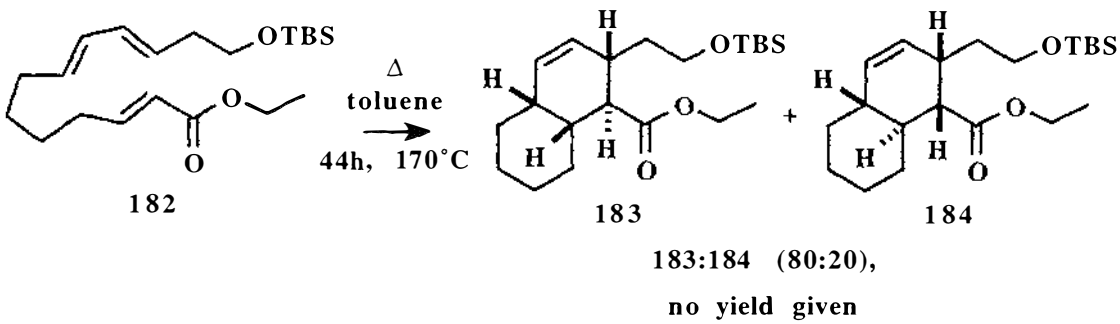


Figure 1.57

The enantioselective synthesis of (-)-oblongolide (**186**) is shown in **Figure 1.58**.[32] This reaction has the same *exo:endo* selectivity as the example shown in **Figure 1.56** although a higher temperature was required for the cycloaddition to occur. The presence of the methyl group in the carbon tether between the diene and dienophile of starting material **185** was sufficient to provide excellent diastereofacial selectivity for the desired natural product.

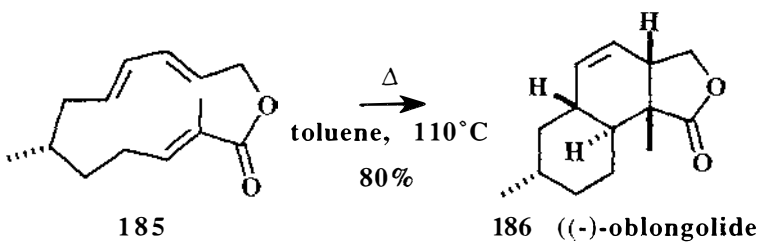


Figure 1.58

The starting material in the final example (compound **187**, **Figure 1.59**), investigated as an approach to Nargenicin A1,[33] has many more stereochemical features than the previous two. The *cis* fused product (**188**) was obtained in high yield and no other adducts were detected.

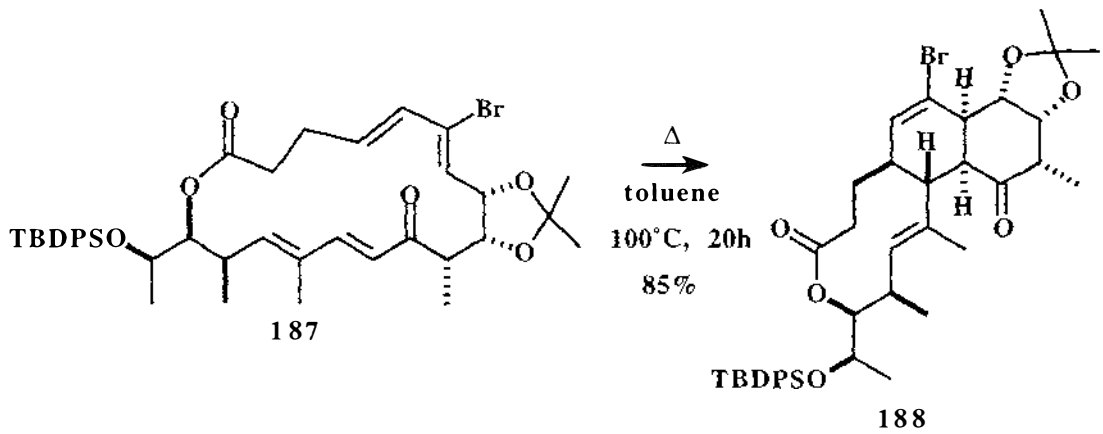
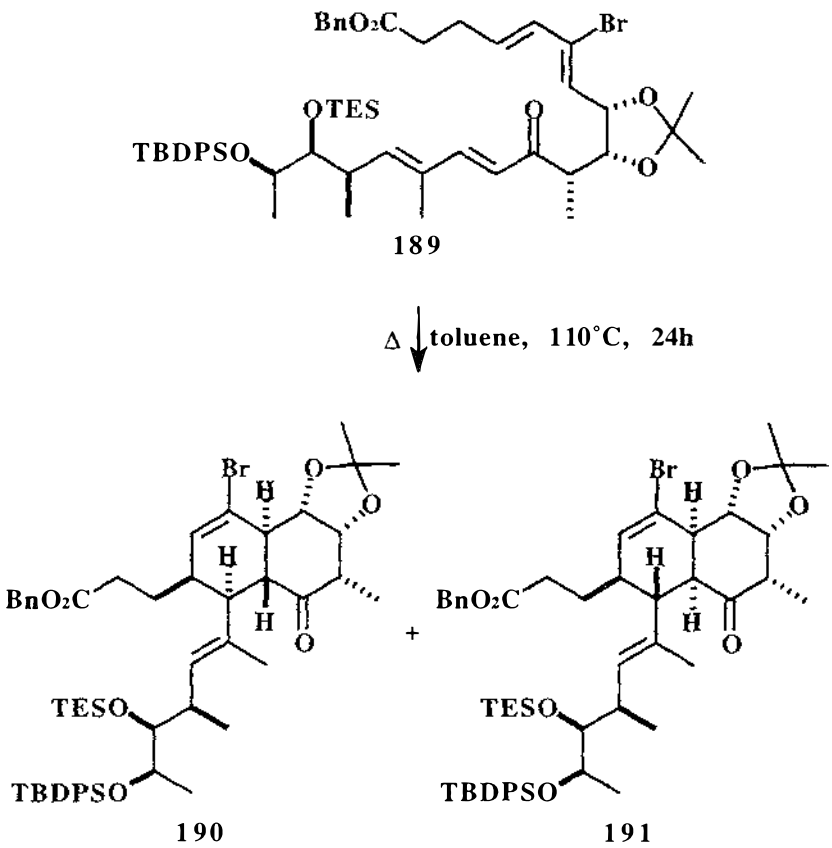


Figure 1.59

The IMDA reaction in **Figure 1.60** is much less stereoselective than the TDA reaction in **Figure 1.59**. Also, the main product which resulted was *trans* fused adduct **189**. This gives weight to the hypothesis that the *exo:endo* diastereoselectivity in the former reaction is due to conformational preferences of macrocycle **187**. The minor product from the IMDA reaction (**190**) has the same absolute stereochemistry as the compound obtained from the TDA reaction (**188**) and the configuration of the carbon atom in the ring junction closest to the acetonide group is the same for all three adducts (**188**, **189** and **190**). This indicates that the diastereofacial selectivity arises from the same stereocontrolling element in each case. The origin of this selectivity is the 1,3-allylic strain[155] between the bulky bromine atom and the acetonide moiety, which raises the energy of the transition state leading to one of the two facial isomers.



190:191 (67:33), 83%

Figure 1.60

2 Remote stereocontrol of ETDA reactions[156]

2.1 Introduction

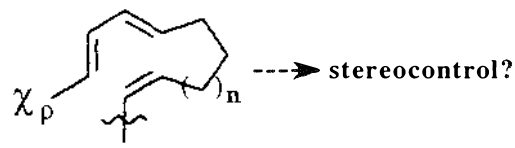


Figure 2.1

The absolute stereoselectivity of IMDA reactions can be controlled by incorporating stereogenic centres into the tether connecting the diene and the dienophile; by attaching a chiral auxiliary to the dienophile terminus; or by enantioselective catalysis of an achiral triene (**Section 1.2.2**). However, the effect of placing a stereogenic centre allylic to the diene but remote from the tether (**Figure 2.1**) is an unexplored method of controlling the π-facial selectivity of IMDA reactions. Four examples in which the IMDA precursor has a stereogenic centre in this position are discussed below.

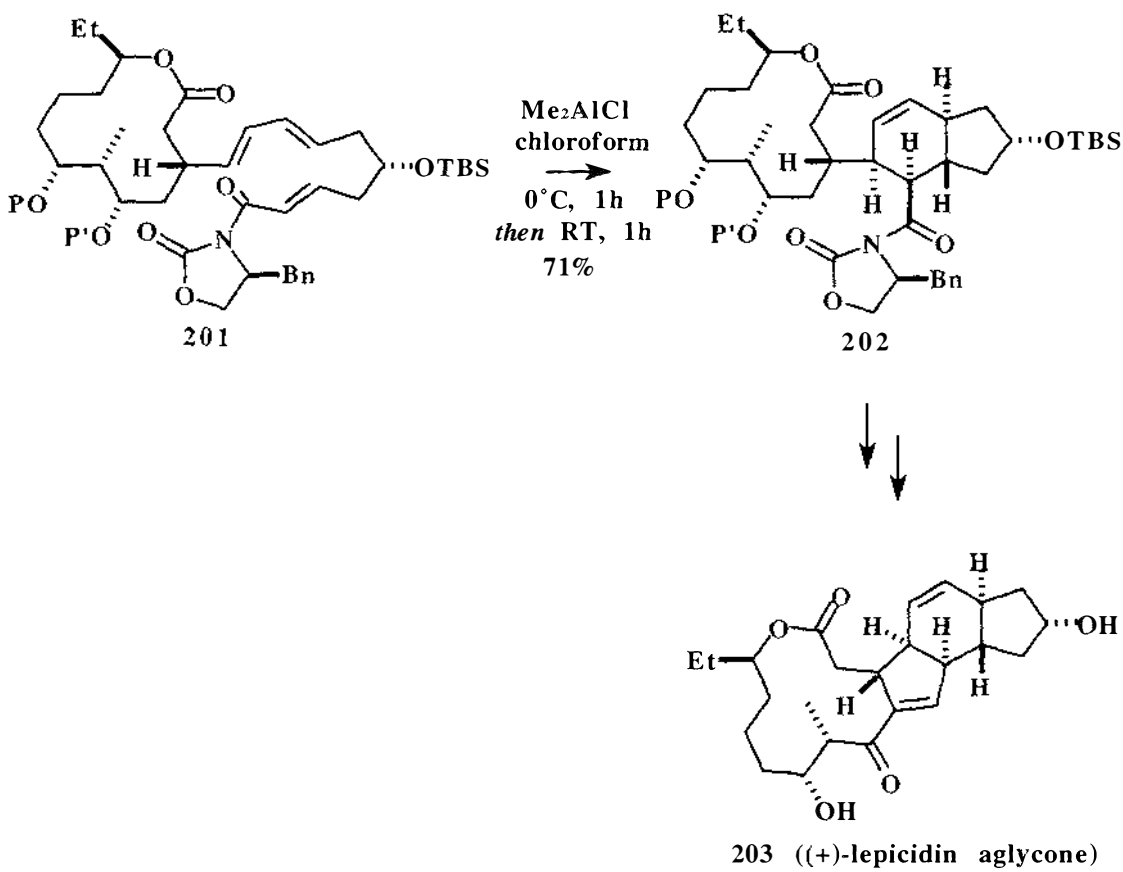
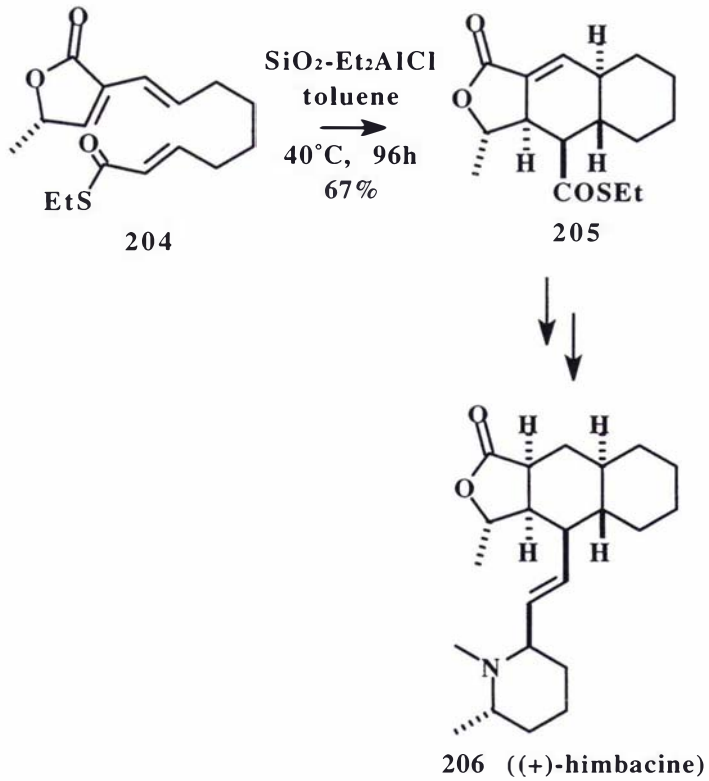


Figure 2.2

The diastereoselective IMDA reaction of **201** (**Figure 2.2**) occupied a central position in the strategy developed for the synthesis of **203** (the aglycone of (+)-lepicidin).[21] The IMDA precursor has a number of stereogenic centres which could affect the overall stereoselectivity: in the tether; in the dienophile auxiliary; and in the macrolide. The observed diastereoselectivity (91:9) could also have been influenced by chelation of the Lewis acid catalyst. It is therefore not possible to gauge the contribution of the chiral lactone to the overall stereoselectivity which was observed, or even to determine whether it had any effect at all. In fact, the outcome of this reaction is comparable to the outcome of the IMDA reaction of **142b** (**Entry 2**, **Figure 1.46**, **Section 1.2.2.2**) in which neither the tether group nor the chiral lactone were present in the starting material.

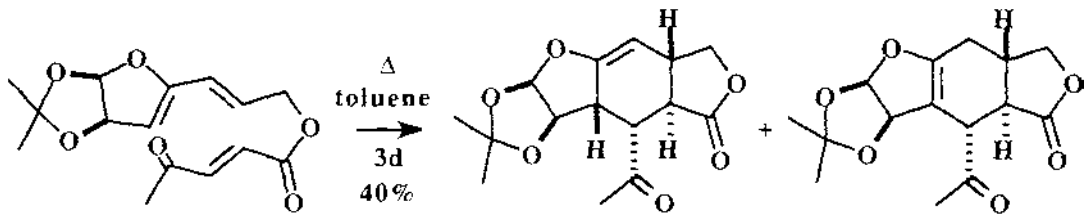
An IMDA reaction also played a central role in a recent synthesis of (+)-himbacine (**206**)[22] (**Figure 2.3**). The diene in starting material **204** had a remote chiral allylic substituent, which engendered a useful diastereoselectivity for adduct **205**. However, in this example the diene is semicyclic and the stereogenic centre is located within the lactone ring. Prediction of the π-facial selectivity is more straightforward in this case since bond rotation at the stereogenic centre cannot occur (i.e. the dienophile is expected to approach the diene from above, as drawn in **Figure 2.3**). A number of similar syntheses of himbacine (or derivatives) involving this strategy have been reported.[157-159]



204 205 206 ((+)-himbacine)

Figure 2.3

A semicyclic diene was also utilized in the ETDA reaction depicted in **Figure 2.4**.[160] Under the reaction conditions employed, the major product from the reaction (**209**) arises from double bond migration of ETDA adduct **208**. Although the combined yield of compounds **208** and **209** was low, no other cycloaddition products (or compounds derived from them) were isolated with yields of greater than 1%, which could indicate that the dioxolane ring conferred a high level of diastereoselectivity in the initial ETDA reaction.



207 **208** **209**

208:209 (25:75)

Figure 2.4

An ETDA reaction involving an acyclic precursor is shown in **Figure 2.5**.[161] In this case the starting material (**210**) has a stereogenic centre allylic to the diene, but the tether connecting the diene and dienophile was also asymmetric. In addition, the starting material consisted of mixture of diastereomers, epimeric at the remote allylic position. The authors commented that the tether substituent provided good stereochemical transcription at the adjacent ring junction site for major isomers **212** and **214**, however, there was little *endo:exo* discrimination. Because the starting material contains a mixture of epimers at the remote allylic site it is possible for double stereodifferentiation[162] to occur. For this reason, each of the products isolated (**212-214**) need not contain equimolar amounts of their component diastereomeric epimers, however, no information about this was provided. Consequently, it is not possible to extract any useful information about the effect of the remote allylic substituent from this very complicated example.

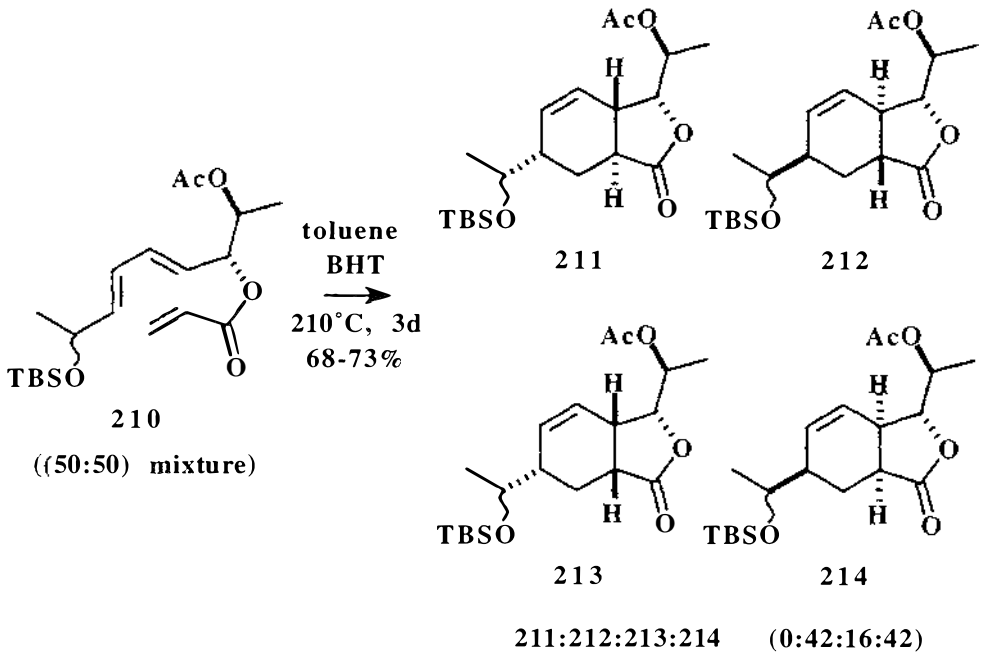


Figure 2.5

Placing substituents allylic to the diene but remote from the tether could potentially provide a new and versatile way of controlling the stereochemical outcome of IMDA reactions. With the exception of the stereochemically biased semicyclic dienes, very little information can be gained about the stereocontrolling effect of the remote allylic substituent in the examples shown above, so it was decided to undertake a systematic study of reactions on simple ETDA precursors, unburdened by extra stereocontrolling elements, of the type shown in **Figure 2.6**.

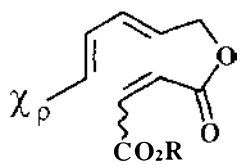


Figure 2.6

Ester tethered substrates were chosen for a number of reasons. There are very few examples of asymmetric ETDA reactions and stereocontrol cannot normally be augmented by the addition of Lewis acid catalysts (**Section 1.2.1.1**), so it is desirable to find alternative methods. The ester tether itself provides a convenient means of attaching the diene to the dienophile, allowing a range of IMDA precursors to be constructed from simple chiral dienols. By activating the dienophile with a second (terminal) EWG the rate retarding effect of the ester tether is largely compensated for. The inherent flexibility of this system means that the effect of the dienophile geometry can also be readily investigated (by preparing maleate and fumarate derivatives), as can the nature of the dienophile which can be terminated with either a carboxylic acid or a derivative thereof (**Chapter 3**).

In order to ascertain whether or not it is possible to control the stereochemical outcome of ETDA reactions using a remote chiral allylic substituent, an initial investigation involving maleate esters of the type shown in **Figure 2.7** was undertaken. It was anticipated that *exo* adducts **217** and **218** would be favoured since the dienophile portion was terminated with a methyl ester group (**Section 1.2.1.1**). It was also hoped that the asymmetric moiety would provide a high level of π-facial stereoselectivity, such that one of the *exo* adducts (**217** or **218**) would be produced in good yield with a high diastereomeric excess.

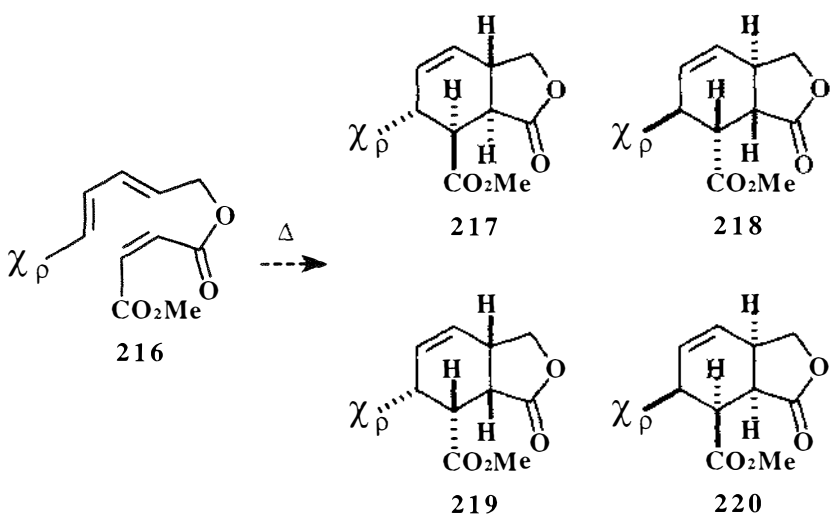


Figure 2.7

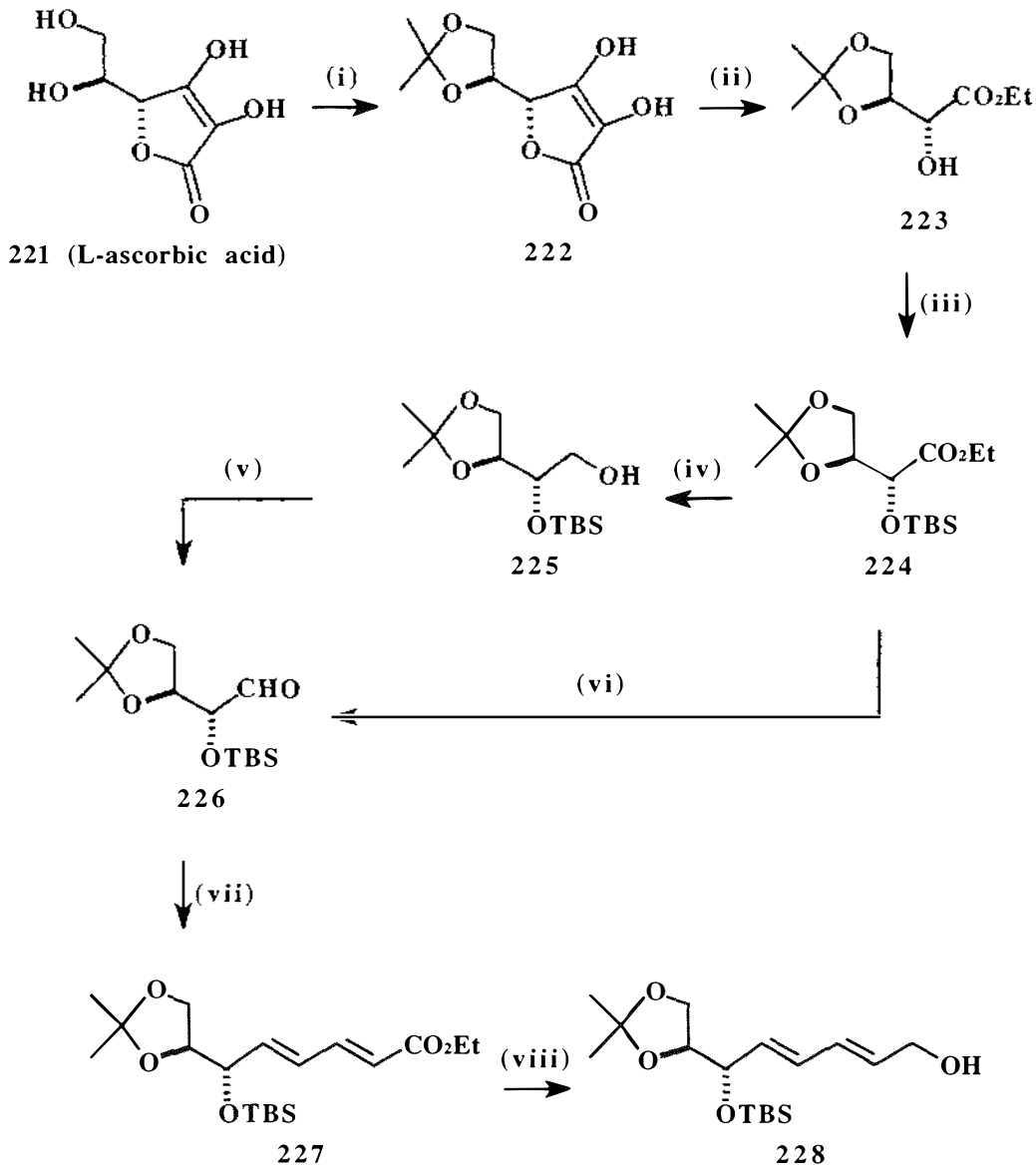
2.2 Synthesis of dienols

The synthesis of the two chiral dienols, which were used to prepare precursors for subsequent ETDA reactions, are discussed in **Sections 2.2.1** and **2.2.2**.

2.2.1 Synthesis of TBS dienol

L-ascorbic acid (**221**) was treated with acetone (**Scheme 2.1**) according to the method of Jung and Shaw[163] to give acetonide **222** as a white crystalline solid. Oxidative cleavage of **222** was accomplished with potassium carbonate and hydrogen peroxide in water and the resulting potassium salt (potassium (2*R*,3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate) was treated with ethyl iodide to give α-hydroxy ester **223** according to the method of Abushanab *et al.*[164] (This paper provides a detailed experimental procedure for preparing an epimer of **223** from D-isoascorbic acid. An earlier reference by the same author[165] outlines the synthesis of the corresponding methyl ester of **223**. Although both of these papers refer to the preparation of compound **223**, neither of them report the physical properties of this material.)

Treatment of α-hydroxy ester **223** with *tert*-butyldimethylsilyl chloride[166] produced silyl ether **224**, which could be purified conveniently by distillation. Reduction of **224** with DIBALH (1.1eq) at -78°C produced a mixture of alcohol **225**, aldehyde **226** and unreacted starting material. Addition of further DIBALH (1.1eq) produced alcohol **225** cleanly and this material could then be oxidized to aldehyde **226** by the addition of the Dess-Martin periodinane[167] (**Section 6.6.1**). It was subsequently found that ester **224** could be reduced directly to aldehyde **226** provided that the temperature was maintained at -100°C, rapid stirring was applied and the DIBALH was added slowly using a syringe pump. The yield of aldehyde **226** achieved using this method was 86% after distillation.



221 (L-ascorbic acid) 222 223 224 225 226 227 228

Conditions: (**i**) acetone, CH_3COCl, RT, 8h, 76%; (**ii**) K_2CO_3, H_2O_2, H_2O, RT, 24h *then* CH_3CH_2I, CH_3CN, reflux, 44h, 83%; (**iii**) TBSCl, imid., DMF, RT, 30min, 68%; (**iv**) DIBALH, CH_2Cl_2, -78°C, 10min *then* RT, 1h; (**v**) Dess-Martin periodinane, CH_2Cl_2, RT, 1h, 58% (2 steps); (**vi**) DIBALH, CH_2Cl_2, -100°C, 86%; (**vii**) $Ph_3PCHCHCHCO_2Et$, CH_2Cl_2, reflux, 1.5h *then* thiophenol, AIBN, PhH, reflux, 3h; (**viii**) DIBALH, CH_2Cl_2, -78°C, 58% (3 steps).

Scheme 2.1

Treatment of aldehyde **226** with the stabilized ylid ethyl 4-(triphenylphosphoranylidene)-(2*E*)-2-butenoate[168, 169] (**Section 6.6.2**) in refluxing dichloromethane produced homologated ester **227** as a mixture of *Z*- and *E*-stereoisomers[†] (79:21) with a yield of 78% after chromatography. Radical isomerisation of the *Z*-stereoisomer was accomplished by treating the mixture with catalytic thiophenol and AIBN in the presence of ultraviolet light.[170] It was found that complete isomerisation could only be achieved by recharging the reaction mixture with fresh thiophenol and AIBN at 1h intervals, with a total reaction time of 3h. The crude product from the isomerisation was used in the subsequent steps without additional purification. Reduction of homologated ester **227** with DIBALH produced TBS dienol **228** as a colourless oil in 58% yield from aldehyde **226** after chromatography.

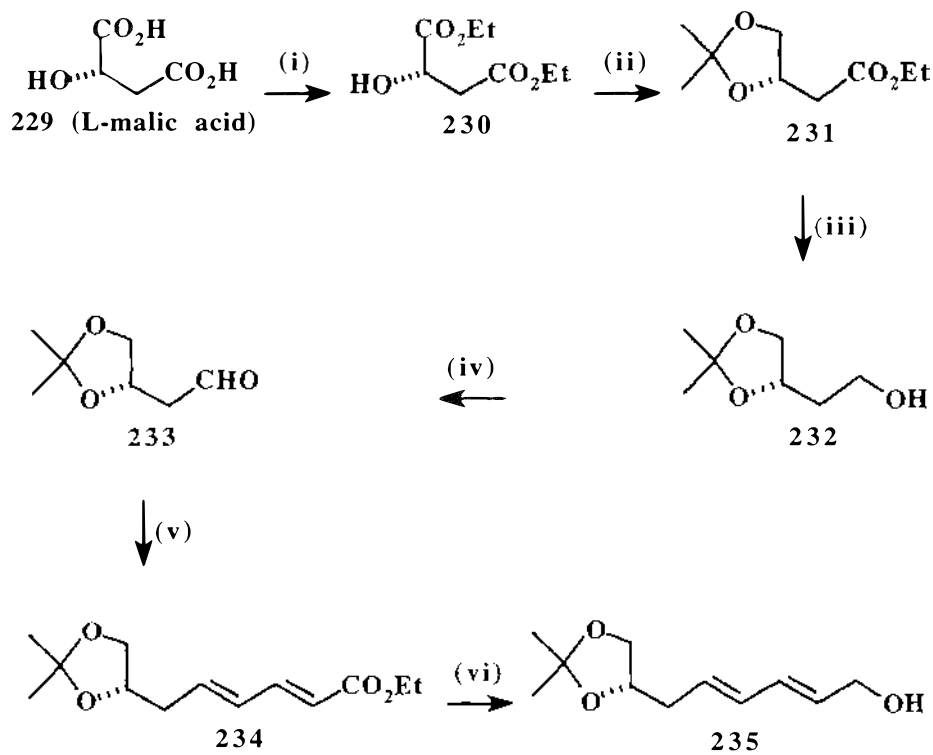
2.2.2 Synthesis of *deoxy* dienol

Diethyl L-malate (**230**) was prepared from L-malic acid (**229**) by refluxing in ethanol (**Scheme 2.2**) in the presence of catalytic sulphuric acid. Regioselective reduction of **230** with borane-dimethyl sulphide complex, followed by treatment of the resulting diol (ethyl (3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate) with 2,2-dimethoxypropane according to the method of Saito *et al.*[171] produced acetonide **231** in 70% yield after distillation.

Attempted preparation of aldehyde **233** directly from acetonide **231** with DIBALH at -100°C (using the method devised for aldehyde **226**, **Section 2.2.1**) inexplicably resulted in yields ranging from 4-10%. For this reason it was more practical to prepare aldehyde **233** using a two step procedure. Acetonide **231** was cleanly reduced with lithium aluminium hydride in refluxing THF, producing a 92% yield of alcohol **232** after Kugelrohr distillation. (Reduction of the corresponding methyl ester with lithium aluminium hydride can be accomplished at room temperature.[171]) Oxidation of alcohol **232** with the Dess-Martin periodinane[167] (**Section 6.6.1**) furnished aldehyde **233** in 78% yield after chromatography.

[†] *E*- and *Z*- refer to the geometry of the newly formed double bond.

Homologation of aldehyde **233** with ethyl 4-(triphenylphosphoranylidene)-(2*E*)-2-butenoate[168, 169] (**Section 6.6.2**) produced diene ester **234** as a mixture of *Z*- and *E*-stereoisomers (50:50) in a 35% yield after chromatography. (An attempt to increase the yield of this reaction using triethyl (2*E*)-4-phosphono-2-butenoate and sodium hydride in THF[172] did not produce any of the desired product by TLC, but resulted in complete destruction of the starting material.) Isomerisation of the *Z*-stereoisomer was accomplished by treating the mixture with thiophenol and AIBN[170] using the method developed for homologated ester **227** (**Section 2.2.1**), although it was only necessary to recharge the reaction mixture once with fresh reagents and shorter reaction times were used. The yield of pure diene ester **234** was 78% after chromatography. Reduction of **234** with DIBALH at -78°C gave *deoxy* dienol **235** in 40% yield as a colourless oil. It is not clear why the reactions in this sequence produced low yields compared to those in **Section 2.2.1**, but since a quantity of *deoxy* dienol was available it was decided to postpone optimization of these procedures in favour of carrying out the subsequent ETDA reactions.



Conditions: (**i**) EtOH, H_2SO_4, reflux, 16h, 76%; (**ii**) BMS, $NaBH_4$, THF, RT, 30min *then* DMP, *p*-TsOH.H_2O, acetone, RT, 30min, 70% (2 steps); (**iii**) $LiAlH_4$, THF, reflux, 14h, 92%; (**iv**) Dess-Martin periodinane, CH_2Cl_2, 16h, 78%; (**v**) $Ph_3PCHCHCHCO_2Et$, CH_2Cl_2, reflux, 1.5h 35% *then* thiophenol, AIBN, PhH, reflux, 1h, 78%; (**vi**) DIBALH, CH_2Cl_2, -78°C, 40%.

Scheme 2.2

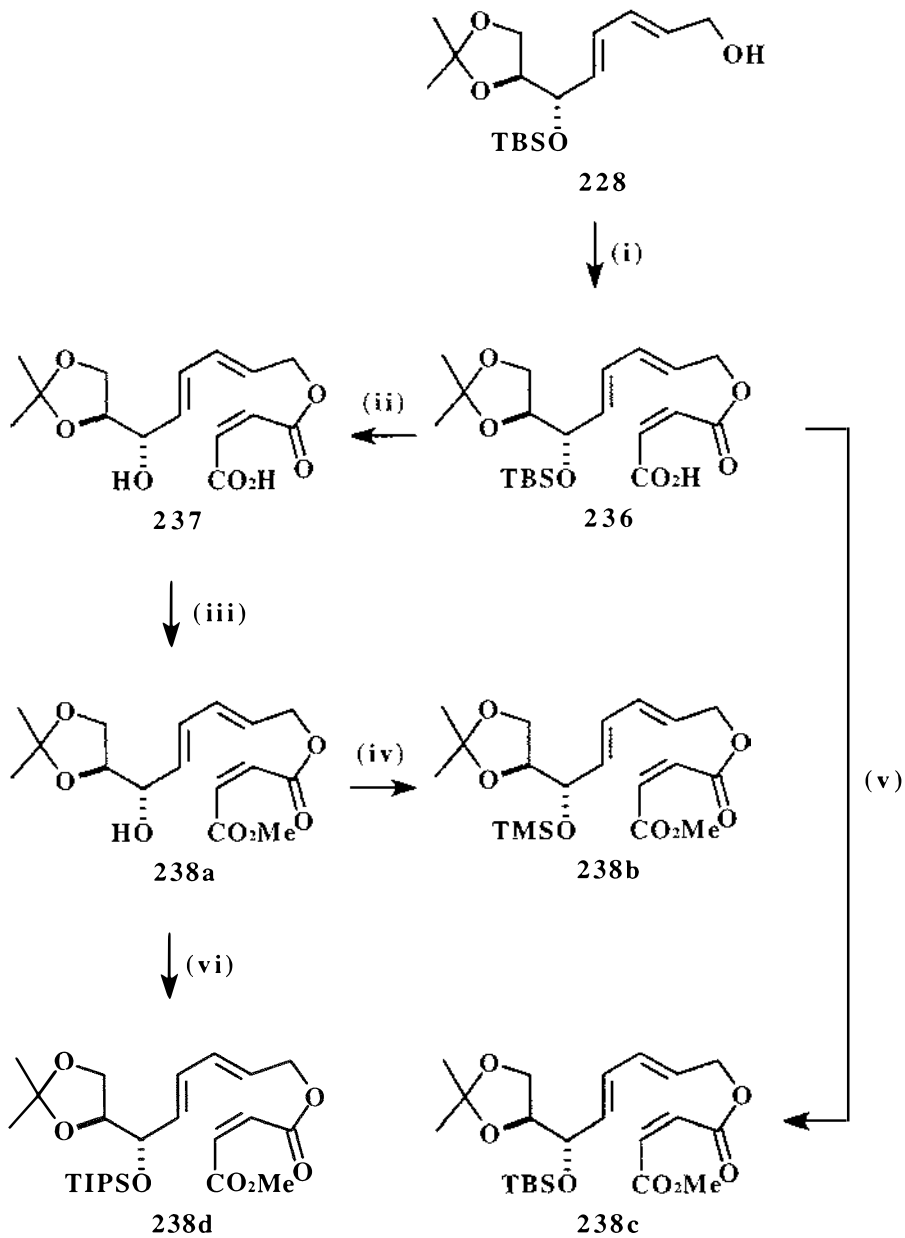
2.3 Synthesis of ETDA precursors

The preparation of a range of ETDA precursors from the two chiral dienols (**Section 2.2**) and maleic anhydride, followed by treatment with diazomethane[173] (**Section 6.6.3**) are given in **Sections 2.3.1** and **2.3.2**.

2.3.1 Synthesis of *hydroxy* and *silyloxy* precursors

Dienol **228** (**Section 2.2.1**) was reacted with maleic anhydride[174] (**Scheme 2.3**) to form carboxylic acid **236** in near quantitative yield after chromatography. Deprotection of the silyl group[166] gave alcohol **237** which was converted to methyl ester **238a** using an ethereal solution of diazomethane[173] (**Section 6.6.3**). Compound **238a** was used to prepare trimethylsilyl derivative **238b** and triisopropylsilyl derivative **238d** using the appropriate trialkylsilyl triflate.[175] The poor reactivity of the 2° alcohol was highlighted by the long reaction times which were required and the modest yields which were obtained, in spite of the highly reactive reagents used. (No reaction was observed between alcohol **238a** and triisopropylsilyl chloride in the presence of imidazole and DMAP.[176]) Treatment of carboxylic acid **236** with diazomethane[173] (**Section 6.6.3**) gave *tert*-butyldimethylsilyl derivative **238c**.

Outwardly, a more economical strategy can be devised in which silyl ether **238c** is deprotected to form alcohol **238a**, thereby eliminating one step (formation of compound **237**) from the overall scheme. In practice this approach was rendered undesirable because treatment of *tert*-butyldimethylsilyl ether **238c** with tetrabutylammonium fluoride gave rise to an unacceptably low yield of secondary alcohol **238a** (26%).

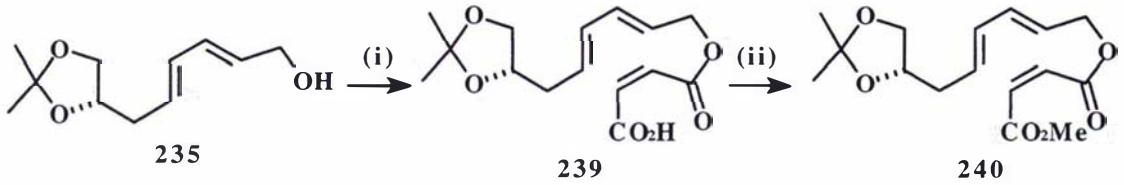


Conditions: (**i**) TEA, MA, DMAP, CH_2Cl_2, RT, 10min, 99%; (**ii**) TBAF, THF, RT, 16h, 85%; (**iii**) CH_2N_2, diethyl ether, 0°C, 74%; (**iv**) TMSOTf, TEA, DMAP, CH_2Cl_2, RT, 2.5h, 51%; (**v**) CH_2N_2, diethyl ether, RT, 80%; (**vi**) TIPSOTf, TEA, CH_2Cl_2, RT, 20h, 58%.

Scheme 2.3

2.3.2 Synthesis of *deoxy* precursors

Treatment of alcohol **235** with maleic anhydride[174] (**Scheme 2.4**) produced carboxylic acid **239** in quantitative yield after chromatography. The yield of methyl ester **240** obtained from acid **239** by treatment with diazomethane[173] (**Section 6.6.3**) was discouraging and unexpected. From this point on it was decided to carry out small scale diazomethane reactions at low temperatures (< 0°C) and to follow the reactions by TLC, rather than follow the standard procedure which is to add the reagent until a yellow colour persists and evolution of nitrogen subsides. In this way it was hoped to minimize side reactions (such as addition to activated alkenes to form 4,5-dihydro-3,4-pyrazoles[177, 178]) which could cause low yields in the highly functionalised olefins reported here.



235 239 240

Conditions: **(i)** TEA, MA, DMAP, CH_2Cl_2, RT, 30min, 100%; **(ii)** CH_2N_2, diethyl ether, RT, 18%.

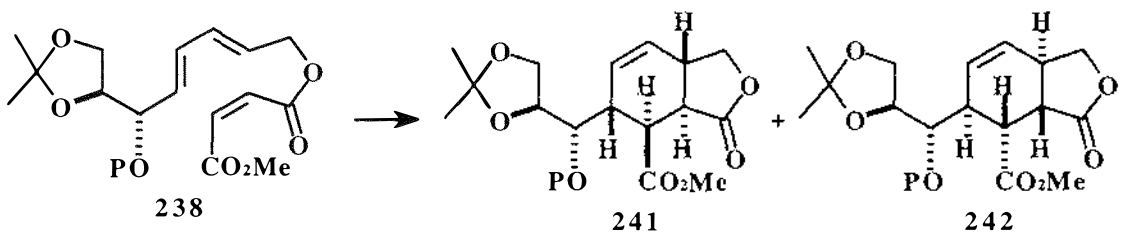
Scheme 2.4

2.4 ETDA reactions

Each of the ETDA precursors prepared in **Section 2.3** was heated in refluxing toluene under an argon atmosphere. Dilute solutions of the starting material (5mmol/L) were used in order to minimize BDA reactions and a small amount of 2,6-di-*tert*-butyl-4-methylphenol (0.20eq) was added to prevent oxidation of the conjugated diene moiety of the starting material. The same conditions were employed in each case to allow direct comparisons with other ETDA reactions to be made. Product ratios were determined from proton NMR spectra of crude reaction mixtures and yields were calculated from the amount of material isolated after chromatography.

2.4.1 ETDA reactions of the *hydroxy* and *silyloxy* precursors

The ETDA reactions of precursors **238a-d** each produced a mixture of isomers **241** and **242** (**Scheme 2.5**). In all of the isomers (**241a-d** and **242a-c**) the coupling constant between the two hydrogen atoms at the ring junction was found to be 13.6-13.8Hz, which indicates that the two rings are *trans* fused in each case.[98] It can be deduced from this that the ETDA adducts originated from *exo* transition states (**Section 1.2**). (Unfortunately it was not possible to characterize compound **242d** since the amount of it produced was very small and it could not be isolated in pure form.) Trace amounts of other compounds could be detected in the proton NMR spectra of the crude reaction mixtures which may have been due to *endo* adducts, however, it was not possible to isolate sufficient quantities of these very minor components to allow full characterization.



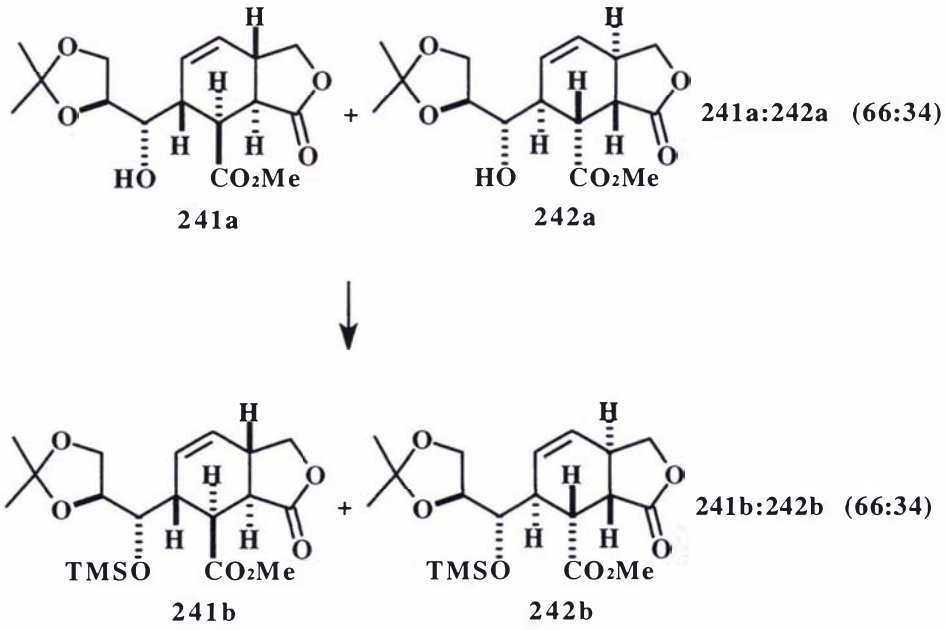
238	P	t/h	241:242	%
a	H	5	66:34	86
b	TMS	12	82:12	67
c	TBS	15	91:9	80
d	TIPS	18	96:4	68

Conditions: BHT, toluene, reflux.

Scheme 2.5

Diastereofacial selectivity was observed in all of the ETDA reactions and in each case the major isomer produced had general structure **241** (**Section 2.4.1.1**). As expected the lowest level of stereocontrol was observed for alcohol **238a** and this increased according to the size of the silyl protecting group. The triisopropylsilyl derivative[179] **238d** exhibited the largest ratio between structures **241** and **242** (96:4) corresponding to a diastereomeric excess of 92%. This remarkable level of diastereocontrol (coupled with the favourable yield of the major isomer and the ease with which it could be isolated) signals the power of remote allylic substituents to control the π-facial selectivity of IMDA reactions.

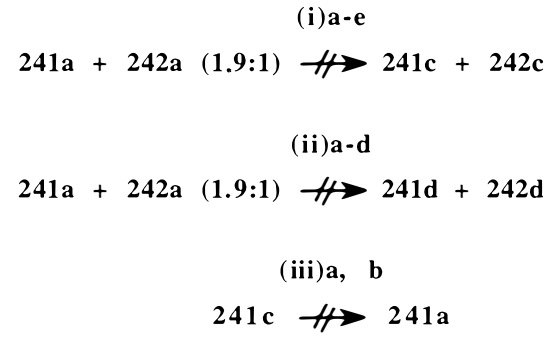
It was not possible to separate dienols **241a** and **242a**, however, it was possible to unambiguously show that the major diastereomer from the ETDA reactions of precursors **238a** and **238b** had identical stereochemistry. A mixture of alcohols **241a** and **242a** (66:34) was treated with trimethylsilyl chloride[166] to produce ether derivatives **241b** and **242b** (66:34) in 61% yield (**Scheme 2.6**). The major and minor isomers in this reaction were identical in every respect to those produced in the ETDA reaction of precursor **238b** (**Scheme 2.5**). This could indicate that the transition states responsible for stereocontrol of the ETDA reactions of silyl precursors **238b-d** might be similar to those involved in the formation of **241a** and **242a** (**Section 2.4.1.2**).



Conditions: TMSCl, imid., DMF, RT, 74%.

Scheme 2.6

Several attempts were made to prepare the *tert*-butyldimethylsilyl and triisopropylsilyl derivatives (reactions **(i)a-e** and **(ii)a-d** respectively) from a mixture of alcohols **241a** and **242a** (66:44) (**Scheme 2.7**).[166, 175, 179] These reactions were not successful and generally resulted in complex mixtures or recovery of the starting material. Two unsuccessful attempts (**(iii)a, b**) were also made to deprotect the *tert*-butyldimethylsilyl derivative **241c**.[166, 180] The first resulted in degradation of the starting material, whereas no reaction was observed in the second. These unsuccessful reactions all highlight the steric inaccessibility of the secondary alcohol or ether group adjacent to the bicyclic framework in compounds **241a-d** and **242a-c**.



Conditions: **(i)a** TBSCl, imid., DMAP, DMF, RT, 24h; **(i)b** TBSCl, pyr., DMAP, CH_2Cl_2, 80°C, 5h, **(i)c** TBSCl, imid, DMF, 80°C, 18h; **(i)d** TBSCl, DMAP, DMF, 80°C, 18h; **(i)e** TBSOTf, TEA, DMAP, CH_2Cl_2, RT, 18h; **(ii)a** TIPSCl, imid., DMAP, DMF, RT, 24h; **(ii)b** TIPSCl, pyr., DMAP, CH_2Cl_2, 80°C, 18h; **(ii)c** TIPSCl, 2,6-lutidene, DMAP, DMF, 80°C; **(ii)d** TIPSOTf, TEA, CH_2Cl_2, DMAP, RT, 18h; **(iii)a** TBAF, THF, RT, 15min; **(iii)b** KF, 18-Crown-6, THF, RT, 48h.

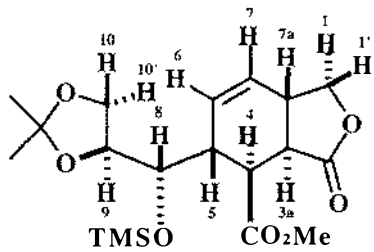
Scheme 2.7

2.4.1.1 Determination of the stereochemisty of the *hydroxy* and *silyloxy* ETDA adducts

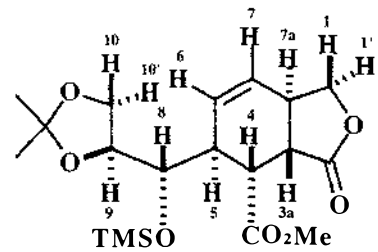
COSY spectra (**Appendices 1.2C** and **1.3C**) were used to confirm the connectivity of the major and minor adducts produced in the ETDA reaction of **238b** (**Section 2.4.1**), then NOESY spectra (**Appendices 1.2N** and **1.3N**) were used to determine the relative stereochemistry. The absolute stereochemistry of the starting material was known and proton NMR spectra indicated that both of the ETDA adducts possessed *trans* fused ring systems. This limited the structures of the two products to **241b** and **242b**, but it was still necessary to determine which isomer was which. Fortunately the nOe's observed for hydrogen atoms in the side chain were strikingly different for the two adducts (**Figure 2.8**). These facts, combined with conformational analysis using molecular models, enabled a confident assignment of the absolute stereochemistry of each isomer to be made.

Selected data from the NOESY spectrum observed for the major adduct is given in **Figure 2.8** along with the two *trans* fused bicyclic structures which are possible for this compound.

major adduct	
H	**nOe**
4	8
5	8, 10
6	9
8	4, 5
9	6
10	5



241b

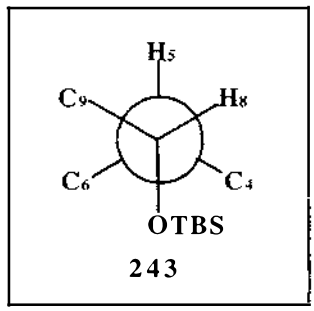


242b

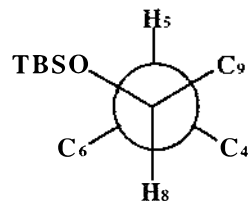
The numbering system used to identify the hydrogen atoms in structures 241b and 242b has been customized to simplify the explanation of the observed nOe's. This numbering system has also been used to identify the carbon and oxygen atoms to which the respective hydrogen atoms are attached.

Figure 2.8

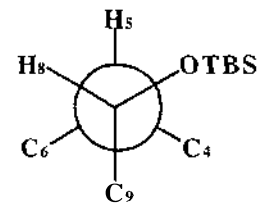
Rotation of C5-C8 bond in structures **241b** or **242b** gives rise to three staggered conformations, each of which corresponds to an energy minimum. The three conformations for structure **241b** (**243**, **244** and **255**) are illustrated in **Figure 2.9**.



243



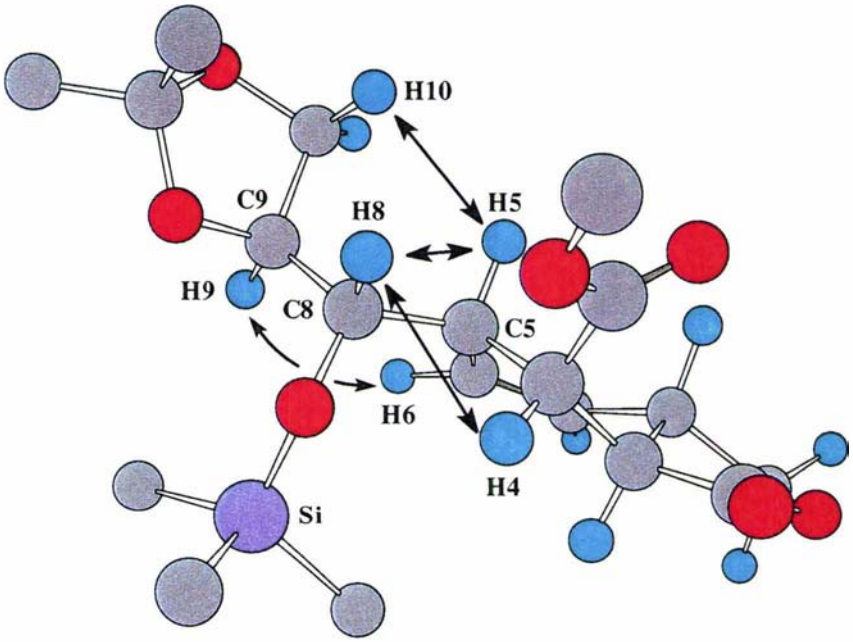
244



255

Figure 2.9

A molecular model (MM2 force field,[181, 182] local minimum) for conformation **243** of structure **241b** is shown **Figure 2.10**. (In order to see the pertinent atoms more clearly, the hydrogen atoms attached to the methyl groups in the molecule have been removed.) In this conformation, the dihedral angle between hydrogen atom H5 and the oxygen atom on C8 bearing the trimethylsilyl group is approximately 180°. Rotation about the C8-C9 bond places the molecule in a conformation that simultaneously situates hydrogen atom H8 proximate to H4 and H5; H9 to H6; and H10 to H5. This corresponds to the nOe's observed for the major adduct of the ETDA reaction (**Figure 2.8**). No other reasonable conformation can simultaneously give rise to these four nOe's.

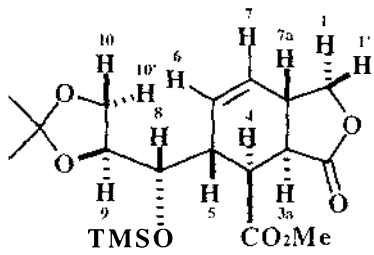


A molecular model (MM2 forcefield, local minimum) of compound 241b (with 24 hydrogen atoms removed) in conformation 243 (Figure 2.9). The arrows indicate hydrogen atoms which are in close proximity.

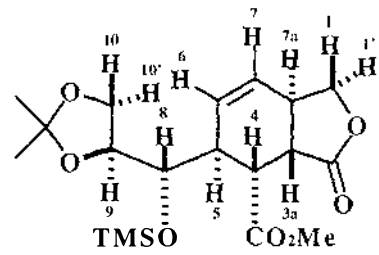
Figure 2.10

Selected data from the NOESY spectrum observed for the minor adduct is given in **Figure 2.8** along with the two possible *trans* fused bicyclic structures.

minor adduct	
H	**nOe**
4	9
5	8, 10
6	8
8	5, 6
9	4
10	5



241b

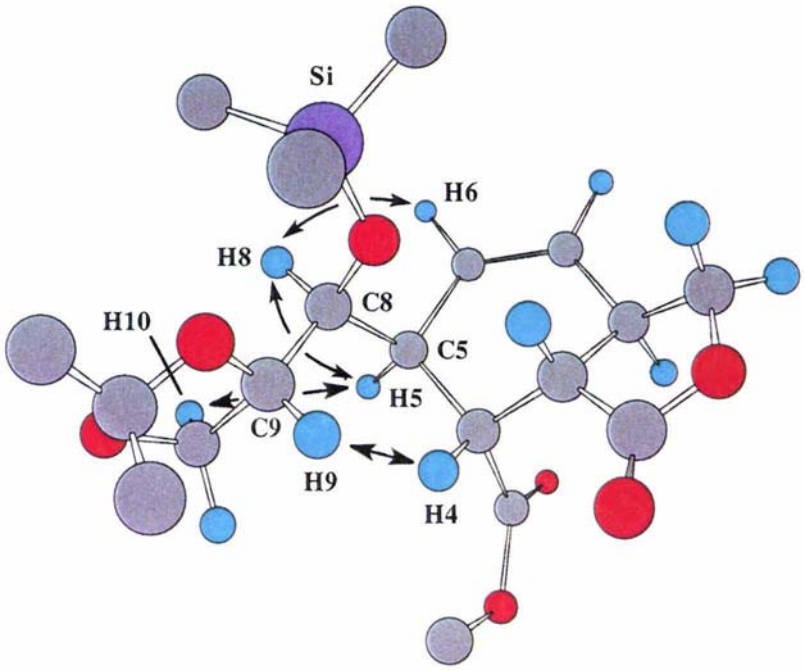


242b

The numbering system used to identify the hydrogen atoms in structures 241b and 242b has been customized to simplify the explanation of the observed nOe's. This numbering system has also been used to identify the carbon and oxygen atoms to which the respective hydrogen atoms are attached.

Figure 2.11

A similar conformational analysis to the one carried out for structure **241b** was carried out for structure **242b.** **Figure 2.12** shows structure **242b** in a staggered conformation, where the dihedral angle between hydrogen atom H5 and the oxygen atom on C8 bearing the trimethylsilyl group is approximately 180° (analogous to conformation **243** of structure **241b** in **Figures 2.9** and **2.10**). Rotation about the C8-C9 bond places the molecule in a conformation that simultaneously brings hydrogen atom H8 close to H5 and H6; H9 to H4; and H10 to H5. This corresponds to the nOe's observed for the minor adduct of the ETDA reaction (**Figure 2.11**). No other reasonable conformation brings these atoms into close proximity at the same time.



A molecular model (MM2 forcefield, local minimum) of compound 242b (with 24 hydrogen atoms removed). The arrows indicate hydrogen atoms which are in close proximity.

Figure 2.12

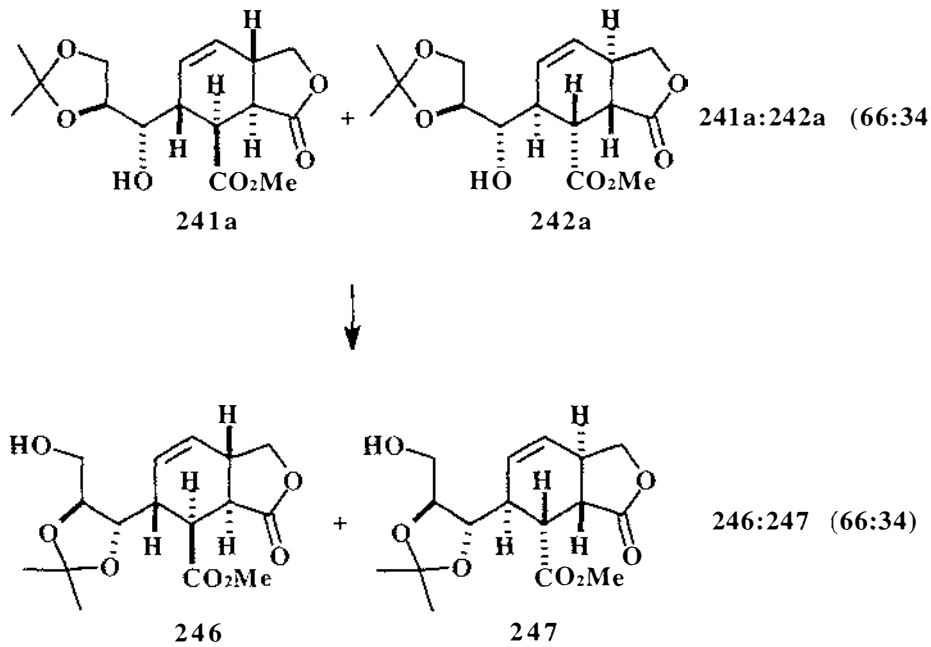
The previous discussion demonstrates that structure **241b** has access to a staggered conformation which is expected to simultaneously give rise to all of the nOe's observed in the NOESY spectrum of the major adduct of the ETDA reaction of **238b**. Likewise, one of the staggered conformations available to structure **242b** is expected to generate the nOe's observed for the minor adduct concurrently. Even more importantly than this, there is no single conformation for structure **241b** (staggered or eclipsed) which can simultaneously account for the nOe's observed for the minor adduct. In addition, structure **242b** cannot be placed in any conformation which would simultaneously give rise to the nOe's observed for major adduct. These observations provide convincing evidence that the major adduct from the ETDA reaction of **238b** has structure **241b** and the minor adduct has structure **242b**. Although this analysis does not constitute unequivocal proof of the absolute stereochemistry of these compounds, it does allow a confident stereochemical assignment of each adduct to be made.

It is important to stress that this argument rests on the fact that there is constant rotation about the C5-C8 bond, but in certain conformations the molecule experiences energy minima. Statistically, it is likely that at any given point in time the number molecules with this conformation would be disproportionately high and that nOe's would be observed for the hydrogen atoms which are placed in close proximity because of it. It follows that the number of molecules in less favourable conformations, at the same point in time, would be lower and that the nOe's arising from them would be weaker. For conformations corresponding to energy maxima, the nOe's might even fall below detectable levels. The fact that strong nOe's were observed for some of the protons in each of the NOESY spectra (but not for the others) is evidence of this effect; the fact that the NOESY spectra are different for each of the adducts is a consequence of their dissimilar structure; and the fact that only one of the structures can adequately explain the origin of the nOe's in each NOESY spectrum, permits the stereochemical assignment of each ETDA adduct to be made. (The configuration of the C1-C14 side chain of maitotoxin has been determined using a similar approach.[183])

The NOESY spectra elicited for **241c** and **241d** were similar to that obtained for **241b** (**Appendix 1.2C**), hence the major isomer has the same relative stereochemistry throughout the series. This is also substantiated by the fact that the ratio of the major adduct to the minor adduct increased as the size of the silyl protecting group was increased from trimethylsilyl to triisopropylsilyl (**Section 2.4.1**). (Unfortunately it wasn't possible to obtain reliable NOESY spectra for minor adduct **242c** because the amount of material isolated was too small. Even when FID's were collected for a period of 64h the nOe's were not large enough to be detected.)

Further evidence for these stereochemical assignments was sought from X-Ray crystallographic studies which necessitated the derivation of alcohols **241a** and **242a** into separable, crystalline products. Esterification of the alcohol mixture (**241a:242a** (66:34)) with acetic anhydride (using triethylamine and DMAP in dichloromethane) or 4-nitrobenzoyl chloride (with pyridine and DMAP in dichloromethane) gave mixtures of the corresponding esters (66:34) in yields of 62% and 100% respectively, but in each case the adducts were found to be chromatographically inseparable. No reaction was observed with 3,5-dinitrobenzoyl chloride or 4-biphenylcarbonyl chloride (using the same conditions as those used for 4-nitrobenzoyl chloride), further highlighting the low reactivity of the secondary alcohol group.

A mixture of alcohols **241a** and **242a** (66:34) was treated with sulfonic acid resin in acetone, resulting in transetherification of the starting materials to derivatives **246** and **247** (66:34) respectively (**Scheme 2.8**). Transetherification to the more highly substituted acetonide is possible where the two secondary alcohols bear a *trans* relationship to each other in the incipient five membered ring.[132] Whereas **241a** could not be separated from **242a**, **246** was separable from **247** using standard chromatographic techniques.



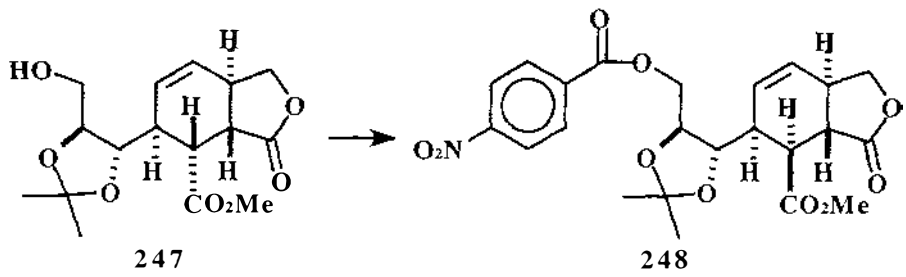
241a 242a

246 247

Conditions: Amberlist IR-118 resin, acetone, RT, 21h, 96%.

Scheme 2.8

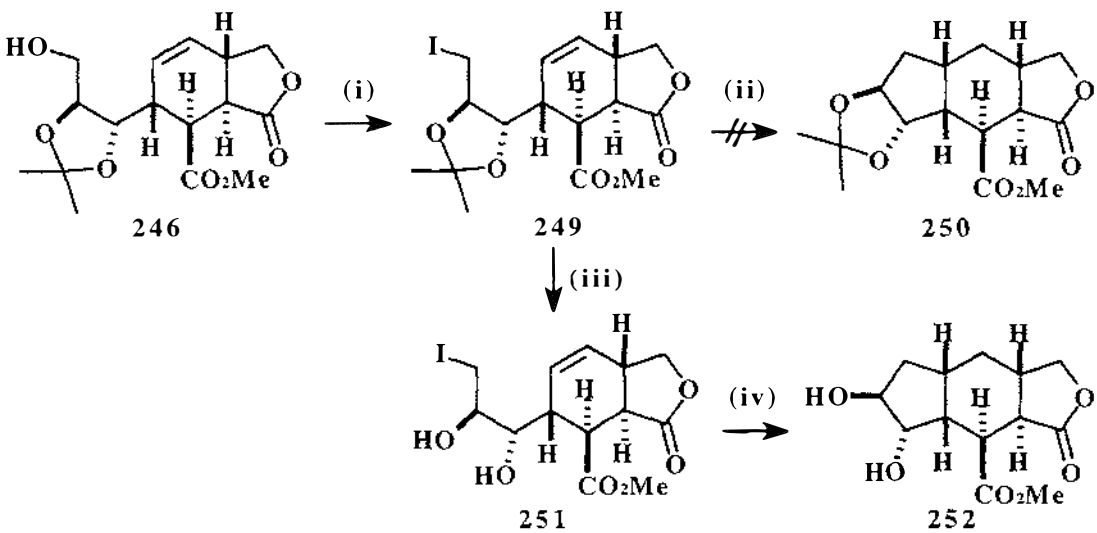
Treatment of **247** with 4-nitrobenzoyl chloride produced ester derivative **248** (**Scheme 2.9**). This material was found to be unsuitable for X-Ray crystallographic analysis since it was not crystalline. Preparation of a range of derivatives in the hope that one of them might produce crystals suitable for X-Ray analysis could have proven to be a futile exercise, hence it was decided to abandon this strategy in favour of preparing adducts suitable for carrying out further nOe difference experiments, which do not rely on the physical state of the material.



Conditions: 4-nitrobenzoyl chloride, pyr., DMAP, CH_2Cl_2, RT, 2h, 71%.

Scheme 2.9

In order to ensure that the nOe difference experiments were successful it was decided to form a tricyclic derivative of alcohol **246**, thereby restricting the conformational mobility of the side chain. Iodination[184] of alcohol **246** (**Scheme 2.10**) gave compound **249** in good yield, however, radical cyclisation of the primary iodide to the alkene using *tris*-(trimethylsilyl)silane[185] did not occur. This was presumably due to the conformational restrictions imposed on the side chain by the isopropylidene group. These restrictions were alleviated by removing the isopropylidene group using sulfonic acid resin in a protic solvent to form diol **251**. This was treated with *tris*-(trimethylsilyl)silane[185] to form tricycle **252** in 64% yield. The two hydrogen atoms at the newly formed ring junction are *cis* to each other because conformational restraints inherent in the three carbon chain between the bicyclic portion of the molecule and the primary alkyl radical mean that radical addition must occur to the bottom face of the alkene.[186, 187]



Conditions: **(i)** imid., triphenyphosphine, I_2, CH_2Cl_2, RT, 20h, 67%; **(ii)** *tris*-(trimethylsilyl)silane, AIBN, benzene, reflux, 4h; **(iii)** Amberlite IR-118 resin, MeOH:H_2O (5:1), reflux, 18h, 82%; **(iv)** *tris*-(trimethylsilyl)silane, AIBN, benzene, reflux, 45min, 64%.

Scheme 2.10

The nOe difference experiments carried out on tricycle **252** (**Figure 2.13**) corroborate the stereochemical assignments for the major ETDA adduct proposed earlier. If alcohol **247** were to be treated in an analogous manner to **246** (**Scheme 2.10**) then tricycle **253** would be produced. However, tricycle **253** cannot produce the large nOe differences observed for tricycle **252**, since the hydrogen atoms at the newly formed ring junction are on the opposite side of the molecule to the requisite hydrogen atom in the cyclopentane ring.

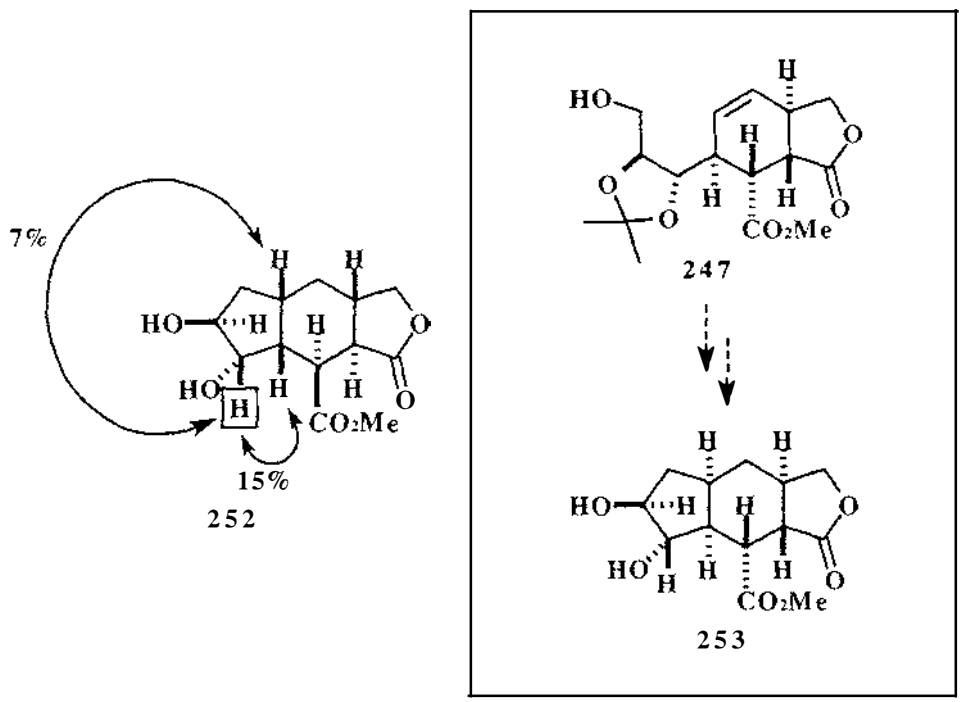
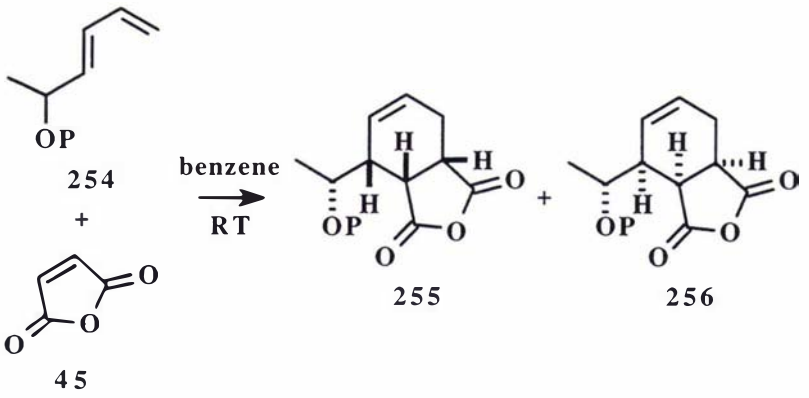


Figure 2.13

2.4.1.2 The origin of the diastereofacial selectivity

Exo:endo stereocontrol of IMDA reactions was discussed in **Section 1.2**, however, it still remains to discuss the origin of the π-facial selectivity observed for the *hydroxy* and *silyloxy* precursors in **Section 2.4.1**. In open chain molecules containing an existing stereogenic centre there are two criteria which must be satisfied in order for asymmetric induction to occur. First, the number of conformations available to the molecule in the transition state must be severely restricted, preferably to one. Second, the preferred conformation must allow differentiation between the diastereotopic faces or groups present in the molecule by the incoming reagent. This differentiation can be due to a bulky group on the existing stereogenic centre which shields one of the diastereotopic faces of the molecule, or one of the groups can coordinate to the incoming reagent and deliver it to one face at the expense of the other.[155]

Since the present study is the first one in which the π-facial stereoselectivity of an IMDA reaction has been controlled by the presence of a remote allylic stereogenic centre on an acyclic diene, the conformational preferences of such molecules have not been investigated. However, there have been a number of studies carried out on the analogous BDA case.[188-190] The examples most closely related to ours[188] are shown in **Figure 2.14**. Racemic dienols **254a-c** reacted with maleic anhydride (**45**) to form mixtures of racemic *endo* adducts with structures **255** and **256**. (The corresponding *exo* adducts were not reported.) The π-facial selectivity of **254a** was increased by protecting the alcohol with a trimethylsilyl or *tert*-butyldimethylsilyl group, although the level of stereocontrol was still low.



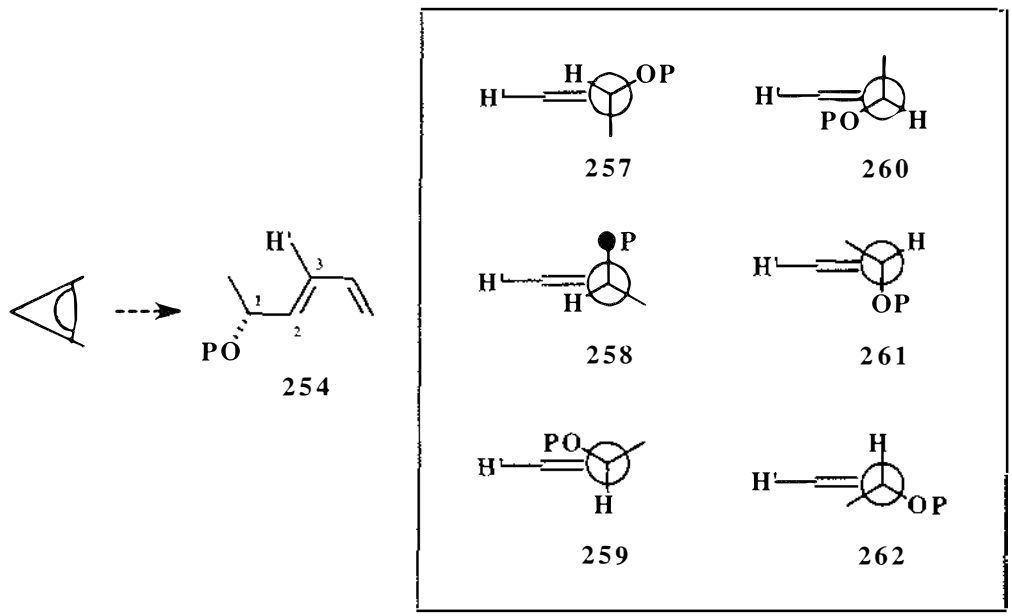
254	P	t/d	255:256	%
a	H	3	27:73	83
b	TMS	5	20:80	69
c	TBS	7	15:85	65

All of the compounds represented in this Figure are racemic. Structures 255 and 256 indicate relative stereochemistry only.

Figure 2.14

The investigators[188] attempted to rationalize their results based on a consideration of conformers **257-262** (**Figure 2.15**). Each conformer has the diene in the s-*cis* conformation required for the DA reaction, but differs from the others due to rotation about the C1-C2 bond. (It is apparent that there are three pairs of conformers which would be expected to provide almost the same level of π-facial stereoselectivity, but in the opposite sense: **257** and **260**; **258** and **261**; and **259** and **262**.) The major product in each reaction (**56a-c**, **Figure 2.13**) arises from approach of the dienophile to the upper

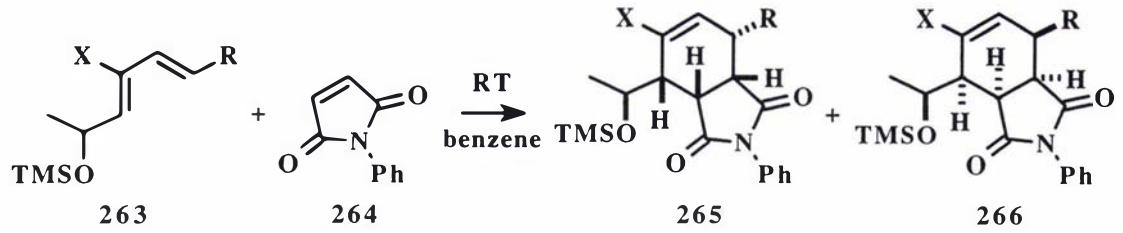
face of the diene and it was proposed that conformers **257**[191] and **258**[192] might be actively involved in the transition state responsible for the π-facial selectivity that was observed.



Six conformations which can be adopted by compound 254 are shown inside the box. Compound 254 is racemic, but for simplicity only the conformations for one of the enantiomers are shown.

Figure 2.15

In substrates where the hydrogen atom H' is replaced by a larger group, conformations **257** and **258** are favoured because they are significantly lower in energy (3-4kcal/mol in both the ground and excited states[193]) than **259-262**, due to 1,3-allylic strain.[155] In this case conformations **257** and **258** both strongly influence the dienophile to approach from above the plane of the diene, due to steric and electronic effects respectively and this usually results in high levels of stereocontrol.[189] An example of the enhanced stereoselectivity made possible by the incorporation of a bulky group to provide 1,3-allylic strain is illustrated in **Figure 2.16**. The methoxymethyl ether in compound **263b**[191] provided a dramatic improvement in stereocontrol compared to compound **263a**[188] which had a hydrogen atom in this position.



263	R	X	t/d	%	265:266
a	CH_3	H	1	75	88:12
b	$CH(CH_3)_2$	OMOM	3-5	-	>99:1*

*** *Endo:exo* (97:3). All of the compounds represented in this Figure are racemic. Structures 265 and 266 indicate relative stereochemistry only.**

Figure 2.16

In the absence of significant 1,3-allylic strain, the difference in energy between the six conformers in **Figure 2.15** is low.[189] This means that the transition state conformation of the molecule may be affected by subtle stereoelectronic effects,[194] due to a conformational preference for a particular alignment of the C1-OP bond with the π system of the diene or the type of dienophile used. In addition, computational studies have shown that a number of transition states may be available and there is no simple parameter which can accurately predict the stereochemical outcome of a particular reaction.[195] As a consequence of this, the stereochemical outcomes of these reactions are difficult to explain and the stereoselectivities obtained are often characteristically low.

The major product from the ETDA reaction of **238c** (**Section 2.4.1**) and the BDA reaction of **254c** are illustrated in **Figure 2.17**. The *endo:exo* stereoselectivity is opposite in the two reactions and so is the π- facial stereocontrol. *Endo* adduct **256c**, in which the dienophile approaches the diene from above, is favoured in the BDA reaction, whereas exo adduct **241c**, in which the dienophile approaches the diene from below, is favoured in the ETDA reaction. Conformations **257** and **258** are thought to direct the dienophile to the top face of the diene in the transition state leading to the BDA reaction, leaving conformations **259-262** to account for the results observed in the ETDA case.

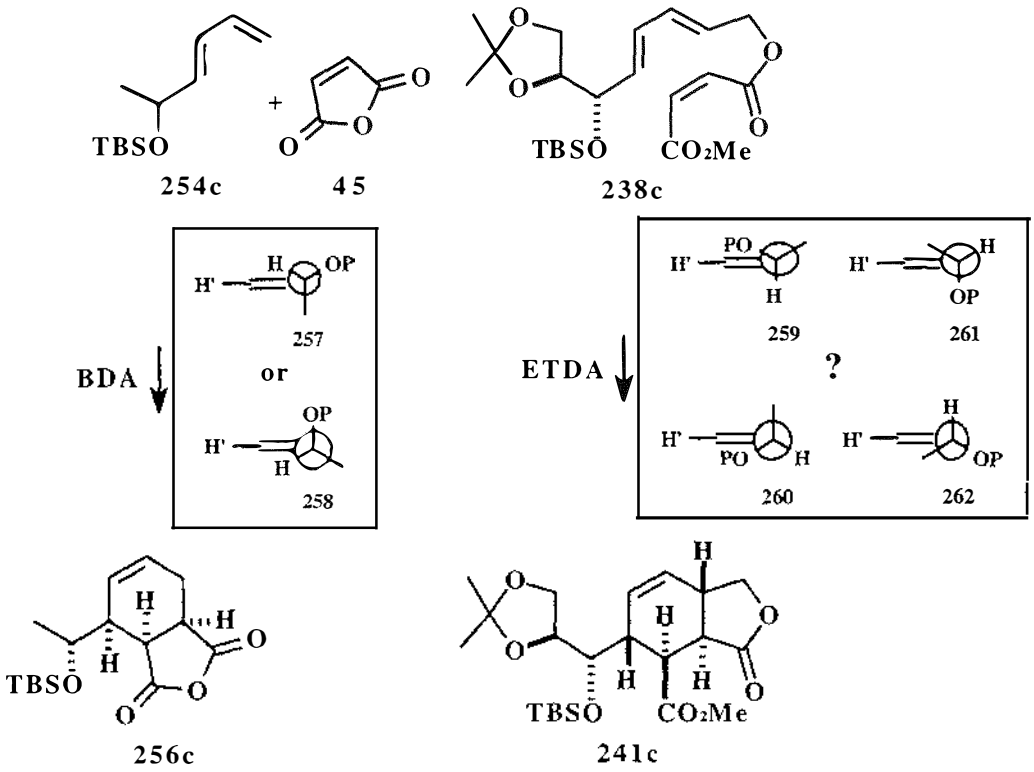
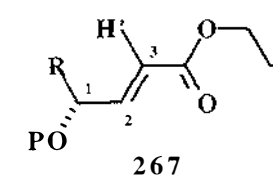
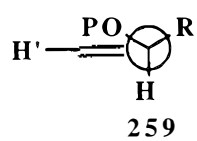


Figure 2.17

Gung *et al.*[196-198] have shown that conjugated chiral alkenes having the general structure **267** (**Figure 2.18**) generally prefer to adopt conformation **259** in which the C1-OP oxygen atom is eclipsed with C3. Precursor **238c** (**Figure 2.19**) may also prefer this conformation in the transition state. Conformation **259** can be imagined to lead to major product **241c** since the lower face of the diene is only shielded by the hydrogen atom on C1, whereas the a dienophile approaching the upper face encounters the more sterically demanding **R** and **OP** (dioxolane and *tert*-butyldimethylsilyl) groups.



267



259

		R			
		Me	Et	iPr	tBu
P	H	*	*	*	*
	TMS	*	*	*	*
	TES	*	*	*	*
	TBS	*	*	*	*
	TPS	*	*	*	
	TIPS	*	*	*	

*** Favoured conformations for 259 for each of the combinations of P and R. The compounds used in this study were racemic, but for simplicity only one of the enantiomers is shown for structure 267 and conformation 259.**

Figure 2.18

Conformation **259** may be involved in the transition states which lead to major adduct **241c**, however, the precise conformational nature of the transition state remains to be experimentally determined. Many factors could affect this conformation including: the steric constraints imposed on the molecule by the ester tether; the effect of the twist and stretch asynchronicity (**Section 2.1**); dominant HOMO-LUMO interactions; or stereoelectronic effects arising due to the dioxolane ring, the dienophile terminus and the nature of the protecting group. These factors contribute to the propensity of IMDA reactions to give *exo* adducts (instead *endo* adducts as in the BDA case) and they are also likely to affect the π-facial selectivity.

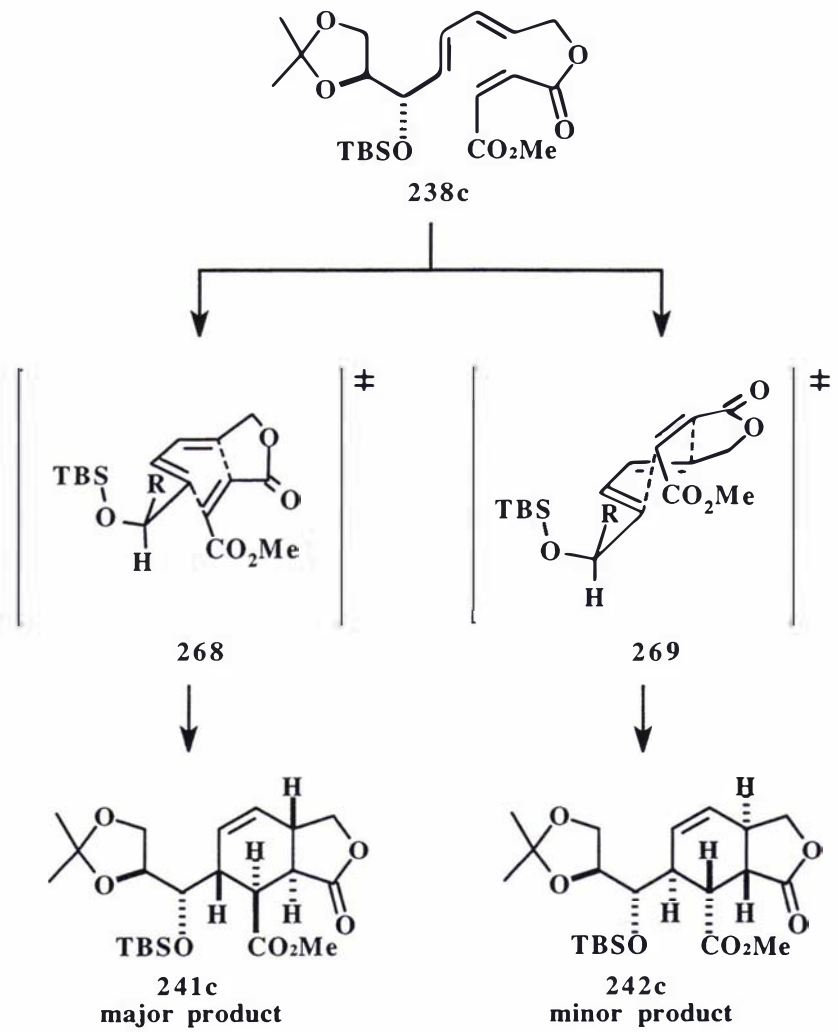
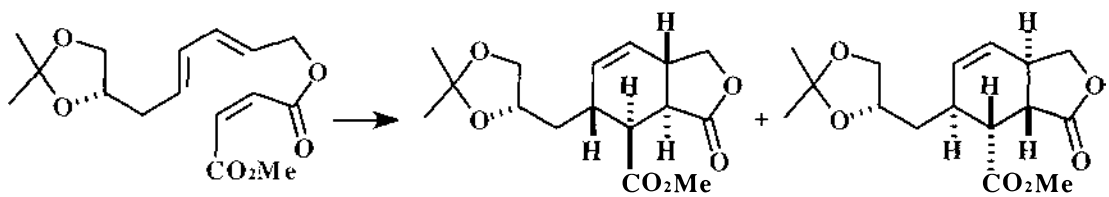


Figure 2.19

It is clear that the situation is complicated, but when the factors responsible for the π-facial selectivity are eventually uncovered valuable information may be gained about the conformational preferences involved in the transition states of IMDA reactions. This discussion is continued in **Section 3.3.3**.

2.4.2 ETDA reaction of the *deoxy* precursor

In order to be sure that the diastereofacial stereoselectivities observed for the ETDA reactions in **Section 2.4.1** were due to the stereogenic centre in the position allylic to the diene, an analogous reaction was carried out on precursor **240** (**Scheme 2.11**). This precursor does not have a stereogenic centre allylic to the diene but it still has a chiral dioxolane moiety in the same position as compounds **238a-d**. (The stereogenic centre in precursor **240** has the opposite absolute configuration to the one in the analogous position in precursors **238a-d**, however, this is not important because the present study is designed to gauge the *ability* of remote stereogenic centres to control the stereochemical outcome of IMDA reactions, which does not depend on the absolute stereochemistry of the starting materials.)



240 **270** **271**

Conditions: BHT, toluene, reflux, 18h, 89%, **270:271** (50:50).

Scheme 2.11

The ETDA reaction of **240** led to a mixture of **270** and **271** in excellent yield, although it was not possible to separate the adducts chromatographically. The proton NMR spectrum of the purified mixture contained a pair of overlapping doublet of doublets at 2.34 and 2.39ppm (**Figure 2.20**). Each doublet of doublets is due to the hydrogen atom at the ring junction adjacent to the lactone carbonyl in one of the ETDA adducts. Analysis of the splitting pattern for each doublet of doublets reveals that the coupling constant between the two hydrogen atoms on the ring junction for each adduct is 13.6Hz, indicating that both isomers possess *trans* fused rings.[98] Traces of other compounds could be detected in the proton NMR spectrum of the crude reaction mixture, which may have been due to small amounts of *endo* products. However, the amount of these was negligible, indicating that the ETDA reaction had again proceeded with a high degree of *exo:endo* stereocontrol. Integration of the signals shown in **Figure 2.20** (and others in the spectrum) showed that the ratio of the two major isomers was 50:50, indicating that the homoallylic stereogenic centre in the dioxolane ring did not produce any detectable facial diastereoselectivity. (Even though this stereogenic centre did not control the facial stereoselectivity in the ETDA reaction of compound **240**, this does not mean that it is unimportant in the corresponding reactions of precursors **238a-d**. Further

experiments are necessary to establish whether the second chiral entity contributes to the overall stereoselectivity in those cases.)

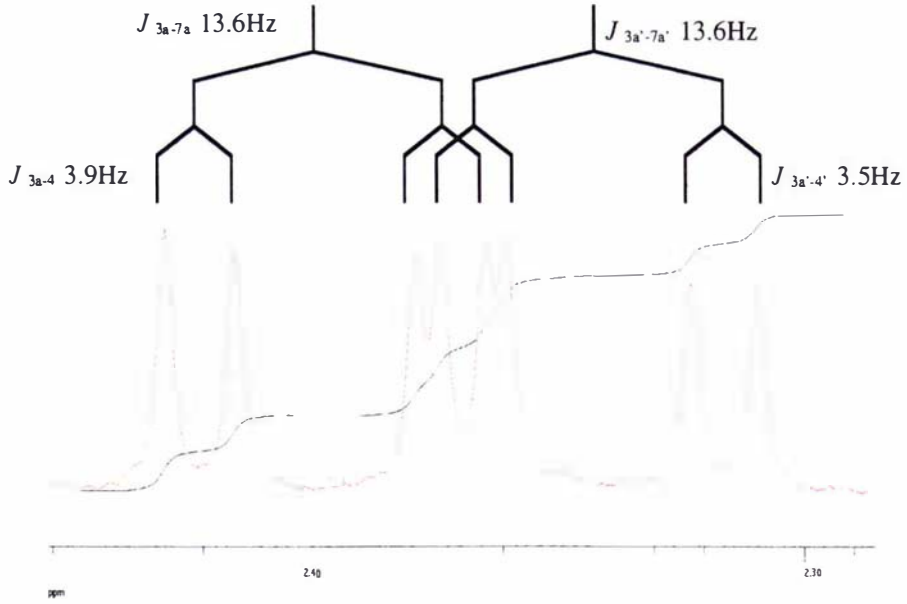


Figure 2.20

This result is commensurate with the IMDA reaction of **272** (**Figure 2.21**),[199] which contains a chiral homoallylic *tert*-butyldimethylsilyl group. This reaction proceeded without *endo:exo* or diastereofacial control to produce equal amounts of each of the four possible IMDA adducts **273-276**. (Compound **272** consisted of a mixture of *E*- and *Z*-stereoisomers of which only the latter underwent cycloaddition. Sigmatropic rearrangement of the *E*-stereoisomer occurred and the product of the rearrangement was recovered in 20% yield, along with a further 10% of unreacted starting material.)

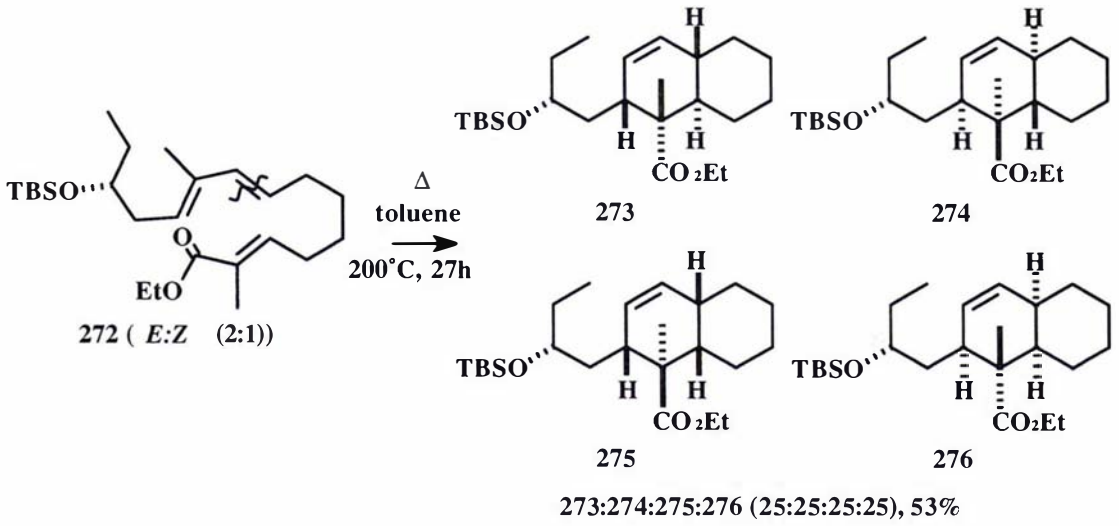
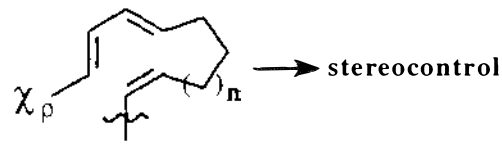


Figure 2.21

2.5 Conclusion

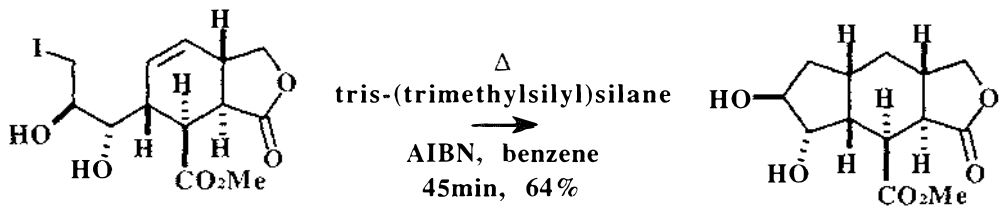
In this **Chapter** two chiral dienols were prepared and these were used to synthesize a range of precursors for investigation of asymmetric induction in ETDA reactions. The results (**Sections 2.4.1** and **2.4.2**) demonstrate that it is possible to achieve a high level of diastereofacial control in ETDA reactions in which the starting material has a stereocontrolling element remote from the tether and allylic to the diene (**Figure 2.22**). Diastereofacial selectivity was shown to depend on the size of the stereocontroling element that was attached to the diene terminus and no π-facial stereocontrol was observed when a stereocontroling element was placed in the homoallylic position (**Section 2.4.2**). If this method of stereocontrol proves to be applicable to other related systems then it represents a powerful new method for achieving asymmetric induction in IMDA reactions.



The attachment of a bulky chiral group to the diene provides a novel method for providing stereochemical control in IMDA reactions.[156]

Figure 2.22

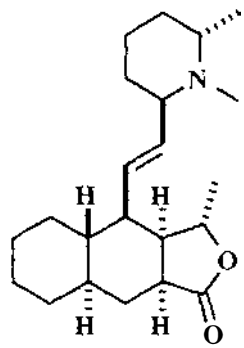
Determination of the stereochemistry of the adducts which were generated in these stereochemical studies was accomplished by taking into account the absolute stereochemistry of the existing stereogenic centres, coupling constants between protons in the bicyclic five-six ring system that formed, COSY and NOESY spectra obtained for the ETDA adducts and molecular models. Further evidence for these stereochemical assignments was obtained from nOe difference experiments carried out on a tricyclic derivative (**52**) (**Figure 2.23**) prepared from one of the ETDA adducts. A tentative proposal for the origin of the observed stereochemistry has also been provided.



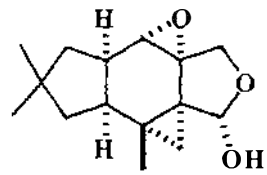
251 **252**

Figure 2.23

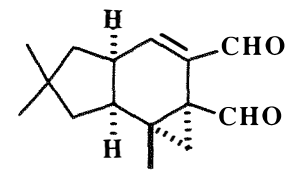
Radical cyclisation of **251** serves as a model study for the synthesis of himbacine (**206**) and velutinal (**277**) (**Figure 2.24**), both of which possess a similar carbocyclic backbone to tricycle **252** (**Figure 2.23**). Himbacine, which is found in the bark of *Galbulimima baccata.*,[200] is a lead compound in the treatment of Alzheimer's disease.[201] Velutinal is a marasmane sesquiterpene found in the tissue of several genera of *Basidiomycetes*.[202] Damage to the surface of the fungi causes conversion of velutinal into isovaleral (**278**) by an unknown mechanism.[203, 204] This compound is a potent antifungal and antibacterial agent as well as a powerful antifeedant for the opossum.[205]



206 (himbacine)



277 (velutinal)



278 (isovaleral)

Figure 2.24

3 The effect of the dienophile

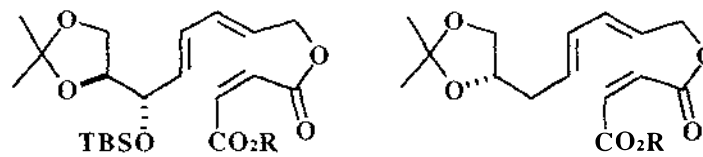
3.1 Introduction

In **Chapter 2** it was demonstrated that the diastereofacial stereoselectivity of ETDA reactions can be controlled by placing a stereogenic centre allylic to the diene and remote from the ester tether. It was also observed that ETDA reactions carried out on maleate esters of this type occur with high levels of *exo* stereocontrol. In this **Chapter** the effect of dienophile geometry and functionality is investigated, since these have been reported to significantly affect the stereochemical outcome and rate of ETDA reactions (**Section 1.2.1**).

3.2 Preparation of ETDA precursors

3.2.1 Maleate precursors

ETDA reactions were carried out on methyl esters **238c** and **240** (**Figure 3.1**) in **Sections 2.4.1** and **2.4.2**. ETDA reactions on the corresponding carboxylic acids **36** and **39** (**Sections 2.3.1** and **2.3.2**) are reported in **Section 3.3.1**.

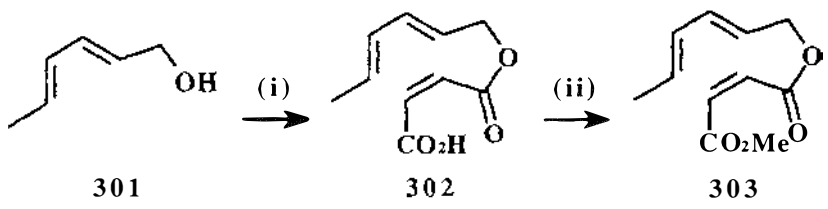


236: R = H
238c: R = Me

239: R = H
240: R = Me

Figure 3.1

In order to compare the *endo:exo* stereoselectivity of the precursors in **Figure 3.1** with less complicated systems, the sterically unencumbered achiral precursors in **Scheme 3.1** were also prepared. Sorbyl alcohol (**301**) was treated with maleic anhydride to produce carboxylic acid **302**,[174] which was then reacted with diazomethane[173] (**Section 6.6.3**) to produce methyl ester **303**. The yield of compound **303** was moderate, reinforcing the observation that trienes such as **302** are sensitive to addition of diazomethane (**Section 2.3.2**).



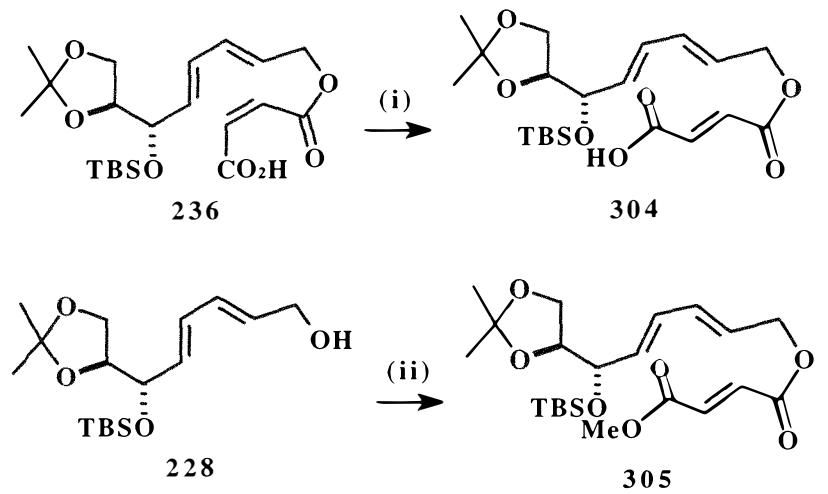
301 302 303

Conditions: (i) TEA, MA, DMAP, CH_2Cl_2, RT, 15min, 88%; (ii) CH_2N_2, diethyl ether, 0°C, 58%.

Scheme 3.1

3.2.2 Fumarate precursors

Carboxylic acid **304** (**Scheme 3.2**) was prepared by isomerisation of maleate precursor **236** (**Section 2.3.1**) with thiophenol and 2,2'-azo-*bis*-isobutyronitrile.[170] It was fortunate that this isomerisation was possible, since the transformation requires the starting material to be irradiated with ultraviolet light in refluxing benzene. The rate of the competing ETDA reactions (of **236** and **304**) were sufficiently slow to allow a good yield of the isomerised product to be obtained. Methyl ester **305** was obtained *via* a straightforward esterification[206] of dienol **228** (**Section 2.2.1**) and methyl hydrogen fumarate.[207]



236 304

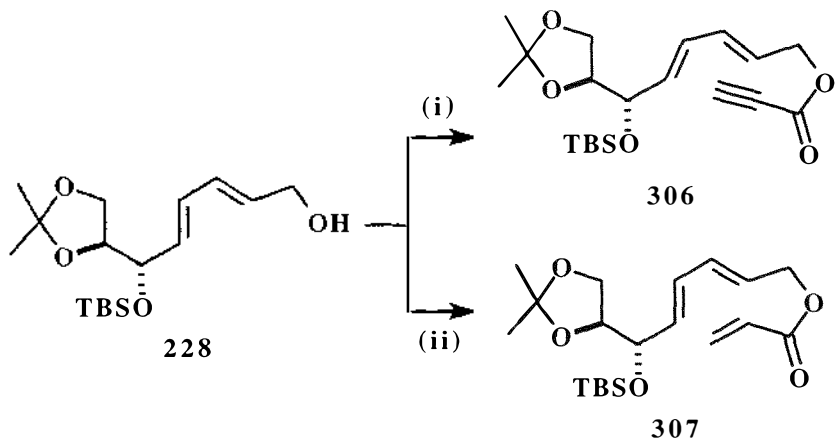
228 305

Conditions: (i) thiophenol, AIBN, benzene, reflux, 2h 65%; (ii) methyl hydrogen fumarate, DCC, DMAP, diethyl ether, 22h, 96%.

Scheme 3.2

3.2.3 Propiolate and acrylate precursors

Propiolate precursor **306** and acrylate precursor **307** (**Scheme 3.3**) were both prepared by esterification[206] of TBS dienol **228** (**Section 2.2.1**).



Conditions: (**i**) propiolic acid, DCC, DMAP, diethyl ether, 0°C for 30min *then* 30°C for 1h, 65%; (**ii**) acrylic acid, DCC, DMAP, diethyl ether/CH_2Cl_2, 9d, 47%.

Scheme 3.3

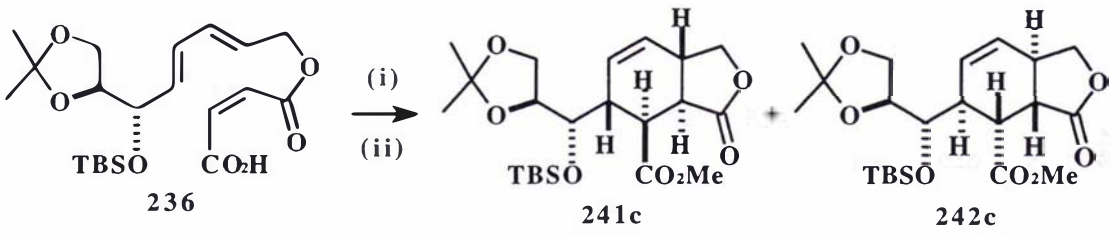
3.3 ETDA reactions

Each of the carboxylic acid precursors prepared in **Section 3.2** was heated in refluxing toluene (5mmol/L) under an argon atmosphere in the presence of 2,6-di-*tert*-butyl-4-methylphenol (0.20eq). The reaction mixture was then cooled and diazomethane[173] (**Section 6.6.3**) was added dropwise to the stirred solution. Product ratios were determined from proton NMR spectra of crude reaction mixtures (before and after the addition of diazomethane) and yields were calculated from the amount of material isolated after chromatography. The other precursors prepared in **Section 3.2** were treated in an identical fashion, except that the diazomethane was not added.

3.3.1 Maleates

After precursor **236** had been heated in refluxing toluene for 17h (**Scheme 3.4**) proton NMR analysis indicated that there were two major products present in the crude reaction mixture. In order to simplify the purification procedure the reaction mixture was cooled and treated with diazomethane[173] (**Section 6.6.3**) to convert the carboxylic acid adducts to the corresponding methyl esters. Proton NMR analysis of the crude mixture of esters confirmed the presence of two products and it was clear that the ratio of these two compounds (89:11) was not affected by the addition of the diazomethane.

The diazomethane treatment also facilitated direct comparison of the products formed in the ETDA reaction of carboxylic acid **236** and methyl ester **238c** (**Section 2.4.1**). Astonishingly, it was determined that the products had identical stereochemistry regardless of whether the dienophile was terminated with a carboxylic acid or a methyl ester group. In both of the ETDA reactions *exo* adducts were produced with a high level of stereocontrol. In addition, the major product was the same in each reaction, indicating that the transition states providing π-facial stereoselectivity of the methyl ester and the carboxylic acid may also be similar. The level of π-facial stereocontrol was only slightly greater in the case of the methyl ester (91:9) than the carboxylic acid (89:11). This is surprising since the steric bulk of the methyl group is significantly greater than the hydrogen atom. However, the position of the methyl group in the transition state may cause it to play a minor role in the stereoselectivity of the reaction (**Section 3.3.3**).

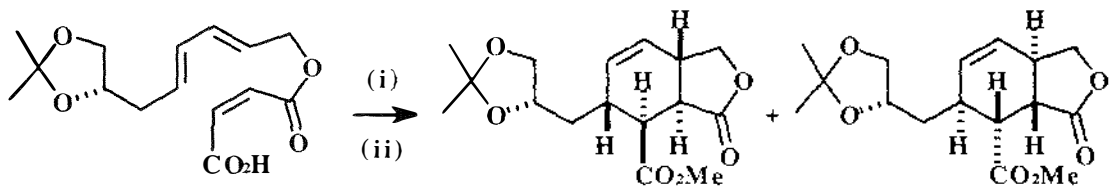


Conditions: **(i)** BHT, toluene, reflux, 17h; **(ii)** 0°C, CH_2N_2, 62% (2 steps), **241c:242c** (89:11).

Scheme 3.4

Formation of *exo* adducts from ETDA reactions of carboxylic acids is counter to previous literature reports (**Section 1.2.1.1**). However, none of the previously reported examples had a bulky group at the diene terminus. It was envisioned that the bulky terminal substituent might be responsible for the formation of *exo* adducts during the ETDA reaction of carboxylic acid **236**. For example, the acid could adopt an *exo* conformation in the transition state to place the carboxylic acid moiety as far away from the terminal substituent as possible, in order to minimize unfavourable steric interactions between the two groups. This might override the factors which normally influence carboxylic acids to cyclise *via endo* transition states.

For the reasons outlined above it was decided to investigate the ETDA reaction of *deoxy* precursor **239** (**Scheme 3.5**). After the crude reaction mixture had been refluxed in toluene for 6h it was treated with diazomethane[173] (**Section 6.6.3**) whereupon proton NMR analysis revealed that the products (**270** and **271**) were identical to those formed in the ETDA reaction of the methyl ester derivative of **239** (compound **240**, **Section 2.4.2**). The carboxylic acid again exclusively gave rise to *exo* adducts. (In congruity with the ETDA reaction of **240**, there was no diastereofacial selectivity and equimolar amounts of each *exo* adduct were observed.)

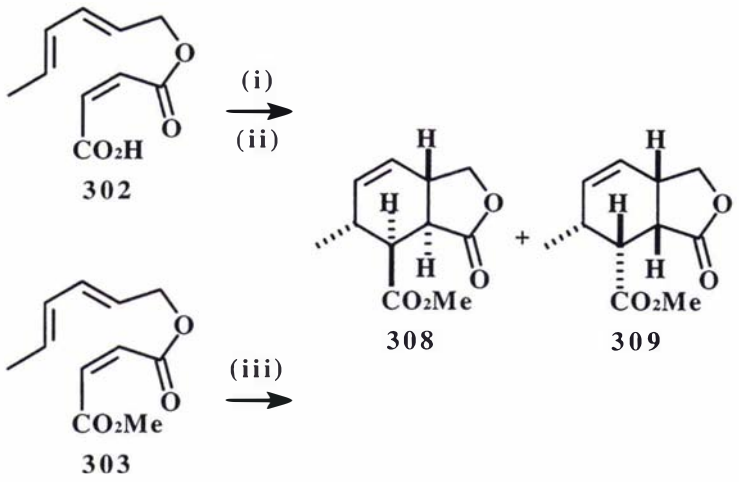


239 **270** **271**

Conditions: **(i)** BHT, toluene, reflux, 6h; **(ii)** 0°C; CH_2N_2, 66% (2 steps), **270:271** (50:50).

Scheme 3.5

The generality of these results was investigated by comparing the ETDA reactions of carboxylic acid **302** and methyl ester **303** (**Scheme 3.6**). These sterically unencumbered, achiral starting materials clearly illustrate the underlying *exo:endo* preference for ETDA reactions of precursors with three atom tethers. The ETDA reactions of compounds **302** and **303** were both rapid but they proceeded with only modest levels of *exo:endo* stereocontrol. These observations may indicate that both of the starting materials possess elevated levels of conformational freedom compared to the chiral trienes described above, although electronic factors cannot be excluded at this stage. In each case *trans* fused adduct **308** (identified from the coupling constant of 13.5Hz between the two hydrogen atoms at the ring junction[98]) was the major isomer, accounting for nearly 70% of the material isolated in the ETDA reaction of carboxylic acid **303**.



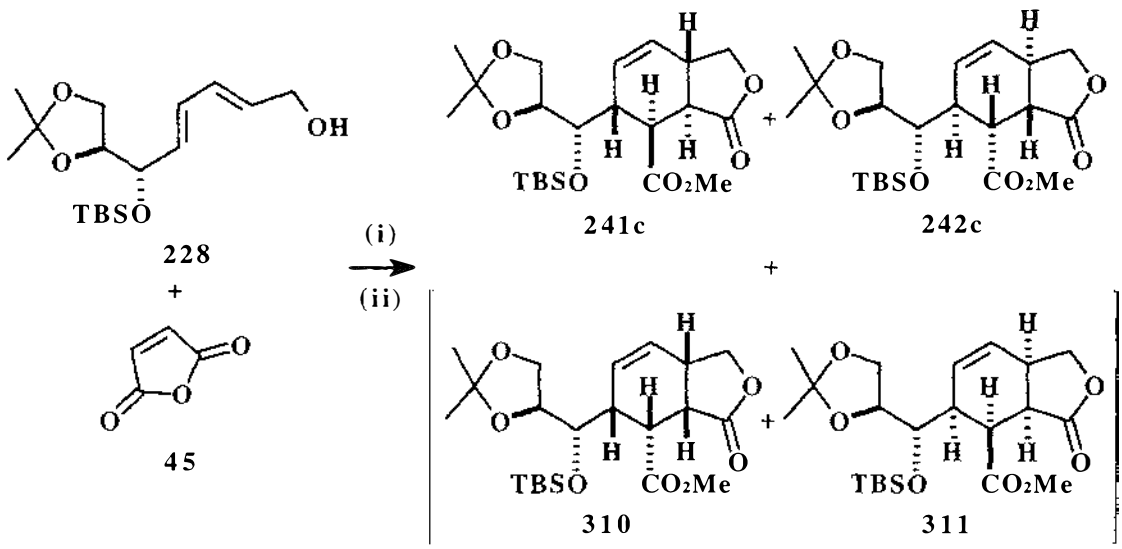
Conditions: (i) BHT, toluene, 2h; (ii) 0°C, CH_2N_2, 83% (2 steps), **308:309** (69:31); (iii) BHT, toluene, reflux, 2h, 79%, **308:309** (79:21).

Scheme 3.6

In agreement with the previous examples, there was little difference in the *endo:exo* stereoselectivity of carboxylic acid **302** and methyl ester **303**. With hindsight there is scant evidence that carboxylic acids and esters should behave differently in ETDA reactions, yet this assertion[98, 103, 101] has gone unchallenged for nearly twenty years. The reasons for this apparent anomaly will be discussed in **Chapter 4**.

3.3.1.1 Comparison of reactions of maleate derivatives with those involving maleic anhydride

For completeness, two DA reactions involving TBS dienol **228** (**Section 2.2.1**) and sorbyl alcohol (**301**) with maleic anhydride (**45**) were also investigated (**Schemes 3.7** and **3.8**). These reactions were carried out by heating a mixture of the alcohol and maleic anhydride (1:1) in refluxing toluene with 2,6-di-*tert*-butyl-4-methylphenol (0.20eq). Concentrated solutions of the starting materials (0.1mol/L) were used in order to ameliorate the BDA reactions. Once the starting materials were consumed (TLC) the reaction mixtures were cooled and diazomethane[173] (**Section 6.6.3**) was added dropwise.

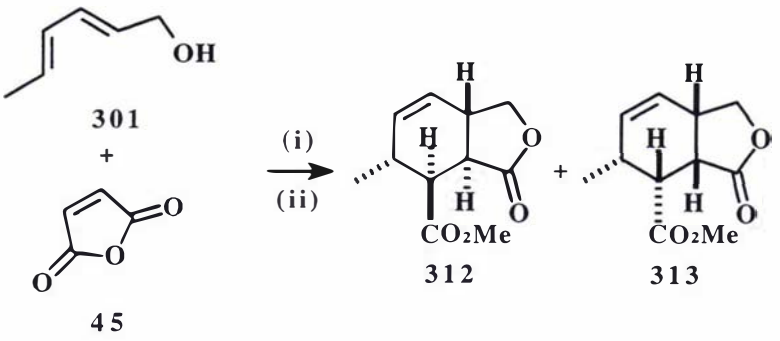


Conditions: **(i)** BHT, toluene, reflux, 67h; **(ii)** -65°C, CH_2N_2, 45% (2 steps), **241c:242c:310:311** (42:4:27:27).

Scheme 3.7

TBS dienol **228** reacted slowly with the maleic anhydride to produce a mixture of adducts **241c**, **242c**, **310** and **311** (42:4:27:27) in modest yield. In BDA reactions, *endo* adducts are favoured,[51] however, in this case a significant amount of the *exo* adducts were produced as well. It is likely that these products formed subsequent to esterification of the reactive primary alcohol with maleic anhydride, since the BDA reaction is hindered by the bulky groups allylic to the diene. Evidence for this is twofold: compound **236** (**Section 3.4**) was observed in proton NMR spectra of the crude reaction mixture in the early stages of the reaction; and the same ratio was observed between **241c** and **242c** (90:10) as in the ETDA reaction of **236** described in **Section 3.3.1**. There did not appear to be any π-facial discrimination between *endo* adducts **310** and **311**. Only one of the adducts **310** and **311** could be isolated and characterized. The coupling constant between the two hydrogen atoms at the ring junction was 11Hz for the isolated compound (**310**) indicating that the two rings were *cis* fused,[98] but it was not possible to determine the relative stereochemistry of this adduct. The structure of the unisolated compound (**311**) is speculative and based on limited proton NMR analysis of mixtures only.

It is interesting to compare these results with the BDA reaction of sorbyl alcohol (**301**) and maleic anhydride (**45**) (**Scheme 3.8**). In this case the BDA reaction was not hampered by steric factors and proceeded rapidly to produce *endo* adduct **313** with a high level of stereoselectively and in excellent yield.



Conditions: **(i)** BHT, toluene, reflux, 70min; **(ii)** -65°C, CH_2N_2, 90% (2 steps), **312:313** (4:96).

Scheme 3.8

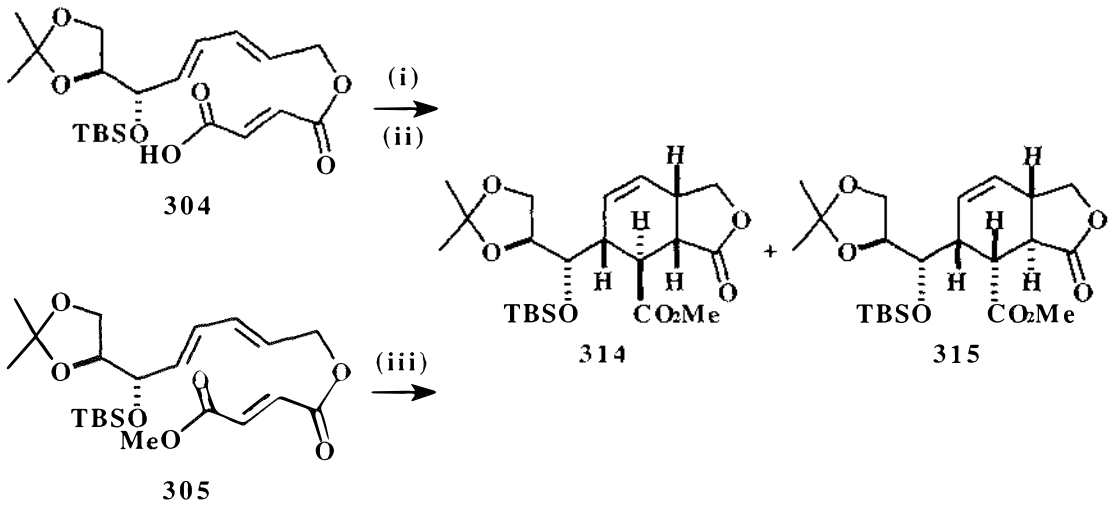
3.3.2 Fumarates

Fumarate half ester **304** and diester **305** were treated in an analogous fashion to the maleate examples reported in **Section 3.3.1** (**Scheme 3.9**). As in the previous examples, each of the ETDA reactions gave rise to two major products which were identical regardless of whether the dienophile in the starting material was terminated with either a carboxylic acid or methyl ester group. It was also noted that adduct **314** was the major product in each case, although the ratio of the two adducts was greater for the methyl ester (86:14) than the carboxylic acid (71:29).

Closer inspection revealed a significant difference between the ETDA reactions of the fumarates and the maleates. The coupling constant between the two hydrogen atoms at the ring junction for minor cycloadduct **315** was 13.4Hz indicating that the two rings were *trans* fused,[98] but no such coupling constant could be distinguished for major product **314**. Each of the hydrogen atoms at the ring junction in this compound gave rise to complicated multiplets which were only partially resolved at 500MHz.[†] However, it was apparent that neither of these multiplets contained a coupling constant in the range 13-14Hz, indicating that the compound was *cis* fused and had been formed by an *endo* transition state.[98]

Details of the way in which the stereochemistry of each of these adducts was determined are presented in **Section 3.3.2.1** and an attempt to explain the stereoselectivity of these results appears in **Section 3.3.3**. It is noteworthy that the hydrogen atoms allylic to the alkene have the same absolute configuration in adducts **314** and **315** which means that the dienophile has approached the lower face of the diene in both cases.

[†] Proton NMR recorded on a Varian Unity Series 500MHz instrument.



Conditions: (i) BHT, toluene, 142h; (ii) 0°C, CH_2N_2, 42% (2 steps), **314:315** (71:29); (iii) BHT, toluene, reflux, 167h, 76% (69% conversion), **314:315** (86:14).

Scheme 3.9

A literature example of an ETDA reaction carried out on a fumarate diester[125] is illustrated in **Figure 3.2**. In this case a high proportion of *endo* adduct **318** was produced but the major adduct still contained a *trans* fused ring system. There are two structural differences between substrates **305** and **316**: the diene terminus; and the dienophile terminus. Which of these two structural features plays the dominant role in determining the *endo:exo* stereoselectivity is unclear at this stage. These ideas are discussed further in **Section 3.3.3**.

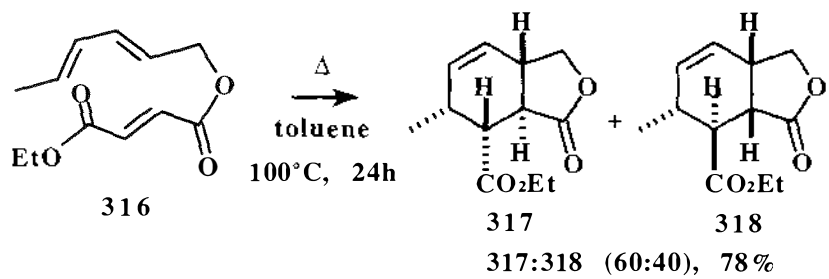


Figure 3.2

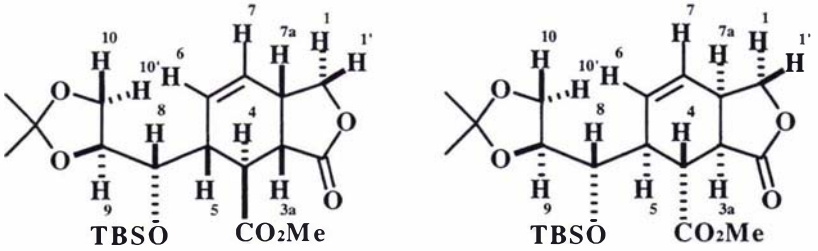
3.3.2.1 Determination of the stereochemistry of the fumarate cycloadducts

COSY spectra (**Appendices 1.4C** and **1.5C**) were used to confirm the connectivity of the major and minor adducts produced in the ETDA reaction of **304** and **305** (**Section 3.3.2**), then NOESY spectra (**Appendices 1.4N** and **1.5N**) were used to determine the relative stereochemistry. The absolute stereochemistry of adducts **314** and **315** (**Section 3.3.2**) were determined by considering the stereochemistry of the starting material, the coupling constants for the protons at the ring junction, NOESY spectra for each adduct and molecular models. (This method was used earlier to determine the absolute stereochemistry of adducts **241b** and **242b** (**Section 2.4.1.1**)).

Selected data from the NOESY spectrum of major adduct **314** is given in **Figure 3.3**. The signals for hydrogen atoms H3a and H4 overlap. (The complete NOESY spectrum is provided in **Appendix 1.4N**) Because it has a *cis* fused ring system, the absolute stereochemistry of adduct **80** is limited to either structure **314a** or **314b**. The *cis* fused ring system is also confirmed by the nOe between H5 and H3a.

major adduct, 314

H	nOe
3a/4	5, 8
5	3a/4, 8, 9, 10, 10'
6	5, 9
8	3a/4, 5
9	5, 6
10	5
10'	5

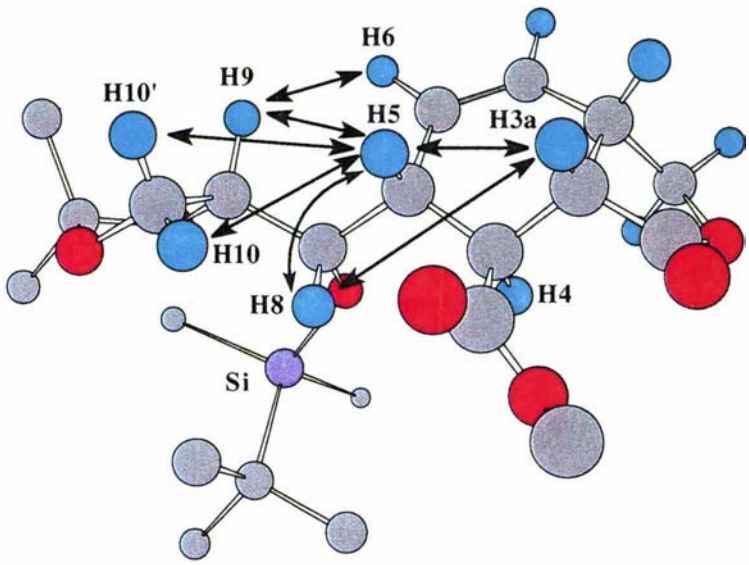


314a **314b**

The purpose of the numbering system illustrated here is to simplify the discussion of the nOe's, *vide infra*. (The side chain would not normally be numbered this way.)

Figure 3.3

Molecular models indicate that there is one C5-C9 staggered conformation for structure **314a** which can simultaneously generate all of the nOe's observed for major adduct **314**. A molecular model (MM2 force field,[181, 182] localized minimum) of this conformation is given in **Figure 3.4** and the proximal hydrogen atoms are indicated by double headed arrows. (In this conformation, the dihedral angle between hydrogen atom H5 and the oxygen atom on C8 bearing the *tert*-butyldimethylsilyl group, is approximately 180°.) Conversely, there is no conformation (staggered or eclipsed) for structure **314b** which can simultaneously give rise to the nOe's observed for the major adduct. These observations suggest that the major product of the ETDA reaction has the absolute stereochemistry associated with structure **314a**.



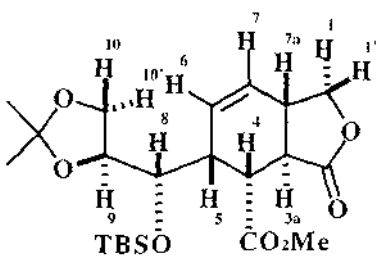
A molecular model (MM2 forcefield, local minimum) of structure 314a (with 24 hydrogen atoms removed). The arrows indicate hydrogen atoms which are in close proximity.

Figure 3.4

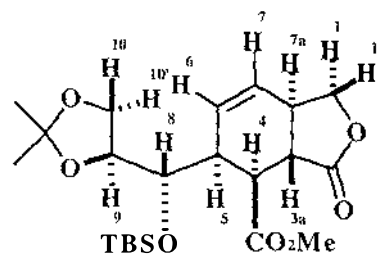
Selected data from the NOESY spectrum of minor adduct **315** is given in **Figure 3.5**. (The complete NOESY spectrum is provided in **Appendix 1.5N**) The absolute stereochemistry of adduct **315** is limited to either structure **315a** or **315b**, since this compound has been shown to contain a *trans* fused ring system.

minor adduct, 315

H	nOe
5	8, 9, 10, 10'
6	9
8	5
9	5, 6
10	5
10'	5



315a

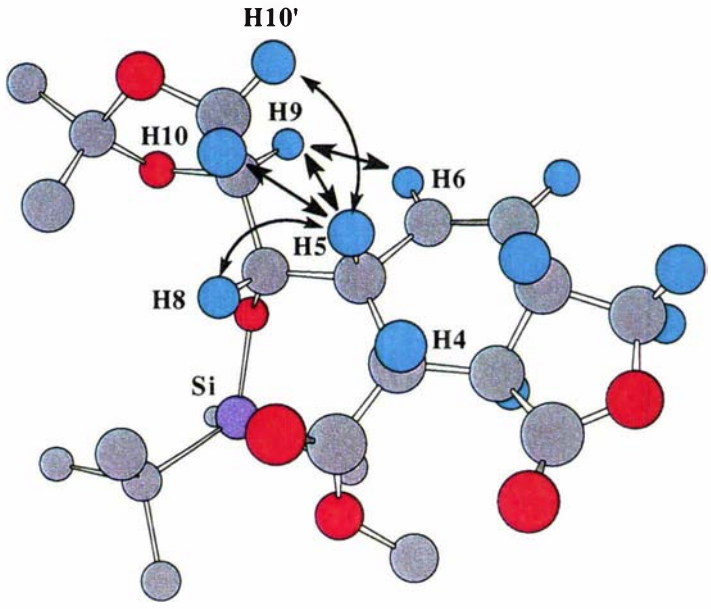


315b

The purpose of the numbering system illustrated here is to simplify the discussion of the nOe's, *vide infra*. (The side chain would not normally be numbered this way.)

Figure 3.5

Molecular models indicate that there is one staggered conformation for structure **315a** which simultaneously generates all of the nOe's observed for major adduct **315**. A molecular model (MM2 force field,[181, 182] localized minimum) of this conformation is given in **Figure 3.6** and the proximal hydrogen atoms are indicated by double headed arrows. (In this conformation, the dihedral angle between hydrogen atom H5 and the oxygen atom on C8 bearing the *tert*-butyldimethylsilyl group is again approximately 180°.) As in the previous case, there is no conformation (staggered or eclipsed) for the alternate structure (**315b**) which can simultaneously give rise to the observed nOe's. These observations suggest that the minor product of the ETDA reaction has the absolute stereochemistry associated with structure **315a**.



A molecular model (MM2 forcefield, local minimum) of structure 315a (with 24 hydrogen atoms removed). The arrows indicate hydrogen atoms which are in close proximity.

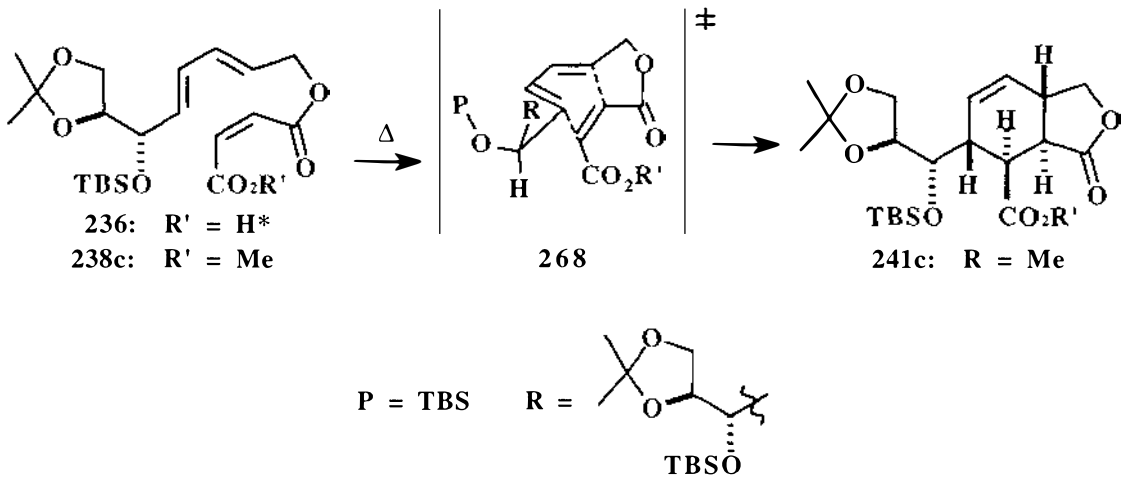
Figure 3.6

These stereochemical assignments would be reinforced if data for both of the possible *exo* and *endo* compounds were available and comparison of the NOESY spectra of all four adducts could be made. However, if the structure of adduct **314** is compared with the major adducts generated by precursors **238a-d** (**Section 2.4.1.1**) it is apparent that the π-facial selectivity is consistent throughout the series. In each case the dienophile approaches from below the plane of the diene. In addition, each of the conformations which account for the observed nOe's (**Figures 2.10**, **2.11**, **3.4** and **3.6**) have approximately the same dihedral angle between hydrogen atom H5 and the oxygen atom on C8. If all of the possible structures and the myriad of conformations available to each one are considered, logic precludes this from being coincidental.

3.3.3 A discussion of the stereoselectivity arising in ETDA reactions of maleates and fumarates

Simple *endo:exo* stereocontrol was discussed in **Section 1.2** and in **Section 2.4.1.2**, transition state **268** (**Figure 3.7**) was proposed to explain the preferential formation of major adduct **241c** from the ETDA reaction of **238c.** It is likely that the π-facial stereoselectivity arises because of steric interactions between the dienophile and the chiral allylic moiety which cause the dienophile to approach from below the plane of the diene. However, each of these effects is likely to influence the other. Based on a simple steric argument these transition states can also be used to account for the observation that

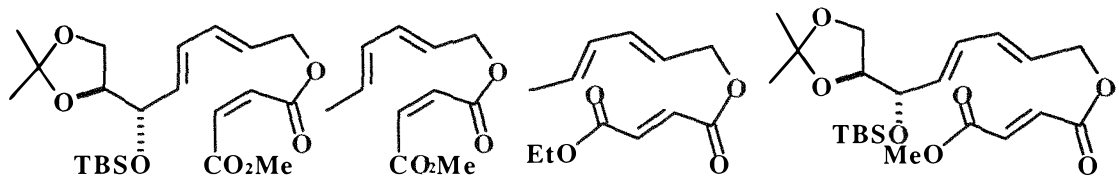
a slightly lower π-facial selectivity is observed for carboxylic acid **36** than methyl ester **38c** (**Sections 3.3.1**), since the hydrogen atom is considerably smaller than the methyl group. However, the difference in selectivity between the carboxylic acid and the methyl ester is minor suggesting that it may be the terminal hydrogen of the dienophile which is involved in stereocontrol. Other factors may also be involved, since the electronic demands of ester groups and carboxylic acids are quite different.



*** In the case of carboxylic acid 236, the major ETDA adduct is converted to methyl ester 241c with diazomethane after cycloaddition.**

Figure 3.7

As is the case with maleate precursors **238c** and **236** (**Section 2.4.1**) the π-facial stereoselectivity of fumarate precursors **304** and **305** (**Section 3.3.2**) arises mainly from approach of the dienophile to the lower face of the diene. The fundamental difference between these ETDA reactions is that the former mainly proceed *via exo* transition states and the latter *via endo* transition states. Before a discussion of the π-facial selectivity of fumarates **304** and **305** is undertaken, it is pertinent to consider the *endo:exo* selectivity of achiral esters **303** (**Section 3.3.1**) and **316**[125] shown in **Figure 3.8**.



238c 303 316 305

Entry	SM	*exo:endo*	Yield (%)
1	238c	100:0	80
2	303	79:21	79
3	316	60:40	78
4	305	9:91	76

Overall *exo:endo* selectivites are given in the table above. Two adducts were produced in the ETDA reaction of 238c, but they were both *exo* adducts.

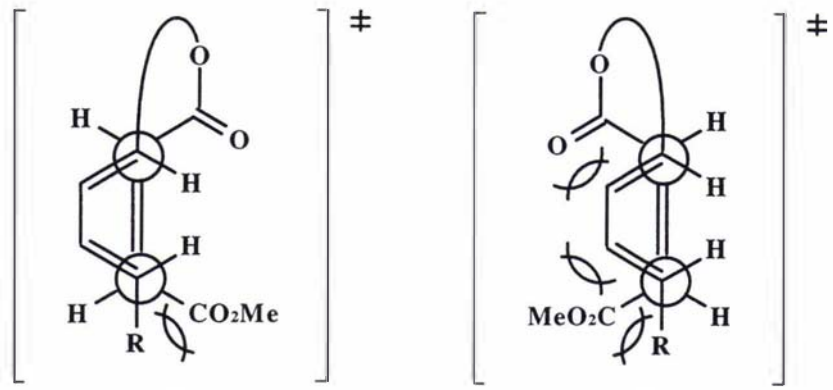
Figure 3.8

A gradual change in *exo:endo* stereoselectivity is observed for cycloaddition of precursors **238c-305**. *Exo* products are favoured for maleate precursor **238c**, which has a bulky group attached to the diene terminus, whereas compound **303** produces a significant amount of the *endo* adduct. The *exo* adduct is not favoured to such an extent for fumarate precursor **316** and addition of the bulky group to the diene terminus results in a high level of *endo* stereoselectivity for compound **305**. (The difference in the *endo:exo* stereoselectivity observed for compounds **316** and **305** may be due in part to the dienophile terminating group, but the size of the groups attached to the dienophile do not normally have a significant impact on stereocontrol.[208])

The trend illustrated in **Figure 3.8** can be explained by considering the transition states postulated in **Figure 3.9**. For the maleates, the *endo* transition state has more unfavourable intramolecular steric interactions than the *exo* transition state which leads to a preference for the *exo* adducts. This steric effect (specifically the steric effect between the **-CO_2Me** group and the **R** group) is increased if the size of **R** is increased. For the fumarates, the situation is not so clear-cut. The *exo* transition state has two significant steric interactions, both of which are located at the peripheral σ-bond. The *endo* transition state also has two significant steric interactions, one of which is near the tether and the other at a distance from it. If the size of the **R** group is increased it is conceivable that there might be a greater amount of steric compression generated in the *exo* transition

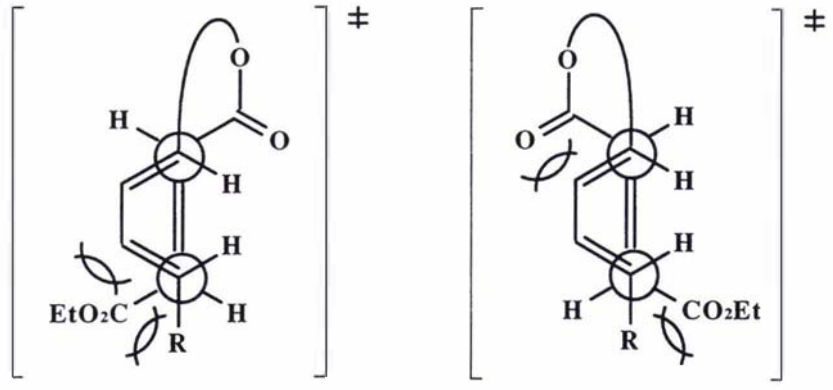
state, leading to increased stereoselectivity for *endo* adducts, such as that observed for compound **305**.

Maleate series.



exo **transition state** *endo* **transition state**

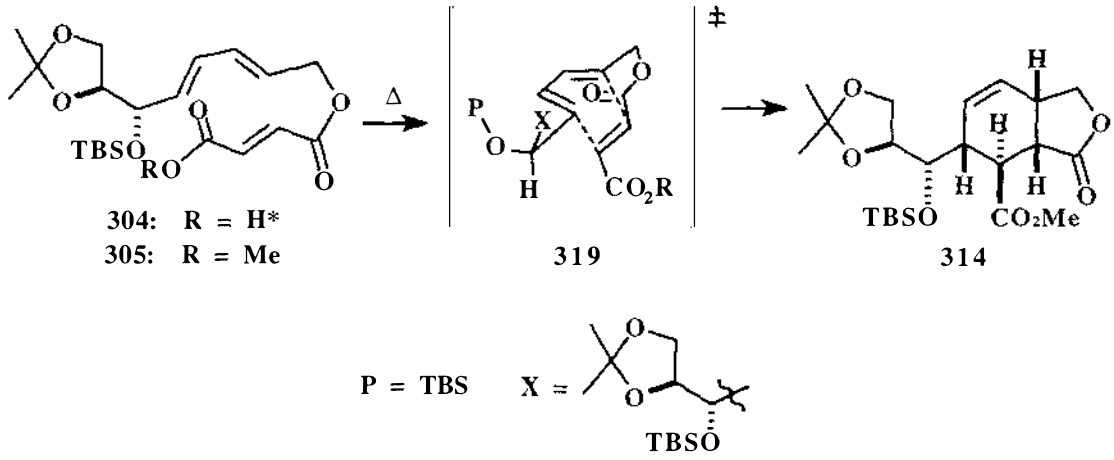
Fumarate series.



exo **transition state** *endo* **transition state**

Figure 3.9

The π-facial stereoselectivity of fumarates **304** and **305** is the final aspect to be considered. The products of these reactions arise because the dienophile approaches from below the plane of the diene. In this case the major product arises from an *endo* transition state, but the conformational preferences of the chiral allylic substituent may well be similar to those for maleate precursors **238c** (**Section 2.4.1.2**). Consequently the transition state which is involved in the formation of the major adduct in the fumarate series may resemble **319** (**Figure 3.10**). Although the major product arises from an *endo* transition state, the top face of the diene might be shielded in a similar to the way it is shielded in the *exo* transition state of the maleate series (**Figure 3.7**). Greater *endo:exo* stereocontrol was observed for methyl ester **305** than carboxylic acid **304**, which can also be explained in terms of simple steric effects.



*** In the case of carboxylic acid 304, the major ETDA adduct is converted to methyl ester 305 with diazomethane.**

Figure 3.10

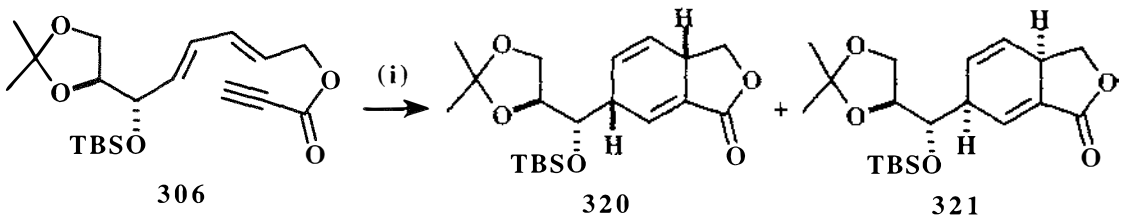
It is necessary to stress that the preceding discussion is speculative and based on the results of a limited number of experiments. It is clear that a complex situation exists and there may be a number of crucial factors, significantly affecting the stereochemical outcome of ETDA reactions, which have yet to be determined. What is presented here is a simple 'working model' which explains the observed stereoselectivities in a consistent manner and paves the way for further investigation to be made.

3.3.4 Propiolates and acrylates

The successful reactions of the fumarate and maleate derivatives described above provided the impetus to investigate the π-facial selectivity involved in the ETDA reactions of the chiral propiolates and acrylates shown below.

Propiolate ester **306** reacted readily in refluxing toluene to produce adducts **320** and **321** in good yield with modest π-facial stereoselectivity (**Scheme 3.10**). In this case only two products are possible since the *exo* and *endo* transition states which arise at each face of the diene yield identical products. Unfortunately the NOESY spectra for these two compounds were identical so it was not possible to distinguish the two adducts. (This is presumably because rotation of the side chain is less hindered than in the maleate or fumarate adducts (**Sections 2.4.1.2** and **3.3.1.1**) so the conformational preferences of the molecules are less well defined and nOe's unique to each molecule do not arise.) The absolute stereochemistry of the two adducts has been tentatively assigned

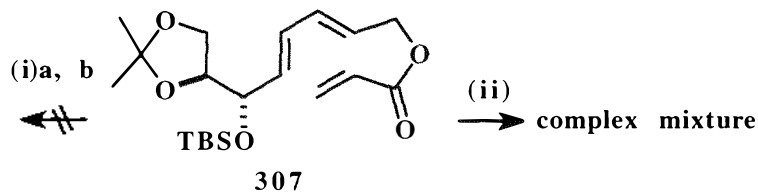
based on previous experience with the maleate and fumarate derivatives, where the major product of the reaction arose from approach from the lower face of the diene in each case.



Conditions: BHT, toluene, 29h, 85% (72% conversion), **320:321** (65:35).

Scheme 3.10

As expected (**Section 1.2.1.3**), the reactivity of acrylate ester **57** was much lower than propiolate ester **56** (**Scheme 3.11**). No reaction was observed in refluxing toluene after a period of 43h, or in refluxing xylene after a period of 23h. A separate sample was heated to 210°C in toluene in a sealed tube for 30h. Some starting material (39%) was recovered, but the reaction was not clean and produced a complex mixture of products without any apparent stereocontrol. These products were chromatographically inseparable and so it was not possible to identify them.



Conditions: **(i)a** BHT, toluene, 43h; **(i)b** BHT, xylene, 23h; **(ii)** BHT, toluene, 210°C, 30h.

Scheme 3.11

3.4 Conclusion

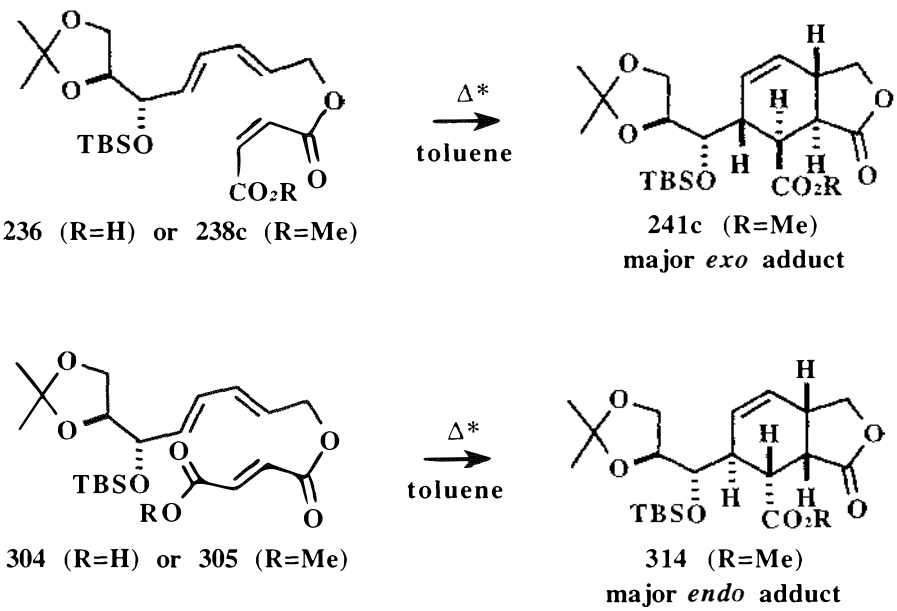
The examples presented in **Chapter 3** challenge the current understanding of stereocontrol of IMDA reactions. The π-facial stereoselectivity of IMDA reactions of maleates, fumarates and propiolates can be controlled by placing a sterically demanding chiral substituent allylic to the diene and remote from the tether, although the stereoselectivity observed in the last case was modest. For maleates there is a clear preference for *exo* adducts regardless of whether the dienophile is terminated with a carboxylic acid or an ester group. (This was observed with both complicated chiral starting materials and simpler achiral examples.) The reasons why apparent anomalies can be found in previous literature reports concerning carboxylic acids (**Section 1.2.2.1**) will be investigated further in **Chapter 4**. Placement of a bulky substituent

allylic to the diene in fumarates can alter the expected *endo:exo* stereoselectivity causing methyl esters, as well as carboxylic acids, gave rise to *endo* adducts as the major products. These results can be rationalized by consideration of developing steric effects in the triene during the intramolecular cycloaddition.

4 ETDA reactions of citraconate esters

4.1 Introduction

The effect of the dienophile terminating group on the stereochemical outcome of ETDA reactions of maleate and fumarate precursors was investigated in **Sections 3.3.1** and **3.3.2**. Sorbyl maleates gave rise to mixtures of *exo* and *endo* adducts, but when a larger group was incorporated at the diene terminus, *exo* adducts were favoured. This was observed regardless of whether the *Z*-dienophile was terminated with a carboxylic acid or a methyl ester group. The nature of the functional group at the dienophile terminus also had little effect on the *exo:endo* stereoselectivity of fumarate precursors. When a bulky group was incorporated at the terminus of the diene, *endo* adducts were produced with a high level of stereocontrol regardless of whether fumarate diesters or half esters were employed. The results for the precursors prepared from TBS dienol **228** (**Section 2.2.1**) are illustrated in **Figure 4.1**.



236 (R=H) or 238c (R=Me)

241c (R=Me)
major *exo* adduct

304 (R=H) or 305 (R=Me)

314 (R=Me)
major *endo* adduct

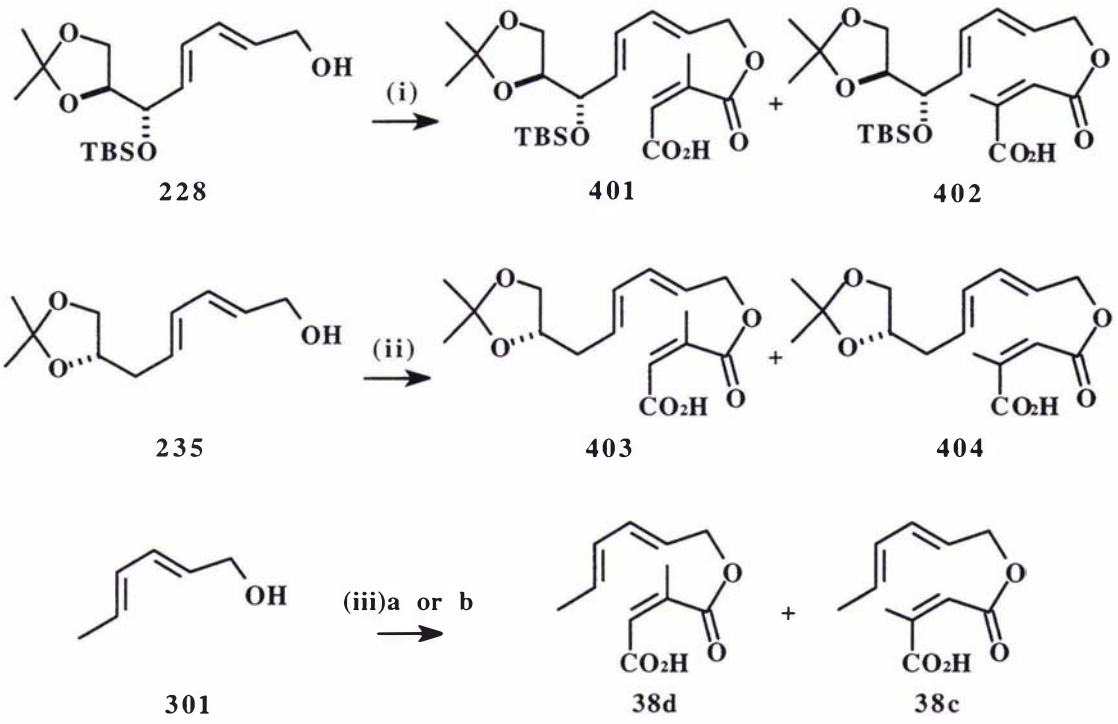
*** The cycloaddition products prepared from carboxylic acids 236 and 304 were converted to methyl esters using diazomethane.**

Figure 4.1

These results were unexpected since ETDA reactions of carboxylic acids have been reported to give *endo* adducts exclusively (**Section 1.2.2.1**). The assertion that citraconate diesters form *exo* adducts and half esters form *endo* adducts [97, 98] has been reinvestigated and this **Chapter** describes the surprising results that were obtained.

4.2 Preparation of citraconate precursors

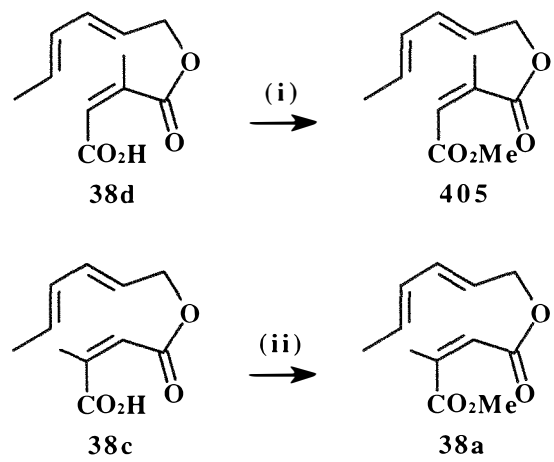
Citraconate half esters were prepared from dienols **228** (**Section 2.2.1**), **235** (**Section 2.2.2**) and **301** by treating the starting material with citraconic anhydride in the presence of triethylamine and N,N-dimethylaminopyridine (**Scheme 4.1**).[174] In addition, the esterification of sorbyl alcohol (**301**) was carried out at 50°C with pyridine in benzene according to the method of White *et al.*[98] Although this paper reported that half esters **38d** and **38c** were inseparable, it was found that separation could be achieved by repeated chromatography, using polar solvents spiked with methanol:acetic acid (1:1, 0.5%) to reduce the effect of tailing. (Since these compounds were not separated in the original paper their physical properties were not reported.)



Conditions: (i) TEA, citraconic anhydride, DMAP, CH_2Cl_2, RT, 1h, 62%, **401:402** (77:23); (ii) TEA, citraconic anhydride, DMAP, CH_2Cl_2, RT, 21h, 77%, **403:404** (67:33); (iii)a TEA, citraconic anhydride, DMAP, CH_2Cl_2, RT, 3h, 100%, **38d:38c** (86:14); (iii)b pyr., citraconic anhydride, benzene, 50°C, 8h, 89%, **38d:38c** (50:50).

Scheme 4.1

Sorbyl citraconate precursors **38d** and **38c** were treated with diazomethane[173] (**Section 6.6.3**) to form the corresponding methyl esters in good yield (**Scheme 4.2**).



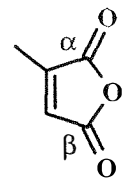
38d **405**

38c **38a**

Conditions: **(i)** CH_2N_2, CH_2Cl_2, RT, 81%; **(ii)** CH_2N_2, CH_2Cl_2, RT, 85%.

Scheme 4.2

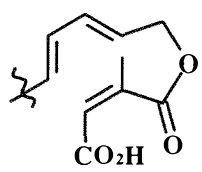
Initially, it was not possible to *unequivocally* assign the regiochemistry of any of the compounds illustrated in **Schemes 4.1** or **4.2** spectroscopically (using NMR or IR) or spectrometrically (using mass spectrometry) since the spectra of the two compounds in each regioisomeric pair did not allow bond connectivity to be established. However, it was possible to unequivocally distinguish the regiochemistry of compound **38a** since the structure of one of the ETDA adducts generated from it (compound **39a**, **Section 4.4.2**) was determined by X-Ray crystallographic analysis. Once compound **38a** had been identified it was possible to deduce the structures of compounds **38d**, **38c** and **405**.



406

Figure 4.2

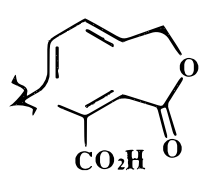
The regiochemistry of compounds **401-404** could not be determined using the same method as that used for compound **38a**, since they did not produce crystalline ETDA adducts (**Section 4.3**). In spite of this there were a number of observations which enabled confident structural assignments of each of these citraconate half esters to be made (by analogy with the assignment of **38d-38a**). Nucleophilic addition to citraconic anhydride (**406**) (**Figure 4.2**) normally occurs at the more sterically demanding α–carbonyl[209] (since it has the larger LUMO coefficient of the two carbonyl carbons[210]) which leads to major regioisomers **401**, **403** and **38d**. The relative polarity of the major and minor regioisomers was similar for each regioisomeric pair. (The R_f of the major isomer was always significantly higher than the minor isomer by TLC analysis on silica plates.) The chemical shift of the dienophile hydrogen atom and methyl group in each compound (**Figure 4.3**) also provided data which enabled the regiochemistry to be determined. The chemical shifts of the dienophile substituents of the major isomers produced in each reaction are very similar, as are those of the minor isomers, yet the chemical shifts obtained for the major and minor isomers are quite different from each other. Since the structure of compounds **38d** and **38c** were known, it was possible to determine the regiochemistry of citraconate half esters **401-404** on this basis. (This was confirmed by spectral data obtained on the adducts produced in subsequent ETDA reactions.)



major regioisomer

chemical shift (∂/ppm)

adduct	H, CH3	H, CH3
401	2.09	5.88
403	2.08	5.89
38d	2.07	5.85



minor regioisomer

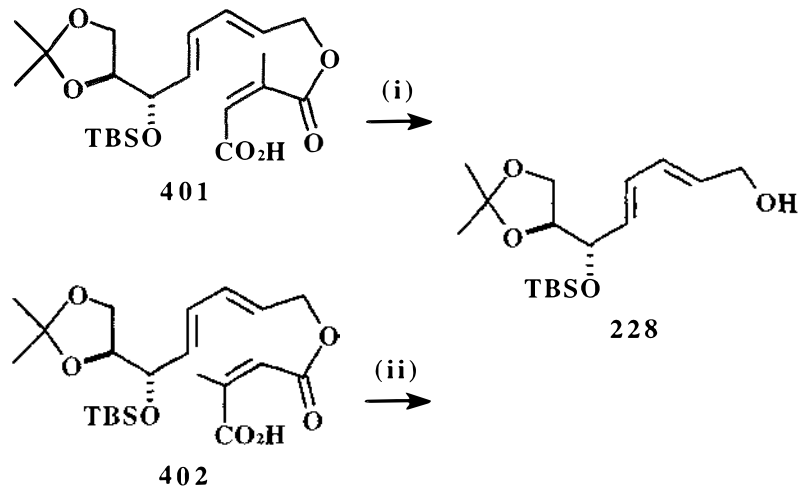
adduct	CH3, H	CH3, H
402	2.15	6.16
404	2.17	6.25
38c	2.14	6.16

Figure 4.3

4.3 Attempted ETDA reactions on citraconate half esters

When compound **401** (**Scheme 4.3**) was heated under standard conditions (**Section 2.4**) in refluxing toluene for 12h in the presence of BHT there was no evidence for the formation of the expected ETDA adducts. Instead, the material isolated from the reaction mixture once the solvent had been evaporated was TBS dienol **228**. Initially it was suspected that this outcome was the result of contamination of the solvent with trace amounts of moisture, leading to acid-catalyzed hydrolysis of the ester linkage of the starting material. For this reason the toluene was redistilled from sodium benzophenone ketyl and a second ETDA reaction was attempted, but this gave the same result as the previous reaction. Although these ETDA reactions were carried out under an argon atmosphere using oven dried glassware, it was conceivable that adventitious moisture might still be affecting the reaction. For this reason an ETDA reaction was carried out in toluene in the presence of 4Å molecular sieves, but this still resulted in formation of TBS dienol **228**. In a fourth reaction the starting material was heated in refluxing toluene in the presence of 4Å molecular sieves and anhydrous potassium carbonate (equimolar with the starting material) in order to neutralize the citraconate half ester and prevent any acid catalyzed processes from occurring. This too resulted in hydrolysis of the ester linkage of the starting material. In a final attempt to cyclise this starting material it was heated in refluxing xylene, but TBS dienol **228** was still produced.

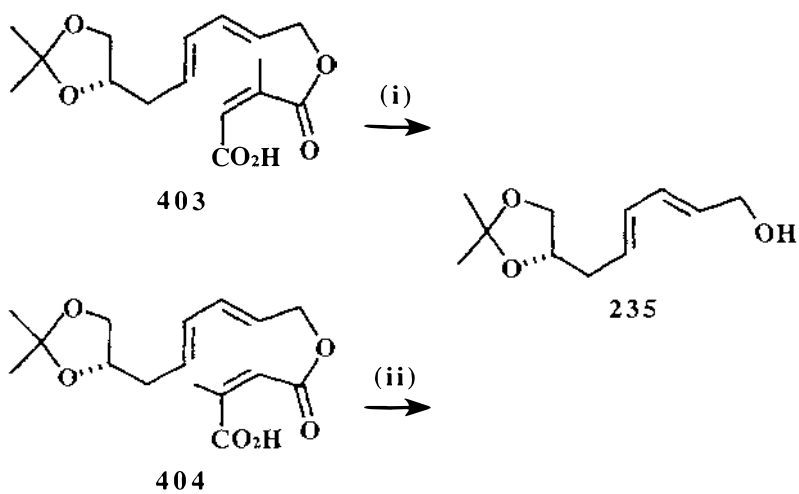
It soon became clear that the formation of TBS dienol **228** was not due to inadequacies in the experimental methods employed, but resulted from unexpected thermal lability of the ester tether. For this reason it was decided to investigate the behaviour of regioisomeric acid **402** (**Scheme 4.3**) under the standard ETDA reaction conditions. Not unexpectedly, this also resulted in the exclusive formation of TBS dienol **228**.



Conditions: (i) BHT, toluene, reflux, 12h, 61%; (ii) BHT, toluene, reflux, 24h, 57%.

Scheme 4.3

It was proposed that the bulky substituent at the diene terminus in precursors **401** and **402** might be responsible for the anomalous results of these citraconate half esters (cf. the maleate half ester series (**Section 3.3.1**)). Hence it was decided to attempt ETDA reactions on *deoxy* dienol derivatives derivatives **403** and **404** (**Scheme 4.4**). In each case the expected ETDA reaction did not occur and *deoxy* dienol **235** was produced instead.



Conditions: (i) BHT, toluene, reflux, 3h, 63%; (ii) BHT, toluene, reflux, 5h, 54%.

Scheme 4.4

Formation of dienols **228** and **235** when half esters **401-404** were heated was completely unexpected and totally different from the results reported for citraconate derivatives of sorbyl alcohol,[97, 98] therefore it was decided to carefully reinvestigate these published results. It was reported[97, 98] that a mixture of the two regioisomeric acids **38d** and **38c** (50:50) was heated in xylene under a nitrogen atmosphere for 15h (**Figure 4.4**). The solvent was then removed yielding a thick brown oil which partially crystallized on standing. Trituration of this material with chloroform:cyclohexane followed by recrystallisation gave a 32% yield of adduct **40c** (based on the mass of compound **38c**). It was reported that a substantial amount of polymeric material was formed, but there was no evidence for the formation of any other adducts. From these observations it was concluded that compound **38c** reacted exclusively *via* the *endo* mode of cycloaddition and compound **38d** was apparently destroyed through "autocatalytic polymerization".[98]

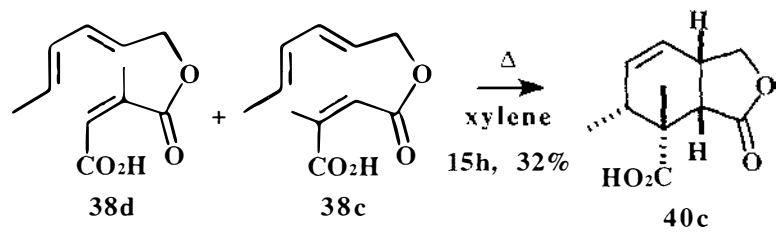


Figure 4.4

In general, for IMDA reactions in which the tether contains three atoms, *exo* adducts are formed (**Section 1.2**). This is the case for ETDA reactions in which the dienophile of the precursor is terminated with an ester group, however, when the dienophile is terminated with a carboxylic acid, formation of *endo* adducts has come to be expected. The reaction illustrated in **Figure 4.4** is one of the most frequently cited examples[14, 15, 17, 19] of the apparently anomalous behaviour of carboxylic acids, however, no satisfactory explanation of this phenomenon has yet been provided.

It was decided to repeat the reaction shown in **Figure 4.4** using the same solvent (xylene), reaction time (15h) and concentration (115mmol/L) that was used by the original investigators.[98] Proton NMR analysis of the crude reaction mixture after removal of the xylene (**Figure 4.5**) revealed that a very complicated mixture containing several distinct products was produced.

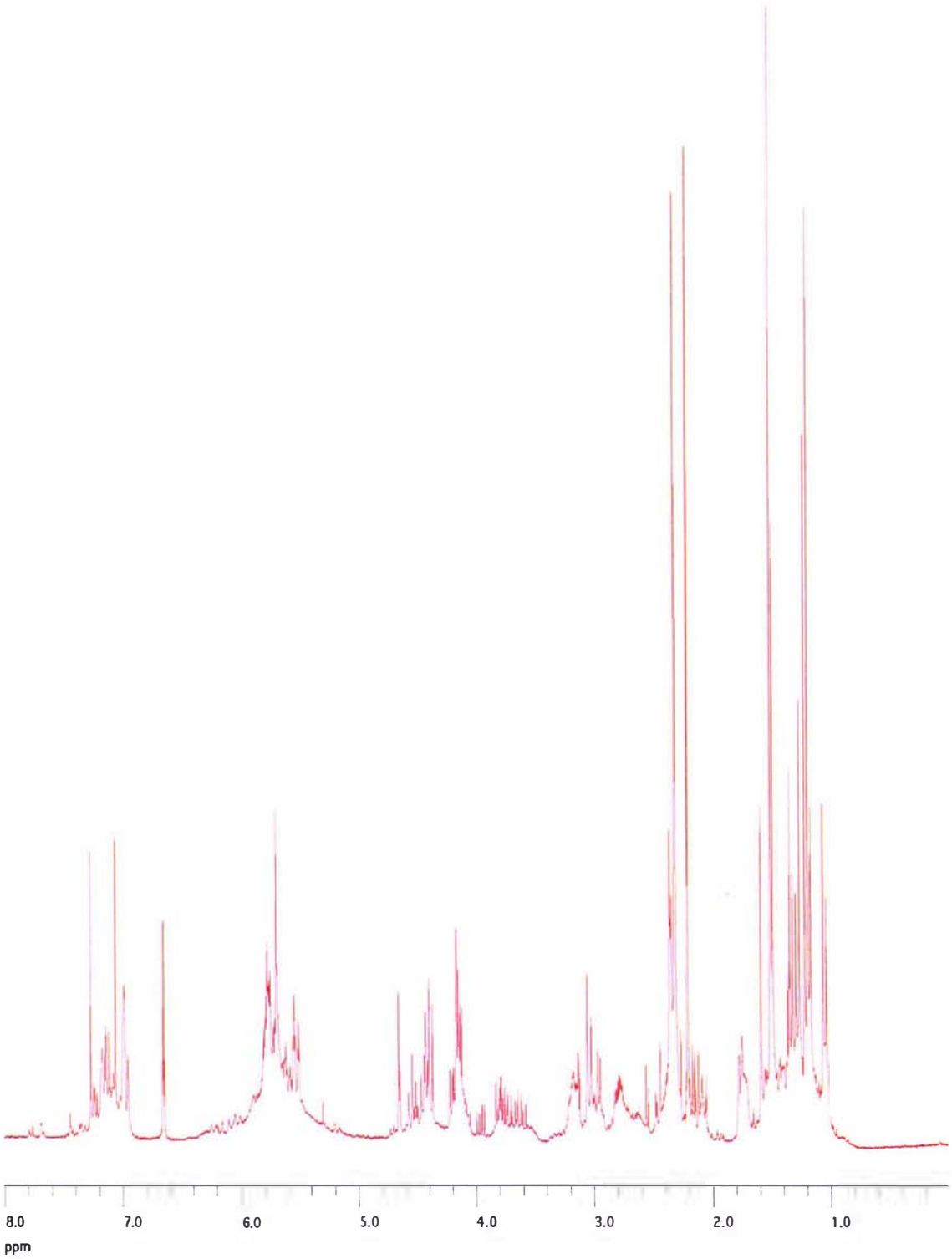
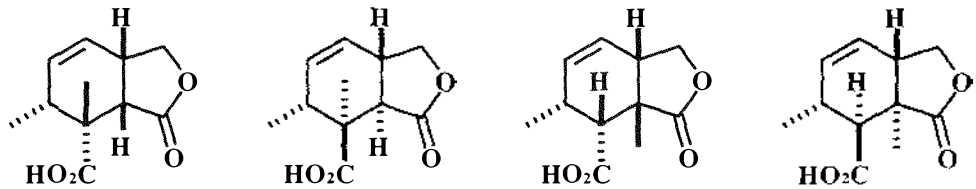


Figure 4.5

Assuming a standard IMDA reaction pathway it is possible for four products to be formed in this reaction (**Figure 4.6**) and at least four products were present in the reaction mixture. It was determined that separation of these adducts was not practical and that independent syntheses of each of the individual compounds would be more expedient. These syntheses are discussed in **Section 4.4**.



The structures represent relative stereochemistry only. Each of these cycloadducts is produced as a racemate. Only adduct 40c was isolated by White *et al.*[98]

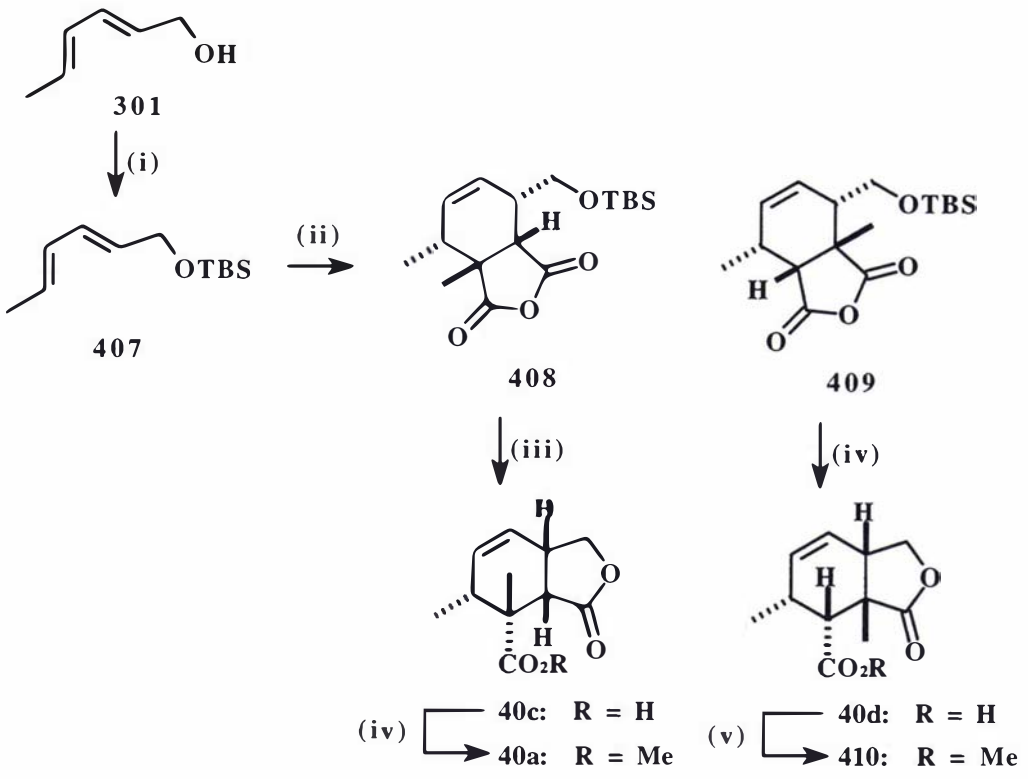
Figure 4.6

4.4 Synthesis of ETDA adducts of sorbyl citraconates

Synthesis of the four adducts shown in **Figure 4.6** (**Section 4.3**) are discussed in this **Section** as well as the formation of methyl ester derivatives of each one.

4.4.1 *Endo* adducts

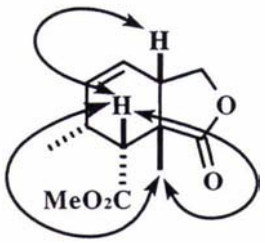
The *endo* adducts of citraconate half esters **38d** and **38c** (i.e. compounds **40c** and **40d**) were prepared by using a BDA reaction (**Scheme 4.5**). Sorbyl alcohol (**301**) was treated with *tert*-butyldimethylsilyl chloride[176] to form silyl ether **407** which was then reacted with citraconic anhydride in refluxing toluene to form a mixture of *endo* adducts **408** and **409**. (Equimolar amounts of the two starting materials were used and the concentration of each was 0.50mol/L.) The regioisomeric cycloadducts were easily separated, then treated with trifluoroacetic acid to cleave the *tert*-butyldimethylsilyl groups and form γ-lactones **40c** and **40d** in a single step. Treatment of each of these lactones with diazomethane[173] (**Section 6.6.3**) formed methyl esters **40a** and **410** respectively in high yield. It is likely that the regioselectivity observed in this reaction is due to unfavourable steric interactions between the bulky *tert*-butyldimethylsilyl group on the diene and the methyl group on the dienophile.



Conditions: (i) TBSCl, imid., CH_2Cl_2, RT, 30min, 97%; (ii) citraconic anhydride, BHT, toluene, reflux, 36h, 93% (at 80% conversion), **408:409** (76:24); (iii) TFA, CH_2Cl_2, RT, 2h, 94%; (iv) TFA, CH_2Cl_2, RT, 2h, 76%; (iv) CH_2N_2, diethyl ether, -65°C, 95%; (v) CH_2N_2, diethyl ether, -65°C, 95%.

Scheme 4.5

Methyl ester **40a** had identical physical properties to those reported in the previously published paper by White *et al.*[98] for which the investigators obtained X-Ray crystallographic data. The regiochemistry of adduct **410** was obtained from a COSY spectrum. Unfortunately it was not possible to determine the ring junction stereochemistry of this compound using coupling constants, since it has a methyl group in this position. However, the NOESY spectrum of **410** showed strong interactions between the two hydrogen atoms and the methyl group which are pointing up in **Figure 4.7**, establishing that this compound has a *cis* fused ring system.

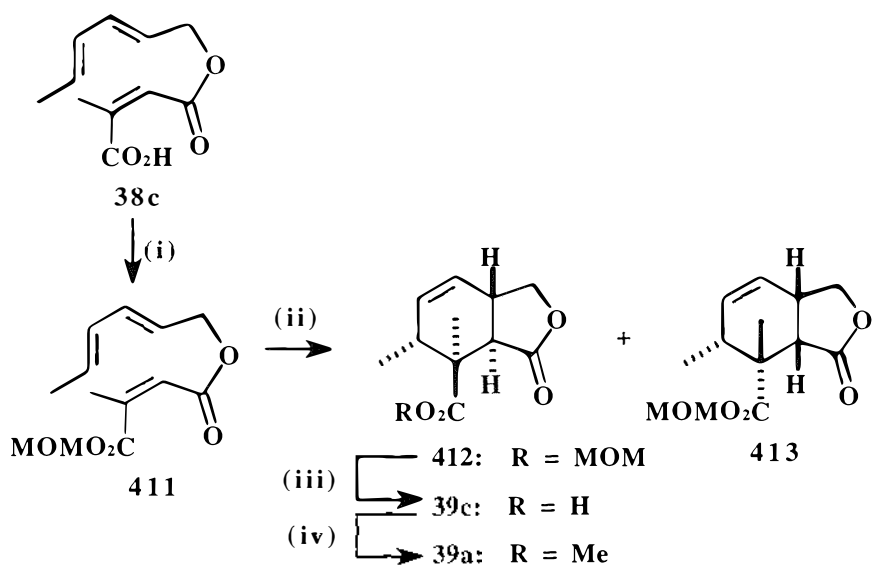


410

Figure 4.7

4.4.2 *Exo* adducts

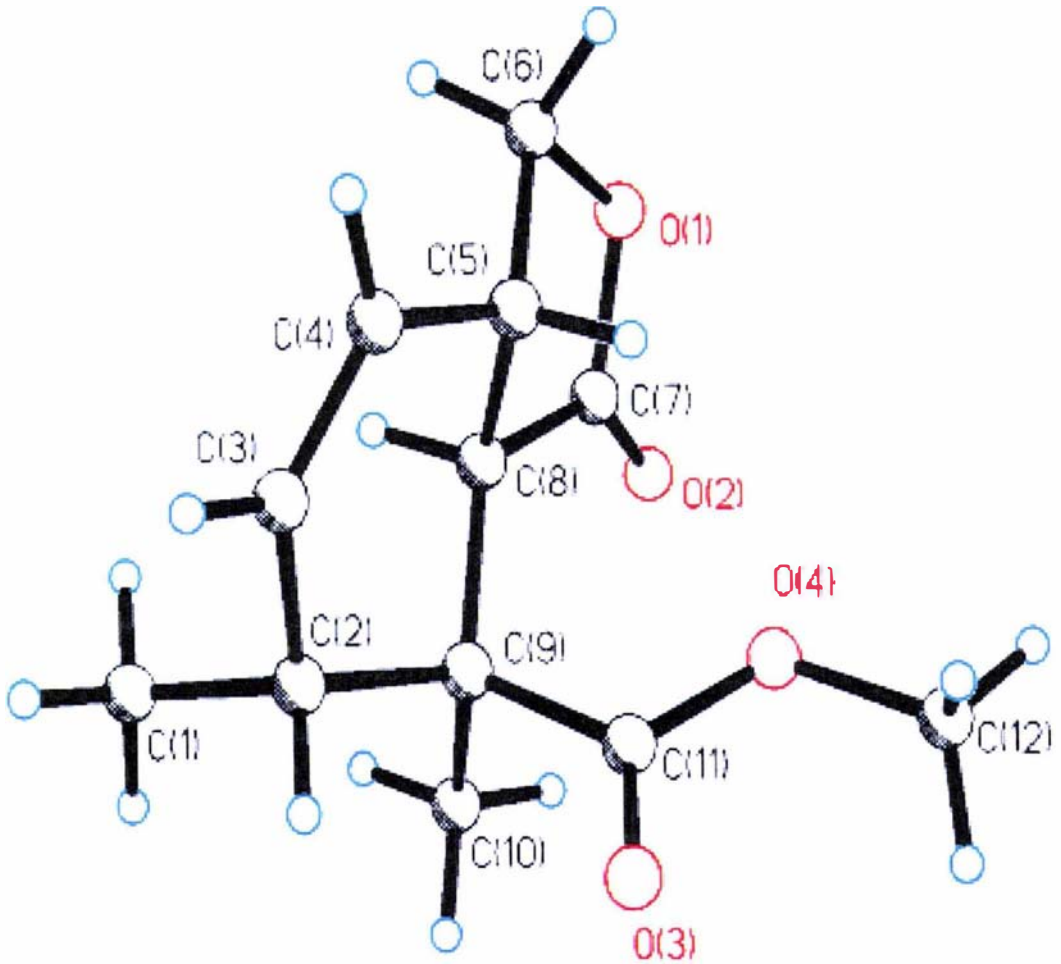
Exo cycloadducts adducts can be readily prepared from ETDA reactions (**Section 1.2.1.1**), however, in the case of the citraconate half esters it was first of all necessary to protect the carboxylic acid groups as labile esters. Citraconate half ester **38c** (**Scheme 4.6**) was treated with chloromethyl methyl ether to form diester **411**, which was then refluxed in toluene to give cycloadducts **412** and **413**. Major compound **412** had a coupling constant of 13.6Hz between the hydrogen atoms at the ring junction indicating that they are *trans* fused, whereas the coupling constant between the same protons in minor compound **413** was only 9.2Hz corresponding to a *cis* fused ring system.[98] Treatment of cyclic methoxymethyl ester **412** with trifluoroacetic acid exposed carboxylic acid **39c** which was then treated with diazomethane[173] (**Section 6.6.3**) to furnish methyl ester **39a**. This adduct had identical physical properties to the previously published compound.[98]



Conditions: (**i**) MOMCl, TEA, CH_2Cl_2, RT, 10min, 59%; (**ii**) BHT, toluene, reflux, 22h, 96% **412:413** (88:12); (**iii**) TFA, CH_2Cl_2, RT, 18h, 96%; (**iv**) CH_2N_2, diethyl ether, -65°C, 66%.

Scheme 4.6

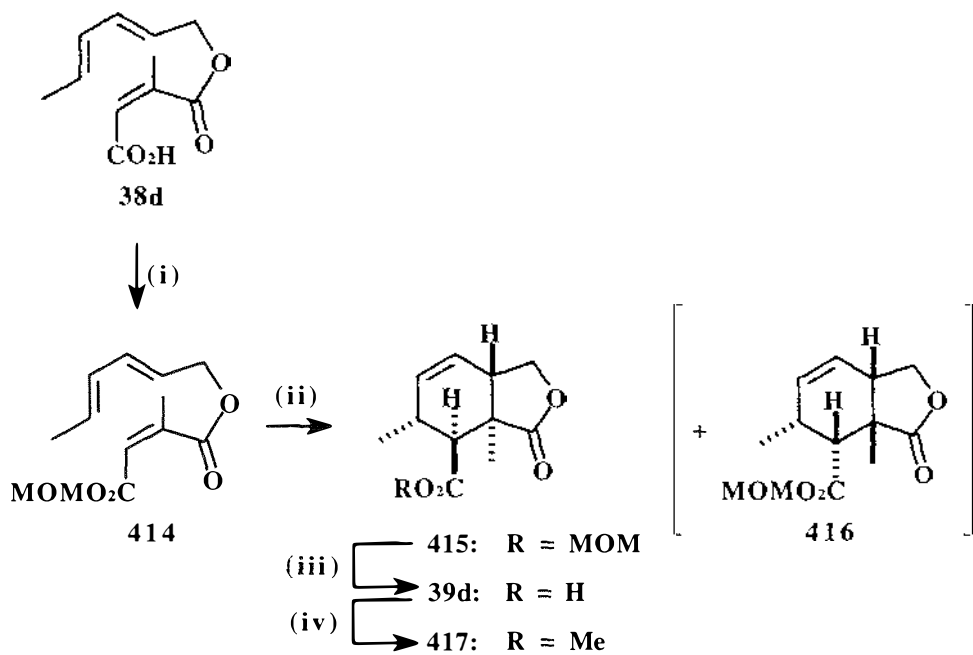
Methyl ester **39a** was highly crystalline and a sample suitable for single crystal X-Ray diffraction was obtained after recrystallisation from *tert*-butyl methyl ether. The crystal structure of this compound is shown in **Figure 4.8**. (Other parameters are summarized in **Appendix 2**) It is clear from the structure that the two rings are *trans* fused and therefore the compound was formed *via* an *exo* transition state. The structure also unequivocally proves the regiochemistry of the molecule, establishing that the methyl group of the dienophile in compound **38c** is distal to the ester tether. (From this it was possible to deduce the regiochemistry of each of the citraconate precursors prepared in **Section 4.2**.)



X-Ray crystallographic structure of adduct 39a, recrystallised from *tert*-butyl methyl ether.

Figure 4.8

The protocol which was used to prepare adducts **39c** and **39a** from carboxylic acid **38c** was repeated on regioisomeric acid **38d** (**Scheme 4.7**). The highly stereoselective ETDA reaction of **82** produced a mixture of two adducts (**415** and **416**), which were assumed to be the *exo* and *endo* products respectively. (It is likely that the *exo:endo* stereoselectivity is greater the ETDA reaction of **38d** than **38c** due to the position of the vinylic methyl group of the dienophile. The steric compression around the developing internal σ-bond will be more acute in compound **38d**, resulting in higher *exo* stereoselectivity.) Major adduct **415** was treated with trifluoroacetic acid to form carboxylic acid **39d** and this was subsequently treated with diazomethane[173] (**Section 6.6.3**) to form methyl ester **417**.

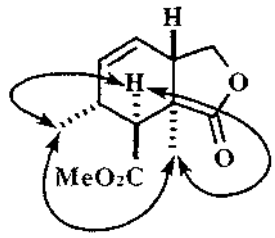


Conditions: (**i**) MOMCl, TEA, CH_2Cl_2, RT, 5min, 86%; (**ii**) BHT, toluene, reflux, 22h, 99%, **415:416** (93:7); (**iii**) TFA, CH_2Cl_2, RT, 6h, 89%; (**iv**) CH_2N_2, diethyl ether, -65°C, 100%.

Scheme 4.7

The regiochemistry of compound **417** was established using a COSY spectrum. It was not possible to use coupling constants to determine the stereochemistry at the ring junction in **417** since there is a methyl group in that position. However, the NOESY spectrum of this compound indicated strong through-space coupling between the hydrogen atom and the two methyl groups pointing down in structure **417** (**Figure**

4.9). The nOe between the two methyl groups is indicative that the cycloadduct formed *via* an *exo* transition state. (Because of the high stereoselectivity of the ETDA reaction of **414** (**415:416**, (93:7)) and difficulties encountered during chromatography, it was not possible to isolate a pure sample of compound **416**. However, based on the result of the ETDA reaction of **411** (**Scheme 4.6**) it seems likely that it should have structure shown.)



417

Figure 4.9

4.5 Reinvestigation of DA reactions on sorbyl citraconate precursors

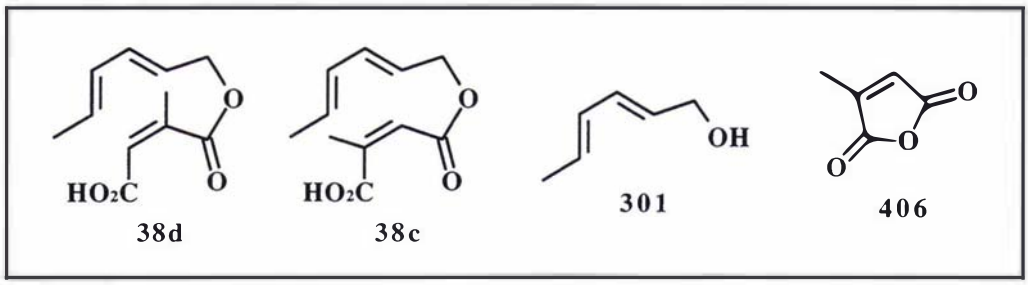
With the four possible regioisomeric and stereoisomeric adducts **40c**, **39c**, **40d** and **39d** in hand (**Section 4.4**) it was possible to analyze the proton NMR spectrum of the ETDA reaction of the 50:50 mixture of citraconate half esters **38d** and **38c** (**Figure 4.5**). Similar reactions were carried out on pure samples of precursors **38d** and **38c**, and the reaction of sorbyl alcohol (**301**) with citraconic anhydride (**406**) was also investigated. These results are discussed in **Section 4.5.1**.

4.5.1 Comparison of the reactions of the sorbyl hydrogen citraconates and the reaction of sorbyl alcohol with citraconic anhydride

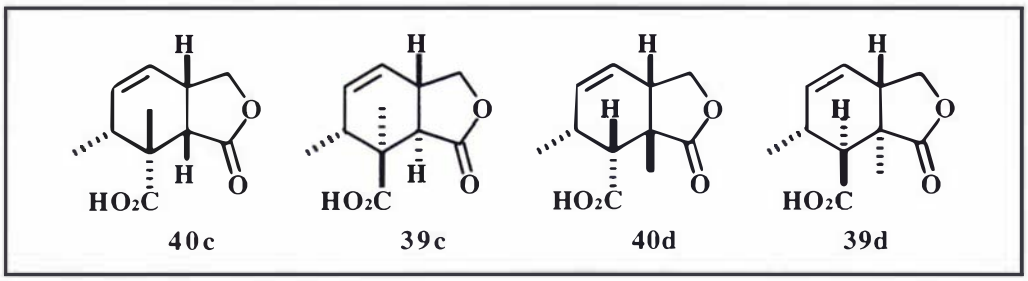
The DA reactions carried out on the citraconate half esters (**38d** and **38c**) and sorbyl alcohol (**301**) with citraconic anhydride (**406**) are illustrated in **Scheme 4.8**. For ease of interpretation each of the starting materials is illustrated, as are the four possible products. The reactions which were carried out are tabulated directly below this. In each case the starting materials were heated to reflux in xylene under an argon atmosphere for 15h using exactly the same conditions as White *et al.*[98] After this, the solvent was removed *in vacuo*, the residue was dissolved in deuterated chloroform and a proton NMR spectrum was recorded. These samples were then dissolved in dichloromethane and treated with trifluoroacetic acid to ensure that any unlactonised BDA *endo* adducts underwent intramolecular esterification to form the required γ-lactones. The trifluoroacetic acid and dichloromethane were then evaporated and proton NMR spectra were again obtained in deuterated chloroform. (The trifluoroacetic acid treatment was found to simplify the proton NMR spectra of the crude materials, but it did not appear to have a significant effect on the product ratios observed.)

When a mixture of the two regioisomeric citraconate half esters **38d** and **38c** (50:50) was heated (**Entry 1**), all of the four possible adducts (**40c**, **39c**, **40d** and **39d**) were produced. This is in direct contrast to the published results,[98] which specify that *only* adduct **40c** was formed under these conditions. When reactions were carried out separately on pure samples of regioisomeric acids **38d** and **38c** (**Entries 2** and **3**

respectively), each of the four adducts was again produced. In a fourth experiment (**Entry 4**), sorbyl alcohol (**301**) was heated with citraconic anhydride (**406**) to produce the same four products. In each case (**Entries 1-4**) the product ratio was almost identical. *Endo* adducts were favoured over *exo* adducts (*ca. endo:exo* (60:40)) and adduct **40c** represented approximately 50% of the material produced in each case.



(i) ↓ (ii)



Entry	Starting materials	40c:39c:40d:39d (i)	40c:39c:40d:39d (ii)	Mass Balance (%)
1	38d + 38c (50:50)	51:16:27:6	50:14:28:8	89
2	38d	55:7:28:10	53:11:29:7	91
3	38c	54:11:24:11	52:12:29:7	90
4	301+406 (50:50)	57:7:30:6	58:7:29:7	95

Conditions: (i) xylene (115mmol/L), reflux, 15h; (ii) TFA, dichloromethane, RT, 24h.

Scheme 4.8

These results have a significant impact upon the mechanism of product formation. There is no mechanism by which citraconate **38d** can form adduct **40c** *via* a normal ETDA reaction, since it would require migration of the methyl group of the dienophile from the ring junction to the adjacent carbon atom in the product. The only way in which adduct **40c** can form under the reaction conditions used is if the ester tether between the diene and the dienophile is cleaved prior to the DA reaction, resulting in the reformation of sorbyl alcohol (**301**) and citraconic anhydride (**406**). Once this has occurred, a BDA reaction can follow between the diene and the dienophile, or re-esterification can ensue followed by a subsequent ETDA reaction. Formation of *endo* adducts is favoured in BDA reactions[51] and so it seems likely that this is what occurs. These ideas are illustrated in **Figure 4.10**.

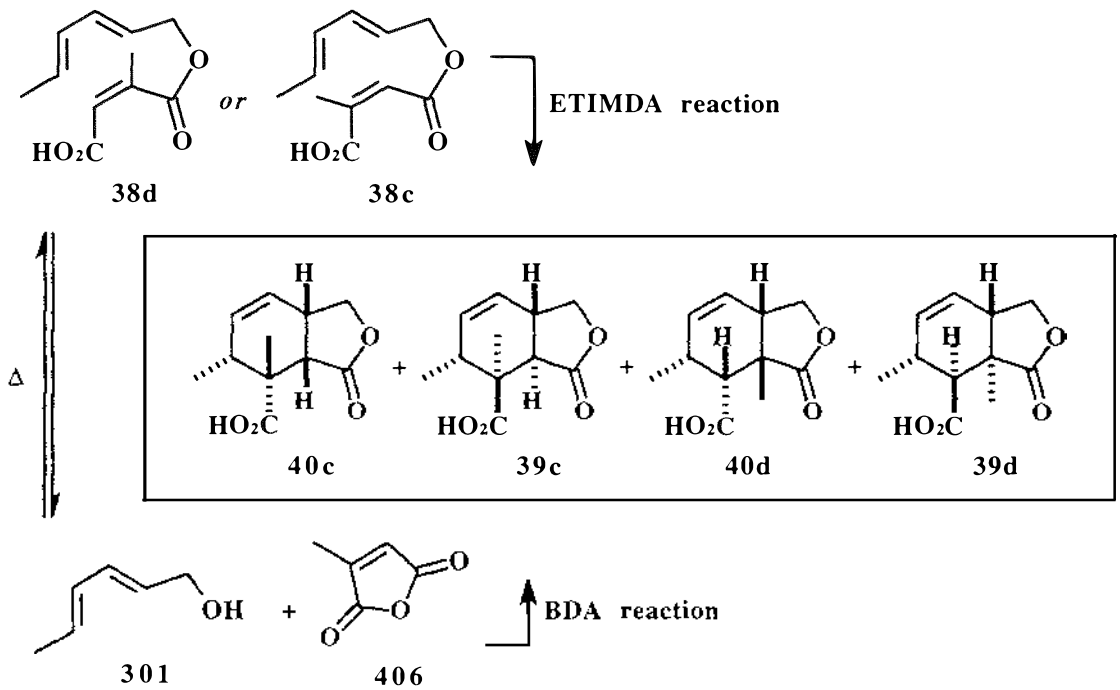


Figure 4.10

4.5.2 Proton NMR experiments

In order to reinforce this postulated mechanism, it was decided to heat precursors **38d** and **38c** separately in refluxing d_8-toluene in an NMR tube, at the same concentration (115mmol/L) as that used for the reactions in **Section 4.5.1**. The results of these experiments are illustrated in time-lapse NMR spectra in **Figures 4.11** to **4.14**. (The quintet at 2.3ppm is due to toluene. Toluene also has three broad multiplets at 7.15-7.35ppm but these are not shown in **Figures 4.11-4.14**.)

The time-lapse NMR spectra in **Figure 4.11** and **4.12** show the results obtained when precursor **38d** was heated. **Figure 4.11** includes chemical shifts form 0.0-7.0ppm, whereas the range has been reduced to 0.7-2.0ppm in **Figure 4.12** to allow some of the extra detail to be observed.

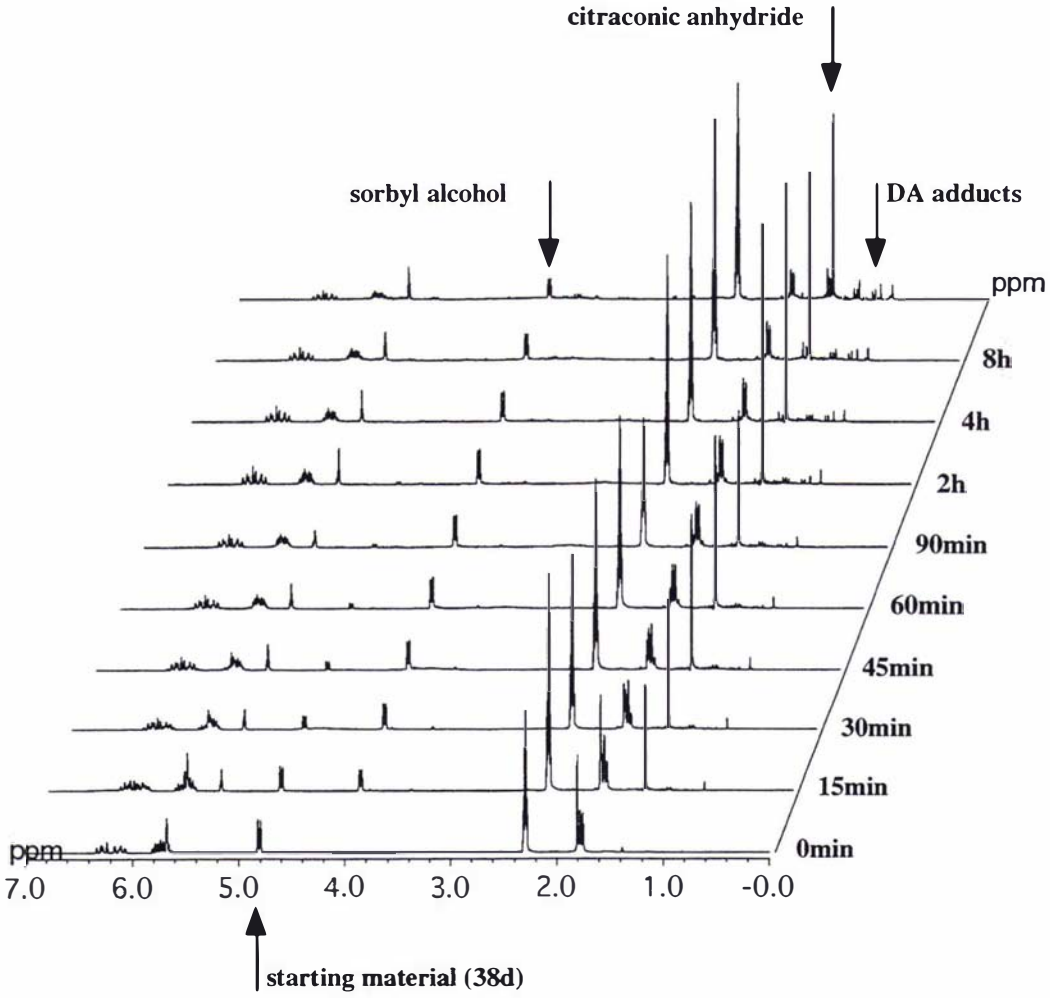


Figure 4.11

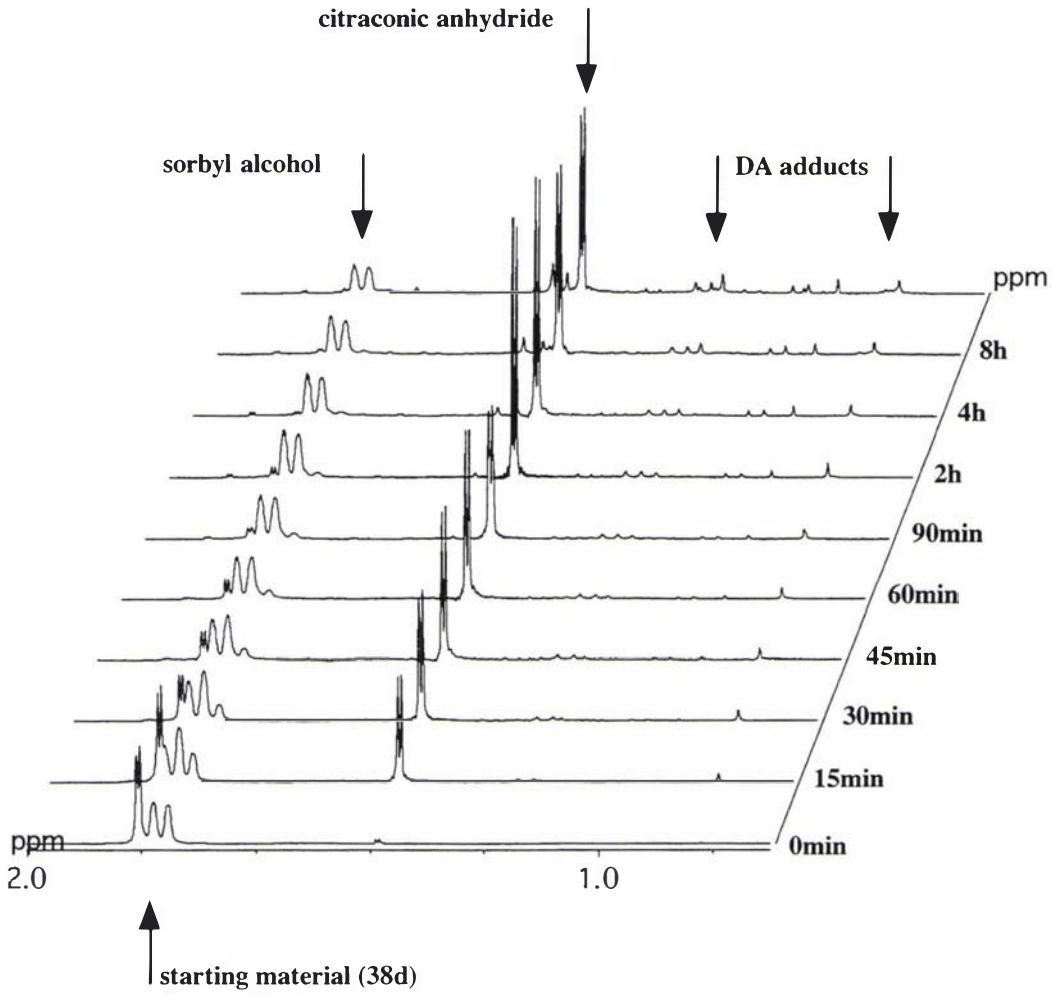


Figure 4.12

After fifteen minutes in refluxing toluene, approximately 50% of precursor **38d** has been cleaved into sorbyl alcohol (**301**) and citraconic anhydride (**406**). After one hour there is only a small amount of compound **64** left in the reaction mixture. DA adducts begin to form subsequent to this.

Similar spectra were also observed when precursor **38c** was heated in d_8-toluene. The time-lapse NMR spectra for this precursor are illustrated in **Figures 4.13** and **4.14**. The results for precursor **38c** were almost identical to those obtained for precursor **38d**, with approximately 50% of the starting material cleaved within the first fifteen minutes and the remainder cleaved after one hour.

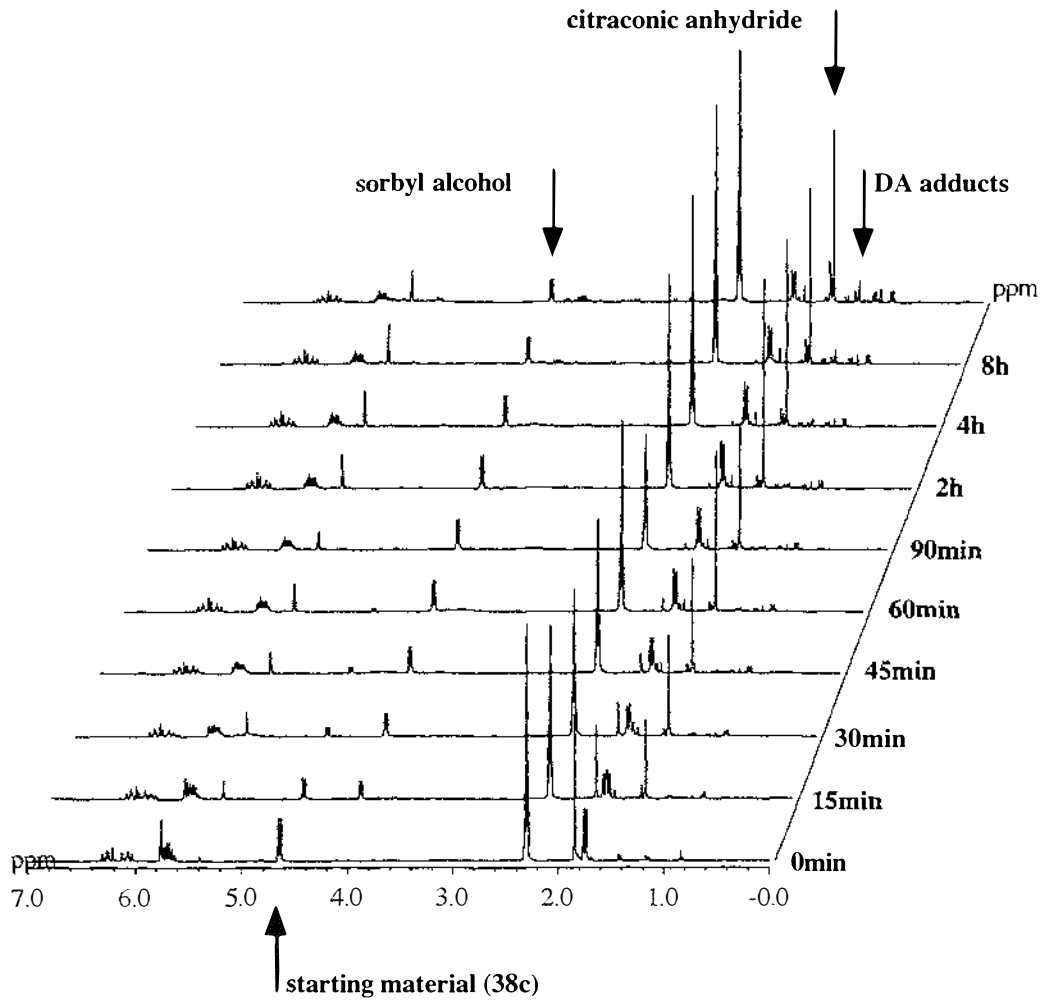


Figure 4.13

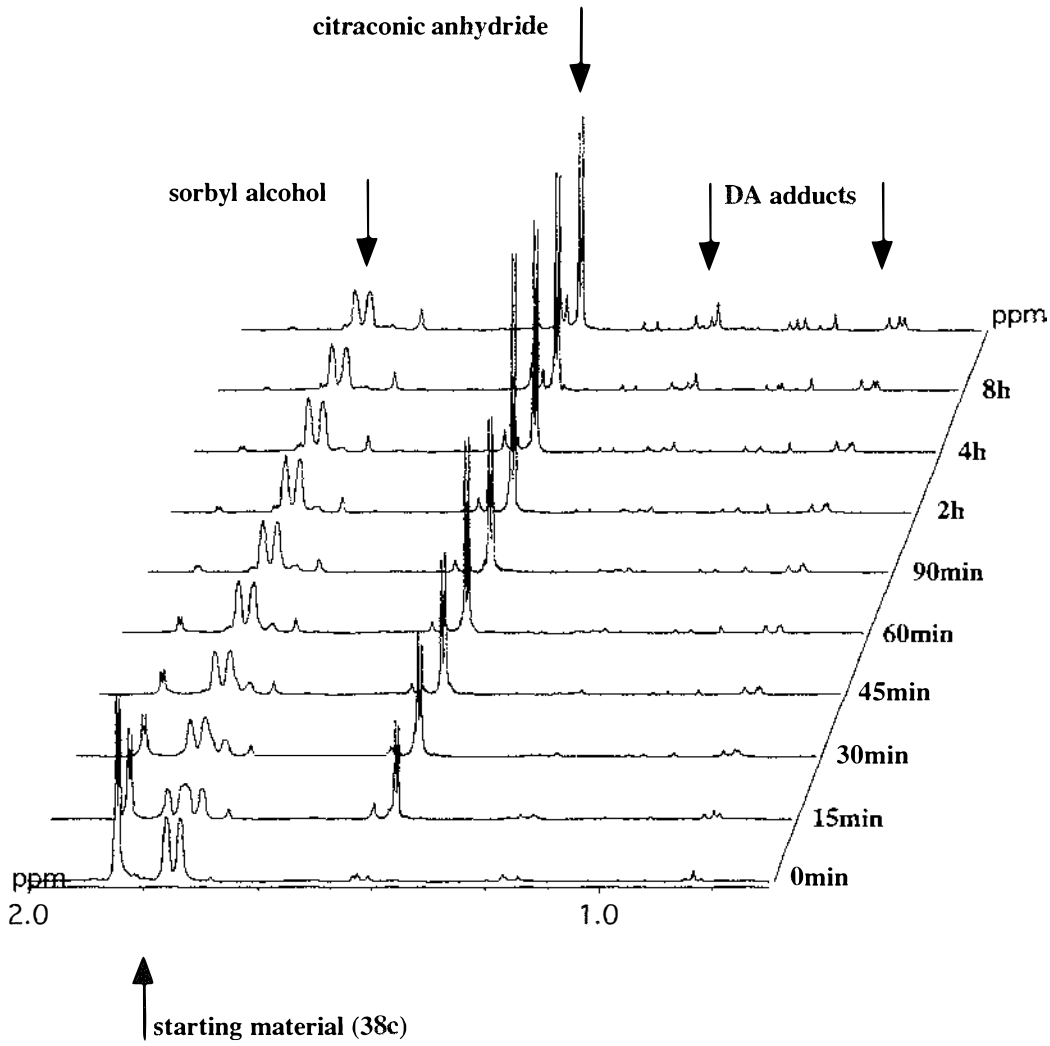


Figure 4.14

Thermal lability of citraconate half esters has no precedent in the literature[†] and it is difficult to explain why the ester bond in these compounds should be so much more labile than those of maleate and fumarate half esters. However, all of the solvents and glassware used in these experiments were carefully dried and the reactions were carried out under an argon atmosphere, therefore it is not reasonable to propose that hydrolysis is responsible for the rapid cleavage of the ester tether. An alternative mechanism (illustrated in **Figure 4.15**) entails protonation of the carbonyl group of the tether, then proton exchange, intramolecular addition of the weakly nucleophilic carboxylate ion and subsequent cleavage of the ester bond. The citraconate half esters are clearly more susceptible to this process than the maleate or fumarate derivatives. This could be due to steric compression of bond angles by the dienophile methyl group, facilitating the protonation and nucleophilic addition steps. Reformation of citraconic anhydride may be

[†] An STN REACS search was conducted in February, 1998. Sincere thanks is extended to Associate Professor Damon Ridley for helping with this search.

more favoured than maleic anhydride because the alkene in the product is more highly substituted and therefore it has greater stability. (In the case of the fumarate derivatives it is not possible for an anhydride to form, unless isomerisation of the double bond occurs.)

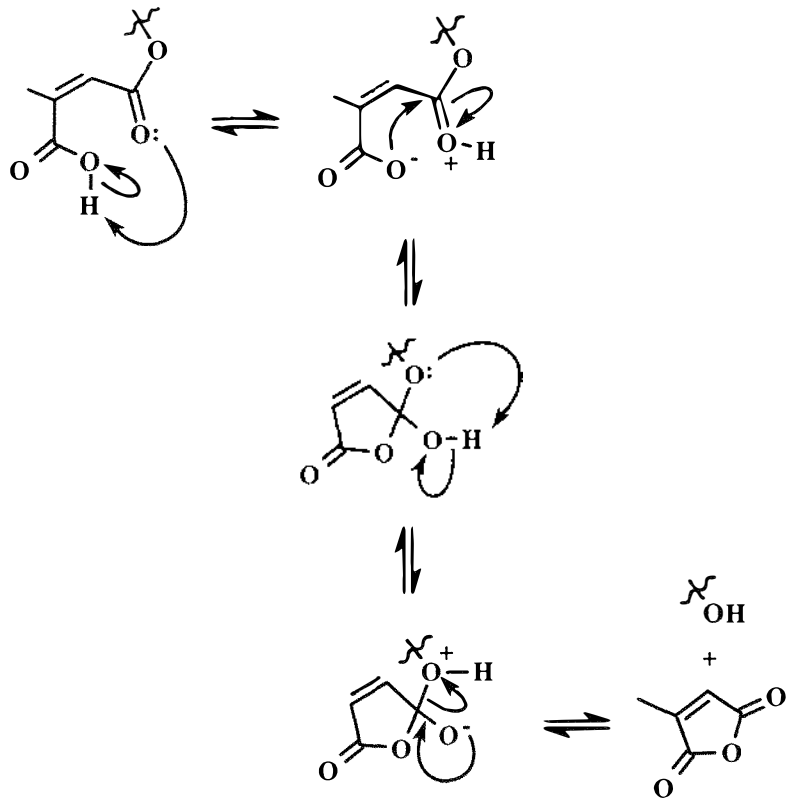
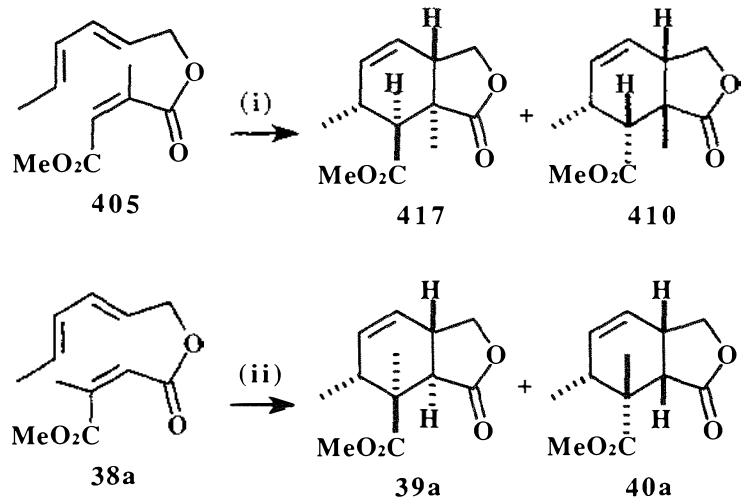


Figure 4.15

4.5.3 ETDA reactions of methyl sorbyl citraconates

For completeness, the ETDA reactions of methyl ester derivatives **66** and **67** are reported in **Scheme 4.9**. In this case (as with the MOM esters in **Section 4.4.2**) the reformation of sorbyl alcohol and citraconic anhydride is prevented by the presence of a terminal methyl ester on the dienophile. In each case the *exo* adduct is favoured, as is usual for ETDA reactions of esters (**Chapters 1**, **2** and **3**). In an analogous fashion to the MOM esters in **Section 4.4.2** the *exo* stereoselectivity was greater in the ETDA reaction of **405** than 38a, due to the position of the vinylic methyl group of the dienophile . Previously, the ETDA reaction of compound **67** was carried out in refluxing xylene,[98] resulting in a 40% yield of **81** after 24h, however, the authors did not mention the presence of adduct **76**.



Conditions: (i) BHT, toluene, reflux, 24h, 71% (95% conversion), **417:410** (93:7); (ii) BHT, toluene, reflux, 24h, 65% **39a:40a** (84:16).

Scheme 4.9

4.6 Conclusion

The assertion that citraconate half esters form *endo* adducts *via* ETDA reactions has gone unchallenged for over twenty years.[97, 98] In this **Chapter** it has been demonstrated that citraconate half esters are thermally labile and break down when heated in refluxing solvent to form citraconic anhydride and an alcohol. This has a big impact upon the commonly held belief that citraconate half esters formed from dienols undergo ETDA reactions to form predominantly *endo* adducts. In fact, the reaction proceeds *via* initial cleavage of the ester tether, followed by a BDA reaction and then an intramolecular esterification, leading to the formation of *cis* fused bicyclic lactone acids. The isolation of chiral dienols **228** and **235** (**Figures 4.3 and 4.4**) from heating dilute solutions of precursors **401** or **402** and **403** or **404** respectively, is consistent with these new mechanistic insights. Clearly, if *exo* cycloadducts are required then citraconate diesters, such as methoxymethyl esters **411** and **414** (**Schemes 4.6** and **4.7**) or methyl esters **405** and **38a** (**Scheme 4.9**) must be employed.

There are two further examples in which ester tethered precursors were preformed, isolated and then subjected to conditions which would normally lead to ETDA reactions.[100, 101] These derivatives are shown in **Figure 4.16**. Dichloromaleate **41f** and bromomaleate **41g** have one structural feature in common with the citraconate half esters already discussed, which is the presence of substituents (other than hydrogen atoms) on the dienophile. It is proposed that dichloromaleate **41f** generates *endo* adduct **43f** *via* the same mechanism as the citraconate half esters **38d** and **38c** form **40c** and

40d (**Figure 4.15**). The reaction of bromomaleate **41g** is not reported to produce ETDA adducts, but instead results in extensive polymerization. Based on the results described for the citraconate half esters in this **Chapter**, it is likely that this process begins with cleavage of the ester tether.

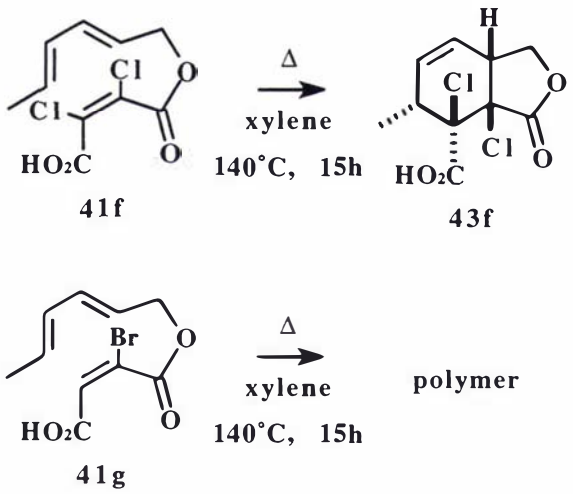


Figure 4.16

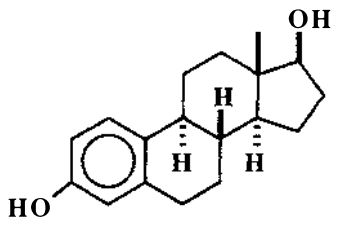
5 Attempted transannular Diels-Alder (TDA) and tandem IMDA (TIMDA) reactions

5.1 Introduction

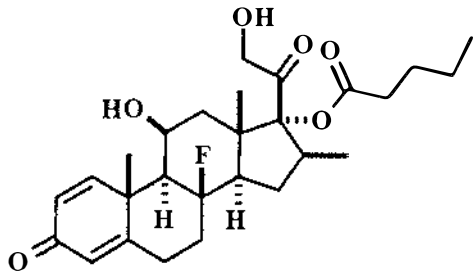
Steroids feature prominently in the regulation of metabolism in every organ of the human body.[211] They are also responsible for initiating all of the major physiological changes an individual goes through during the course of their life and for controlling the reproductive cycle.[212] As a consequence of this they are used extensively in the treatment of a wide variety of diseases and they are the major active ingredients of the contraceptive pill. Steroids therefore represent attractive targets for synthetic organic chemists[213] and a number of strategies involving DA reactions have been reported.[214-216]

Steroids have featured in the development of some recent therapeutic agents with diverse delivery systems[217] (**Figure 5.1**). These include: oestradiol (**1**) which has been incorporated into patches for transdermal hormonal replacement in menopausal women; hydrocortisone derivatives such as betamethasone valerate (**2**) which is the active ingredient in creams for the treatment of inflammatory skin conditions such as psoriasis; and beclomethasone dipropionate (**3**) which is inhaled directly into the lungs for the control asthma. Plant natural extracts containing steroids have been known for much longer. Digoxin (**4**) is a steroid glycoside found in foxgloves (*Digitalis purpurea* or *Digitalis lanata*) which can be administered intravenously in the emergency treatment of cardiac arrest. The efficacy of foxglove extracts in the treatment of heart ailments was reported as early as 1250[218] and the active agents contained in these extracts have not been improved upon.[219]

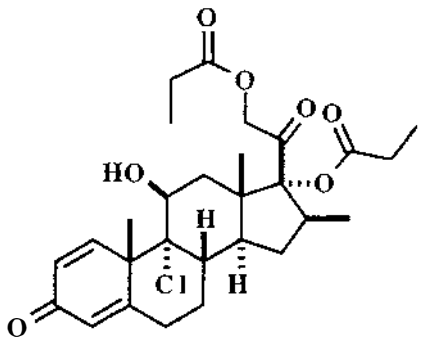
New steroids are constantly being isolated from diverse sources and some of these are unsurpassed in their biological activity.[220, 221] However, in their natural setting, many of these compounds occur in only trace amounts and synthesis is the only way that they can become readily available.



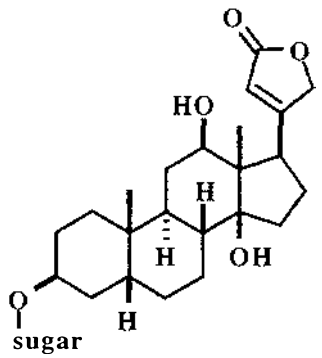
501 (oestradiol)



502 (betamethasone valerate)



503 (beclomethasone dipropionate)



504 (digoxin)

Figure 5.1

Any synthetic approach to a specific molecule, which is ultimately intended for pharmacological use, must meet a set of strict criteria in order for commercial manufacture to be considered economically viable. The synthesis must be short, the starting materials and reagents must be inexpensive, the reactions must be easily and safely carried out on large scale and the products must be obtained in enantiomerically pure form.[222]

Synthesis of steroids *via* a tandem transannular Diels-Alder (TTDA) reaction of a macrocyclic precursor, containing a *bis*-diene (in the form of a conjugated tetraene) and a *bis*-dienophile, should satisfy all of the criteria listed above. This novel approach is illustrated retrosynthetically (from the cyclopentano perhydrophenanthrene nucleus (**X**) of steroids) in **Figure 5.2**. Esterification is a convenient way of attaching the *bis*-diene to the *bis*-dienophile and the inclusion of a stereogenic centre in lactone **7** provides a potential method for controlling the stereochemical outcome of the TTDA reaction. A high level of stereochemical control is essential in this setting because the TTDA reaction generates eight new stereogenic centres in a single step. It was anticipated that the low reactivity of the singly activated *E*-dienophiles in structure **7** (**Sections 1.2.1.3**, **3.3.2** and **3.3.4**) and the rate retarding effect of the two ester tethers (**Section 1.2.1.2**) might be compensated for by the entropic advantage inherent in the TTDA reaction.

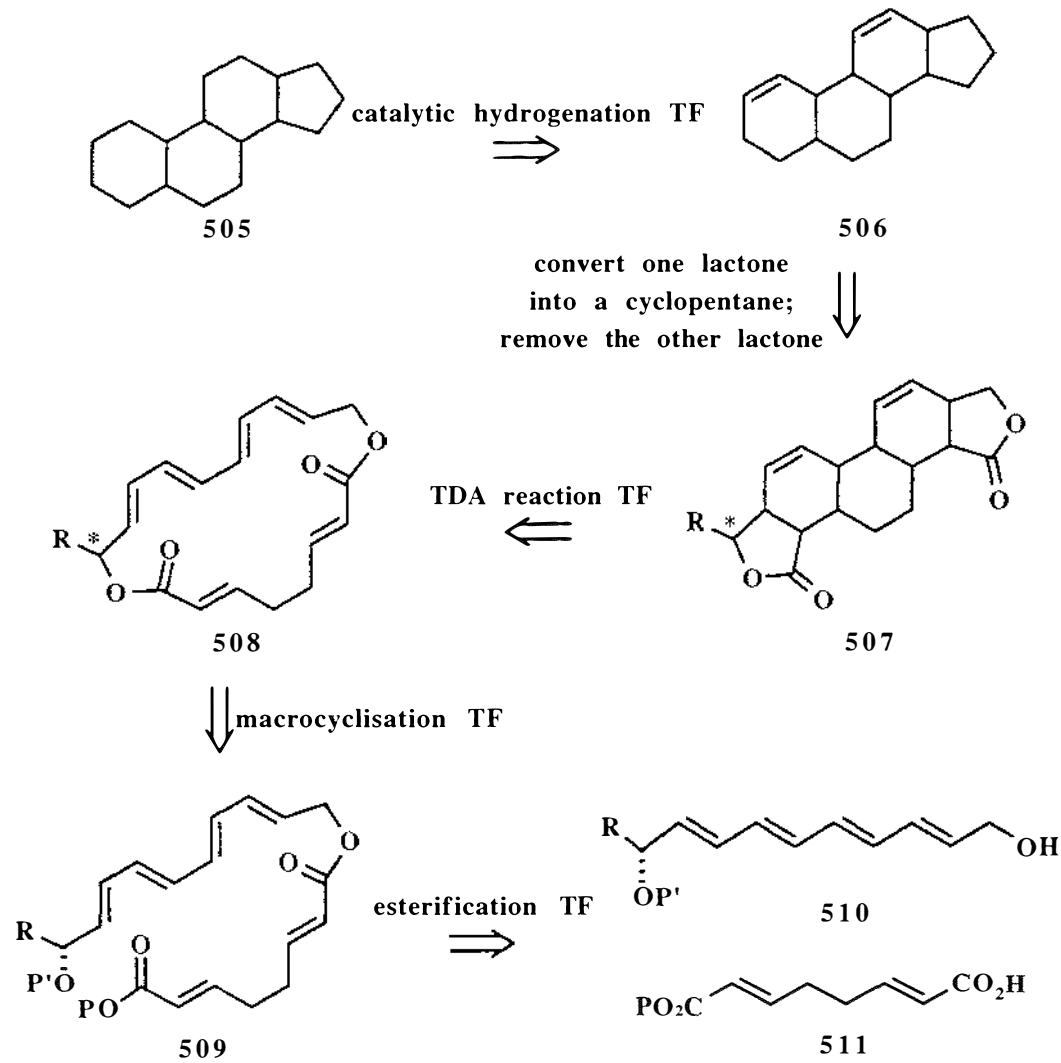
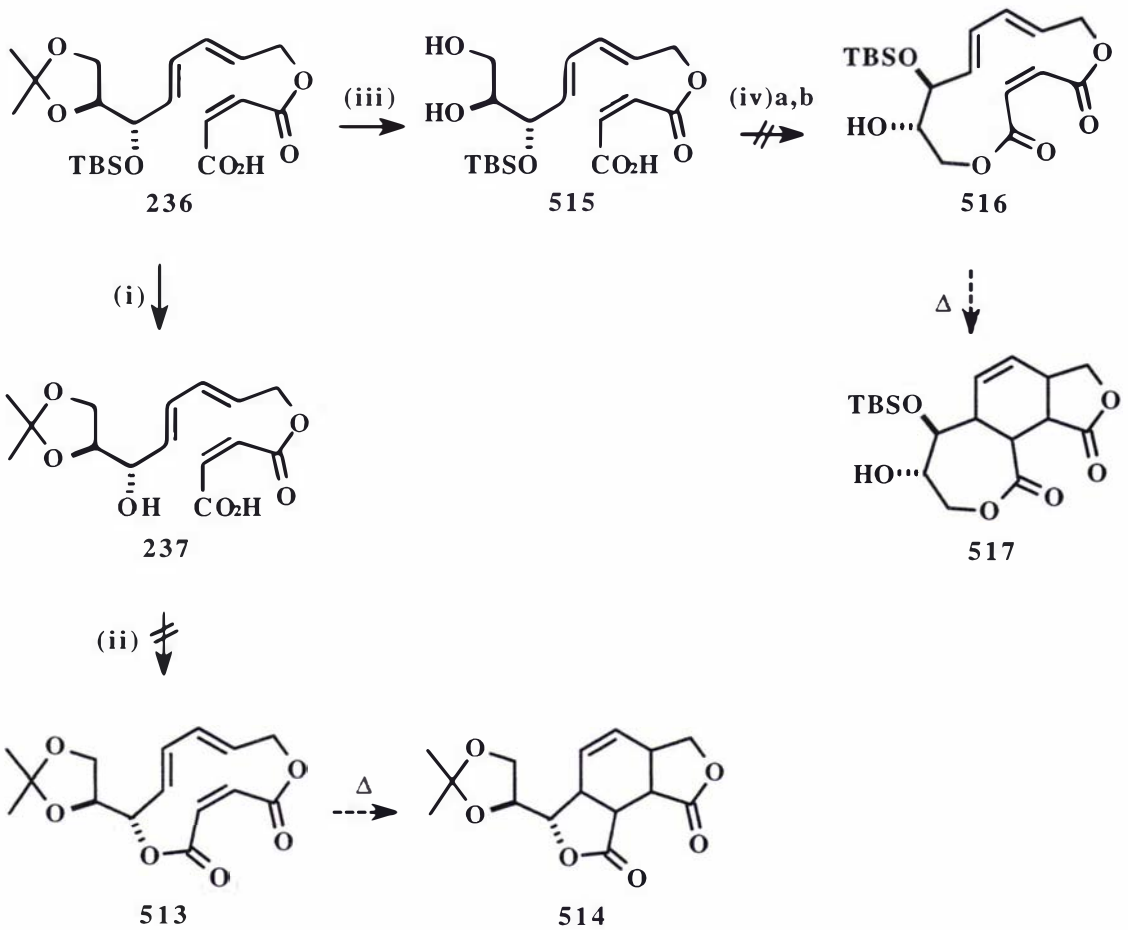

catalytic hydrogenation TF
505
506
convert one lactone
into a cyclopentane;
remove the other lactone
TDA reaction TF
508
507
macrocyclisation TF
esterification TF
509
510
511

Figure 5.2

5.2 Attempts to synthesize single TDA reaction precursors

Because of the complexity of precursors such as **508** (**Figure 5.2**) it was decided to carry out a model study involving the TDA reaction of a macrocycle containing a single diene and dienophile, as illustrated in **Scheme 5.1**.

Carboxylic acid **236** was treated with tetrabutylammonium fluoride[166] to expose the secondary alcohol, then a modified Yamaguchi macrocyclisation protocol[223] was attempted on compound **237** with 2,4,6-trichlorobenzoyl chloride, but the latter reaction was not successful. The reason for this was revealed by inspecting Dreiding models of compound **237**, which indicated that a very high level of strain would need to be overcome in order for lactonisation to occur.



Conditions: **(i)** TBAF, THF, RT, 16h, 85%; **(ii)** TEA, 2,4,6-trichlorobenzoyl chloride, toluene, RT, 2h, *then* DMAP, 10h; **(iii)** TFA, CH_2Cl_2, RT, 20min, 59%; **(iv)a** TEA, 2,4,6-trichlorobenzoyl chloride, toluene, RT, 18h, *then* DMAP; 3h; **(iv)b** DCC, DMAP, TfOH, chloroform, (slow addition of **53** *via* syringe pump), RT, 8h.

Scheme 5.1

Due to the difficulties encountered in the macrocylisation of compound **237**, it was decided to attempt to form a larger macrocycle with significantly more inherent conformational mobility. This strategy has the advantage that the bulky *tert*-butyldimethylsilyl group (which is intended to control the stereoselectivity in the ensuing TDA reaction) is retained. Carboxylic acid **236** was treated with trifluoroacetic acid[224] to form diol **515** in modest yield. Macrocyclisation of **515** using the modified Yamaguchi protocol[223] was then attempted. Unfortunately this reaction did not occur although a variety of solvents (benzene, toluene and xylene), starting material concentrations (1-10mmol/L) and reagent equivalents were tested. Mass spectral data (EI, 70eV) of the crude reaction mixture produced in reaction **(iv)a** disclosed fragments which had masses in excess of 700amu, indicating that intermolecular esterification may have been more rapid than macrolactonisation, in spite of the high dilution (up to 1mmol/L) that was used. A modified Steglich esterification protocol[225] using dicyclohexylcarbodiimide was also attempted, however, this too was unsuccessful.

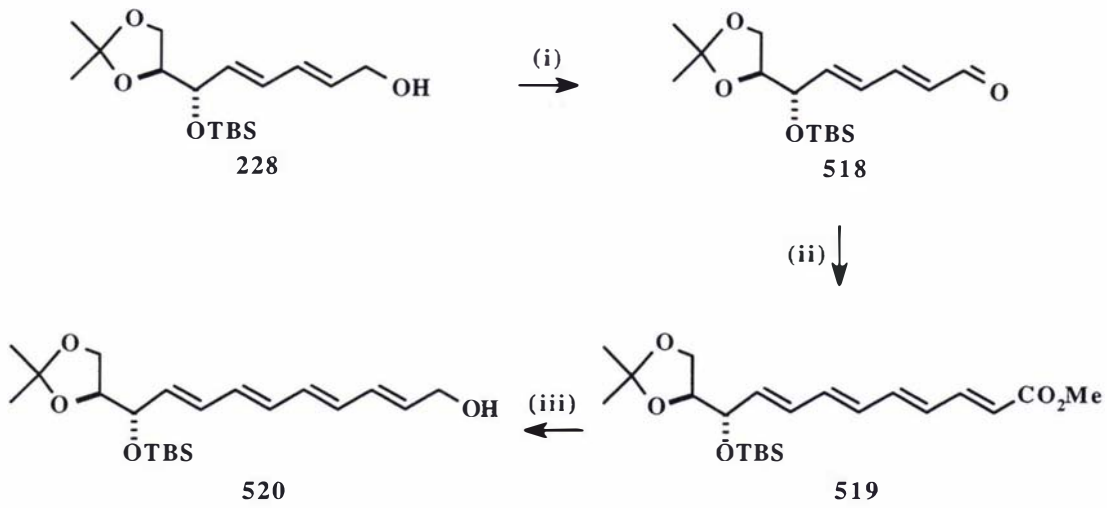
5.3: Attempts to synthesize TTDA reaction precursors

In spite of the lack of success with the model system (**Section 5.2**), synthesis of macrocyclic precursors for a TTDA reactions was still attempted. This involved three stages: synthesis of a *bis*-diene in the form of a conjugated tetraene (**Section 5.3.1**); synthesis of a *bis*-dienophile (**Section 5.3.2**) with an appropriate protecting group; and formation of the macrocycle (**Section 5.3.3**).

5.3.1 Synthesis of a chiral tetraenol

Dienol **228** (**Section 2.2.1**) was treated with Dess-Martin periodinane[167] (**Section 6.6.1**) to form aldehyde **518** in high yield (**Scheme 5.2**). This was then homologated with methyl 4-triphenyphosphoranylidene)-(2*E*)-2-butenoate[168, 169] (**Section 6.6.2**) to give tetraene ester **519** as a mixture of *E*- and *Z*-stereoisomers in modest yield. It was found that isomerisation with thiophenol and AIBN[170] was ineffective. Treatment of ester **519** with catalytic iodine in dichloromethane[226] afford the *E*-stereoisomer although nearly 40% of the material was unaccounted for. (This may have been due to loss of the isopropylidene group,[227] since isomerisation required the addition of extra iodine (0.2 equivalents) in this case.) It was found that the addition of 2,6-di-*tert*-butyl-4-methylphenol (0.2 equivalents) in the esterification step increased the yield of compound **519** to 78%, however, the presence of minute traces of the

antioxidant was detrimental to the subsequent isomerisation. Reduction of ester **519** with diisobutyl aluminium hydride afforded conjugated tetraenol **520** in excellent yield.

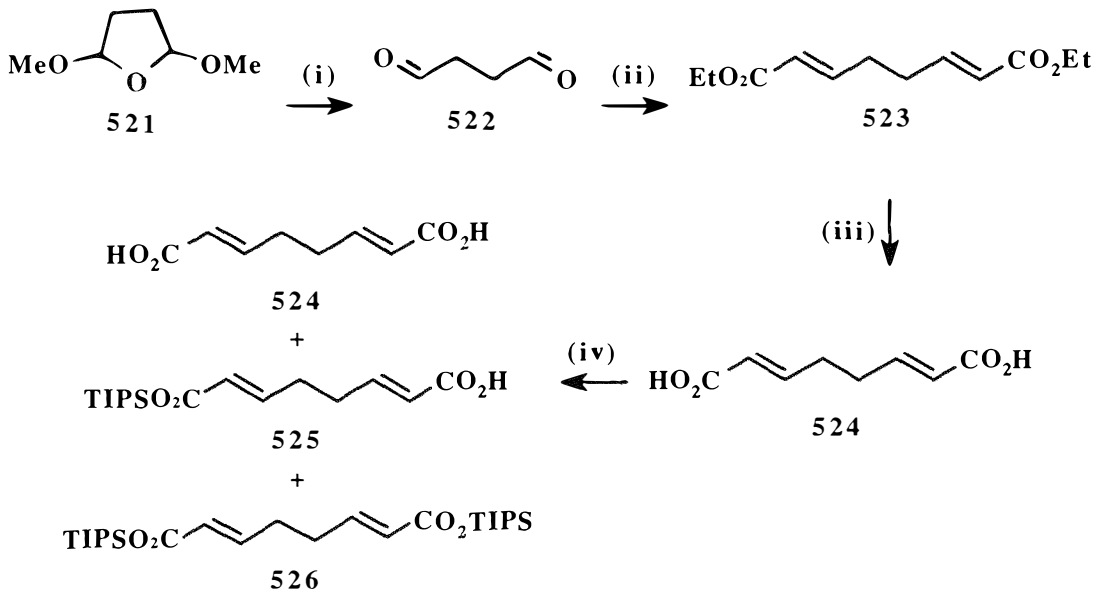


Conditions: **(i)** Dess-Martin Periodinane, CH_2Cl_2, RT, 30min, 83%; **(ii)** Ph_3P=CHCHCHCO$_2$Me, CH_2Cl_2, reflux, 3h, 46% *then* I_2, CH_2Cl_2, 5h, 59%; **(iii)** DIBALH, CH_2Cl_2, -110°C to -80°C, 88%.

Scheme 5.2

5.3.2 Synthesis of a *bis*-dienophile

A monoprotected *bis*-dienophile was prepared (**Scheme 5.3**) from 2,5-dimethoxytetrahydrofuran (**521**) *via* succinaldehyde[11] (**522, Section 6.6.4**). The dialdehyde was homologated with ethyl (triphenyphosphoranylidene)ethanoate to form diene **524** in excellent yield. Unlike previous reactions involving the related ylid (**Sections 2.2.1**, **2.2.2** and **5.3.1**), the *E*-stereoisomer was produced exclusively and no isomerisation was necessary after the Wittig reaction. Hydrolysis of the diester **524** with aqueous potassium hydroxide in tetrahydrofuran (followed by solvent extraction of the aqueous phase with diethyl ether, adjustment to pH 1 and filtration) produced diacid **525** in 68% yield. One equivalent of triisopropylsilyl chloride was slowly added to the diacid and triethylamine in dichloromethane producing monoprotected *bis*-dienophile **525** with an overall yield of 46% (along with disubstituted adduct **526** (22%) and recovered diacid **524** (20%))

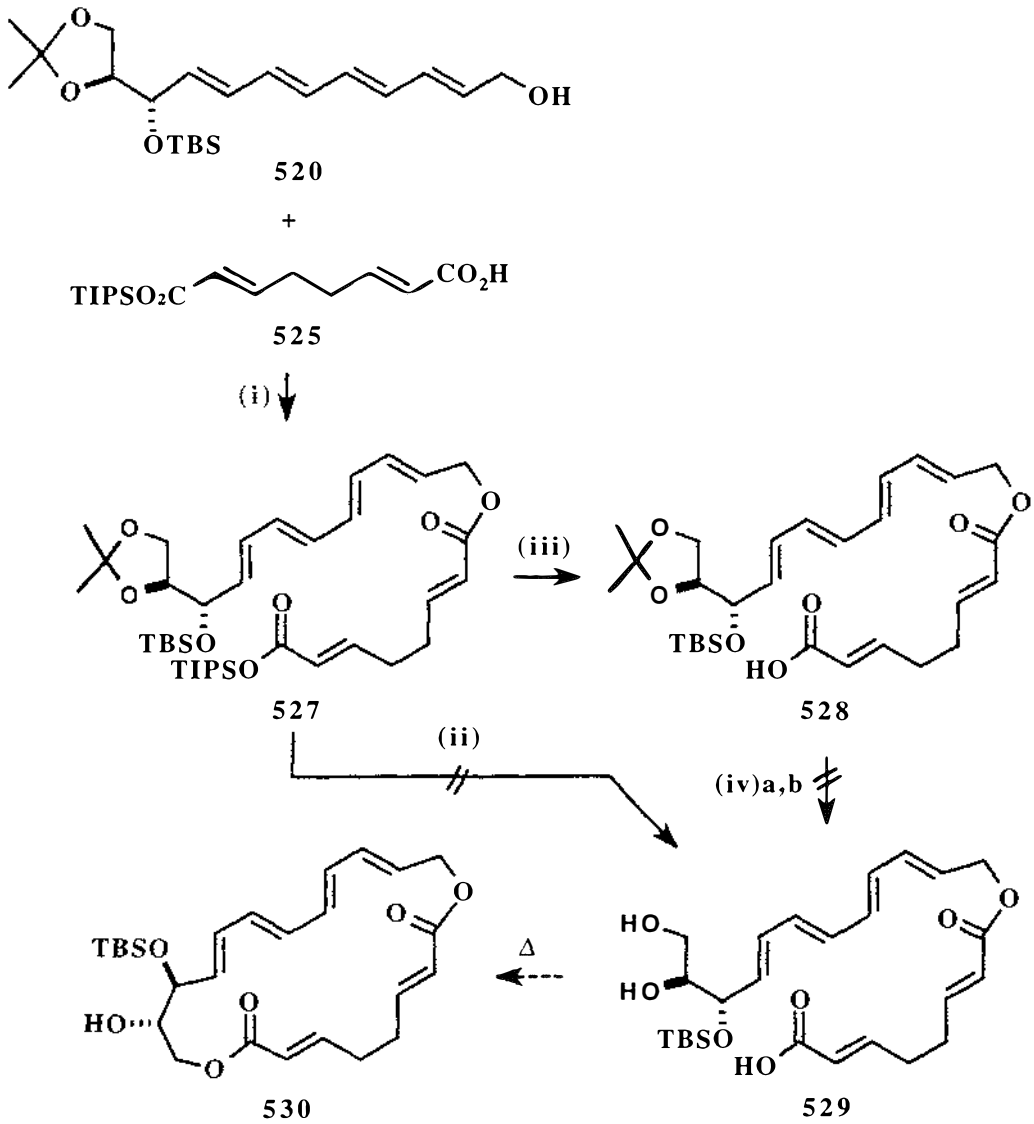


Conditions: **(i)** 0.6N HCl, RT, 1h, 78% (crude); **(ii)** $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, reflux, 64h, 88%; **(iii)** KOH, H_2O, THF, RT, 2h, 68%; **(iv)** TEA, TIPSCl, CH_2Cl_2, RT, 1h, 88%, **524:525:526** (23:52:25).

Scheme 5.3

5.3.3 Attempts to synthesize TTDA precursors

Esterification[206] of tetraenol **520** and monoprotected dienedioic acid **525** (**Scheme 5.4**) proved to be difficult to accomplish and yields were generally lower than 40%. However, compound **527** was isolated cleanly and exhibited infrared, NMR, UV and mass spectra commensurate with the structure shown.[228-231] An attempt was made to simultaneously remove the isopropylidene group[224] and triisopropyl group in compound **527** using trifluoroacetic acid, but the product (**529**) could not be identified in the crude reaction mixture, so it was decided to attempt these deprotections separately. Triisopropylsilyl esters are conveniently removed using potassium carbonate in methanol[232] and a quantitative yield was realized in the conversion of compound **527** to carboxylic acid **528**. Attempted removal of the isopropylidene group from **528** with trifluoroacetic acid caused decomposition of the starting material and so the deprotection was attempted using milder conditions. Aqueous acetic acid in THF has been successfully used to deprotect isopropylidene groups[224] and to deprotect primary TBS ethers in the presence of secondary ones.[233-235] In one example the starting material also incorporated an ester funtionality.[236] This protocol was investigated in an attempt to deprotect compound **528** and proton NMR analysis indicated that some level of success may have been achieved. However, optimal conditions need to be found for this difficult deprotection. (Catalytic iodine in methanol is another gentle method which can be used to remove isopropylidene groups.[227])



Conditions: **(i)** DCC, DMAP, CH_2Cl_2, RT, 3h, 34%; **(ii)** TFA, CH_2Cl_2, RT, 30min; **(iii)** K_2CO_3, methanol, RT, 10min, 100%; **(iv)a** TFA, CH_2Cl_2, RT, 30min; **(iv)b** AcOH, THF, H_2O, RT, 24h.

Scheme 5.4

Because it was not possible to form compound **529**, the macrocyclisation step could not be attempted. However, if conditions cannot be found which facilitate access to compound **529**, other strategies are available (**Figure 5.3**). Removal of the *tert*-butyldimethylsilyl group in compound **528** reveals a secondary alcohol group which has the potential to lactonise with the carboxylic acid group, but Dreiding models suggest that dilactone **532** would be highly strained. This strain could provide the impetus for a TTDA reaction to occur, but it also renders the dilactone difficult to form. One way of relieving some of this strain could be to isomerise acid **531** into **533** with sulphonic acid resin in acetone[132] (**Section 2.4.1.1**) and then attempt the macrocyclisation reaction.

The advantage which compound **533** has over **529** is that there is only one hydroxyl group which can participate in the macrocyclisation (although the secondary alcohol in compound **529** would be appreciably less reactive than the primary one). Compound **533** does not have the bulky *tert*-butyldimethylsilyl group to direct the stereochemical outcome of the TDA reaction, but it does have an isopropylidene group which would increase the conformational rigidity of the dilactone, which might lead to a measure of stereoselectivity.

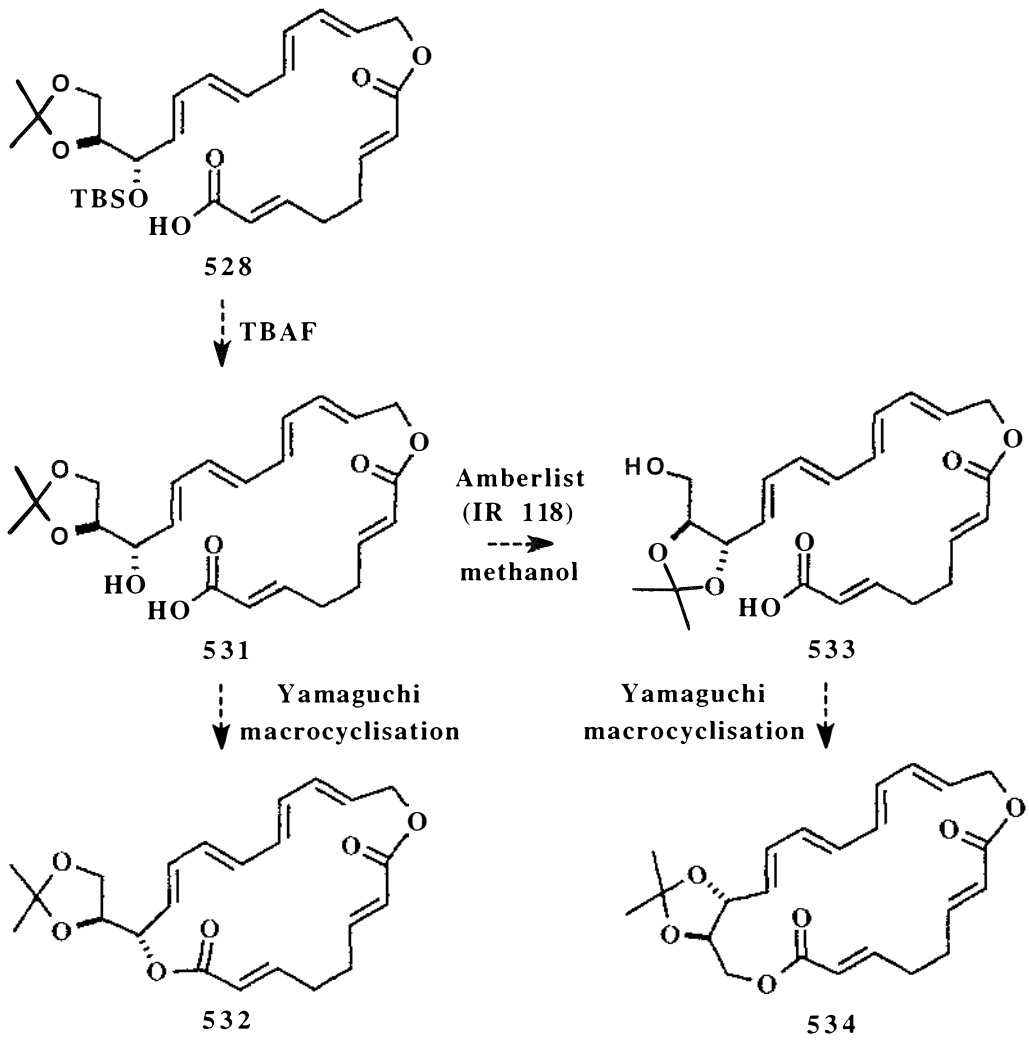


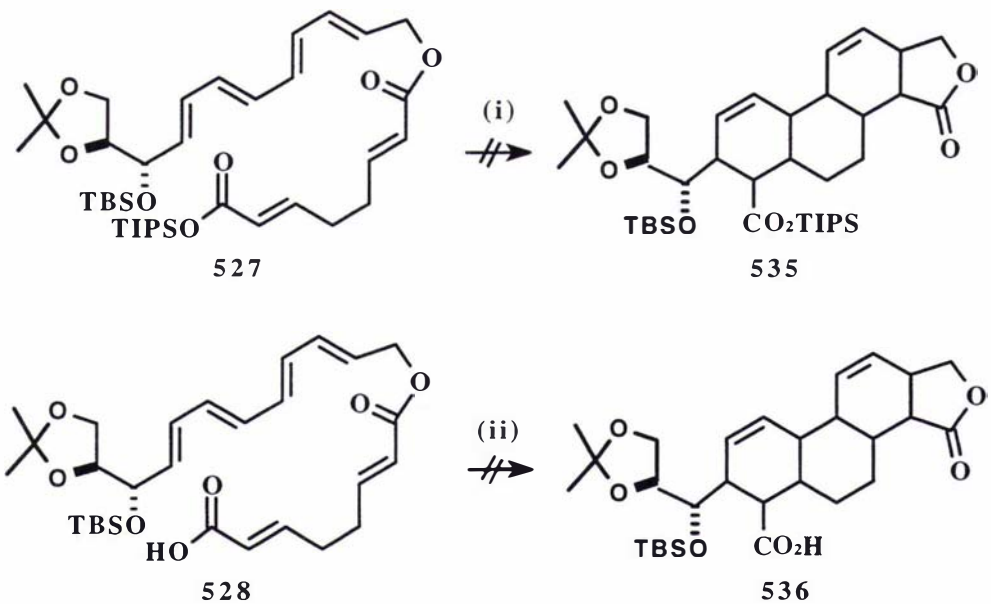
Figure 5.3

5.3.4 Attempted TIMDA reactions

Since the substrates were available, it was decided to attempt TIMDA reactions on compounds **527** and **528** (**Scheme 5.5**). It was anticipated that the singly activated *E*-dienophile in compound **527** (**Sections 1.2.1.3**, **3.3.2** and **3.3.4**) and the rate retarding effect of the ester tether (**Section 1.2.1.2**) would cause the molecule to be resistant to cycloaddition, therefore it was decided to carry out an ETDA reaction in d_6-DMSO to allow the reaction to be monitored easily by proton NMR analysis and to permit high temperatures to be used. The reaction was carried out for 11h at 110°C in an NMR tube, but unfortunately the starting material was completely destroyed under these conditions.

A TIMDA reaction was carried out on compound **528** in water with ten equivalents of sodium bicarbonate. (The sodium bicarbonate was added to solubilise the starting material, which proved to be successful at elevated temperatures.) It was thought that the water might force the hydrophobic molecule to coil in upon itself bringing the alkene moieties together to provide the impetus for a TIMDA reaction to occur.[237] However, refluxing for five days did not cause any change in the starting material.

It is apparent from these reactions that more forcing conditions are required to secure a TIMDA reaction. A number of options are available, including the application of high pressure.[237] These studies await future investigation.



Conditions: **(i)** d_6-DMSO, 110°C, 11h; **(ii)** $NaHCO_3$, H_2O, reflux, 5d.

Scheme 5.5

5.5 Conclusion

Whist the reactions in this **Section** were not all successful, the elegance of the strategy to form steroid skeletons *via* TTDA reactions is still compelling. A chiral conjugated tetraenol (**520**) has been prepared, as has a monoprotected dienedioic acid containing a suitable *bis*-dienophile moiety (**525**). Esterification of these materials produced a TIMDA precursor (**527**), albeit in modest yield. Selective deprotection of this TIMDA precursor was also achieved, but some of the other deprotections were troublesome. Preliminary investigations carried out on TIMDA precursors (**527** and **528**) confirm the fact that forcing conditions will be necessary to cause cycloaddition to occur. Formation of macrocyclic dilactones was difficult and, due to time constraints, this prevented any TTDA reactions from being attempted. However, a number of strategies are still available which may eventually enable stereocontrolled TTDA reactions to be carried out on these systems.

6 Experimental

6.1 Introduction

All moisture sensitive reactions were done under an argon atmosphere using oven dried (150°C) glassware. Benzene, toluene, xylene, THF and diethyl ether were purified and dried by distillation from sodium benzophenone ketyl.[238] Dichloromethane was distilled from calcium hydride.[238] Other commercial reagents were used as supplied (except in specific cases as indicated in the appropriate text).

Reactions were normally monitored by thin layer chromatography (TLC) on aluminium backed 60 F254 silica gel plates (Merck). Unless otherwise specified, compounds were detected by visualization under an ultraviolet lamp followed by treatment with alkaline potassium permanganate dip[239] and strong heating. In some cases reactions were followed by proton NMR analysis, *vide infra*.

Slow addition of solutions to reaction mixtures was accomplished using a Cole Parmer 74900 series syringe pump. Organic solvents partitioned against water as part of an aqueous work up were dried with anhydrous magnesium sulphate:sodium sulphate (3:1) prior to filtration and evaporation of the solvent *in vacuo*. Celite (Serva 545, 0.020-0.044mm) was occasionally used as a filtration aid. Kugelrohr distillation was carried out on a Buchi GKR-51.

Flash column chromatography and rapid vacuum filtration were carried out using oven dried (150°C) 60 silica gel (40-63μm, Merck). Radial chromatography was carried out with a Harrison Research 7924T chromatotron using 230mm diameter glass plates, precoated with a slurry of silica gel 60 HF254 (63-200μm, Merck):calcium sulphate hemihydrate (BDH) (17.5:1) and oven dried overnight (150°C). Hexane and ethyl acetate (distilled from laboratory grade solvents) were the principal eluents, although diethyl ether, dichloromethane, methanol and acetic acid (analytical grades) were also used when required. Product ratios were determined by integration of proton NMR spectra of crude reaction mixtures prior to chromatography. Unless indicated otherwise yields were determined from actual masses of material isolated in analytically pure form. Where diastereomeric mixtures were produced the overall yield given includes the contribution made from mixed fractions in which the individual stereoisomers could be identified by NMR spectra and were shown to be free of other impurities.

Melting points of crystalline materials were measured on a Reichert hot stage apparatus and are uncorrected. Optical rotation ($[\alpha]_D$) was measured on an Optical Activity Limited AA-100 polarimeter. The path length for neat samples was 0.05dm and 1.0dm was used for solutions. Infrared measurements were carried out on a Perkin-Elmer Paragon 1000 FT-IR spectometer. (Only the major peaks have been reported.) Proton and carbon nuclear magnetic resonance (NMR) spectra were recorded on a Jeol JNM-GX270W instrument. The following abbreviations were used: s, singulet; d, doublet; t, triplet, q, quartet; m, multiplet; b, broad; and obs, obscured (where the multiplicity could not be determined due to the position of a much larger peak). Unless otherwise specified chemical shifts (δ) are reported in parts per million values (ppm) relative to chloroform as the internal standard (7.27ppm for ^{1}H NMR and 77.0ppm for ^{13}C NMR respectively) and coupling constants (*J*) are given in hertz (Hz). Where necessary DEPT, APT, HETCOR, HSQC, HMQC, ROESY, phase sensitive COSY, NOESY and nOe difference experiments were performed. (A summary of the two dimensional NMR experiments carried out is contained in **Appendix 2**.) Ultraviolet-visible spectra were recorded on a Shimadzu UV-3101PC scanning spectrophotometer. (Spectroscopic grade methanol was used throughout.) Mass spectral measurements were made on a VG Instruments VG70-250S double focusing magnetic sector mass spectrometer. Electron Impact (EI) was carried out at 40, 70 or 80eV and Chemical Ionization (CI) was accomplished at 40eV and 70eV with ammonia gas. The source temperature was 180-200°C, the trap current was 200μA and for high resolution experiments a resolving power of 5000-6000 was used. Crystallographic analysis was performed on an Enraf Nonius Delft Diffractus 586 diffractometer.

6.1.1 General procedure for ETDA reactions

To a stirred solution of the starting material (5mmol/L) in benzene, toluene or xylene was added 2,6-di-*tert*-butyl-4-methylphenol (0.2eq) under argon. The solution was heated to reflux and heating continued until the starting material was consumed (as judged by proton NMR analysis or TLC of crude reaction mixtures), whereupon the solvent was evaporated and the products were separated chromatographically. (Proton NMR analysis of the crude reaction mixtures was used to determine the product ratios.)

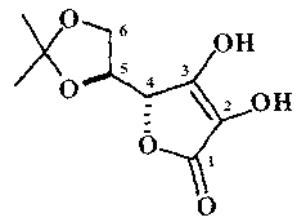
6.1.2 General procedure for ETDA reactions of carboxylic acids

To a stirred solution of the starting material (5mmol/L) in benzene, toluene or xylene was added 2,6-di-*tert*-butyl-4-methylphenol (0.2eq) under argon. The solution was heated to reflux and heating continued until the starting material was consumed (as judged by proton NMR analysis or TLC of crude reaction mixtures), whereupon the reaction mixture was cooled to RT, 0°C or -60°C and diazomethane[173] (**Section 6.6.3**) was added. The solvent was then evaporated and the products were separated chromatographically. (Proton NMR analysis of the crude reaction mixtures (before and after the addition of diazomethane) was used to determine the product ratios.)

6.2 Experimental for Chapter Two

6.2.1 Preparation of chiral dienols

5,6-*O*-isopropylidene-L-ascorbic acid (222)

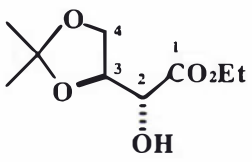


222

Protection of L-ascorbic acid (**221**) was based on the method of Jung and Shaw.[163] To a stirred solution of L-ascorbic acid (**221**) (100g, 0.568mol) in acetone (400mL, 5.68mol, 10eq) at RT under a calcium chloride drying-tube was added acetyl chloride (10.0mL, 1.50mol, 2.64eq). Further acetone (200mL) was subsequently added to aid stirring, which was continued for 8h. The mixture was refrigerated overnight and the resulting precipitate rinsed with cold acetone (3 x 100mL) then dried under vacuum yielding the **title compound (222)** (93.6g, 0.433mol, 76%) as a white crystalline solid: mp 217-219°C dec. [lit.[163] 214-218°C dec.]; $[\alpha]_D^{21}$ = +25.7° (c = 1.00, water) [lit.[240] $[\alpha]_D^{19}$ = +25.3° (c = 1.00, water)]; (Found: M^+, 216.0632. $C_9H_{12}O_6$ requires M, 216.0633); ν_{max} (KBr disc) 3243, 3074, 2992, 1754 and 1664cm^{-1}; δ_H (270MHz, d_6-DMSO/internal reference 2.50ppm) 1.25 (6H, s, -C(CH_3)$_2$-), 3.17-3.64 (2H, m, -CO*H*=CO*H*-), 3.88 (1H, dd, *J* 6.4, 8.3Hz, C6-*H*), 4.09 (1H, dd, *J* 7.2, 8.3Hz, C6-*H'*), 4.26 (1H, m, C5-*H*) and 4.70 (1H, d, *J* 2.9Hz, C4-*H*); δ_C (68.1MHz,

d_6-DMSO/internal reference 39.7ppm) 25.7, 26.0, 65.0, 73.6, 74.4, 109.1, 118.2, 152.4 and 170.2; *m/z* (CI/NH_3, 40eV) 216 (8%), 201 (45), 101 (89), 59 (48) and 43 (100).

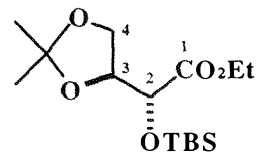
ethyl (2*R*, 3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate (223)



223

Oxidative cleavage of 5,6-*O*-isopropylidene-L-ascorbic acid (**222**) and esterification of the the resulting potassium salt was based on the method of Abushanab *et al.*[165, 164] To a stirred solution of 5,6-*O*-isopropylidene-L-ascorbic acid (**222**) (93.6g, 0.433mol) in water (457mL) containing potassium carbonate (119g, 0.866mol, 2eq), chilled in an ice bath and maintained below 20°C, was added 30% hydrogen peroxide (95.0mL, 0.866mol, 2eq). On completion of the addition the solution was warmed to RT and stirring was continued for 24h. The solvent was evaporated and the moist solid extracted with boiling absolute ethanol (6 x 200mL). After filtration and evaporation the material was dried under vacuum to give crude potassium (2*R*,3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate salt (107g) as a white powder. To a stirred solution of the crude salt in acetonitrile (500mL) at RT under argon was added ethyl iodide (55mL, 1.5mol, *ca* 3.5eq) and the solution was warmed to reflux. Stirring was continued for 44h and then the solvent was evaporated. The residue was partitioned between water (100mL) and dichloromethane (3 x 100mL). The combined organic layers were then washed with water (100mL), brine (2 x 100mL), dried, filtered and evaporated to produce the crude product (73.2g) as an orange oil. Distillation gave the **title compound (223)** (69.0g, 0.338mol, 78%) as a yellow oil: bp 84-88°C/0.5mmHg; $[\alpha]_D^{21}$ = +4.2° (c = 1.50, methanol); R_f = 0.20 (hexane:ethyl acetate (5:1)); (Found: M^+-CH_3, 189.0762. $C_8H_{13}O_5$ requires *M*, 189.0763); ν_{max} (film) 3489, 2986, 2937, 2906 1743 and 1208cm^{-1}; δ_H (270MHz, $CDCl_3/D_2O$ shake) 1.29 (3H, t, *J* 7.3Hz, -OCH_2CH_3), 1.34 and 1.41 (6H, 2 x s, -$C(CH_3)_2$-), 3.99 (1H, dd, *J* 7.0, 8.3Hz, C4-*H*), 4.08 (1H, dd, *J* 6.6, 8.3Hz, C4-*H'*), 4.09 (1H, d, *J* 3.1Hz, C2-*H*), 4.26 and 4.27 (2H, 2 x q, *J* 7.3Hz, -OCH_2CH_3) and 4.35 (1H, ddd, *J* 3.1, 6.6, 7.0Hz, C3-*H*); δ_C (68.1MHz, $CDCl_3$) 14.2, 25.4, 26.1, 61.9, 65.6, 70.4, 76.4, 109.8 and 171.8; *m/z* (EI, 40eV) 189 (73%), 131 (28), 101 (100), 60 (54) and 42 (84).

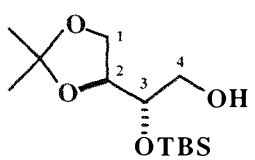
ethyl (2*R*,3*S*)-3,4-*O*-isopropylidene-2-(1-*tert*-butyl-1,1-dimethylsilyl)oxy -3,4-dihydroxybutanoate (224)



224

To a stirred solution of ethyl (2*R*,3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanoate (**223**) (10.2g, 0.0500mol) in DMF (10mL) at 0°C under argon was added imidazole (4.08g, 0.0600mol, 1.2eq) and *tert*-butyldimethylsilyl chloride (7.90g, 0.0525mol, 1.05eq). 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 (15.9g) as a yellow oil. Distillation gave the **title compound** (**224**) (10.8g, 0.0340mol, 68%) as a colourless oil: bp 148-150°C/14mmHg; $[\alpha]_D^{20}$ = +28.0° (c = 4.65, dichloromethane); R_f = 0.63 (hexane:ethyl acetate (5:1)); (Found: M^+-CH_3, 303.1628. $C_{14}H_{27}O_5Si$ requires *M*, 303.1614); ν_{max} (film) 2985, 2955, 2932, 2896, 2858, 1735, 1473, 1464, 1380, 1370 and 1156cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.08 and 0.11 (6H, 2 x s, -Si(CH_3)$_2$-), 0.92 (9H, s, -C(CH_3)$_3$), 1.30 (3H, t, *J* 7.1Hz, -OCH$_2$$CH_3$), 1.35 and 1.41 (6H, 2 x s, -C(CH_3)$_2$-), 3.97 (1H, dd, *J* 6.4, 8.5Hz, C4-*H*), 4.05 (1H, dd, *J* 6.4, 8.5Hz, C4-*H'*), 4.20 (1H, d, *J* 5.3Hz, C2-*H*), 4.21 and 4.22 (2H, 2 x q, *J* 7.1Hz, -OCH_2CH$_3$) and 4.33 (1H, td, *J* 6.4, 5.3Hz, C3-*H*); δ_C (68.1MHz, $CDCl_3$) -5.17, -4.92, 14.2, 18.4, 25.3, 25.7, 26.3, 60.9, 65.5, 73.3, 77.1, 109.5 and 170.8; *m/z* (EI, 70eV) 303 (22%), 261 (52), 203 (35), 101 (54) and 75 (100).

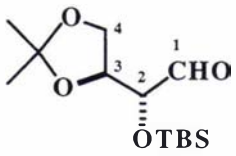
(2*S*,3*S*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2,4-butanetriol (225)



225

To a stirred solution of ethyl (2*R*,3*S*)-3,4-*O*-isopropylidene-2-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-3,4-dihydroxybutanoate (**224**) (4.44g, 0.0157mol) in dichloromethane (200mL) at -78°C under argon was added dropwise diisobutylaluminium hydride (1.0mol/L in toluene, 34.5mL, 0.0345mol, 2.2eq). On completion of the addition stirring was continued for 10min at -78°C then the mixture was allowed to warm to RT and stirred for a further 1h. The excess diisobutylaluminium hydride was quenched at RT with 2% aqueous sodium hydroxide solution (20mL). The material was filtered through celite and the filtrate was rinsed with dichloromethane (3 x 50mL). The combined extracts were washed with water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (3.15g) as a colourless oil. A small portion of the crude material (174mg) was purified on silica (10g) with hexane:ethyl acetate (10:1 then 5:1) to give an analytically pure sample of the **title compound** (**225**) (147mg) as a colourless oil: $[\alpha]_D^{18.5}$ = -11.0° (c = 6.80, dichloromethane); R_f = 0.20 (hexane:ethyl acetate (5:1)); (Found: M^+-CH_3, 261.1522. $C_{12}H_{25}O_4Si$ requires *M*, 261.1522); ν_{max} (film) 3462, 2985, 2954, 2930, 2887, 2858, 1472, 1463, 1380 and 1370cm^{-1}; δ_H (270MHz, $CDCl_3/D_2O$ shake) 0.12 (6H, s, -Si(CH_3)$_2$-), 0.91 (9H, s, -C(CH_3)$_3$), 1.36 and 1.43 (6H, 2 x s, -C(CH_3)$_2$-), 3.53 (1H, dd, *J* 4.7, 11.4Hz, C1-*H*), 3.67 (1H, dd, *J* 4.8, 11.4Hz, C1-*H'*), 3.78-3.89 (2H, m, C2-*H* and C3-*H*), 4.00 (1H, dd, *J* 6.6, 8.3Hz, C4-*H*) and 4.20 (1H, dd, *J* 6.6, 12.6Hz, C4-*H'*); δ_C (68.1MHz, $CDCl_3$) -4.71, -4.59, 18.1, 25.1, 25.8, 26.3, 63.6, 65.3, 72.8, 77.1 and 109.1; *m/z* (EI, 40eV) 261 (10%), 161 (59), 131 (66), 117 (100) and 75 (91).

(2*R*,3*S*)-3,4-*O*-isopropylidene-2-(1-*tert*-butyl-1,1-dimethylsilyl)oxy -3,4-dihydroxybutanal (226)



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Method A

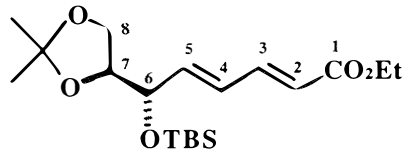
To a stirred solution of crude (2*S*,3*S*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2,4-butanetriol (**225**) (2.98g, *ca* 0.0108mol) in dichloromethane (30mL) was added Dess-Martin periodinane[167] (**Section 6.6.1**) (5.02g, 0.0119mol, *ca* 1.1eq) at RT under argon. After 1h the reaction mixture was filtered and the filtrate was

rinsed with dichloromethane (3 x 15mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (50mL) containing sodium thiosulphate pentahydrate (10g), saturated aqueous sodium bicarbonate (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (3.30g) as a yellow oil. The crude material was adsorbed onto silica (9g) then loaded onto a silica column (36g) and eluted with hexane:ethyl acetate (5:1) to give the **title compound** (**226**) (2.20g, 8.02mmol, 58% (2 steps)) as a colourless oil, *vide infra.*

Method B

To a stirred solution of ethyl (2*R*,3*S*)-3,4-*O*-isopropylidene-2-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-3,4-dihydroxybutanoate (**224**) (10.8g, 0.0338mol) in dichloromethane (100mL) at -100°C under argon was added diisobutylaluminium hydride (1.5mol/L in toluene, 33.8mL, 0.0570mol, 1.5eq) using a syringe pump over 1h. The excess diisobutylaluminium hydride was quenched at -100°C with 2% aqueous sodium hydroxide (30mL) then the mixture was allowed to warm to RT. Water (50mL) and dichloromethane (50mL) were added resulting in an emulsion, which was eliminated by the stepwise addition of saturated aqueous potassium sodium (+)-tartrate. The aqueous layer was extracted with dichloromethane (3 x 50mL) and the combined extracts were washed with 50% aqueous potassium sodium (+)-tartrate (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (11.0g) as a yellow oil. Distillation gave the **title compound** (**226**) (7.97g, 0.0290mol, 86%) as a colourless oil: bp 96°C/0.01mmHg; $[\alpha]_D^{21}$ = +2.0° (c = 4.79, dichloromethane); R_f = 0.46 (hexane:ethyl acetate (5:1)); (Found: M^++H, 275.1671. $C_{13}H_{27}O_4Si$ requires *M*, 275.1679); ν_{max} (film) 2986, 2954, 2931, 2888, 2858, 1737, 1472, 1463, 1380 and 1371cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.09 and 0.11 (6H, 2 x s, -Si(CH_3)$_2$-), 0.94 (9H, s, -C(CH_3)$_3$), 1.35 and 1.42 (6H, 2 x s, -C(CH_3)$_2$-), 3.95 (1H, dd, *J* 6.2, 8.7Hz, C4-*H*), 4.04 (1H, dd, *J* 1.4, 4.7Hz, C2-*H*), 4.07 (1H, dd, *J* 6.4, 8.7Hz, C4-*H'*), 4.32 (1H, ddd, *J* 4.7, 6.2, 6.4Hz, C3-*H*) and 9.70 (1H, d, *J* 1.4Hz, -*CH*O); δ_C (68.1MHz, $CDCl_3$) -5.00, -4.68, 18.3, 25.1, 25.7, 26.1, 65.1, 76.4, 77.7, 109.6 and 202.0; *m/z* (EI, 70eV) 275 (3%), 131 (25), 117 (31), 101 (100) and 75 (69).

ethyl (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-7,8-dihydroxy-2,4-octadienoate (227)



227

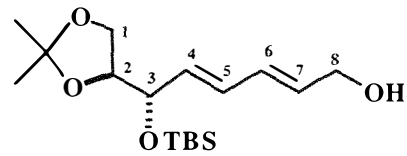
To a stirred solution of (2*R*,3*S*)-3,4-*O*-isopropylidene-2-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-3,4-dihydroxybutanal (**226**) (5.00g, 0.0182mol) in dichloromethane (50mL) at RT under argon was added ethyl 4-(triphenylphosphoranylidene)-(2*E*)-2-butenoate[168, 169] **(Section 6.6.2)** (9.55g, 0.0255mol, 1.4eq) and the resulting mixture warmed to reflux and heating continued for 1.5h. (Consumption of the starting material was monitored by proton NMR analysis.) Evaporation gave the crude product (14.5g) as a yellow oil. This material was adsorbed onto silica (15g) then loaded onto a silica column (15g) and eluted with hexane:ethyl acetate (10:1) to give a mixture of *Z*- and *E*-stereoisomers (79:21) of compound **227** (5.24g, 0.0141mol, 78%).

Isomerisation.

To a stirred solution of the *Z*- and *E*-stereoisomers of compound **227** (5.24g, 0.0141mol) in benzene (50mL) at RT under argon was added thiophenol (0.435mL, 4.23mmol, 0.3eq) and 2,2'-azo-*bis*-isobutyronitrile (0.345g, 0.213mmol, 0.15eq) in three potions at one hour intervals, during which time the reaction mixture was irradiated with ultraviolet light at reflux for a total of 3h. (Isomerisation was monitored by proton NMR analysis.) The solvent was evaporated to give the crude product (5.65g) as a yellow oil, which was used without further purification. A small portion of the crude material (103mg) was purified on silica (10g) with hexane:ethyl acetate (20:1 then 10:1) to give an analytically pure sample of the **title compound (227)** (77.0mg) as a pale yellow oil: $[\alpha]_D^{20}$ = -29.7° (c = 1.84, dichloromethane); R_f = 0.26 (hexane:ethyl acetate (10:1)); (Found: M^+, 370.2174 $C_{19}H_{34}O_5Si$ requires M, 370.2176); ν_{max} (film) 2985, 2956, 2931, 2887, 2858, 1714, 1646, 1620, 1472, 1463, 1380, and 1370cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.048 and 0.071 (6H, 2 x s, -Si(CH_3)$_2$-), 0.894 (9H, s, -C(CH_3)$_3$), 1.29 (3H, t, *J* 7.2Hz, -OCH$_2$$CH_3$), 1.33 and 1.39 (6H, 2 x s, -C(CH_3)$_2$-), 3.77 (1H, dd, *J* 6.0, 8.6Hz, C8-*H*), 3.95 (1H, dd, *J* 6.7, 8.6Hz, C8-*H*'), 4.07-4.15 (1H, m, C7-*H*), 4.20 (2H, q, *J* 7.2Hz, -OCH_2CH$_3$), 4.38 (1H, td, *J* 5.3, 0.8Hz, C6-*H*), 5.88 (1H, d, *J* 15.4Hz, C2-*H*), 6.13 (1H, dd, *J* 5.3, 15.3Hz, C5-*H*), 6.41 (1H, ddd, *J* 0.8, 11.0,

15.3Hz, C4-*H*) and 7.28 (1H, dd, *J* 11.0, 15.4Hz, C3-*H*); δ_C (68.1MHz, $CDCl_3$) -4.76, -4.61, 14.4, 18.3, 25.1, 25.8, 26.4, 60.3, 65.1, 72.8, 78.2, 109.5, 121.5, 129.1, 140.4, 143.4 and 166.7; *m/z* (EI, 70eV) 370 (0.3%), 313 (25), 270 (67), 101 (100) and 73 (62).

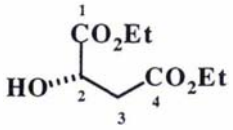
(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (228)



228

To a stirred solution of the crude ethyl (2*E*,4*E*,6*S*,7*S*)-7,8-*O*-isopropylidene-6-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-7,8-dihydroxy-2,4-octadienoate (**227**) (5.55g, *ca* 0.0150mol) in dichloromethane (75mL) at -78°C under argon was added dropwise diisobutylaluminium hydride (1.5mol/L in toluene, 22.0mL, 0.0330mol, *ca* 2.2eq). The starting material was consumed immediately and the excess diisobutylaluminium hydride was quenched at -60°C with 2% aqueous sodium hydroxide (20mL). Saturated aqueous potassium sodium (+)-tartrate (50mL) was added to disperse the emulsion which formed and the aqueous layer was extracted with further dichloromethane (3 x 50mL). The combined extracts were washed with brine (50mL) then dried, filtered and evaporated to give the crude product (6.07g) as a yellow oil. The crude product was adsorbed onto silica (10g) then loaded onto a silica column (100g) and eluted with hexane:ethyl acetate (3:1) to give the **title compound** (**228**) (3.50g, 0.0107mol, 58% (3 steps)) as a pale yellow oil: $[\alpha]_D^{24}$ = -26.0° (c = 1.33, dichloromethane); R_f = 0.14 (hexane:ethyl acetate (3:1)); (Found: M^+, 328.2066. $C_{17}H_{32}O_4Si$ requires *M*, 328.2070); ν_{max} (film) 3418, 2954, 2929, 2886, 2857, 1661, 1626, 1472, 1462, 1380, and 1371cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.02 and 0.43 (6H, 2 x s, -Si(CH_3)$_2$-), 0.87 (9H, s, -C(CH_3)$_3$), 1.30 and 1.36 (6H, 2 x s, -C(CH_3)$_2$-), 2.37 (1H, s, -O*H*), 3.75 (1H, dd, *J* 6.2, 8.4Hz, C1-*H*), 3.90 (1H, dd, *J* 6.6, 8.4 Hz, C1-*H'*), 4.05 (1H, m, C2-*H*), 4.14 (2H, d, *J* 5.3Hz, C8-*H*), 4.24 (1H, t, *J* 5.7Hz, C3-*H*), 5.59-5.70 (1H, m, C4-*H*), 5.73-5.88 (1H, m, C7-*H*) and 6.15-6.32 (2H, m, C5-*H* and C6-*H*); δ_C (68.1MHz, $CDCl_3$) -4.75, -4.52, 18.3, 25.2, 25.8, 26.4, 63.0, 65.2, 73.4, 78.6, 109.3, 130.3, 130.9, 131.6 and 132.2; *m/z* (EI, 70eV) 328 (2%), 227 (44), 210 (32), 101 (100) and 73 (77).

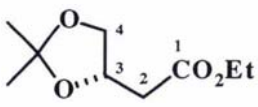
diethyl L-malate (230)



230

To a stirred solution of L-malic acid (**229**) (13.4g, 0.100mol) in ethanol (200mL) was added concentrated sulphuric acid (17.8mol/L, 13.4mL, 0.240mol, 2.4eq) at RT. On completion of the addition the solution was warmed to reflux and stirring was continued for 16h. The ethanol was partially evaporated then the residue was partitioned between dichloromethane (200mL) and saturated aqueous sodium bicarbonate (50mL). Solid sodium bicarbonate was added until effervescence subsided. The extract was washed with water (2 x 50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (21.0g) as a colourless oil. Distillation gave the **title compound** (**230**) (14.4g, 0.0757mol, 76%) as a colourless oil: bp 134-136°C/11mmHg [lit.[241] 85-86°C/0.5mmHg]; $[\alpha]_D^{19}$ = -10.2° (neat) [lit.[241] $[\alpha]_D^{22}$ = -10.4° (neat)]; R_f = 0.48 (hexane:ethyl acetate (2:1)); (Found: M^++H, 191.0923. $C_8H_{15}O_5$ requires M, 191.0919); ν_{max} (film) 3490, 2984, 2940, 2908, 1736, 1374, and 1271cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.26 (3H, t, J 7.3Hz, -$CH_2CO_2CH_2CH_3$), 1.30 (3H, t, J 7.3Hz, -$CHOHCO_2CH_2CH_3$), 2.77 (1H, dd, J 5.9, 16.5Hz, C3-*H*), 2.82 (1H, dd, J 4.6, 16.5Hz, C3-*H'*), 3.27 (1H, d J 5.3Hz, -O*H*), 4.18 (2H, q, J 7.3Hz, -$CH_2CO_2CH_2CH_3$), 4.27 (2H, dq, J 1.1, 7.3Hz, -$CHOHCO_2CH_2CH_3$) and 4.43-4.52 (1H, m, C2-*H*); δ_C (68.1MHz, $CDCl_3$) 14.2 (2 x C), 38.7, 61.0, 62.0, 67.3, 170.3 and 173.2; *m/z* (EI, 70eV) 191 (1%), 149 (6), 117 (100), 89 (36), 71 (94) and 43 (36).

ethyl (3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate (231)

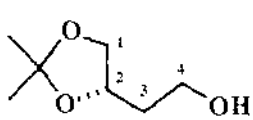


231

Regiochemical reduction of diethyl L-malate (**230**) and protection of the resulting diol was based on the method of Saito *et al.*[171] To a stirred solution of diethyl L-malate (**230**) (9.00g, 0.0473mol) in THF (85mL) at RT under argon in a 500mL flask fitted with a short reflux condenser was added dropwise borane-dimethyl sulphide complex (2.0mol/L in THF, 24.8mL, 0.0496mol, 1.05eq). On completion of the addition stirring

was continued for 30min then the solution was cooled to 10°C and sodium borohydride (0.0882g, 2.33mmol, 0.05eq) was added. After effervescence had ceased the solution was warmed to RT and stirring was continued for 30min. Ethanol (16.2mL, 0.276mol, 5.84eq) and *para*-toluenesulphonic acid monohydrate (0.450g, 2.33mmol, 0.05eq) were added and the resulting cloudy solution was stirred for 30min. Benzene:ethanol (1:1, 220mL) was added and evaporated in two equal portions, followed by benzene (80mL) to give the crude diol (7.82g) as a colourless gum. Chromatography of this material on silica (32g) with ethyl acetate gave ethyl (3*S*)-3,4-dihydroxybutanoate (6.16g, 0.0416mol, 88%) as a colourless oil: R_f = 0.39 (ethyl acetate). To a stirred solution of ethyl (3*S*)-3,4-dihydroxybutanoate (6.16g, 0.0416mol) in acetone (25mL) at RT under argon was added 2,2-dimethoxypropane (6.2mL, 0.050mol, 1.2eq) and *para*-toluenesulphonic acid monohydrate (0.399g, 2.10mmol, 0.05eq). On completion of the addition the solution was stirred for 30min then triethylamine (0.291mL, 2.09mmol, 0.05eq) and diethyl ether (70mL) were added. The reaction mixture was filtered through a silica plug (50g) which was rinsed with diethyl ether (250mL) and the combined extracts were evaporated to give the crude product (7.58g) as an opaque oil. Distillation of this material gave the **title compound** (**231**) (6.16g, 0.0327mol, 69%) as a colourless oil: bp 98°C/11mmHg [lit.[171] bp 110°C/23mmHg]; $[\alpha]_D^{20}$ = +18.5° (c = 1.17, chloroform) [lit.[171] $[\alpha]_D^{20}$ = +27.0° (c = 1.17, chloroform)]; $[\alpha]_D^{20}$ = +6.4° (c = 1.38, ethanol) [lit.[171] $[\alpha]_D^{20}$ = +15.4° (c = 1.38, ethanol)]; R_f = 0.70 (hexane:ethyl acetate (2:1)); (Found: M^+-CH_3, 173.0812. $C_8H_{13}O_4$ requires *M*, 173.0814); ν_{max} (film) 2986, 2936, 1736, 1371, 1380 and 1066cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.3Hz, -OCH_2CH_3), 1.36 and 1.42 (6H, 2 x s, -$C(CH_3)_2$-), 2.52 (1H, dd, *J* 7.3, 15.8Hz, C2-*H*), 2.72 (1H, dd, *J* 6.2, 15.8Hz, C2-*H'*), 3.66 (1H, dd, *J* 6.4, 8.3Hz, C4-*H*), 4.16 (2H, q, *J* 7.3Hz, -OCH_2CH_3), 4.17 (1H, dd, *J* 5.1, 8.3Hz, C4-*H'*) and 4.41-4.53 (1H, m, C3-*H*); δ_C (68.1MHz, $CDCl_3$) 14.2, 25.5, 26.9, 39.0, 60.6, 69.1, 72.0, 109.0 and 170.3; *m/z* (EI, 40eV) 173 (47%), 113 (55), 101 (32), 85 (100) and 42 (81).

(2*S*)-1,2-*O*-isopropylidene-1,2,4-butanetriol (232)

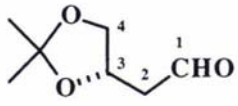


232

To a stirred solution of ethyl (3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate (**231**) (2.16g, 0.0115mol) in THF (30mL) at 0°C under argon was added lithium

aluminium hydride (1.09g, 0.0287mol, 2.5eq). On completion of the addition the solution was warmed to reflux and stirring was continued for 14h. The reaction mixture was diluted with dichloromethane (25mL) and the excess lithium aluminium hydride was quenched with THF:water (1:1, 7.5mL). The reaction mixture was filtered through celite (20g) which was rinsed with dichloromethane (3 x 100mL), then the combined extracts were dried, filtered and evaporated to give the crude product (1.70g) as a colourless oil. Kugelrohr distillation (87.5°C/0.05mmHg) gave the **title compound** (**232**) (1.54g, 0.0105mol, 91%) as a colourless oil: $[\alpha]_D^{19.5}$ = -2.29° (c = 9.80, methanol), [Lit.[242] $[\alpha]_D$= -2.23° (c = 9.80, methanol); R_f = 0.31 (hexane:ethyl acetate (1:1)); (Found: M^+-CH_3, 131.0709. $C_6H_{11}O_3$ requires *M*, 131.0708); ν_{max} (film) 3423, 2985, 2937, 2878, 1421, 1380, 1370, and 1059cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.37 and 1.44 (6H, 2 x d, 0.7Hz, -C(C*H*$_3$)$_2$-), 1.79-1.87 (2H, m, C3-*H*), 2.20-2.26 (1H, m, -O*H*), 3.61 (1H, dd, *J* 7.5, 8.1Hz, C1-*H*), 3.76-3.86 (2H, m, C4-*H*), 4.10 (1H, dd, *J* 6.2, 8.1Hz, C1-*H'*) and 4.23-4.24 (1H, m, C2-*H*); δ_C (68.1MHz, $CDCl_3$) 25.6, 26.8, 35.7, 60.1, 69.3, 74.6 and 108.8; *m/z* (EI, 40eV) 131(57%), 71 (78), 60 (36), 42 (100) and 31 (21).

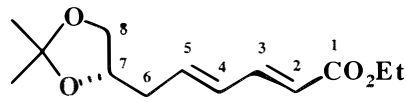
(3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanal (233)



233

To a stirred solution of (2*S*)-1,2-*O*-isopropylidene-1,2,4-butanetriol (**232**) (1.29g, 8.83mmol) in dichloromethane (20mL) at RT under argon was added Dess-Martin periodinane[167] (**Section 6.6.1**) (6.73g, 15.9mmol, 1.8eq). Stirring was continued for 16h then the reaction mixture was filtered through celite (10g) and evaporated to give the crude product (1.54g) as a colourless oil. Chromatography of this material on silica (60g) with hexane:ethyl acetate (2:1) gave the **title compound** (**233**) (0.989g, 6.86mmol, 78%) as a colourless oil: $[\alpha]_D^{20}$ = +15.4° (neat) [Lit.[242] $[\alpha]_D^{20}$ = +16.5° (neat)]; R_f = 0.64 (hexane:ethyl acetate (2:1)); (Found: M^++H, 145.0865. $C_7H_{13}O_3$ requires *M*, 145.0865); ν_{max} (film) 2987, 2937, 2877, 1725, 1372 and 1382cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.31 and 1.36 (6H, 2 x d, 0.7Hz, -C(C*H*$_3$)$_2$-), 2.60 (1H, ddd, *J* 1.3, 6.0, 17.4Hz, C2-*H*), 2.80 (1H, ddd, *J* 1.9, 6.6, 17.4Hz, C2-*H'*), 3.54 (1H, dd, *J* 6.6, 8.3Hz, C4-*H*), 4.14 (1H, dd, *J* 5.9, 8.3Hz, C4-*H'*), 4.43-4.53 (1H, m C3-*H*) and 9.73-9.76 (1H, m, -C*H*O); δ_C (68.1MHz, $CDCl_3$) 25.4, 26.8, 47.7, 69.0, 70.5, 109.0 and 199.6; *m/z* (EI, 40eV) 145 (1%), 129 (15), 69 (100) 59 (18) and 43 (51).

ethyl (2*E*,4*E*,7*S*)-7,8-*O*-isopropylidene-7,8-dihydroxy-2,4-octadienoate (234)



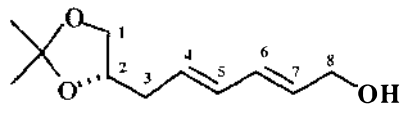
234

To a stirred solution of (3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanal (**233**) (1.02g, 7.06mmol) in dichloromethane (10mL) at RT under argon was added ethyl 4-(triphenylphosphoranylidene)-(2*E*)-2-butenoate[168, 169] (**Section 6.6.2**) (3.70g, 9.89mmol, 1.4eq). On completion of the addition stirring was continued at RT for 1h. Silica gel (7.5g) was added and the solvent was evaporated. This material was loaded onto a silica column (75g) which was eluted with hexane:ethyl acetate (10:1 then 5:1) to give a mixture of *Z*- and *E*-stereoisomers (50:50) of compound **234** (0.598g, 2.49mmol, 35%).

Isomerisation.

To a stirred solution of the *Z*- and *E*-stereoisomers of compound **234** (0.598g, 2.49mmol) in benzene (5mL) at RT under argon was added thiophenol (51.0μL, 0.98mmol, 0.2eq) and 2,2'-azo-*bis*-isobutyronitrile (40.8mg, 0.250mmol, 0.1eq) in two potions at one hour intervals, during which time the reaction mixture was irradiated with ultraviolet light at reflux for a total of 2h. (Isomerisation was monitored by proton NMR analysis.) The solvent was evaporated to give the crude product (0.740g) as a yellow oil. Chromatography of this material on silica (20g) with hexane:ethyl acetate (10:1 then 5:1) gave the **title compound** (**234**) (0.464g, 1.93mmol, 78%) as a colourless oil: $[\alpha]_D^{21}$ = -4.1° (c = 0.40, dichloromethane); R_f = 0.41 (hexane:ethyl acetate (5:1)); (Found: M^+-CH_3, 225.1116. $C_{12}H_{17}O_4$ requires *M*, 225.1127); ν_{max} (film) 2984, 2936, 2904, 2875, 1714, 1644, 1618, 1379, 1369 and 1262cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.3Hz, -OCH_2CH_3), 1.36 and 1.43 (6H, 2 x s, -$C(CH_3)_2$-), 2.34-2.71 (2H, m, C6-*H*), 3.58 (1H, dd, *J* 6.8, 8.0Hz, C8-*H*), 4.04 (1H, dd, *J* 6.2, 8.0Hz, C8-*H'*), 4.20 (2H, q, *J* 7.3Hz, -OCH_2CH_3), 4.14-4.26 (1H, m, C7-*H*), 5.83 (1H, d, *J* 15.6Hz, C2-*H*), 6.03-6.16 (1H, m, C5-*H*), 6.26 (1H, dd, *J* 10.8, 15.1Hz, C4-*H*) and 7.26 (1H, dd, *J* 10.8, 15.6Hz, C3-*H*); δ_C (68.1MHz, $CDCl_3$) 14.4, 25.6, 26.9, 37.2, 60.3, 68.8 74.8, 109.1, 120.4, 130.8, 138.1, 144.1 and 166.8; *m/z* (CI/NH_3, 40eV) 225 (10%), 101 (100), 83 (8), 73 (13) and 43 (28).

(2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-4,6-octdadiene-1,2,8-triol (235)

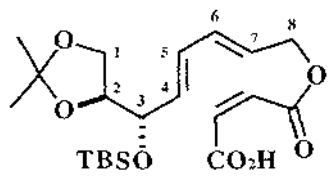


235

To a stirred solution of ethyl (2*E*,4*E*,7*S*)-7,8-*O*-isopropylidene-7,8-dihydroxy-2,4-octadienoate (**234**) (472mg, 1.96mmol) in dichloromethane (20mL) at -80°C under argon was added diisobutylaluminium hydride (1.5mol/L, 2.88mL, 4.32mmol, 2.2eq). On completion of the addition the excess diisobutylaluminium hydride was quenched by the addition of ethyl acetate (1.0mL) and the reaction mixture was diluted with hexane (50mL) and filtered through silica gel (10g) which was eluted with hexane, hexane:ethyl acetate (5:1 then 2:1) and ethyl acetate. Evaporation of the combined extracts gave the crude product (313mg) as a colourless oil. Chromatography of this material on silica (10g) with hexane:ethyl acetate (2:1) gave the **title compound** (**235**) (155mg, 0.782mmol, 40%) as a colourless oil: $[\alpha]_D^{21}$ = +13.2° (c = 0.650, dichloromethane); R_f = 0.32 (hexane:ethyl acetate (2:1)); (Found: M^+, 198.1253. $C_{11}H_{18}O_3$ requires *M*, 198.1255); ν_{max} (film) 3418, 2986, 2934, 2873, 1659, 1455, 1371, 1381 and 1216cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.36 and 1.42 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 1.70 (1H, s, -O*H*), 2.23-2.61 (2H, m, C3-*H*), 3.57 (1H, dd, *J* 7.0, 7.9Hz, C1-*H*), 4.02 (1H, dd, *J* 5.9, 7.9Hz, C1-*H'*), 4.09-4.24 (3H, m, C2-*H* and C8-*H*), 5.67 (1H, dt, *J* 14.5, 7.1Hz, C4-*H*) 5.77 (1H, dt, *J* 14.5, 5.9Hz, C7-*H*) and 6.06-6.29 (2H, m, C5-*H* and C6-*H*); δ_C (68.1MHz, $CDCl_3$) 25.7, 26.9, 36.9, 63.3, 68.8, 75.3, 109.0, 129.2, 130.7, 131.1 and 132.1; *m/z* (EI, 70eV) 198 (2%), 183 (47), 101 (100), 80 (81) and 59 (49).

6.2.2 Prpearation of ETDA precursors

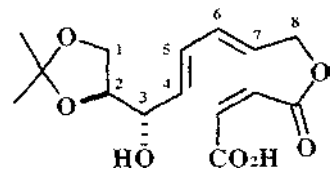
(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (236)



236

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (**228**) (0.492g, 1.50mmol) in dichloromethane (25mL) at RT under argon was added triethylamine (0.334mL, 2.40mmol, 1.6eq), maleic anhydride (0.330g, 3.37mmol, 2.25eq) and N,N-dimethylaminopyridine (0.0180g, 0.150mmol, 0.1eq). Stirring was continued for 10min and the reaction mixture was diluted with dichloromethane (100mL) and partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (0.735g) as a yellow oil. Chromatography of this material on silica (20g) with ethyl acetate:hexane:acetic acid (200:50:1) gave the **title compound** (**236**) (0.631g, 1.48mmol, 99%) as a pale yellow oil: $[\alpha]_D^{18}$ = -39.4° (c = 0.62, dichloromethane); R_f = 0.46 (ethyl acetate:hexane:acetic acid (200:50:1)); (Found: M^+, 426.2043, . $C_{21}H_{34}O_7Si$ requires M, 426.2074); ν_{max} (film) 3175, 2986, 2955, 2930, 2889, 2857, 1732, 1714, 1642, 1472, 1462, 1413, 1382, 1372 and 1256cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.057 and 0.077 (6H, 2 x s, -Si(C*H*$_3$)$_2$-), 0.902 (9H, s, -C(C*H*$_3$)$_3$), 1.34 and 1.40 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 3.79 (1H, dd, *J* 6.0, 8.6Hz, C1-*H*), 3.95 (1H, dd, *J* 6.6, 8.6Hz, C1-*H'*), 4.05-4.16 (1H, m, C2-*H*), 4.32 (1H, t, *J* 5.6Hz, C3-*H*), 4.80 (2H, d, *J* 7.0Hz, C8-*H*), 5.71-5.86 (2H, m, C4-*H* and C7-*H*) 6.20-6.52 (2H, m, C5-*H* and C6-*H*) and 6.39 and 6.46 (2H, 2 x d, B and A of AB, J_{AB} 12.5Hz, -C*H*=C*H*CO$_2$H); δ_C (68.1MHz, $CDCl_3$) -4.73, -4.51, 18.3, 25.1, 25.9, 26.4, 65.1, 67.0, 72.9, 78.4, 109.4, 124.1, 129.0, 129.8, 134.4, 135.6, 136.1, 164.1 and 167.2; *m/z* (EI, 70eV) 426 (0.1%), 227 (24), 210 (44), 101 (100), 75 (69) and 43 (27).

(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl hydrogen maleate (237)

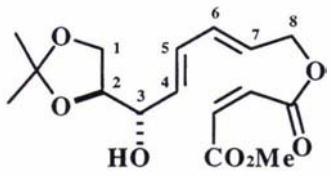


237

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (**236**) (1.20g, 2.81mmol) in THF (15mL) at RT under argon was added tetrabutylammonium fluoride (1.0mol/L in THF, 5.62mL, 5.62mmol, 2eq). On completion of the addition stirring was continued for 16h then the reaction mixture was diluted with dichloromethane (300mL) and partitioned against saturated aqueous ammonium chloride solution (150mL). The

ammonium chloride solution was further extracted with chloroform (2 x 150mL) and the combined extracts were washed with brine (150mL), dried (anhydrous sodium sulphate only), filtered and evaporated to give the crude product (3.35g) as a yellow oil. The crude product was adsorbed onto silica (7.5g) then loaded onto a silica column (55g) and eluted with ethyl acetate:acetic acid (40:1) gave the **title compound** (**237**) (0.751g, 2.41mmol, 85%) as a colourless oil: $[\alpha]_D^{19.5}$ = -16.4° (c = 1.28, dichloromethane); R_f = 0.50 (ethyl acetate:acetic acid (40:1)); (Found: M^+-H, 311.1130. $C_{15}H_{19}O_7$ requires *M*, 311.1131); ν_{max} (film) 3433, 2989, 2937, 2944, 1730, 1713, 1644, 1415, 1383, 1372 and 1215cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.37 and 1.46 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 3.78 (1H, dd, *J* 5.0, 7.8Hz, C1-*H*), 3.96-4.16 (3H, m, C1-*H'*, C2-*H* and C3-*H*), 4.78 (2H, d, *J* 6.4Hz, C8-*H*), 5.62-5.93 (2H, m, C4-*H* and C7-*H*), 6.16-6.47 (2H, m, C5-*H* and C6-*H*) and 6.36 and 6.43 (2H, 2 x d, B and A of AB, J_{AB} 12.5Hz, -C*H*=C*H*CO$_2$H); δ_C (68.1MHz, $CDCl_3$) 25.3, 26.8, 65.8, 66.6, 73.1, 78.6, 109.9, 125.6, 129.1, 131.1, 133.1, 134.7, 135.2, 164.9 and 166.8; *m/z* (EI ,70eV) 311 (2%), 113 (17), 101 (100), 59 (14) and 43 (25).

(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl methyl maleate (238a)

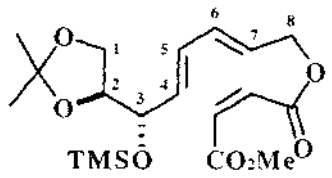


238a

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl hydrogen maleate (**237**) (7.51g, 2.41mmol) in diethyl ether (30mL) at 0°C was added dropwise an ethereal solution of diazomethane[173] (**Section 6.6.3**). On completion of the addition the solvent was evaporated to give the crude product (0.800g) as a yellow oil. Chromatography of this material on silica (25g) with hexane:ethyl acetate (1:1) gave the **title compound** (**238a**) (0.582g, 1.78mol, 74%) as a pale yellow oil: $[\alpha]_D^{20}$ = -14.3° (c = 1.47, dichloromethane); R_f = 0.34 (hexane:ethyl acetate (1:1)); (Found: M^+-H, 325.1282. $C_{16}H_{21}O_7$ requires *M*, 325.1287); ν_{max} (film) 3467, 2987, 2953, 2887, 1731, 1647, 1438, 1372, 1383 and 1215 cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.31 and 1.40 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 2.77 (1H, s, -O*H*), 3.70 (1H, dd, *J* 5.1, 7.7Hz, C1-*H*), 3.72 (3H, s, -CO$_2$C*H*$_3$), 3.87-4.11 (3H, m, C1-*H'*, C2-*H* and C3-*H*), 4.67 (2H, d, *J* 6.4Hz, C8-*H*), 5.64 (1H, dd, *J* 6.4, 14.3Hz, C4-*H*), 5.77 (1H, dt, *J* 14.3, 6.4Hz, C7-*H*), 6.22 (2H, d, *J* 0.4Hz, -C*H*=C*H*CO$_2$CH$_3$) and 6.15-6.38 (2H, m, C5-*H* and

C6-*H*); δ_C (68.1MHz, $CDCl_3$) 25.2, 26.6, 52.1, 65.1, 65.6, 73.1, 78.5, 109.6, 126.7, 129.3, 129.7, 131.2, 132.3, 133.4, 164.5 and 165.3; *m/z* (EI, 70eV) 325 (0.06%), 121 (6), 101 (100), 59 (13) and 43 (45).

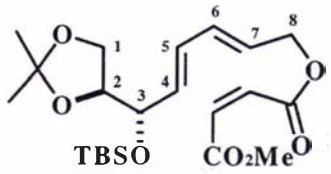
(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238b)



238b

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl methyl maleate (**238a**) (101mg, 0.311mmol) in dichloromethane (5mL) at 0°C under argon was added triethylamine (94.7μL, 0.684mmol, 2.2eq), trimethylsilyl trifluoromethanesulphonate (108μL, 0.559mmol, 1.8eq) and N,N-dimethylaminopyridine (crystal). On completion of the addition the solution was warmed to RT and stirring was continued for 2.5h. The reaction mixture was diluted with diethyl ether (20mL) and partitioned against saturated aqueous sodium bicarbonate (20mL). The aqueous layer was extracted with diethyl ether (2 x 10mL) and the combined extracts were washed with brine (10mL) then dried, filtered and evaporated to give the crude product (0.162g) as a yellow oil. Chromatography of this material on silica (8g) with hexane:ethyl acetate (10:1 then 5:1) gave the **title compound** (**238b**) (63.0mg, 0.159mmol, 51%) as a colourless oil: $[\alpha]_D^{20}$ = -16.2° (c = 0.680, dichloromethane); R_f = 0.28 (hexane:ethyl acetate (5:1)); (Found: M^+, 398.1755. $C_{19}H_{30}O_7Si$ requires *M*, 398.1761); ν_{max} (film) 2986, 2955, 2898, 1732, 1645, 1438, 1380, 1371 and 1213cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.127 (9H, s, -Si(CH_3)$_3$), 1.34 and 1.40 (6H, 2 x s, -C(CH_3)$_2$-), 3.75 (1H, dd, *J* 6.1, 8.4Hz, C1-*H*), 3.79 (3H, s -CO_2CH_3), 3.95 (1H, dd, *J* 6.5, 8.4Hz, C1-*H'*), 4.02-4.10 (1H, m, C2-*H*) 4.19-4.26 (1H, m, C3-*H*), 4.73 (2H, d, *J* 7.0Hz, C8-*H*), 5.66-5.89 (2H, m, C4-*H* and C7-*H*), 6.20-6.40 (2H, m, C5-*H* and C6-*H*) and 6.27 (2H, s, -C*H*=C*H*CO_2CH_3); δ_C (68.1MHz, $CDCl_3$) 0.252, 25.2, 26.4, 52.1, 65.3 (2 x C), 73.5, 78.6, 109.3, 125.9, 129.4, 129.7, 130.4, 133.2, 133.9, 164.6 and 165.3; *m/z* (EI, 40eV) 398 (0.1%), 168 (64), 113 (35), 101 (100) and 73 (31).

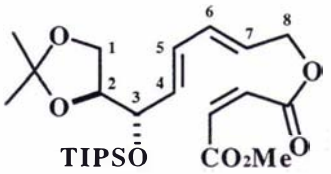
(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238c)



238c

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (**236**) (0.503g, 1.18mmol) in diethyl ether (10mL) at RT was added dropwise an ethereal solution of diazomethane[173] (**Section 6.6.3**). On completion of the addition the solvent was evaporated to give the crude product (0.535g) as a yellow oil. Chromatography of this material on silica (20g) with hexane:ethyl acetate (5:1) gave the **title compound** (**238c**) (0.417g, 0.946mmol, 80%) as a pale yellow oil: $[\alpha]_D^{20}$ = -27.6° (c = 1.89, dichloromethane); R_f = 0.32 (hexane:ethyl acetate (5:1)); (Found: M^+-CH_3, 425.2022. $C_{21}H_{33}O_7Si$ requires *M*, 425.1996); ν_{max} (film) 2985, 2954, 2931, 2887, 2857, 1735, 1472, 1462, 1438, 1380, 1371 and 1253cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.047 and 0.068 (6H, 2 x s, -Si(CH_3)$_2$-), 0.893 (9H, s, -C(CH_3)$_3$), 1.33 and 1.39 (6H, 2 x s, -C(CH_3)$_2$-), 3.77 (1H, dd, *J* 6.3, 8.4Hz, C1-*H*), 3.78 (3H, s, -CO_2CH_3), 3.93 (1H, dd, *J* 6.6, 8.4Hz, C1-*H'*), 4.04-4.12 (1H, m, C2-*H*), 4.29 (1H, t, *J* 5.5Hz, C3-*H*), 4.72 (2H, d, *J* 6.6Hz, C8-*H*), 5.67-5.88 (2H, m, C4-*H* and C7-*H*), 6.21-6.39 (2H, m, C5-*H* and C6-*H*) and 6.27 (2H, s, -C*H*=C*H*COCH$_3$); δ_C (68.1MHz, $CDCl_3$) -4.84, -4.64, 18.2, 25.1, 25.7, 26.3, 52.0, 65.1, 65.2, 73.2, 78.5, 109.2, 125.7, 129.4, 129.6, 130.1, 133.3, 133.9, 164.5 and 165.2; *m/z* (EI, 40eV) 425 (1%), 210 (56), 187 (36), 113 (56) and 101 (100).

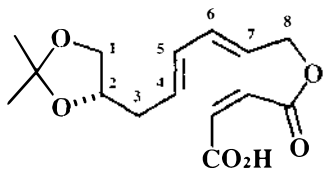
(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1,1,1-triisopropylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238d)



238d

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl methyl maleate (**238a**) (51.5mg, 0158mmol) in dichloromethane (5mL) at 0°C under argon was added triethylamine (49.1μL, 0.347mmol, 2.2eq), triisopropylsilyl trifluoromethanesulphonate (60.8μL, 0.284mmol, 1.8eq) and N,N-dimethylaminopyridine (crystal). On completion of the addition the solution was warmed to RT and stirring was continued for 20h. Additional triethylamine (49.1μL, 0.347mmol, 2.2eq), triisopropylsilyl trifluoromethanesulphonate (60.8μL, 0.284mmol, 1.8eq) and N,N-dimethylaminopyridine (crystal) were added and stirring continued for a further 20h. The reaction mixture was diluted with diethyl ether (20mL) and partitioned against saturated aqueous sodium bicarbonate (20mL). The aqueous layer was extracted with diethyl ether (2 x 10mL) and the combined extracts were washed with brine (10mL) then dried, filtered and evaporated to give the crude product (0.129g) as a yellow oil. Chromatography of this material on silica (6g) with hexane:ethyl acetate (10:1 then 5:1) gave the **title compound** (**238d**) (43.9mg, 0.091mol, 58%) as a colourless oil: $[\alpha]_D^{20}$ = -13.8° (c = 0.26, dichloromethane); R_f = 0.26 (hexane:ethyl acetate (5:1)); (Found: M^+, 482.2720. $C_{25}H_{42}O_7Si$ requires *M*, 482.2700); ν_{max} (film) 2944, 2891, 2867, 1731, 1645, 1462, 1381, 1370 and 1213cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.96-1.13 (21H, m, -Si(C*H*(CH_3)$_2$)$_3$), 1.33 and 1.37 (6H, 2 x s, -C(CH_3)$_2$-), 3.78 (3H, s, -CO_2CH_3), 3.82 (1H, dd, *J* 6.1, 8.6Hz, C1-*H*), 3.95 (1H, dd, *J* 6.8, 8.6Hz, C1-*H'*), 4.14-4.24 (1H, m, C2-*H*), 4.46 (1H, t, *J* 5.4Hz, C3-*H*), 4.73 (2H, d, *J* 6.6Hz, C8-*H*), 5.68-5.89 (2H, m, C4-*H* and C7-*H*), 6.18-6.40 (2H, m, C5-*H* and C6-*H*) and 6.27 (2H, s, -C*H*=C*H*COCH$_3$); δ_C (68.1MHz, $CDCl_3$) 12.4, 18.1, 25.1, 26.3, 52.2, 65.1, 65.5, 73.3, 78.5, 109.3, 125.7, 129.5, 129.7, 130.5, 133.5, 134.0, 164.6 and 165.4; *m/z* (EI, 40eV) 482 (0.7%), 252 (33), 243 (83), 113 (100) and 101 (73).

(2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (239)

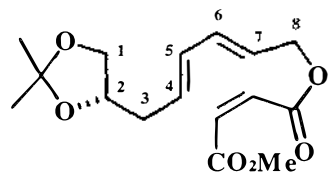


239

To a stirred solution of (2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-4,6-octadiene-1,2,8-triol (**235**) (38.2mg, 0.190mmol) in dichloromethane (10mL) at 0°C under argon was added triethylamine (42,9μL, 0.310mmol, 1.6eq), maleic anhydride (42.5mg, 0.430mmol, 2.25eq) and N,N-dimethylaminopyridine (2.4mg, 0.019mmol, 0.1eq). On completion

of the addition the solution was allowed to warm to RT and stirring was continued for 30min. The solvent was evaporated to give the crude product (0.414g) as a yellow oil. Chromatography of this material on silica (5g) with ethyl acetate:acetic acid:methanol (98:1:1) gave the **title compound** (**239**) (56.3mg, 0.190mmol, 100%) as a colourless oil: $[\alpha]_D^{21}$ = +7.3° (c = 0.510, dichloromethane); R_f = 0.40 (ethyl acetate:acetic acid:methanol (98:1:1)); (Found: M^+, 296.1256. $C_{15}H_{20}O_6$ requires M, 296.1260); ν_{max} (film) 3470, 2986, 2936, 1731, 1714, 1643, 1416, 1382, 1372, and 1214cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.36 and 1.42 (6H, 2 x s, -C(CH_3)$_2$-), 2.27-2.56 (2H, m, C3-*H*), 3.58 (1H, dd, *J* 6.8, 7.9Hz, C1-*H*), 4.04 (1H, dd, *J* 6.0, 7.9Hz, C1-*H'*), 4.11-4.23 (1H, m, C2-*H*), 4.77 (2H, d, *J* 6.8Hz, C8-*H*), 6.63-6.87 (2H, m, C4-*H* and C7-*H*), 6.07-6.50 (2H, m, C5-*H* and C6-*H*) and 6.35 and 6.46 (2H, B and A of AB, J_{AB} 12.6Hz, -C*H*=C*H*CO_2H); δ_C (68.1MHz, $CDCl_3$) 25.7, 26.9, 37.0, 67.1, 68.8, 75.1, 109.1, 123.0, 128.9, 131.3, 131.9, 136.1 (2 x C), 164.6 and 167.1; *m/z* (EI, 70eV) 296 (0.3%), 281 (59), 131 (37), 101 (100) and 72 (43).

(2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (240)



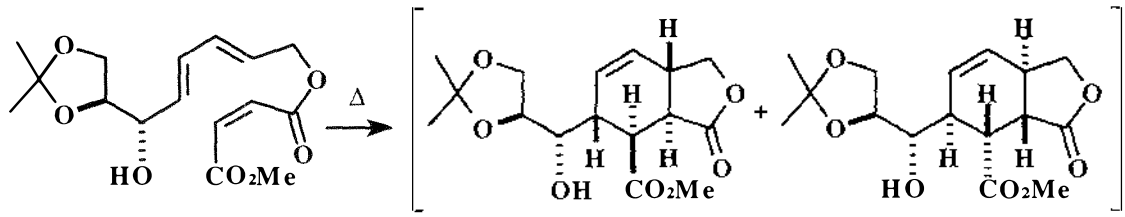
240

To a stirred solution of (2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (**239**) (56.3mg, 0.190mmol) in diethyl ether (5mL) at RT was added dropwise an ethereal solution of diazomethane[173] (**Section 6.6.3**). On completion of the addition the solvent was evaporated to give the crude product (65.0mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate (5:1 then 2:1) gave the **title compound** (**240**) (10.6mg, 0.0342mmol, 18%) as a pale yellow oil: $[\alpha]_D^{21}$ = +5.6° (c = 0.290, dichloromethane); R_f = 0.56 (hexane:ethyl acetate (2:1)); (Found: M^+, 310.1416. $C_{16}H_{22}O_6$ requires M, 310.1416); ν_{max} (film) 2986, 2921, 2851, 1731, 1644, 1437, 1380, 1370 and 1212cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.36 and 1.43 (6H, 2 x s, -C(CH_3)$_2$-), 2.27-2.57 (2H, m, C3-*H*), 3.58 (1H, dd, *J* 6.8, 7.9Hz, C1-*H*), 3.79 (3H, s, -CO_2CH_3), 4.03 (1H, dd, *J* 5.9, 7.9 Hz, C1-*H'*), 4.11-4.21 (1H, m, C2-*H*), 4.71 (2H, d, *J* 6.6Hz, C8-*H*), 5.66-5.80 (2H, m, C4-*H* and C7-*H*), 6.07-6.36 (2H, m, C5-*H* and C6-*H*) and 6.27 (2H, s, -C*H*=C*H*CO_2CH_3); δ_C (68.1MHz, $CDCl_3$) 25.7, 27.0, 37.0, 52.2, 65.6, 68.9, 75.2, 109.0, 124.5, 129.6,

129.7, 130.9, 131.6, 134.8, 164.7 and 165.5; *m/z* (CI/NH_3, 40eV) 310 (3%), 295 (55), 113 (100), 101 (94) and 73 (47).

6.2.3 ETDA reactions

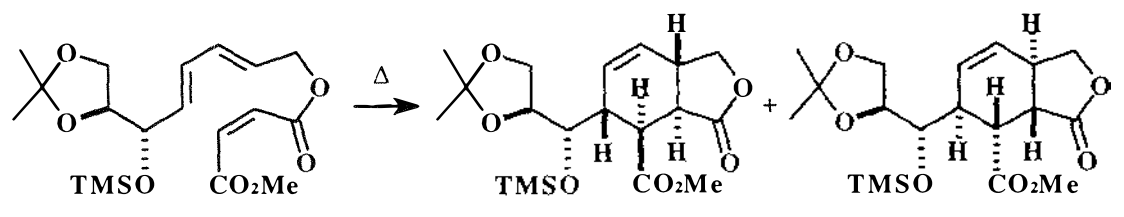
ETDA reaction of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl methyl maleate (238a)



238a **241a** **242a**

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl methyl maleate (**238a**) (0.522g, 1.60mmol) in toluene (320mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (71.0mg, 0.320mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 5h. Evaporation of the solvent gave the crude product (0.640g) as a yellow oil. Chromatography of this material on silica (30g) with hexane:ethyl acetate (1:1) gave the **ETDA adducts** (**241a** and **242a**) as an inseparable mixture (448mg, 1.37mmol, 86%, **241a:242a** (66:34)): R_f (**241a** and **242a**) = 0.24 (hexane:ethyl acetate (1:1)). (Derivatives of these adducts which are separable are described in **Section 6.2.4**).

ETDA reaction of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238b)

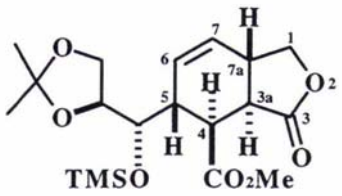


238b **241b** **242b**

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (**238b**) (45.3mg, 0.114mmol) in toluene (27.8mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (6.1mg, 0.0283mmol, 0.2eq). The solution was warmed to reflux and

heating was continued for 12h. Evaporation of the solvent gave the crude product (65.7mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (4:1) gave the **ETDA adducts** (**241b** and **242b**) (30.3g, 0.0760mmol, 67%, **241b:242b** (82:18)), *vide infra.*

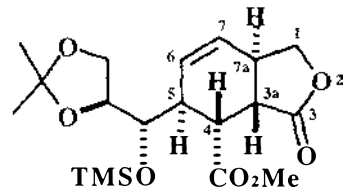
methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (241b)



241b

Colourless oil; $[\alpha]_D^{20}$ = -46.3° (c = 0.990, dichloromethane); R_f = 0.22 (hexane:ethyl acetate (4:1)); (Found: M^+-CH_3, 383.1524. $C_{18}H_{27}O_7Si$ requires *M*, 383.1526); ν_{max} (film) 2985, 2954, 2897, 1789, 1731, 1436, 1379 and 1370cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.144 (9H, s, -Si(CH_3)$_3$), 1.33 and 1.41 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 2.77-2.88 (1H, m, C5-*H*), 2.84 (1H, dd, *J* 3.9, 13.7Hz, C3a-*H*), 3.03-3.21 (1H, m, C7a-*H*), 3.39 (1H, d, *J* 3.9Hz, C4-*H*), 3.57-3.83 (1H, obs, -C*H*H'OC(CH_3)$_2$OCH-), 3.71 (3H, s, -CO_2CH_3), 3.78 (1H, dd, *J* 3.9, 5.5Hz, -C*H*OTMS), 3.85 (1H, dd, *J* 8.0, 11.3Hz, C1-*H*), 4.02 (1H, dd, *J* 6.2, 7.8Hz, -CH*H'*OC(CH_3)$_2$OCH-), 4.03-4.15 (1H, m, -CHH'OC(CH_3)$_2$OC*H*-), 4.52 (1H, dd, *J* 7.0, 8.0Hz, C1-*H'*), 5.63 (1H, dt, *J* 10.2, 3.1Hz, C6-*H*) and 6.02 (1H, dt, *J* 10.2, 2.0Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 13.4, 18.4, 25.5, 26.5, 36.5, 39.1, 42.8, 43.6, 52.2, 66.3, 70.2, 109.4, 126.8, 128.7, 172.8 and 173.9; (HETCOR demonstrated that δ_C for -*C*HOTMS was completely obscured by the 77.0ppm peak of the $CDCl_3$ triplet.); *m/z* (EI, 40eV) 383 (10%), 297 (21), 268 (99), 237 (72) and 73 (100).

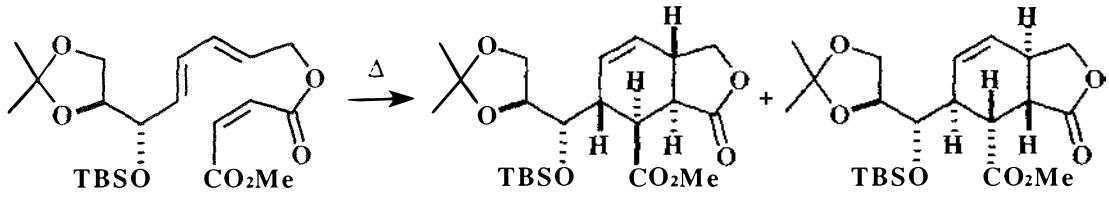
methyl (3a*S*, 4*R*, 5*S*, 7a*R*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (242b)



242b

Colourless oil; $[\alpha]_D^{19.5}$ = +54.5° (c = 0.110, dichloromethane); R_f = 0.26 (hexane:ethyl acetate (4:1)); (Found: M^+-CH_3, 383.1537. $C_{18}H_{27}O_7Si$ requires M, 383.1526); ν_{max} (film) 2986, 2955, 2927, 2855, 1786, 1736, 1437, 1381 and 1371cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.101 (9H, s, -Si(CH_3)$_3$), 1.38 and 1.44 (6H, 2 x s, -C(CH_3)$_2$-), 2.51-2.57 (1H, m, C5-*H*), 2.71 (1H, dd, *J* 4.2, 13.8Hz, C3a-*H*), 3.12-3.30 (1H, m, C7a-*H*), 3.45 (1H, d, *J* 4.2Hz, C4-*H*), 3.59 (1H, t, *J* 8.1Hz, -C*H*H'OC(CH_3)$_2$OCH-), 3.72 (3H, s, -CO_2CH_3), 3.74 (1H, dd, *J* 1.8, 5.0Hz, -C*H*OTMS), 3.80 (1H, dd, *J* 8.1, 11.5Hz, C1-*H*), 4.13 (1H, dd, *J* 6.4, 8.1Hz, -CH*H'*OC(CH_3)$_2$OCH-), 4.19-4.29 (1H, m, -CHH'OC(CH_3)$_2$OC*H*-), 4.53 (1H, dd, *J* 7.2, 8.1Hz, C1-*H'*), 5.56 (1H, dt, *J* 10.0, 3.2Hz, C6-*H*) and 6.01 (1H, dt, *J* 10.0, 2.0Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 0.699, 25.5, 26.8, 35.7, 36.3, 42.2, 42.7, 52.4, 66.2, 70.5, 77.8, 78.0, 109.4, 126.3, 131.9, 172.5 and 174.5; *m/z* (EI, 40eV) 383 (13%), 297 (23), 268 (99), 237 (73), 145 (45), 101 (52) and 73 (100).

ETDA reaction of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238c)

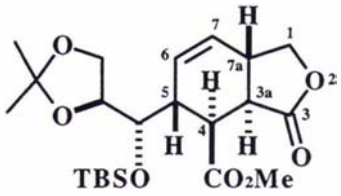


238c **241c** **242c**

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (**238c**) (0.115g, 0.261mmol) in toluene (52.0mL) at RT under argon was added 2,6-di-*tert*-butyl-4-

methylphenol (0.0116g, 0.0522mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 15h. Evaporation of the solvent gave the crude product (0.128g) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (4:1) gave the **ETDA adducts** (**241c** and **242c**) (0.0922g, 0.209mmol, 80%, **241c:242c** (91:9)), *vide infra*.

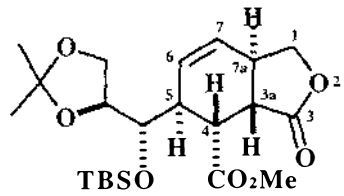
methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1-dimethyl-1-*tert*-butlyldimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (241c)



241c

Yellow oil; $[\alpha]_D^{21}$ = -34.3° (c = 2.98, dichloromethane); R_f = 0.29 (hexane:ethyl acetate (4:1)); (Found: M^+-CH_3, 425.1972. $C_{21}H_{33}O_7Si$ requires *M*, 425.1972); ν_{max} (film) and 2985, 2953, 2892, 2857, 1789, 1731, 1472, 1462, 1436, 1472, 1462 1380and 1370cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.114 (6H, s, -Si(CH_3)$_2$-), 0.903 (9H, s, -C(CH_3)$_3$), 1.31 and 1.42 (6H, 2 x s, -C(CH_3)$_2$-), 2.78 (1H, dd, *J* 4.2, 13.8Hz, C3a-*H*), 2.91-2.97 (1H, m, C5-*H*), 3.05-3.23 (1H, m, C7a-*H*), 3.58 (1H, d, *J* 4.2Hz, C4-*H*), 3.70 (3H, s, -CO_2CH_3), 3.70-3.82 (2H, m, -C*H*H'OC(CH_3)$_2$OCH- and -C*H*OTBS), 3.84 (1H, dd, *J* 7.9, 11.4Hz, C1-*H*), 3.96 (1H, dd, *J* 6.4, 7.9Hz, -CH*H'*OC(CH_3)$_2$OCH-), 4.05-4.16 (1H, m, -CHH'OC(CH_3)$_2$OC*H*-), 4.48-4.70 (1H, m, C1-*H'*), 5.66 (1H, dt, *J* 10.1, 3.1Hz, C6-*H*) and 6.00 (1H, dt, *J* 10.1, 2.2Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) -4.43, -4.32, 18.2, 25.6, 25.9, 26.4, 36.4, 38.0, 42.6, 43.6, 52.0, 66.1, 70.2, 74.6, 76.6, 109.4, 126.7, 128.7, 172.9 and 174.1; *m/z* (EI, 40eV) 425 (7%), 279 (28), 265 (100), 117 (25) and 73 (57).

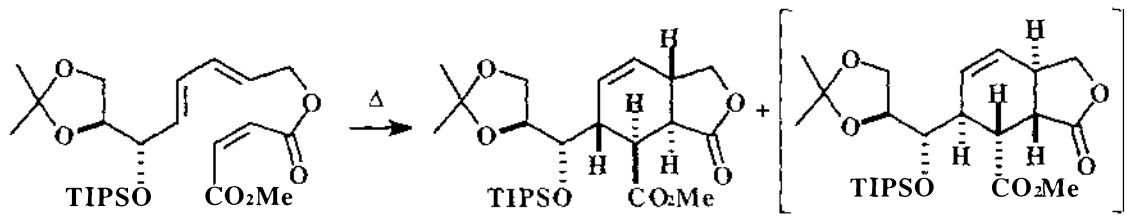
methyl (3a*S*, 4*R*, 5*S*, 7a*R*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1-dimethyl-1-*tert*-butlyldimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (242c)



242c

Colourless oil; $[\alpha]_D^{20}$ = +18.0° (c = 0.100, dichloromethane); R_f = 0.29 (hexane:ethyl acetate (4:1)); (Found: M^+-CH_3, 425.1994. $C_{21}H_{33}O_7Si$ requires M, 425.1996); ν_{max} (film) and 2925, 2853, 1789, 1737, 1463, 1378, 1368 and 1255cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.048 and 0.127 (6H, 2 x s, -Si(CH_3)$_2$-), 0.853 (9H, s, -C(CH_3)$_3$), 1.38 and 1.44 (6H, 2 x s, -C(CH_3)$_2$-), 2.52-2.58 (1H, m, C5-*H*), 2.80 (1H, dd, *J* 4.2, 13.5Hz, C3a-*H*), 3.10-3.32 (1H, m, C7a-*H*), 3.46 (1H, d, *J* 4.2Hz, C4-*H*), 3.57 (1H, t, *J* 8.1Hz, -C*H*H'OC(CH_3)$_2$OCH-), 3.72 (3H, s, -CO_2CH_3), 3.81 (1H, t, *J* 8.1Hz, -C*H*OTBS), 3.82 (1H, dd, *J* 8.0, 13.7Hz, C1-*H*), 4.13 (1H, dd, *J* 6.2, 8.1Hz, -CH*H'*OC(CH_3)$_2$OCH-), 4.20-4.30 (1H, m, -CHH'OC(CH_3)$_2$OC*H*-), 4.54 (1H, dd, *J* 7.2, 8.0Hz, C1-*H'*), 5.60 (1H, dt, *J* 10.0, 3.1Hz, C6-*H*) and 6.01 (1H, dt, *J* 10.0, 2.2Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) -4.14, -3.97, 18.5, 25.5, 26.2, 26.8, 30.4, 35.7, 36.3, 42.3, 42.9, 52.4, 66.2, 70.4, 77.8, 78.3, 109.4, 126.3, 132.3 and 172.5; *m/z* (EI, 70eV) 425 (4%), 279 (17), 265 (100), 101 (100) and 73 (57).

ETDA reaction of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1,1,1-triisopropylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (238d)

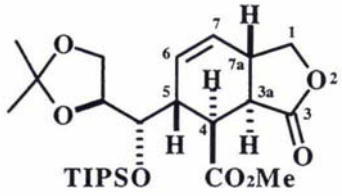


238d **241d** **242d**

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1,1,1-triisopropylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (**238d**) (37.0mg, 0.0767mmol) in toluene (15.3mL) at RT under argon was added 2,6-di-*tert*-butyl-4-

methylphenol (3.4mg, 0.015mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 18h. Evaporation of the solvent gave the crude product (40.3mg) as a yellow oil. Chromatographhy on silica (4g) with hexane:ethyl acetate (4:1) gave the **ETDA adducts** (**241d** and **242d**) (25.1mg, 0.0520mmol, 68%, **241d:242d** (96:4)), *vide infra*. (Adduct **242d** was unable to be isolated and characterised. The structure of this compound is speculative and based on limited proton NMR analysis of mixtures only.)

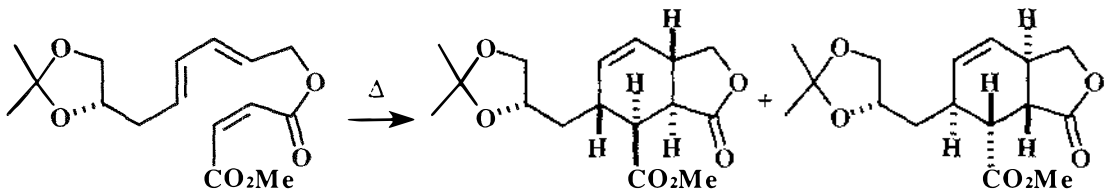
methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1,1-triisopropylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (241d)



241d

Colourless oil; $[\alpha]_D^{21}$ = -50.0° (c = 1.04, dichloromethane); R_f = 0.17 (hexane:ethyl acetate (4:1)); (Found: M^+-CH_3, 467.2466. $C_{24}H_{39}O_7Si$ requires *M*, 467.2465); ν_{max} (film) 2945, 2866, 1789, 1731, 1462, 1380, 1370, 1327, 1317 and1215cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.959-1.20 (21H, m, -Si(C*H*(CH_3)$_2$)$_3$), 1.32 and 1.41 (6H, 2 x s, -C(CH_3)$_2$-), 2.77 (1H, dd, *J* 4.1, 13.7Hz, C3a-*H*), 2.85-2.92 (1H, m, , C5-*H*), 3.00-3.17 (1H, m, C7a-*H*), 3.52 (1H, d, *J* 4.1Hz, C4-*H*), 3.68 (1H, t, *J* 8.0Hz, -C*H*H'OC(CH_3)$_2$OCH-), 3.70 (3H, s, -CO_2CH_3), 3.84 (1H, dd, *J* 8.0, 11.4Hz, C1-*H*), 3.99 (1H, dd, *J* 6.1, 8.0Hz, -CH*H'*OC(CH_3)$_2$OCH-), 4.03 (1H, dd, *J* 3.7, 6.1Hz, -C*H*OTBS), 4.07-4.18 (1H, m, -CHH'OC(CH_3)$_2$OC*H*-), 4.53 (1H, dd, *J* 7.2, 8.0Hz, C1-*H'*), 5.69 (1H, dt, *J* 10.1, 3.0Hz, C6-*H*), 6.01 (1H, dt, *J* 10.1, 2.1Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 13.4, 18.4, 25.5, 26.5, 36.5, 39.1, 42.8, 43.6, 52.2, 66.3, 70.2, 109.4, 126.8, 128.7, 172,8 and 173.9; (HETCOR demonstrated that δ_C for -*C*HOTIPS and -CHH'OC(CH_3)$_2$O*C*H- were obscured by the 76.5 and 77.5ppm peaks of the $CDCl_3$ triplet respectively); *m/z* (EI, 40eV) 467 (4%), 439 (20), 381 (25), 321 (100) and 173 (31).

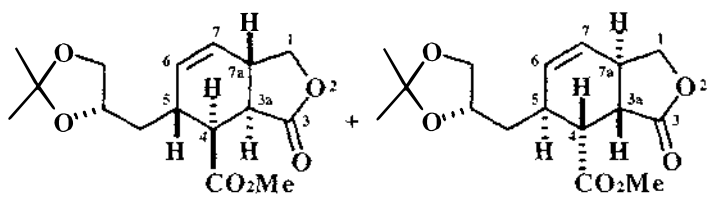
ETDA reaction of (2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (240)



240 270 271

To a stirred solution of (2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl methyl maleate (**240**) (0.9mg, 2.9mmol) in toluene (0.6mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (0.1mg, 0.6mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 18h. Evaporation of the solvent gave the crude product (1.0mg) as a yellow oil. Chromatography of this material on silica (1g) with hexane:ethyl acetate (2:1) gave the **ETDA adducts** (**270** and **271**) (0.8mg, 2.6mmol, 89%, **270:271** (50:50)) as an inseparable mixture, *vide infra*.

methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((2*S*)-1,2-*O*-isopropylidene-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (270) and **methyl (3a*S*, 4*R*, 5*S*, 7a*R*)-5-((2*S*)-1,2-*O*-isopropylidene-1,2-diihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (271) (270:271 (50:50))**



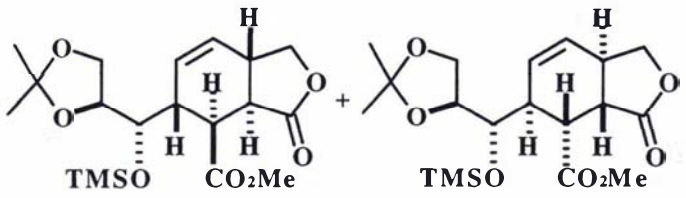
270 271

Colourless oil; R_f = 0.24 (hexane:ethyl acetate (2:1)); (Found: M^+, 310.1418. $C_{16}H_{22}O_6$ requires M, 310.1416); ν_{max} (film) 2985. 2933, 1788, 1731, 1436, 1380, 1371 and 1217cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.35, 1.37, 1.42 and 1.43 (12H, 4 x s, 2 x -C(CH_3)$_2$-), 1.57-1.86 (4H, m, 2 x -C5-CH_2-), 2.34 and 2.39 (2H, 2 x dd, *J* 3.5, 13.6Hz and *J* 3.9, 13.6Hz, 2 x C3a-*H*), 2.92-3.08 (2H, m, 2 x C5-*H*), 3.14-3.34 (2H, m, 2 x C7a-*H*), 3.18 and 3.31 (2H, 2 x d, *J* 3.9Hz and *J* 3.5Hz, 2 x C4-*H*), 3.50-3.58 (2H, m, 2 x -C*H*H'OC(CH_3)$_2$OCH-), 3.72 (6H, s, 2 x -CO_2CH_3), 3.87 (2H, dd, *J* 8.1, 11.4Hz, 2 x C1-*H*), 4.04-4.14 (2H, m, 2 x -CH*H*'OC(CH_3)$_2$OCH-), 4.15-4.30 (2H, m, 2 x

-CHH'OC(CH_3)$_2$OC*H*-), 4.53 and 4.56 (2H, 2 x dd, *J* 1.5, 6.8Hz and *J* 1.8, 6.6Hz, 2 x C1-*H'*), 5.71 and 5.75 (2H, 2 x dt, *J* 9.9, 3.1Hz and *J* 10.3, 3.3Hz, 2 x C6-*H*) and 5.86 and 5.88 (2H, 2 x dt, *J* 10.3, 1.8Hz and *J* 9.9, 2.0Hz, 2 x C7-*H*); δ_C (68.1MHz, $CDCl_3$) 25.8 (2 x C), 27.0, 27.1, 29.7, 36.3, 36.6, 36.7, 37.0, 39.4, 39.8, 40.7, 40.9, 41.7, 41.9, 52.3, 69.4, 69.7, 70.6 (2 x C), 73.5, 74.3, 109.2, 109.3, 124.2, 124.3, 132.6, 133.0, 172.0, 172.2, 174.4 and 174.5; (A Pure Inverse Gated Decoupling NMR experiment was used to confirm that δ_C at 25.8ppm and 70.6ppm each contained two overlapping peaks.); *m/z* (EI, 40eV) 310 (1%), 295 (100), 252 (23), 221 (28), 175 (45), 131 (50), 91 (64), 72 (32), 59 (26) and 43 (71).

6.2.4 Miscellaneous reactions of ETDA adducts

Methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (241b) and **methyl (3a*S*, 4*R*, 5*S*, 7a*R*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1,1-trimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (242b) (241b:242b (66:34))**

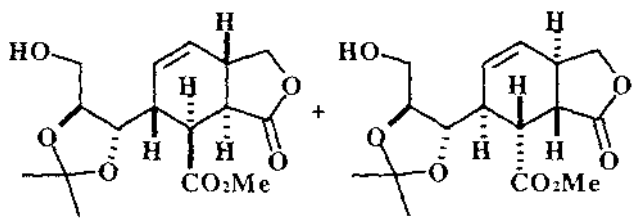


241b **242b**

To a stirred solution of methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (**241a**) and methyl (3a*S*, 4*R*, 5*S*, 7a*R*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate (**242a**) (**241a:242a** (66:34)) (15.0mg, 0.0460mmol) in dimethylformamide (50µL) at RT under argon was added imidazole (18.8mg, 0.276mmol, 6eq) and trimethylsilyl chloride (29.2µL, 0.230mmol, 5eq). Stirring was continued for 20min then the reaction mixture was diluted with dichloromethane (30mL) and partitioned against water (30mL). The aqueous layer was extracted with dichloromethane (2 x 30mL) and the combined extracts were washed with brine (30mL) then dried, filtered and evaporated to give the crude product (25.1mg) as a yellow oil. Chroatography of this material on silica (0.5g) with hexane:ethyl acetate (4:1) gave the **title compounds** (**241b** and **242b**) (11.2mg, 0.0343mmol, 74%, **241b:242b**

(66:34)), *vide supra.*

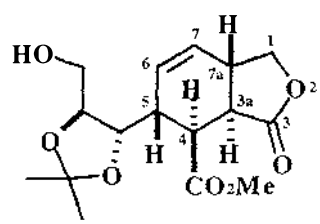
Methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((1*S*,2*S*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (246) and **methyl (3a*S*, 4*R*, 5*S*, 7a*R*)-5-((1*S*,2*S*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate (247) (246:247 (66:34))**



246 247

To a stirred solution of methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (**241a**) and methyl (3a*S*, 4*R*, 5*S*, 7a*R*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexa-hydro-4-isobenzofurancarboxylate (**242a**) (**241a:242a** (66:34)) (36.0mg, 0.110mmol) in acetone (2mL) at RT under argon was added Amberlist IR-118 resin (36mg). Stirring was continued for 21h then the reaction mixture was filtered and evaporated to give the crude product (36.0mg) as a yellow oil. Chromatography of this material on silica (5g) with ethyl acetate:hexane (1.5:1) gave the **title compounds** (**246** and **247**) (34.5mg, 0.106mmol, 96%, **246:247** (66:34)), *vide infra.*

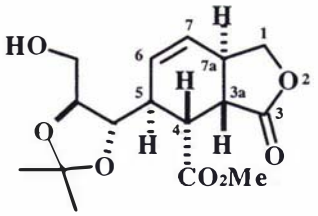
methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((1*S*,2*S*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (246)



246

Colourless oil; $[\alpha]_D^{21}$ = -96.8° (c = 0.440, dichloromethane); R_f = 0.33 (ethyl acetate:hexane (1.5:1)); (Found: M^+-CH_3, 311.1139. $C_{15}H_{19}O_7$ requires *M*, 311.1131); ν_{max} (film) 3468, 2986, 2932, 1783, 1732, 1437, 1381, 1371 and 1218cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.39 and 1.41 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 2.06 (1H, t, *J* 6.0Hz, -O*H*), 2.66 (1H, dd, *J* 3.8, 13.5Hz, C3a-*H*), 2.98-3.05 (1H, m, C5-*H*), 3.11-3.28 (1H, m, C7a-*H*), 3.26 (1H, d, *J* 3.8Hz, C4-*H*), 3.64-3.77 (1H, m, -C*H*H'OH), 3.73 (3H, s, -CO_2CH_3), 3.78-3.95 (1H, m, -CH*H'*OH), 3.88 (1H, dd, *J* 7.9, 11.4Hz, C1-*H*), 3.98-4.06 (2H, m, -C*H*OC(CH$_3$)$_2$OC*H*-), 4.53 (1H, dd, *J* 7.3, 7.9Hz, C1-*H'*), 5.82 (1H, dt, *J* 10.1, 3.3Hz, C6-*H*) and 6.03 (1H, dt, *J* 10.1, 2.2Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 27.3, 27.4, 36.6, 40.1, 40.5, 42.3, 52.5, 62.5, 70.4, 78.7, 80.6, 109.4, 126.7, 127.8, 171.9 and 174.2; *m/z* (EI, 70eV) 311 (12%), 196 (19), 131 (76), 91 (19), 59 (100) and 43 (29).

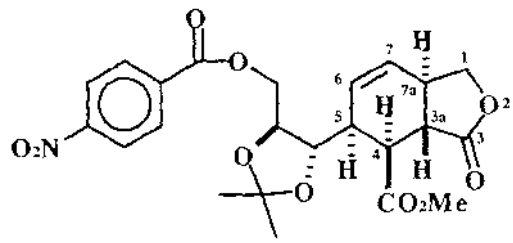
methyl (3a*S*, 4*R*, 5*S*, 7a*R*)-5-((1*S*,2*S*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (247)



247

Colourless oil; $[\alpha]_D^{21}$ = +20.0° (c = 0.460, dichloromethane); R_f = 0.25 (ethyl acetate:hexane (1.5:1)); (Found: M^+-CH_3, 311.1138. $C_{15}H_{19}O_7$ requires *M*, 311.1131); ν_{max} (film) 3458, 2984, 2923, 1782, 1731, 1437, 1380, 1370 and 1215cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.42 and 1.44 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 2.57 (1H, dd, *J* 3.7, 13.6Hz, C3a-*H*), 2.89-2.96 (1H, m, C5-*H*), 3.11-3.30 (1H, m, C7a-*H*), 3.45 (1H, m, C4-*H*), 3.49-3.89 (1H, m, -C*H*H'OH), 3.73 (3H, s, -CO_2CH_3), 3.81-3.93 (1H, m, -CH*H'*OH), 3.91 (1H, dd, *J* 8.1, 11.4Hz, C1-*H*), 4.00-4.06 (2H, m, -C*H*OC(CH$_3$)$_2$OC*H*-), 4.49-4.59 (1H, m, C1-*H'*), 5.67 (1H, dt, *J* 9.9, 3.1Hz, C6-*H*), 6.03 (1H, dt, *J* 9.9, 2.0Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 27.2, 27.3, 36.2, 37.0, 41.2, 42.5, 52.5, 62.1, 70.3, 78.9, 79.1, 109.5, 126.8, 130.0, 172.2 and 174.1; *m/z* (EI, 70eV) 311 (%), 196 (19), 131 (75), 59 (100) and 43 (26).

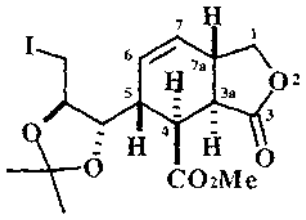
methyl (3a*S*, 4*R*, 5*S*, 7a*R*)-5-((1*S*,2*R*)-1,2-*O*-isopropylidene-3-(4-nitrobenzoyl)oxy-1,2-dihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (248)



248

To a stirred solution of methyl (3a*S*, 4*R*, 5*S*, 7a*R*)-5-((1*S*,2*S*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (**247**) (8.9mg, 0.028mmol) in dichloromethane (1mL) at RT under argon was added pyridine (22μl, 0.27mmol, 10eq), 4-nitrobenzoyl chloride (12.7mg, 0.0684mmol, 2.5eq) and N,N-dimethylaminopyridine (crystal). Stirring was continued for 2h then the reaction mixture was diluted with diethyl ether (60mL) and partitioned against 10% aqueous hydrochloric acid (30mL), water (30mL) and brine (30mL) then dried, filtered and evaporated to give the crude product (22.4mg) as a yellow oil. Chromatography of this material on silica (0.5g) with hexane:ethyl acetate (2:1) gave the **title compound** (**248**) (9.2mg, 0.019mmol, 70%) as a colourless oil: $[\alpha]_D^{19.5}$ = +27.0° (c = 0.300, dichloromethane); R_f = 0.25 (hexane:ethyl acetate (2:1)); (Found: M^+-CH_3, 460.1234. $C_{22}H_{22}NO_{10}$ requires *M*, 460.1244); ν_{max} (film) 2987, 2955, 2926, 2854, 1787, 1731, 1607, 1529, 1381 and 1371cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.43 and 1.47 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 2.60 (1H, dd, *J* 4.0, 13.6Hz, C3a-*H*), 2.83- 3.23 (1H, m, C5-*H*), 3.14-3.30 (1H, m, C7a-*H*), 3.46 (1H, d, *J* 4.0Hz, C4-*H*), 3.73 (3H, s, -CO_2CH_3), 3.92 (1H, dd, *J* 8.2, 11.6Hz, -C*H*H'CHOC(CH3)2OCH-), 4.01 (1H, dd, *J* 4.2, 7.7Hz, C1-*H*), 4.29-4.37 (1H, m, -CHH'C*H*OC(CH3)2OCH-), 4.44-4.64 (1H, m, (1H, dd, C1-*H'*, -CH*H'*CHOC(CH3)2OC*H*-), 5.71 (1H, dt, *J* 9.9, 3.2Hz, C6-*H*), 6.06 (1H, dt, *J* 9.9, 2.0Hz, C7-*H*) and 8.26 and 8.33 (4H, B and A of AB, J_{AB} 8.9Hz, aromatic-*H*); δ_C (68.1MHz, $CDCl_3$) 27.1, 27.2, 36.2, 37.0, 41.3, 42.5, 52.5, 65.8, 70.2, 76.6, 80.2, 109.8, 110.3, 123.6 (2 x C), 127.3, 129.7, 130.8 (2 x C), 164.3, 172.0 and 173.9; *m/z* (EI, 70eV) 450 (5%), 280 (6), 222 (100), 149 (16) and 57 (19).

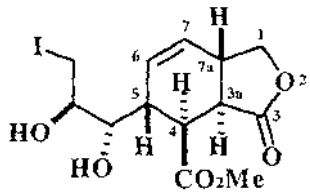
methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((2*R*,3*S*)-1-iodo-2,3-*O*-isopropylidene-2,3-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (249)



249

To methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((1*S*,2*S*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-1-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (**246**) (18.0mg, 0.0552mmol) at RT under argon was added chloroform (1mL) containing imidazole (7.1mg, 0.11mmol 1.9eq), triphenyphosphine (23.2mg, 0.0880mmol, 1.6eq) and iodine (21.0mg, 0.0827mmol, 1.5eq) and the solution was stirred for 8h. An additional volume of the chloroform solution (1mL) was added and stirring was continued for 12h. The reaction mixture was diluted with heaxane:ethyl acetate (20:1, 5mL), silica (0.1g) was added and then rapid vacuum filtration through a silica plug (0.5g) was carried out with hexane:ethyl acetate (20:1 then 5:1) to give the **title compound** (**249**) (15.9mg, 0.0364mmol, 67%) as a yellow oil: $[\alpha]_D^{21}$ = -76.3° (c = 0.79, dichloromethane); R_f = 0.09 (hexane:ethyl acetate (5:1)); (Found: M^+-CH_3, 421.0149. $C_{15}H_{18}O_6I$ requires *M*, 421.0148); ν_{max} (film) 2987, 2932, 1789, 1731, 1435, 1381, 1371 and 1218cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.38 and 1.45 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 2.46 (1H, dd, *J* 4.0, 13.4Hz, C3a-*H*), 3.09-3.15 (1H, m, C5-*H*), 3.16-3.29 (1H, m, C7a-*H*), 3.27 (1H, d, *J* 4.0Hz, C4-*H*), 3.29-3.35 (2H, m, -C*H*$_2$I), 3.74 (3H, s, -CO_2C*H*$_3$), 3.89 (1H, dd, *J* 8.1, 11.4Hz, C1-*H*), 3.95 (1H, dd, *J* 4.6, 6.4Hz, -C*H*OC(CH_3)$_2$OCHCH_2I), 4.01-4.10 (1H, m, -CHOC(CH_3)$_2$OC*H*CH_2I), 4.55 (1H, dd, *J* 7.0, 8.1Hz, C1-*H'*), 5.82 (1H, dt, *J* 10.1, 3.1Hz, C6-*H*) and 6.06 (1H, dt, *J* 10.1, 2.0Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 6.26, 27.8, 27.9, 36.5, 40.4, 41.0, 42.2, 52.5, 70.4, 77.6, 85.0, 110.1, 127.1, 127.3, 171.8 and 174.0; *m/z* (EI, 70eV) 421 (10%), 241 (100), 183 (49), 91 (35) and 43 (44).

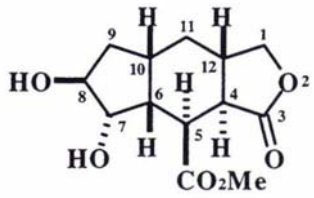
methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((2*R*,3*S*)-2,3-dihydroxy-1-iodo-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (251)



251

To a stirred solution of methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((2*R*,3*S*)-1-iodo-2,3-*O*-isopropylidene-2,3-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (**249**) (13.8mg, 0.0316mmol) in methanol:water (5:1, 1mL) at RT under argon was added Amberlite IR 118 ion exchange resin (16.0mg). On completion of the addition the solution was warmed to 50°C and stirred for 30min. The solution was then warmed to reflux and stirring was continued for 18h. The solution was filtered through cotton wool and evaporated to give the crude product (13.8mg) as a yellow oil. Chromatography of this material on silica (0.5g) with benzene then hexane:ethyl acetate (1:1 then 1:2) gave **recovered starting material** (**249**) (5.8mg, 0.0133mmol, 42%) followed by the **title compound** (**251**) (5.8mg, 0.015mmol, 82% based on 58% conversion) as a yellow oil: $[\alpha]_D^{21} = -28.0°$ (c = 0.054, dichloromethane); R_f = 0.36 (hexane:ethyl acetate (1:2)); (Found: M^++H, 397.0138. $C_{13}H_{18}O_6I$ requires *M*, 397.0148); ν_{max} (film) 3444, 2919, 2850, 1777, 1731, 1435 and 1378cm^{-1}; δ_H (270MHz, $CDCl_3$) 2.60-2.76 (1H, m, -C*H*H'I), 2.71 (1H, dd, *J* 4.2, 13.6Hz, C3a-*H*), 2.95-3.05 (1H, m, C5-*H*), 3.12-3.32 (1H, m, C7a-*H*), 3.32-3.45 (2H, m, C4-*H* and -CH*H*'I), 3.74 (3H, s, -CO_2CH_3), 3.79-3.90 (2H, m, -C*H*OH-C*H*OH-), 3.92 (1H, dd, *J* 8.1, 11.4Hz, C1-*H*), 4.56 (1H, dd, *J* 7.3, 8.1Hz, C1-*H*'), 5.81 (1H, dt, *J* 10.1, 3.1Hz, C6-*H*) and 6.08 (1H, dt, *J* 10.1, 2.2Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 10.5, 36.4, 39.2, 42.5, 42.8, 52.5, 70.4, 71.6, 75.5, 127.4, 127.7, 172.3 and 174.4; *m/z* (EI, 70eV) 397 (2%), 196 (46), 136 (44), 91 (100) and 77 (34).

methyl 2-oxa-3-oxo-[4*R*,5*S*,6*R*,7*S*,8*S*,10*S*,12*S*]-7,8-dihydroxytricyclo-[7.3.0.0^{6,10}]-5-dodecanecarboxylate (252)



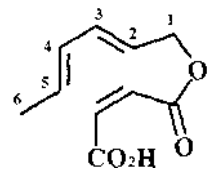
252

To a stirred solution of methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-((2*R*,3*S*)-2,3-dihydroxy-1-iodo-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (**251**) (5.8mg, 0.015mmol) in benzene (0.6mL) at RT under argon was added *tris*-trimethylsilylsilane (5.2μL, 0.016mmol, 1.1eq) and 2,2'-azo-*bis*-isobutyronitrile (crystal). On completion of the addition the solution was warmed to reflux and stirring was continued for 45min. The solvent was evaporated to give the crude product (9.7mg) as a yellow oil. Chromatography of this material on silica (0.5g) with ethyl acetate gave the **title compound** (**252**) (2.6mg, 0.0096mmol, 64%) as a colourless oil: $[\alpha]_D^{21}$ = -6.0° (c = 0.100, dichloromethane); R_f = 0.40 (ethyl acetate); (Found: M^++H, 271.1196. $C_{13}H_{19}O_6$ requires *M*, 271.1181); ν_{max} (film) 3440, 2920, 2851, 1731 and 1426cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.21-1.41 (1H, m, C11-*H*), 1.84 (1H, ddd, *J* 4.0, 8.2, 14.3Hz, C9–*H*), 1.95 (1H, ddd, *J* 2.4, 6.3, 12.0Hz, C11-*H'*), 2.03 (1H, ddd, *J* 2.4, 6.8, 14.3Hz, C9-*H'*), 2.18-2.37 (1H, m, C10-*H*), 2.67 (1H, dd, *J* 5.8, 7.6Hz, C6-*H*), 2.72-2.89 (2H, m, C4-*H* and C12-*H*), 3.40 (1H, d, *J* 4.2Hz, C5-*H*), 3.72 (3H, s, -CO_2CH_3), 3.81 (1H, dd, *J* 8.3, 11.1Hz, C1-*H*), 4.13-4.25 (2H, m, C7-*H* and C8-*H*) and 4.42 (1H, dd, *J* 6.4, 8.3Hz, C1-*H'*); δ_C (68.1MHz, $CDCl_3$) 29.8, 34.6, 35.4, 37.5, 37.9, 42.4, 44.2, 52.2, 72.1, 79.4, 83.0, 173.4 and 176.4; *m/z* (EI, 70eV) 271 (3%), 192 (48), 91 (100), 105 (46) and 77 (70).

6.3 Experimental for Chapter Three

6.3.1 Preparation of ETDA Precursors

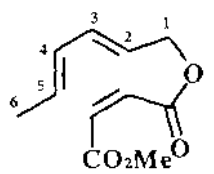
(2*E*,4*E*)-2,4-hexadien-1-yl hydrogen maleate (302)



302

To a stirred solution of (2*E*,4*E*)-2,4-hexadien-1-ol (**301**) (0.500g, 5.10mmol) in dichloromethane (25mL) at 0°C under argon was added triethylamine (1.14mL, 8.20mmol, 1.6eq), maleic anhydride (1.12g, 11.5mmol, 2.25eq) and N,N-dimethylaminopyridine (0.0620g, 0.508mmol, 0.1eq). Stirring was continued for 15min and the reaction mixture was diluted with diethyl ether (100mL) and partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (1.25g) as a yellow oil. Chromatography of this material on silica (30g) with hexane:ethyl acetate:acetic acid:methanol (20:20:1:1) gave the **title compound** (**302**) (0.880g, 4.49mmol, 88%) as a pale yellow oil: R_f = 0.49 (hexane:ethyl acetate:acetic acid:methanol (20:20:1:1)); (Found: M^+, 196.0738. $C_{10}H_{12}O_4$ requires *M*, 196.0736); ν_{max} (film) 3153, 3025, 2963, 2691, 1735, 1636, 1413 and 1210cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.75 (3H, d, *J* 6.6Hz, C6-*H*), 4.71 (2H, d, *J* 6.8Hz, C1-*H*), 5.21-5.86 (2H, m, C2-*H* and C5-*H*), 5.98-6.10 (1H, m, C4-*H*), 6.21-6.34 (1H, m, C3-*H*) and 6.35 (2H, d, *J* 0.4Hz, -C*H*=C*H*CO_2H);δ_C (68.1MHz, $CDCl_3$) 18.1, 66.9, 121.7, 129.9, 130.0, 132.0, 133.0, 136.3, 166.3, and 166.5; *m/z* (EI, 70eV) 196 (7%), 107 (79), 97 (100), 91 (67) and 79 (65).

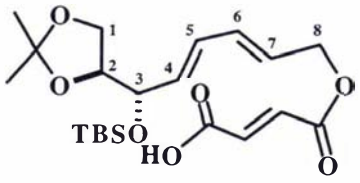
(2*E*,4*E*)-2,4-hexadien-1-yl methyl maleate (303)



303

To a stirred solution (2*E*,4*E*)-2,4-hexadien-1-yl hydrogen maleate (**302**) (0.463g, 2.36mmol) in diethyl ether (20mL) at 0°C was added dropwise an ethereal solution of diazomethane[173] (**Section 6.6.3**). On completion of the addition the solvent was evaporated to give the crude product (0.480g) as a yellow oil. Chromatography of this material on silica (20g) with hexane:ethyl acetate (10:1 then 5.1) gave the **title compound** (**303**) (0.287g, 1.37mmol, 58%) as a colourless oil: R_f = 0.33 (hexane:ethyl acetate (10:1)); (Found: M^+, 210.0891. $C_{11}H_{14}O_4$ requires M, 210.0892); ν_{max} (film) 3023, 2953, 2881, 2853, 1730, 1647, 1438, 1397, 1378, 1367 and 1214cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.73 (3H, d, *J* 6.8Hz, C6-*H*), 3.74 (3H, s, -CO_2CH_3), 4.65 (2H, d, *J* 6.8Hz, C1-*H*), 5.61 (1H, dt, *J* 15.2, 6.8Hz, C2-*H*), 5.75 (1H, dq, *J* 14.9, 6.8Hz, C5-*H*), 5.94-6.09 (1H, m, C3-*H*), 6.22 (2H, s, -C*H*=C*H*CO_2CH_3) and 6.25 (1H, dd, *J* 10.1, 14.9Hz, C4-*H*); δ_C (68.1MHz, $CDCl_3$) 18.1, 52.0, 65.6, 122.7, 129.4, 129.5, 130.1, 131.4, 135.3, 164.6 and 165.3; *m/z* (EI, 70eV) 210 (2%), 113 (64), 97 (100), 85 (12) and 79 (23).

(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen fumarate (304)

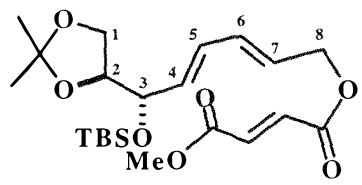


304

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (**236**) (0.682g, 1.68mmol) in benzene (20mL) at RT under argon was added thiophenol (34.4μL, 0.336mmol, 0.2eq) and 2,2'-azo-*bis*-isobutyronitrile (27.6mg, 0.168mmol, 0.1eq) in two potions at one hour intervals, during which time the reaction mixture was irradiated with ultraviolet light at reflux for a total of 2h. (Isomerisation was monitored by proton NMR analysis.) The solvent was evaporated to give the crude product (0.710g) as a yellow oil. Chromatography of this material on silica (10g) with hexane:ethyl acetate:acetic acid (150:150:1) gave the **title compound** (**304**) (0.442g, 1.09mmol, 65%) as a yellow oil: $[\alpha]_D^{21}$ = -21.3° (c = 0.360, diethyl ether); R_f = 0.24 (hexane:ethyl acetate:acetic acid (150:150:1)); (Found: M^+-CH_3, 411.1841. $C_{20}H_{31}O_7Si$ requires M, 411.1839); ν_{max} (film) 3153, 2929, 2856, 1727, 1714, 1644, 1472, 1462, 1380, 1370 and 1258cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.061 and 0.080 (6H, 2 x s, -$Si(CH_3)_2$), 0.905 (9H, s, -$C(CH_3)_3$), 1.34 and 1.41 (6H, 2 x s, -$C(CH_3)_2$-), 3.79 (1H, dd, *J* 6.2, 8.6Hz,

C1-*H*), 3.95 (1H, dd, *J* 6.7, 8.6Hz, C1-*H'*), 4.05-4.14 (1H, m, C2-*H*), 4.31 (1H, t, *J* 5.6Hz, C3-*H*), 4.75 (2H, d, *J* 6.6Hz, C8-*H*), 5.69-5.89 (2H, m, C4-*H* and C7-*H*) 6.20-6.41 (2H, m, C5-*H* and C6-*H*) and 6.87 and 6.96 (2H, 2 x d, B and A of AB, J_{AB} 15.7Hz, -C*H*=C*H*CO_2H); δ_C (68.1MHz, $CDCl_3$) -4.74, -4.52, 18.3, 25.7, 25.8, 26.4, 65.2, 65.6, 73.1, 78.5, 109.5, 125.5, 130.2, 132.9, 133.5, 134.2, 135.0, 164.2 and 168.9; *m/z* (EI, 40eV) 411 (2%), 369 (12), 210 (18), 173 (37), 143 (27), 101 (100) and 73 (35).

(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl fumarate (305)

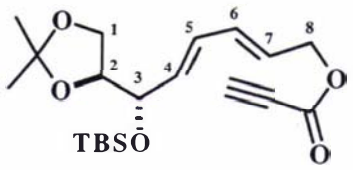


305

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (**228**) (297mg, 0.903mmol) in diethyl ether (15mL) at RT under argon was added methyl hydrogen fumarate[207] (141mg, 1.08mmol, 1.2eq), dicyclohexylcarbodiimide (242mg, 1.17mmol, 1.3eq) and N,N-dimethylaminopyridine (11.0mg, 0.0900mmol, 0.1eq). Stirring was continued for 19h then furhter methyl fumarate (71mg, 0.59mmol, 0.60eq), dicyclohexylcarbodiimide (0.121mg, 0.585mmol, 0.65eq) and N,N-dimethylaminopyridine (5.0mg, 0.045mmol, 0.05eq) was added and the solution was stirred for a further 3h. The reaction mixture was filtered and the solvent evaporated to give the crude product (0.621g) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl aceatate (8:1) gave the **title compound** (**305**) (0.383g, 0.869mmol, 96%) as a colourless oil: $[\alpha]_D^{21}$ = -25.6° (c = 8.60, dichloromethane); R_f = 0.20 (hexane:ethyl acetate (8:1)); (Found: M^+, 440.2240. $C_{22}H_{36}O_7Si$ requires *M*, 440.2230); ν_{max} (film) 2986, 2953, 2931, 2857, 1727, 1645, 1472, 1462, 1437, 1380 and 1370cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.035 and 0.055 (6H, 2 x s, -Si(C*H*$_3$)$_2$-), 0.879 (9H, s, -C(C*H*$_3$)$_3$), 1.31 and 1.37 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 3.75 (1H, dd, *J* 6.2, 8.5Hz, C1-*H*), 3.79 (3H, s, -CO_2C*H*$_3$), 3.92 (1H, dd, *J* 6.6, 8.5Hz, C1-*H'*), 4.02-4.11 (1H, m, C2-*H*), 4.28 (1H, t, *J* 5.6Hz, C3-*H*), 4.71 (2H, d, *J* 6.4Hz, C8-*H*), 5.67-5.86 (2H, m, C4-*H* and C7-*H*), 6.19-6.38 (2H, m, C5-*H* and C6-*H*) and 6.86 (2H, s, -C*H*=C*H*COCH$_3$); δ_C (68.1MHz, $CDCl_3$) -4.77, -4.55, 18.3, 25.2, 25.8, 26.4, 52.3, 65.2, 65.4, 73.1, 78.5, 109.3, 125.6, 130.1, 133.3,

133.4, 133.5, 134.0, 164.4 and 165.1; *m/z* (EI, 40eV) 440 (0.1%), 383 (13), 210 (28), 187 (33), 101 (100) and 73 (30).

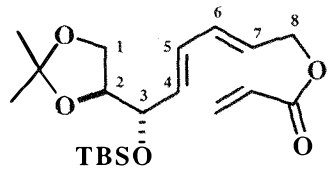
(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl propiolate (306)



306

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (**228**) (0.515g, 1.57mmol) in diethyl ether (20mL) at 0°C under argon was added propiolic acid (0.174mL, 2.82mmol, 1.8eq), dicyclohexylcarbodiimide (0.647g, 3.13mmol, 2eq) and N,N-dimethylaminopyridine (0.0290g, 0.235mmol, 0.15eq). Stirring was continued for 30min then a further amount of propiolic acid (0.087mL, 1.4mmol, 0.9eq) and dicyclohexylcarbodiimide (0.323g, 1.57mmol, 1eq) were added. After 30min the reaction mixture was warmed to 30°C and stirring continued for 1h. The reaction mixture was filtered and the filtrate was rinsed with diethyl ether (20mL), then the supernatant was partitioned against saturated aqueous sodium bicarbonate (20mL), water (20mL) and brine (20mL) then dried, filtered and evaporated to give the crude product (1.237g) as a yellow oil. Chromatography of this material on silica (30g) with hexane:ethyl acetate (10:1, then 5:1, then 2:1) gave the **title compound** (**306**) (0.388g, 1.02mmol, 65%) as a colourless oil: $[\alpha]_D^{19}$ = -26.9° (c = 5.4, dichloromethane); R_f = 0.62 (hexane:ethyl acetate (2:1)); (Found: M^+, 380.2039. $C_{20}H_{32}O_5Si$ requires *M*, 380.2019); ν_{max} (film) 3256, 2987, 2955, 2931, 2887, 2858, 2120, 1716, 1472, 1462, 1381, 1371 and 1222cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.057 and 0.077 (6H, 2 x s, -Si(C*H*$_3$)$_2$-), 0.90 (9H, s, -C(C*H*$_3$)$_3$), 1.34 and 1.40 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 2.91 (1H, s, -CC*H*), 3.78 (1H, dd, *J* 6.2, 8.6Hz, C1-*H*), 3.94 (1H, dd, *J* 6.6, 8.6Hz, C1-*H'*), 4.05-4.13 (1H, m, C2-*H*), 4.30 (1H, t, *J* 5.6Hz, C3-*H*), 4.73 (2H, d, *J* 6.8Hz, C8-*H*), 5.69-5.89 (2H, m, C4-*H* and C7-*H*) and 6.22-6.41 (2H, m, C5-*H* and C6-*H*); δ_C (68.1MHz, $CDCl_3$) -4.70, -4.49, 18.3, 25.2, 25.8, 25.9, 26.4, 65.3, 66.3, 73.3, 74.6, 74.8, 109.4, 125.0, 130.1, 133.9, 134.7 and 152.1; *m/z* (EI, 40eV) 380 (0.1%), 323 (11), 210 (34), 101 (100) and 73 (34).

(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl acrylate (307)

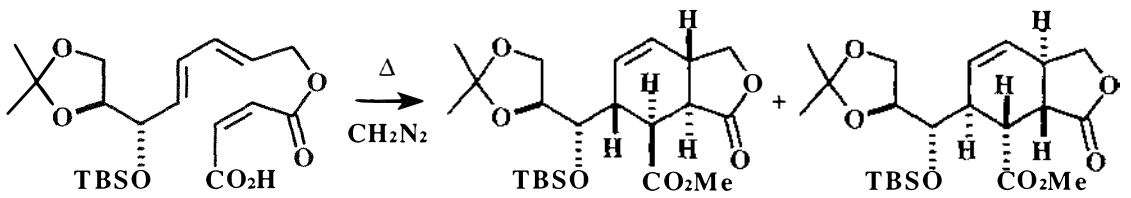


307

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (**228**) (98.3mg, 0.299mmol) in diethyl ether (2.5mL) at RT under argon was added acrylic acid (36.9μL, 0.539mmol, 1.8eq), dicyclohexylcarbodiimide (123mg, 0.598mmol, 2eq) and N,N-dimethylaminopyridine (5.5mg, 0.045mmol, 0.15eq). The reaction mixture was stirred for 2d then the solvent was evaporated and replaced with dichloromethane (2.5mL) and stirring was continued for a further 7d. The reaction mixture was filtered through celite and evaporated to give the crude product (0.176mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (10:1 then 3:1) gave the **title compound** (**307**) (54.0mg, 0.141mmol, 47%) as a colourless oil: $[\alpha]_D^{20}$= -27.4° (c = 1.51, dichloromethane); R_f = 0.32 (hexane:ethyl acetate (10:1)); (Found: M^+-CH_3, 367.1949. $C_{19}H_{31}O_5Si$ requires *M*, 367.1941); ν_{max} (film) 2985, 2954, 2930, 2886, 2857, 1728, 1472, 1462, 1407, 1380, and 1370cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.45 and 0.065 (6H, 2 x s, -Si(CH_3)$_2$-), 0.889 (9H, s, -C(CH_3)$_3$), 1.32 and 1.38 (6H, 2 x s, -C(CH_3)$_2$-), 3.76 (1H, dd, *J* 6.3, 8.5Hz, C1-*H*), 3.92 (1H, dd, *J* 6.7, 8.5Hz, C1-*H'*), 4.03-4.12 (1H, m, C2-*H*), 4.30 (1H, t, *J* 5.5Hz, C3-*H*), 4.69 (2H, d, *J* 6.4Hz, C8-*H*), 5.68-5.84 (2H, m, C4-*H* and C7-*H*), 5.84 (1H, dd, A of ABX, J_{AB} 1.5Hz and J_{AX} 10.4Hz, -CH=C*H*H'), 6.17 (1H, dd, X of ABX, J_{AX} 10.4Hz and J_{BX} 17.4Hz, -C*H*=CHH'), 6.20-6.37 (2H, m, C5-*H* and C6-*H*) and 6.43 (1H, dd, B of ABX, J_{AB} 1.5Hz andJ_{BX} 17.4Hz , -CH=CH*H'*); δ_C (68.1MHz, $CDCl_3$) -4.73, -4.51, 18.3, 25.2, 25.9, 26.4, 64.7, 65.2, 73.3, 78.6, 109.3, 126.4, 128.2, 130.3, 130.8, 133.1, 133.5 and 165.7; *m/z* (EI, 70eV) 367 (0.4%), 325 (7), 281 (11), 210 (28), 195 (18), 129 (42), 101 (100), 73 (44), 55 (52) and 43 (19).

6.3.2 ETDA reactions

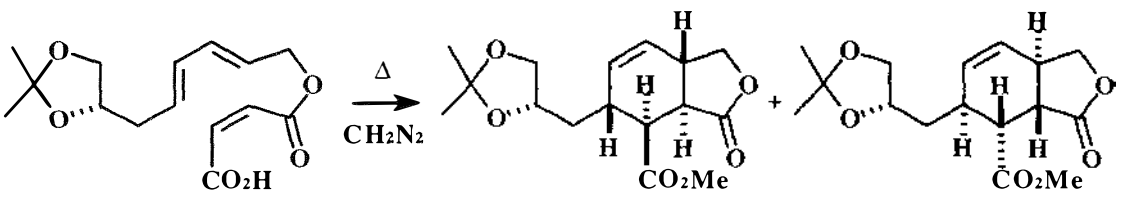
ETDA reaction of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (236)



236 **241c** **242c**

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (**236**) (137mg, 0.322mmol) in toluene (64.4mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (14.2mg, 0.0646mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 17h. The solution was cooled to 0°C, then an ethereal solution of diazomethane[173] (**Section 6.6.3**) was added. On completion of the addition the solvent was evaporated to give the crude product (148.1mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (4:1) gave the **ETDA adducts** (**241c** and **242c**) (86.3mg, 0.196mmol, 62%, **241c:242c** (89:11)), *vide supra.*

ETDA reaction of (2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (239)

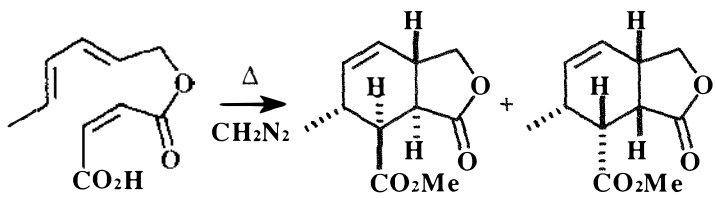


239 **270** **271**

To a stirred solution of (2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (**239**) (8.7mg, 0.029mmol) in toluene (5.9mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (1.3mg, 0.0059mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 6h. The solution was cooled to 0°C, then an ethereal solution of diazomethane[173] (**Section 6.6.3**) was

added. On completion of the addition the solvent was evaporated to give the crude product (10.0mg) as a yellow oil. Chromatography of this material on silica (1g) with hexane:ethyl acetate (2:1) gave the **ETDA adducts** (**270** and **271**) (5.9mg, 0.019mmol, 66%, **270:271** (50:50)), *vide supra.*

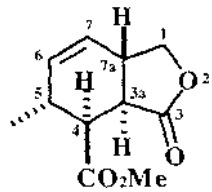
ETDA reaction of (2*E*,4*E*)-2,4-hexadien-1-yl hydrogen maleate (302)



302 **308** **309**

To a stirred solution of (2*E*,4*E*)-2,4-hexadien-1-yl hydrogen maleate (**302**) (36.0mg, 0.180mmol) in toluene (36.6mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (8.1mg, 0.037mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 2h. The solution was cooled to 0°C, then an ethereal solution of diazomethane[173] (**Section 6.6.3**) was added. On completion of the addition the solvent was evaporated to give the crude product (45.0mg) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (5:1 then 2:1) gave the **ETDA adducts** (**308** and **309**) (31.6mg, 0.150mmol, 83%, **308:309** (69:31)), *vide infra.*

***rel*-methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-5-methyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (308)**

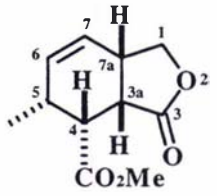


308

Colourless oil; R_f = 0.23 (hexane:ethyl acetate (5:1)); (Found: M^+, 210.0891. $C_{11}H_{14}O_4$ requires M, 210.0892); ν_{max} (film) 3026, 2959, 2901, 1782, 1732, 1437, 1326, 1312 and 1216cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.18 (3H, d, *J* 7.3Hz, C5-C*H*$_3$), 2.35 (1H, dd, *J* 3.6, 13.5Hz, C3a-*H*), 2.87-2.99 (1H, m, C5-*H*), 2.96 (1H, d, *J* 3.6Hz, C4-*H*), 3.11-3.27 (1H, m, C7a-*H*), 3.69 (3H, s, -CO_2CH_3), 3.87 (1H, dd, *J* 7.9, 11.4Hz, C1-*H*),

4.51 (1H, dd, *J* 7.3, 7.9Hz, C1-*H'*), 5.65 (1H, dt, *J* 10.0, 3.3Hz, C6-*H*) and 5.72 (1H, dt, *J* 10.0, 1.9Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 22.0, 34.1, 36.4, 41.5, 42.7, 52.1, 70.6, 123.0, 134.5, 172.1 and 174.6; *m/z* (EI, 70eV) 210 (0.5%), 179 (13), 105 (100), 91 (61) and 77 (20).

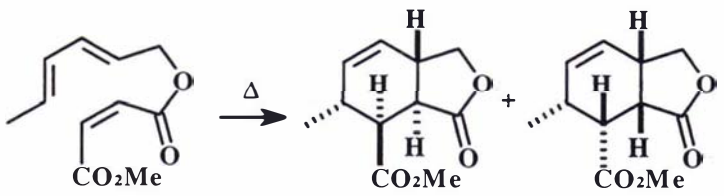
rel-methyl (3a*S*, 4*R*, 5*R*, 7a*S*)-5-methyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxyl-ate (309)



309

Colourless oil; R_f = 0.13 (hexane:ethyl acetate (2:1)); (Found: M^+, 210.0893. $C_{11}H_{14}O_4$ requires *M*, 210.0892); ν_{max} (film) 3022, 2953, 2913, 1770, 1732 1435 and 1212cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.16 (3H, d, *J* 7.5Hz, C5-C*H*$_3$), 2.62-2.77 (1H, m, C5-*H*), 3.09 (1H, t, *J* 5.3Hz, C4-*H*), 3.14-3.26 (1H, m, C7a-*H*), 3.33 (1H, dd, *J* 5.3, 9.7Hz, C3a-*H*), 3.75 (3H, s, -CO_2CH_3), 4.17 (1H, dd, *J* 4.4, 8.6Hz, C1-*H*), 4.44 (1H, dd, *J* 7.8, 8.6Hz, C1-*H'*), 5.60 (1H, dt, *J* 10.1, 2.4Hz, C7-*H*) and 5.82 (1H, ddd, *J* 2.4, 4.0, 10.1Hz, C6-*H*); δ_C (68.1MHz, $CDCl_3$) 17.8, 30.3, 35.3, 38.6, 42.1, 51.8, 71.4, 124.3, 133.9, 171.7 and 177.0; *m/z* (EI, 70eV) 210 (19%), 178 (59), 150 (55), 105 (56) and 93 (100).

ETDA reaction of (2*E*,4*E*)-2,4-hexadien-1-yl methyl maleate (303)

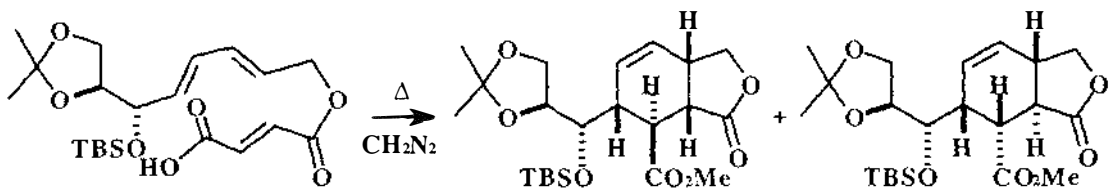


303 **308** **309**

To a stirred solution of (2*E*,4*E*)-2,4-hexadien-1-yl methyl maleate (**303**) (37.0mg, 0.176mmol) in toluene (35.2mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (7.8mg, 0.035mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 2h. Evaporation of the solvent gave the crude product (45.0mg) as a yellow oil. Chromatography of this material on silica (4g) with

hexane:ethyl acetate (5:1 then 2:1) gave the **ETDA adducts** (**308** and **309**) (29.2mg, 0.139mmol, 79%, **308:309** (79:21)), *vide supra*.

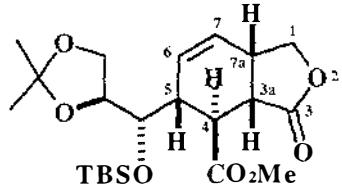
ETDA reaction of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen fumarate (304)



304 **314** **315**

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen fumarate (**304**) (97.0mg, 0.239mmol) in toluene (47.8mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (10.5mg, 0.0477mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 142h. The solution was cooled to 0°C, then an ethereal solution of diazomethane[173] (**Section 6.6.3**) was added. On completion of the addition the solvent was evaporated to give the crude product (117mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (5:1 then 2:1) then ethyl acetate gave the **ETDA adducts** (**314** and **315**) (44.6mg, 0.101mmol, 42%, **314:315** (71:29)), *vide infra*.

methyl (3a*S*, 4*S*, 5*R*, 7a*S*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1-dimethyl-1-*tert*-butlyldimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (314)

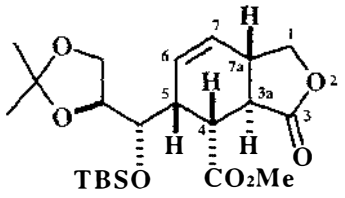


314

Colourless oil; $[\alpha]_D^{21}$ = -66.1° (c = 1.20, dichloromethane); R_f = 0.50 (hexane:ethyl acetate (2:1)); (Found: M^+-CH_3, 425.1996. $C_{21}H_{33}O_7Si$ requires M, 425.1996); ν_{max} (film) 2984, 2953, 2930, 2897, 2856, 1787, 1738, 1472, 1462, 1435, 1380, 1370 and

1208cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.46 and 0.88 (6H, 2 x s, -Si(CH_3)$_2$-), 0.863 (9H, s, -C(CH_3)$_3$), 1.35 and 1.40 (6H, 2 x s, -C(CH_3)$_2$-), 2.40-2.50 (1H, m, C5-*H*), 2.91-3.06 (2H, m, C3a-*H* and C4-*H*), 3.07-3.25 (1H, m, C7a-*H*), 3.57 (1H, t, *J* 8.2Hz, -C*H*H'OC(CH_3)$_2$OCH-), 3.62 (1H, dd, *J* 2.8, 7.3Hz, -C*H*OTBS), 3.77 (3H, s, -CO_2CH_3), 3.91 (1H, t, *J* 8.8Hz, C1-*H*), 3.97 (1H, dd, *J* 6.2, 8.2Hz, -CH*H'*OC(CH_3)$_2$OCH-), 4.17-4.27 (1H, m, -CHH'OC(CH_3)$_2$OC*H*-), 4.49 (1H, dd, *J* 8.0, 8.8Hz, C1-*H'*), 5.70 (1H, dt, *J* 10.4, 3.3Hz, C7-*H*) and 5.94 (1H, dt, *J* 10.4, 2.2Hz, C6-*H*); δ_C (68.1MHz, $CDCl_3$) -5.18, -3.86, 18.5, 25.5, 26.1, 26.6, 35.0, 40.4, 40.5, 40.7, 52.2, 66.0, 71.6, 73.9, 78.0, 109.3, 123.8, 129.2, 173.6 and 176, 3; *m/z* (EI, 40eV) 425 (12%), 383 (28), 339 (66), 325 (85), 293 (89), 265 (64), 89 (42) and 73 (100).

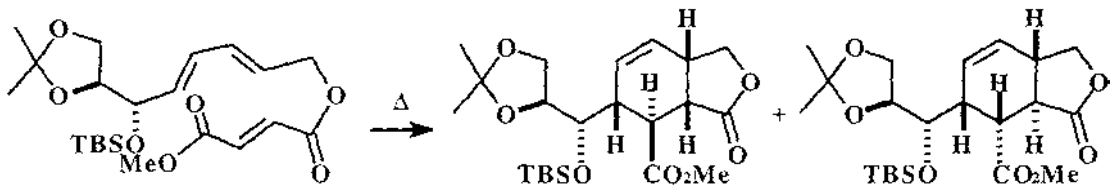
methyl (3a*R*, 4*R*, 5*R*, 7a*S*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1-dimethyl-1-*tert*-butlyldimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (315)



315

Colourless oil; $[\alpha]_D^{19.5}$ = -137° (c = 0.190, dichloromethane); R_f = 0.42 (hexane:ethyl acetate (2:1)); (Found: M^+-CH_3, 425.1999 $C_{21}H_{33}O_7Si$ requires *M*, 425.1996); ν_{max} (film) 2984, 2952, 2928, 2855, 1789, 1738, 1471, 1462, 1435, 1380 and 1370cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.118 (6H, s, -Si(CH_3)$_2$-), 0.878 (9H, s, -C(CH_3)$_3$), 1.35 and 1.41 (6H, 2 x s, -C(CH_3)$_2$-), 2.54-2.62 (1H, m, C5-*H*), 2.70-2.86 (1H, m, C7a-*H*), 2.96 (1H, dd, *J* 7.2, 11.6Hz, C4-*H*), 3.16 (1H, dd, *J* 11.6, 13.4Hz, C3a-*H*), 3.56 (1H, t, *J* 8.1Hz, -C*H*H'OC(CH_3)$_2$OCH-), 3.79 (1H, dd, *J* 2.0, 7.5Hz, -C*H*OTBS), 3.80 (3H, s, -CO_2CH_3), 3.90 (1H, dd, *J* 8.0, 11.4Hz, C1-*H*), 3.99 (1H, dd, *J* 6.4, 8.1Hz, -CH*H'*OC(CH_3)$_2$OCH-), 4.08-4.19 (1H, m, -CHH'OC(CH_3)$_2$OC*H*-), 4.45 (1H, dd, *J* 6.6, 8.0Hz, C1-*H'*), 5.74 (1H, dt, *J* 9.9, 3.5Hz, C6-*H*) and 5.96 (1H, dt, *J* 9.9, 2.0Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) -4.53, -3.64, 18.6, 25.5, 26.3, 26.6, 40.7, 41.1, 41.4, 44.1, 51.9, 66.2, 70.1, 74.9, 78.3, 109.6, 124.7, 129.1, 170.7 and 173.7; *m/z* (EI, 70eV) 425 (9%), 383 (19), 339 (65), 325 (61), 293 (55), 265 (49), 89 (36) and 75 (100).

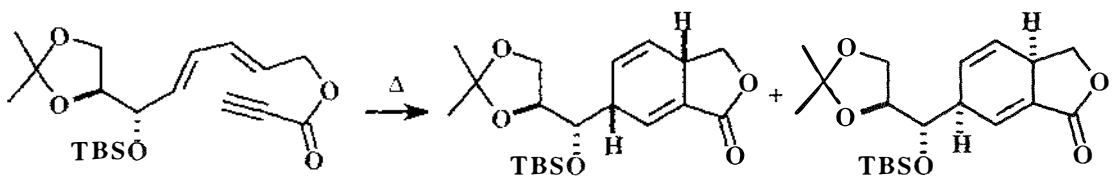
ETDA reaction of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl fumarate (305)



305 **314** **315**

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl methyl fumarate (**305**) (92.5mg, 0.210mmol) in toluene (42mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (9.3mg, 0.042mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 167h. Evaporation of the solvent gave the crude product (98.9mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (5:1 then 3:1) gave **recovered starting material** (**305**) (29.4mg, 0.067mmol, 31%) followed by the **ETDA adducts** (**314** and **315**) (48.3mg, 0.110mmol, 76% (at 69% conversion), **314:315** (86:14)), *vide supra.*

ETDA reaction of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl propiolate (306)

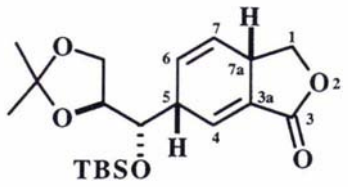


306 **320** **321**

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl propiolate (**306**) (97.1mg, 0.255mmol) in toluene (51.0mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (5.6mg, 0.026mmol, 0.1eq). The solution was warmed to reflux and heating was continued for 29h. Evaporation of the solvent gave the crude product (0.101g) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (3:1) gave **recovered starting material** (**56**) (27.2mg,

0.0715mmol, 28%) followed by the **ETDA adducts** (**320** and **321**) (59.6mg, 0.157mmol, 85% (at 72% conversion), **320:321** (65:35)), *vide infra*.

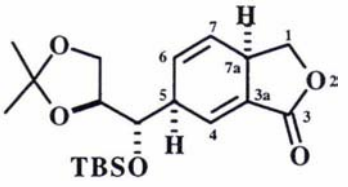
(5*R*, 7a*S*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1-dimethyl-1-*tert*-butlyldimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,5,7a-tetrahydroisobenzofuran (320)



320

Colourless oil; $[\alpha]_D^{20}$ = -13.5° (c = 1.12, dichloromethane); R_f = 0.30 (hexane:ethyl acetate (3:1)); (Found: M^+, 380.2030. $C_{20}H_{32}O_5Si$ requires M, 380.2019); ν_{max} (film) 2984, 2954, 2929, 2897, 2856, 1769, 1482, 1471, 1380 and 1370cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.080 and 0.112 (6H, 2 x s, -Si(C*H*$_3$)$_2$-), 0.871 (9H, s, -C(C*H*$_3$)$_3$), 1.33 and 1.41 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 3.05-3.16 (1H, m, C5-*H*), 3.46-3.59 (1H, m, C7a-*H*), 3.58 (1H, t, *J* 8.1Hz, -C*H*H'OC(CH$_3$)$_2$OCH-), 3.82 (1H, t, *J* 8.6Hz, C1-*H*), 3.85 (1H, dd, *J* 4.4, 8.1Hz, -CH*H'*OC(CH$_3$)$_2$OCH-), 3.92 (1H, dd, *J* 3.7, 6.6Hz, -C*H*OTBS), 4.00-4.10 (1H, m, CHH'OC(CH$_3$)$_2$OC*H*-), 4.64 (1H, dd, *J* 8.2, 8.6Hz, C1-*H'*), 5.76-5.93 (2H, m, C6-*H* and C7-*H*) and 6.96-7.01 (1H, m, C4-*H*); δ_C (68.1MHz, $CDCl_3$) -4.74, -4.18, 18.3, 25.7, 25.9, 26.6, 37.8, 42.8, 65.9, 70.4, 75.2, 77.9, 108.9, 123.8, 127.5, 128.0, 135.1 and 168.9; *m/z* (EI, 40eV) 380 (0.3%), 187 (35), 131 (59), 101 (39), 91 (42) and 73 (100).

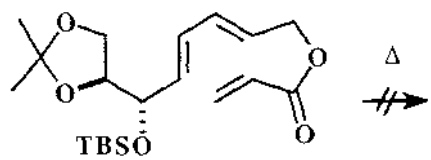
(5*S*, 7a*R*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1-dimethyl-1-*tert*-butlyldimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,5,7a-tetrahydroisobenzofuran (321)



321

Colourless oil; $[\alpha]_D^{20}$ = +51.8° (c = 0.36, dichloromethane); R_f = 0.39 (hexane:ethyl acetate (3:1)); (Found: M^+, 380.1999 $C_{20}H_{32}O_5Si$ requires M, 380.2019); ν_{max} (film) 2984, 2953, 2929, 2897, 2856, 1770, 1697, 1471, 1462, 1380, 1370 and 1206cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.052 and 0.098 (6H, 2 x s, -Si(C*H*$_3$)$_2$-), 0.841 (9H, s, -C(C*H*$_3$)$_3$), 1.35 and 1.41 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 2.95-3.05 (1H, m, C5-*H*), 3.46-3.63 (1H, m, C7a-*H*), 3.61 (1H, t, *J* 8.1Hz, -C*H*H'OC(CH$_3$)$_2$OCH-), 3.82 (1H, dd, *J* 8.3, 10.4Hz, C1-*H*), 3.87-3.95 (2H, m, -CH*H'*OC(CH$_3$)$_2$OC*H*-), 4.13-4.22 (1H, m, -C*H*OTBS), 4.65 (1H, t, *J* 8.3Hz, C1-*H'*), 5.82-5.99 (2H, m, C6-*H* and C7-*H*) and 6.86-6.90 (1H, m, C4-*H*); δ_C (68.1MHz, $CDCl_3$) -4.74, -4.10, 18.3, 25.6, 25.9, 26.6, 37.8, 42.0, 65.8, 70.4, 75.7, 78.1, 109.2, 123.2, 128.8, 130.4, 133.3 and 168.9; *m/z* (EI, 40eV) 380 (0.1%), 265 (25), 187 (36), 131 (69), 91 (50) and 73 (100).

Attempted ETDA reactions of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl acrylate (307)



307

Method A

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl acrylate (**307**) (17.5mg, 0.0457mmol) in toluene (9.2mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (2.0mg, 0.0091mmol, 0.2eq). The solution was warmed to reflux and heating continued for 43h, but no reaction was detected by TLC. The solvent was evaporated and replaced with xylene (9.2mL), then the solution was warmed to reflux and heating was continued for 23h. No change was detected by TLC.

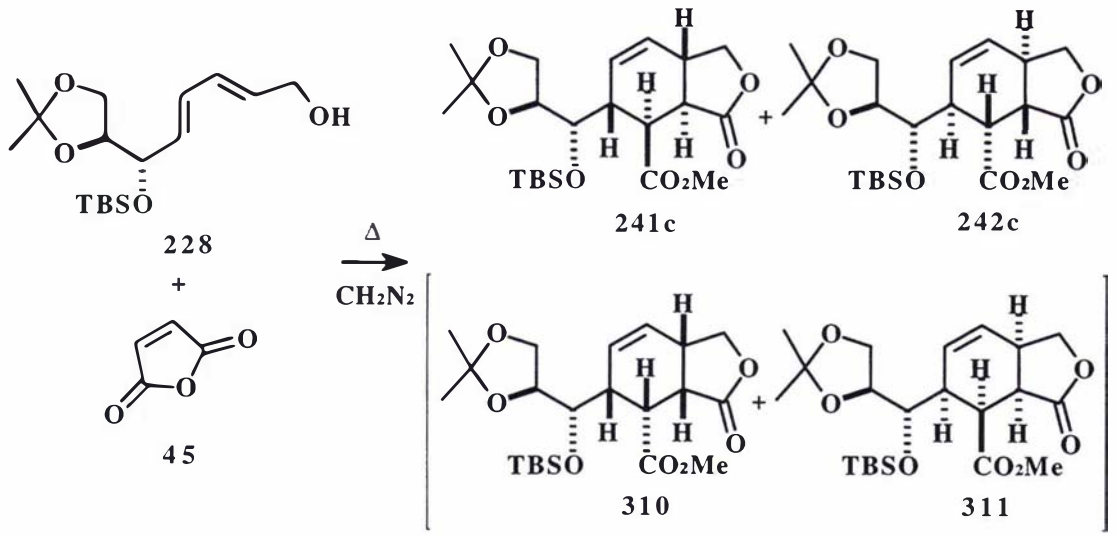
Method B

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl acrylate (**307**) (30.2mg, 0.0789mmol) in toluene (9.2mL) was added 2,6-di-*tert*-butyl-4-methylphenol (3.5mg, 0.016mmol, 0.2eq) under argon. The solution was heated to 210°C in a sealed tube

(without refluxing) for 30h. TLC indicated that a portion of the starting material was consumed, so the solvent was evaporated to give the crude product (29.6mg) as a yellow oil. Chromatography of this material on silica (1g) with dichloromethane:hexane:ethyl acetate gave **recovered starting material (307)** (6.1mg, 0.016mmol, 39%) followed by a mixture of compounds which were found to be chromatographically inseparable in a range of solvent systems. (Proton NMR analysis indicated that a complex mixture of compounds was produced.)

6.3.3 Miscellaneous DA reactions

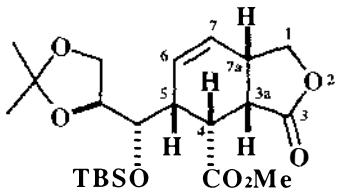
DA reaction between (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-4,6-octadien-1,2,8-triol (228) and maleic anhydride (45).



To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-4,6-octadien-1,2,8-triol (**228**) (100mg, 0.304mmol) in toluene (3.0mL) at RT under argon was added maleic anhydride (**45**) (29.8mg, 0.304mmol, 1eq) and 2,6-di-*tert*-butyl-4-methylphenol (13.4mg, 0.0608mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 67h. The solution was cooled to -65°C then an ethereal solution of diazomethane[173] (**Section 6.6.3**) was added dropwise. On completion of the addition the solvent was evaporated to the give the crude product (126.9mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (3:1) then ehtyl acetate gave the **DA adducts (241c, 242c, 310** and **311)** (60.3mg, 0.137mmol, 45%, **241c:242c:310:311** (42:4:27:27)), *vide supra/infra*. (Only one of the adducts **310** and **311** was able to be isolated and characterised. Coupling constants for the isolated compound (**310**) indicated that the two

rings were *cis* fused, but it was not possible to determine the relative stereochemistry of this adduct. The structure of the unisolated compound (**311**) is speculative and based on limited proton NMR analysis of mixtures only.

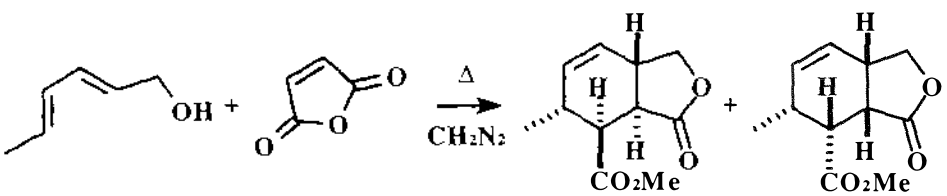
methyl (3a*S*, 4*R*, 5*R*, 7a*S*)-5-((2*S*,3*S*)-1,2-*O*-isopropylidene-3-(-1,1-dimethyl-1-*tert*-butlyldimethylsilyl)oxy-1,2-dihydroxy-3-propanyl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (310)



310

Colourless oil; $[\alpha]_D^{21}$ = +4.3° (c = 0.31, dichloromethane); R_f = 0.45 (hexane:ethyl acetate (3:1)); (Found: M^+-CH_3, 425.1990. $C_{21}H_{33}O_7Si$ requires *M*, 425.1996); ν_{max} (film) 2953, 2928, 2856, 1769, 1738, 1473, 1463, 1436, 1380 and 1370cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.073 and 0.115 (6H, 2 x s, -Si(CH_3)$_2$-), 0.870 (9H, s, -C(CH_3)$_3$), 1.35 and 1.42 (6H, 2 x s, -C(CH_3)$_2$-), 2.40-2.49 (1H, m, C5-*H*), 2.97 (1H, dd, *J* 6.2, 11.0Hz, C3a-*H*), 3.13-3.29 (1H, m, C7a-*H*), 3.42 (1H, dd, *J* 4.2, 6.2Hz, C4-*H*), 3.65 (3H, s, -CO_2CH_3), 3.77 (1H, dd, *J* 7.3, 8.3Hz, -C*H*H'OC(CH_3)$_2$OCH-), 4.01 (1H, dd, *J* 4.6, 8.3Hz, -CH*H'*OC(CH_3)$_2$OCH-), 4.04 (1H, t, *J* 8.3Hz, C1-*H*), 4.20 (1H, dd, *J* 6.2, 7.3Hz, -C*H*OTBS), 4.39-4.47 (1H, m, -CHH'OC(CH_3)$_2$OC*H*-), 4.51 (1H, dd, *J* 8.3, 9.6Hz, C1-*H'*), 5.65 (1H, dt, *J* 10.1, 2.9Hz, C7-*H*) and 5.91 (1H, dt, *J* 10.1, 2.2Hz, C6-*H*); δ_C (68.1MHz, $CDCl_3$) -4.80, -4.03, 18.6, 24.9, 26.2, 26.4, 34.3, 39.6, 40.9, 41.6, 51.7, 65.3, 71.6, 73.6, 77.9, 109.3, 124.2, 129.5, 171.6 and 177.1; *m/z* (EI, 70eV) 425 (7%), 383 (19), 339 (77), 325 (100), 265 (34) and 73 (77).

DA reaction between (2*E*,4*E*)-2,4-hexadien-1-ol (228) and maleic anhydride (45)



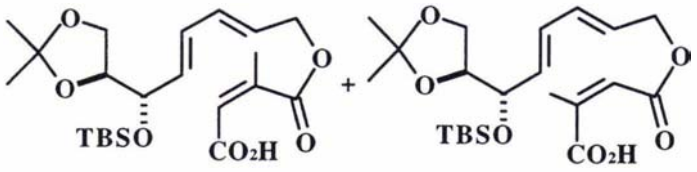
228 **45** **312** **313**

To a stirred solution of (2*E*,4*E*)-2,4-hexadien-1-ol (**228**) (103mg, 1.05mmol) in toluene (2.00mL) at RT under argon was added maleic anhydride (**45**) (103mg, 1.05mmol, 1eq) and 2,6-di-*tert*-butyl-4-methylphenol (44.1mg, 0.200mmol, 0.2eq) . The solution was warmed to reflux and heating was continued for 70min. Toluene (10mL) was added and the solution was cooled to -65°C then an ethereal solution of diazomethane[173] (**Section 6.6.3**) was added dropwise. On completion of the addition the solvent was evaporated to give the crude product (250mg) as a yellow oil. Chromatography of this material on silica (10g) with hexane:ethyl acetate (5:1 then 2:1) gave the **DA adducts** (**312** and **313**) (198mg, 0.942mmol, 90%, **312:313** (4:96)), *vide supra.*

6.4 Experimental for Chapter four

6.4.1 Preparation of citraconate precursors

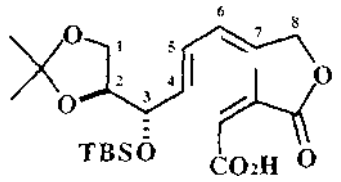
1-((2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (401) and **1-((2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (402)**



401 **402**

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol (**228**) (102mg, 0.310mmol) in dichloromethane (10mL) at RT under argon was added triethylamine (69.2µL, 0.497mmol, 1.6eq), citraconic anhydride (62.6µL, 0.699mmol, 2.25eq) and N,N-dimethylaminopyridine (crystal). Stirring was continued for 1h then the reaction mixture was diluted with diethyl ether (50mL) and partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (152mg) as a yellow oil. Chromatography of this material on silica (5g) with ethyl acetate:hexane (2:1) then ethyl acetate:acetic acid (100:1) gave the **title compounds** (**401** and **402**) (84.7mg, 0.192mmol, 62%, **401:402** (77:23)), *vide infra.*

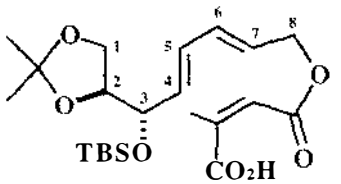
1-((2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (401)



401

Colourless oil; $[\alpha]_D^{21}$ = -27.4° (c = 1.29, dichloromethane); R_f = 0.70 (ethyl acetate:acetic acid (100:1)); (Found: M^+, 440.2220. $C_{22}H_{36}O_7Si$ requires M, 440.2230); ν_{max} (film) 3437, 3157, 2950, 2930, 2857, 1732, 1714, 1651, 1471, 1462, 1382 and 1372cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.047 and 0.67 (6H, 2 x s, -Si(CH_3)$_2$-), 0.891 (9H, s, -C(CH_3)$_3$), 1.33 and 1.39 (6H, 2 x s, -C(CH_3)$_2$-), 2.09 (3H, d, *J* 1.5Hz, -CH=CCH_3-), 3.78 (1H, dd, *J* 6.2, 8.6Hz, C1-*H*), 3.93 (1H, dd, *J* 6.7, 8.6Hz, C1-*H'*), 4.04-4.12 (1H, m, C2-*H*), 4.29 (1H, t, *J* 5.5Hz, C3-*H*), 4.73 (2H, d, *J* 6.6Hz, C8-*H*), 5.69-5.83 (2H, m, C4-*H* and C7-*H*), 5.88 (1H, q, *J* 1.5Hz, -C*H*=CCH$_3$-) and 6.21-6.39 (2H, m, C5-*H* and C6-*H*); δ_C (68.1MHz, $CDCl_3$) -4.75, -4.50, 18.3, 20.9, 25.2, 25.9, 26.4, 65.2, 65.9, 73.2, 78.5, 109.4, 120.7, 125.5, 130.2, 133.3, 134.3, 147.3, 168.4 and 168.6; *m/z* (CI/NH_3, 40eV) 440 (0.03%), 271 (13), 227 (33), 210 (24), 101 (100), 75 (76) and 39 (30).

1-((2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (402)

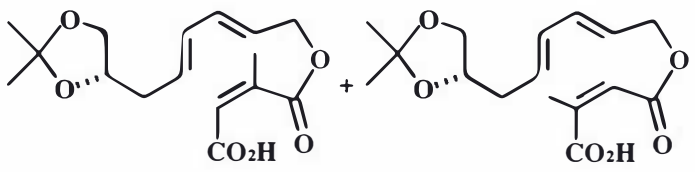


402

Colourless oil; $[\alpha]_D^{21}$ = -26.1° (c = 0.88, dichloromethane); R_f = 0.33 (ethyl acetate:acetic acid (100:1)); (Found: M^+, 440.2212 $C_{22}H_{36}O_7Si$ requires M, 440.2230); ν_{max} (film) 3468, 3155, 2985, 2954, 2930, 2893, 2857, 1730, 1714, 1472, 1462, 1447, 1380, 1370 and 1255cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.055 and 0.075 (6H, 2 x s, -Si(CH_3)$_2$-),

0.900 (9H, s, -C(CH_3)$_3$), 1.34 and 1.40 (6H, 2 x s, -C(CH_3)$_2$-), 2.15 (3H, d, *J* 1.5Hz, -CH=CCH_3-), 3.79 (1H, dd, *J* 6.0, 8.6Hz, C1-*H*), 3.95 (1H, dd, *J* 6.6, 8.6Hz, C1-*H'*), 4.05-4.14 (1H, m, C2-*H*), 4.27-4.34 (1H, m, C3-*H*), 4.72 (2H, d, *J* 6.6Hz, C8-*H*), 5.69-5.83 (2H, m, C4-*H* andC7-*H*), 6.16 (1H, q, *J* 1.5Hz, -C*H*=CCH$_3$-) and 6.20-6.42 (2H, m, C5-*H* and C6-*H*); δ_C (68.1MHz, $CDCl_3$) -4.71, -4.50, 18.3, 22.2, 25.2, 25.9, 26.4, 65.1, 66.1, 73.0, 78.5, 109.5, 122.6 (2 x C), 125.0, 130.0, 133.8, 134.7 and 166.4 (2 x C); *m/z* (EI, 70eV) 440 (0.05%), 271 (15), 227 (36), 210 (33), 101 (100), 75 (81) and 39 (37).

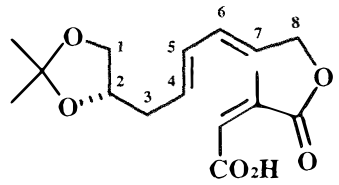
1-((2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (403) and **1-((2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (404)**



403 **404**

To a stirred solution of (2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-4,6-octdadiene-1,2,8-triol (**235**) (45.5mg, 0.230mmol) in dichloromethane (5mL) at 0°C under argon was added triethylamine (48.0µL, 0.0.345mmol, 1.5eq), citraconic anhydride (25.7µL, 0.290mmol, 1.25eq) and N,N-dimethylaminopyridine (crystal). Stirring was continued for 3h then a further amount of triethylamine (48.0µL, 0.0.345mmol, 1.5eq) and citraconic anhydride (25.7µL, 0.290mmol, 1.25eq) was added and the solution was warmed to RT and stirred for 18h. The reaction mixture was diluted with diethyl ether (50mL) and partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (140mg) as a yellow oil. Chromatography of this material on silica (10g) with ethyl acetate:acetic acid:methanol (200:1:1 then 20:1:1) gave the **title compounds (403** and **404)** (55.0mg, 0.177mmol, 77%, **403:404** (67:33)), *vide infra*.

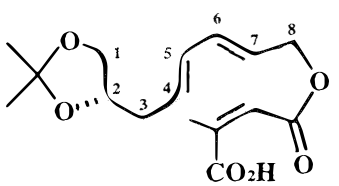
1-((2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (403)



403

Colourless oil; $[\alpha]_D^{21} = +8.5^{\circ}$ (c = 0.41, dichloromethane); R_f = 0.69 (ethyl acetate:acetic acid:methanol (20:1:1)); (Found: M^+, 310.1418. $C_{16}H_{22}O_6$ requires M, 310.1416); ν_{max} (film) 3435, 3151, 3028, 2986, 2934, 2883, 1731, 1654, 1448, 1379, 1369 and 1340cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.35 and 1.42 (6H, 2 x s, -C(CH_3)$_2$-), 2.08 (3H, d, *J* 1.5Hz, -CH=CCH_3-), 2.24-2.55 (2H, m, C3-*H*), 3.57 (1H, dd, *J* 6.8, 8.0Hz, C1-*H*), 4.02 (1H, dd, *J* 6.0, 8.0Hz, C1-*H'*), 4.16 (1H, m, C2-*H*), 4.72 (2H, d, *J* 6.7Hz, C8-*H*), 5.83-5.62 (2H, m, C4-*H* and C7-*H*), 5.89 (1H, q, *J* 1.5Hz, -C*H*=CCH_3-) and 6.13 and 6.29 (2H, 2 x dd, *J* 10.4, 15.1 Hz and *J* 10.4, 15.1 Hz, C5-*H* and C6-*H*); δ_C (68.1MHz, $CDCl_3$) 21.0, 25.7, 26.9, 37.0, 66.1, 68.8, 75.2, 109.0, 121.7, 124.2, 130.9, 131.7, 135.1, 146.5, 168.0 and 168.4; *m/z* (CI/NH_3, 40eV) 310 (0.02%), 183 (13), 101 (100), 80 (27), 68 (35) and 43 (24).

1-((2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (404)

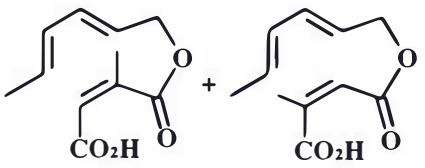


404

Colourless oil; $[\alpha]_D^{21} = +6.3^{\bullet}$ (c = 0.58, dichloromethane); R_f = 0.44 (ethyl acetate:acetic acid:methanol (2:1:1)); (Found: M^+, 310.1400. $C_{16}H_{22}O_6$ requires M, 310.1416); ν_{max} (film) 3435, 3153, 2984, 2935, 2877, 1729, 1653, 1447, 1380 and 1370cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.36 and 2.17 (6H, 2 x d, 0.5Hz, -C(CH_3)$_2$-), 2.17 (3H, d, *J* 1.5Hz, -CH=CCH_3-), 2.28-2.53 (2H, m, C3-*H*), 3.58 (1H, dd, *J* 6.8, 8.0Hz, C1-*H*), 4.04 (1H, dd, *J* 6.8, 8.0Hz, C1-*H'*), 4.17 (1H, m, C2-*H*), 4.74 (2H, d, *J* 6.8Hz, C8-*H*), 5.62-5.85 (2H, m, C4-*H* and C7-*H*), 6.08-6.39 (2H, m, C5-*H* and C6-*H*) and 6.25

(1H, q, *J* 1.5Hz, -C*H*=CCH$_3$-); δ_C (68.1MHz, $CDCl_3$) 22.9, 25.7, 27.0, 37.0, 66.7, 68.8, 75.1, 109.1, 123.2, 123.4, 131.4, 131.7, 135.7, 147.7, 166.4 and 167.2; *m/z* (CI/NH_3, 40eV) 310 (0.2%), 295 (6), 183 (39), 101 (100), 80 (74), 68 (86) and 43 (81).

1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (38d) and **1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (38c)**



38d **38c**

Method A

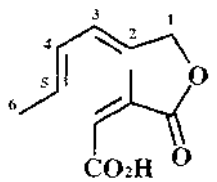
To a stirred solution of (2*E*,4*E*)-2,4-hexadien-1-ol (**301**) (2.00g, 20.4mmol) in dichloromethane (100mL) at 0°C under argon was added triethylamine (3.00mL, 21.5mmol, 1.05eq), citraconic anhydride (2.74mL, 30.6mmol, 1.5eq) and N,N-dimethylaminopyridine (0.124g, 1.01mmol, 0.05eq). On completion of the addition the solution was warmed to RT and stirring was continued for 30min. An extra amount of triethylamine (1.56mL, 11.2mmol, 0.55eq), citraconic anhydride (1.60mL, 14.3mmol, 0.7eq) and N,N-dimethylaminopyridine (0.124g, 0.510mmol, 0.025eq) was added and stirring was continued for 3h. The reaction mixture was partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (6.021g) as a yellow oil. The crude product was adsorbed onto silica (9g) then loaded onto a silica column (90g) and eluted with hexane:ethyl acetate (2:1), ethyl acetate, ethyl acetate:acetic acid (165:1) then ethyl acetate:acetic acid:methanol (38:1:1) to give the **title compounds** (**38d** and **38c**) (4.30g, 20.4mmol, 100%, **38d:38c** (86:14)), *vide infra*.

Method B

Compounds 38d and **38c** were also prepared using the method of White *et al.*[98] To a stirred solution of (2*E*,4*E*)-2,4-hexadien-1-ol (**301**) (1,96g, 20.0mmol) in benzene (4mL) at RT under argon was added pyridine (1.60mL, 48.3mmol, 2.42eq) and citraconic anhydride (1.80mL, 20.0mmol, 1eq). On completion of the addition the

solution was warmed to 50°C and stirring was continued for 8h. The solvent was evaporated then dichloromethane (50mL) was added and this was partitioned against 10% aqueous hydrochloric acid (2 x 50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (3.87g) as a yellow oil. Half of the crude product (1.91g) was columned in two portions on silica (50g) with hexane:ethyl acetate:acetic acid:methanol (260:130:1:1) to give the **title compounds** (**38d** and **38c**) (1.847g, 8.79mmol, 44% (corresponding to an overall yield of 89%), **38d:38c** (50:50)), *vide infra*.

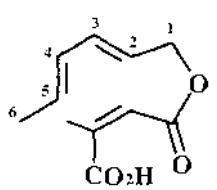
1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (38d)



38d

Wax; R_f = 0.18 (hexane:ethyl acetate:acetic acid:methanol (260:130:1:1); (Found: M^+, 210.0892 $C_{11}H_{14}O_4$ requires *M*, 210.0892); ν_{max} (film) 3432, 3025, 2959, 2915, 1731, 1698, 1650, 1447 and 1343cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.74 (3H, d, *J* 6.8Hz, C6-*H*), 2.07 (3H, d, *J* 1.8Hz, -CH=CCH_3-), 4.69 (2H, d, *J* 7.0Hz, C1-*H*), 5.62 (1H, dt, *J* 15.2, 7.0Hz, C2-*H*), 5.74 (1H, dq, *J* 14.9, 6.8Hz, C5-*H*), 5.85 (1H, q, *J* 1.8Hz, -C*H*=CCH$_3$-), 5.97-6.10 (1H, m, C4-*H*), (1H, dd, *J* 10.3, 15.2Hz, C3-*H*) and 11.0 (1H, br s, -COOH); δ_C (68.1MHz, $CDCl_3$) 18.1, 20.8, 66.2, 120.2, 122.5, 130.2, 131.4, 135.5, 147.6, 168.3 and 169.4; *m/z* (CI/NH_3, 40eV) 210 (7%), 113 (43), 97 (83), 81 (73), 68 (89) and 39 (100).

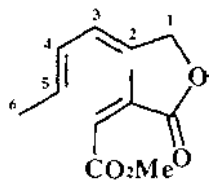
1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (38c)



38c

Wax; R_f = 0.05 (hexane:ethyl acetate:acetic acid:methanol (260:130:1:1); (Found: M^+, 210.0898. $C_{11}H_{14}O_4$ requires M, 210.0892); ν_{max} (film) 3412, 3026, 2936, 1713, 1650, 1446, 1431, 1484, 1474 and 1345cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.78 (3H, d, J 6.6Hz, C6-*H*), 2.14 (3H, d, J 1.5Hz, -CH=CCH_3-), 4.70 (2H, d, J 7.0Hz, C1-*H*), 5.56-5.87 (2H, m, C2-*H* and C5-*H*), 5.99-6.13 (1H, m, C4-*H*), 6.16 (1H, q, J 1.5Hz, -C*H*=CCH$_3$-) and 6.29 (1H, dd, J 10.3, 14.9Hz, C3-*H*); δ_C (68.1MHz, $CDCl_3$) 18.2, 22.2, 66.6, 122.1, 122.9, 130.1, 132.0, 136.1, 146.5, 166.6 and 168.6; *m/z* (EI, 70eV) 210 (2%), 113 (23), 97 (87), 79 (43), 68 (51) and 39 (100).

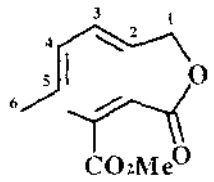
1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-methyl (2*Z*)-2-methyl-2-butenedioate (405)



405

To a stirred solution of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (**38d**) (30.0mg, 0.143mmol) in dichloromethane (10mL) at RT was added dropwise an ethereal solution of diazomethane[173] (**Section 6.6.3**). On completion of the addition the solvent was evaporated to give the crude product (32.0mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate (8:1) gave the **title compound** (**405**) (25.7mg, 0.115mmol, 81%) as a colourless oil: R_f = 0.40 (hexane:ethyl acetate (8:1)); (Found: M^+, 224.1044. $C_{12}H_{16}O_4$ requires M, 224.1049); ν_{max} (film) 3024, 2952, 2853, 1731, 1656, 1446, 1352 and 1268cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.77 (3H, d, J 6.8Hz, C6-*H*), 2.06 (3H, d, J 1.5Hz, -CH=CCH_3-), 3.71 (3H, s, -CO$_2$CH_3), 4.72 (2H, d, J 6.8Hz, C1-*H*), 5.67 (1H, dt, J 15.2, 6.8Hz, C2-*H*), 5.77 (1H, dq, J 15.2, 6.8Hz, C5-*H*), 5.85 (1H, q, J 1.5Hz, -C*H*=CCH$_3$-), 6.00-6.13 (1H, m, C4-*H*) and 6.29 (1H, dd, J 10.5, 15.2Hz, C3-*H*); δ_C (68.1MHz, $CDCl_3$) 18.2, 20.5, 51.8, 66.0, 120.6, 122.9, 130.2, 131.4, 135.3, 145.2, 165.1 and 168.3; *m/z* (CI/NH_3, 40eV) 224 (2%), 128 (100), 113 (18), 97 (37) and 81 (35).

1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-methyl (2*Z*)-3-methyl-2-butenedioate (38a)

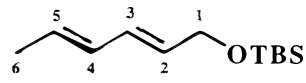


38a

To a stirred solution of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (**38c**) (85.0mg, 0.400mmol) in dichloromethane (10mL) at RT was added dropwise an ethereal solution of diazomethane[173] (**Section 6.6.3**). On completion of the addition the solvent was evaporated to give the crude product (88.1mg) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (10:1 then 5:1) gave the **title compound** (**38a**) (76.4mg, 0.341mmol, 85%) as a colourless oil: R_f = 0.21 (hexane:ethyl acetate (10:1)); (Found: M^+, 224.1042. $C_{12}H_{16}O_4$ requires M, 224.1049); ν_{max} (film) 3023, 2952, 2879, 2853, 1735, 1724, 1654, 1446, 1354 and 1269cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.74 (3H, d, J 6.8Hz, C6-*H*), (3H, d, J 1.5Hz, -CH=CC*H*$_3$-), 3.78 (3H, s, -CO$_2$C*H*$_3$), 4.59 (2H, d, J 6.8Hz, C1-*H*), 5.59 (1H, dt, J 15.2, 6.8Hz, C2-*H*), 5.73 (1H, dq, J 14.9, 6.8Hz, C5-*H*), 5.84 (1H, q, J 1.5Hz, -C*H*=CCH$_3$-), 5.96-6.09 (1H, m, C4-*H*) and 6.23 (1H, dd, J 10.8, 15.2Hz, C3-*H*); δ_C (68.1MHz, $CDCl_3$) 18.1, 20.5, 52.3, 65.2, 120.7, 123.0, 130.2, 131.2, 135.0, 145.2, 164.3 and 169.0; *m/z* (EI, 70eV) 224 (3%), 128 (100), 113 (16), 97 (37), 79 (19) and 38 (16).

6.4.2 Preparation of *endo* adducts

(2*E*,4*E*)-1-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-2,4-hexadiene (407)

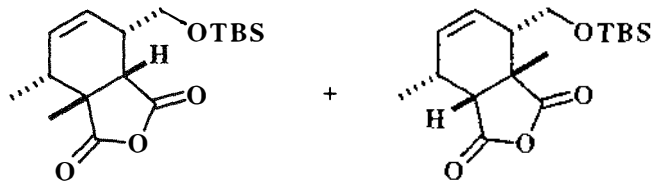


407

To a stirred solution of (2*E*,4*E*)-2,4-hexadien-1-ol (**301**) (0.512g, 5.22mmol) in dichloromethane (5mL) at RT under argon was added imidazole (0.710g, 10.4mmol, 2.0eq), *tert*-butyldimethylsilyl chloride (1.38g, 7.80mmol, 1.5eq) and N,N-dimethylaminopyridine (0.128g, 1.04mmol, 0.2eq).[176] Stirring was continued for 30min then the reaction mixture was diluted with hexane (30mL) and filtered throught a

silica plug (2cm diameter x 4cm deep) which was eluted with hexane:ethyl acetate (20:1 then 10:1 then 5:1) and evaporated to give the **title compound** (**407**) (1.07g, 5.04mmol, 97%) as a colourless oil: R_f = 0.95 (hexane:ethyl acetate (5:1)); (Found: M^+-H, 211.1516 $C_{12}H_{23}OSi$ requires *M*, 211.1518); ν_{max} (film) 3345, 2956, 2930, 2884, 2857, 1654, 1472, 1462, 1462, 1379, 1362 and 1255cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.080 (6H, s, -Si(CH_3)$_2$-), 0.919 (9H, s, -C(CH_3)$_3$), 1.76 (3H, d, *J* 6.6Hz, C6-*H*), 4.20 (2H, d, *J* 5.5Hz, C1-*H*), 5.57-5.77 (2H, m, C2-*H* and C5-*H*) and 6.00-6.25 (2H, m, C3-*H* and C4-*H*); δ_C (68.1MHz, $CDCl_3$) -5.01, 18.2, 18.5, 26.1, 63.7, 128.8, 129.7, 130.1 and 130.9; *m/z* (EI, 40eV) 211 (12%), 169 (12), 89 (10), 75 (100) and 41 (10).

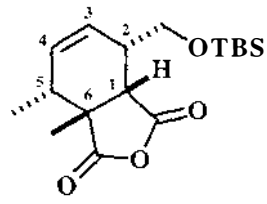
rel-(1*S*,2*S*,5*R*,6*R*)-2-(1-*tert*-butyl-1,1-dimethylsilyl)oxymethyl-5,6-dimethyl-1,2,5,6-tetrahydrophthalic anhydride (408) and **rel-(1*S*,2*S*,5*R*,6*R*)-2-(1-*tert*-butyl-1,1-dimethylsilyl)oxymethyl-1,5-dimethyl-1,2,5,6-tetrahydrophthalic anhydride (409)**



408 **409**

To a stirred solution of (2*E*,4*E*)-1-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-2,4-hexadiene (**407**) (0.429g, 2.02mmol) in toluene (4.0mL) was added citraconic anhydride (181μL, 2.02mmol, 1eq) and 2,6-di-*tert*-butyl-4-methylphenol (89.0mg, 0.40mmol, 0.2eq) at RT under argon. The solution was warmed to reflux and heating continued for 36h. Evaporation of the solvent gave the crude product (700mg) as a yellow oil. Chromatography of this material on silica (35g) with hexane, hexane:diethyl ether (20:1 then 10:1), hexane:ethyl acetate (20:1 then 10:1) then ethyl acetate gave **recovered starting material** (**407**) (86.4mg, 0.406mmol, 20%) followed by the **title compounds** (**408** and **409**) (0.485g, 1.49mmol, 93% (at 80% conversion), **408:409** (76:24)), *vide infra*.

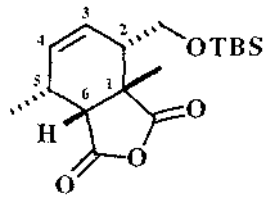
rel-(1*S*,2*S*,5*R*,6*R*)-2-(1-*tert*-butyl-1,1-dimethylsilyl)oxymethyl-5,6-dimethyl-1,2,5,6-tetrahydrophthalic anhydride (408)



408

Crystalline solid; mp 79-80°C (from *tert*-butyl methyl ether); R_f = 0.50 (hexane:ethyl acetate (10:1)); (Found: M^+-CH_3, 309.1532. $C_{16}H_{25}O_4Si$ requires *M*, 309.1522); ν_{max} (KBr disc) 3039, 2982, 2956, 2933, 2881, 2857, 1839, 1777, 1474, 1463 and 1103cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.102 (6H, s, -Si(C*H*$_3$)$_2$-), 0.907 (9H, s, -C(C*H*$_3$)$_3$), 1.29 (3H, d, *J* 7.5Hz, C5-C*H*$_3$), 1.48 (3H, s, C6-C*H*$_3$), 2.05-2.19 (1H, m, C5-*H*), 2.42-2.56 (1H, m, C2-*H*), 3.14 (1H, d, *J* 4.8Hz, C1-*H*), 3.99 (1H, dd, *J* 7.3, 9.9Hz, -C*H*H'-OTBS), 4.17 (1H, dd, *J* 9.0, 9.9Hz, -CH*H'*-OTBS), 5.74 (1H, dt, *J* 9.2, 2.9Hz, C4-*H*) and 5.85 (1H, dt, *J* 9.2, 3.1Hz, C3-*H*); δ_C (68.1MHz, $CDCl_3$) -5.27, -5.25, 15.4, 18.3, 22.1, 25.9, 38.2, 38.7, 49.9, 50.6, 62.2, 131.0, 134.4, 170.7 and 174.0; *m/z* (EI, 40eV) 309 (6%), 267 (100), 209 (45), 195 (32), 89 (92) and 75 (53).

rel-(1*S*,2*S*,5*R*,6*R*)-2-(1-*tert*-butyl-1,1-dimethylsilyl)oxymethyl-1,5-dimethyl-1,2,5,6-tetrahydrophthalic anhydride (409)

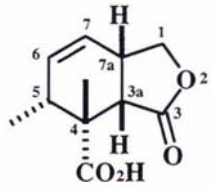


409

Colourless oil; R_f = 0.36 (hexane:ethyl acetate (10:1)); (Found: M^+-CH_3, 309.1511. $C_{16}H_{25}O_4Si$ requires *M*, 309.1522); ν_{max} (film) 2955, 2950, 2883, 2857, 1850, 1780, 1472, 1462 and 1104 cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.071 (6H, s, -Si(C*H*$_3$)$_2$-), 0.885 (9H, s, -C(C*H*$_3$)$_3$), 1.49 (3H, d, *J* 7.3Hz, C5-C*H*$_3$), 1.52 (3H, s, C1-C*H*$_3$), 2.08-2.17 (1H, m, C5-*H*), 2.38-2.51 (1H, m, C2-*H*), 2.86 (1H, d, *J* 5.3Hz, C1-*H*), 3.77 (1H, dd, *J* 7.3, 10.1Hz, -C*H*H'-OTBS), 3.98 (1H, dd, *J* 4.6, 10.1Hz, -CH*H'*-OTBS) and 5.81-5.92 (2H, m, C3-*H* and C4-*H*); δ_C (68.1MHz, $CDCl_3$) -5.42, 16.9, 18.3, 23.0, 25.9,

29.7, 45.5, 48.7, 55.4, 61.8, 130.4, 135.4, 170.5 and 174.4; *m/z* (EI, 40eV) 309 (4%), 267 (100), 209 (30), 89 (29), 81 (24) and 75 (55).

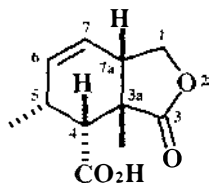
rel-(3a_S_, 4_R_, 5_R_, 7a_S_)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (40c)



40c

To a stirred solution of *rel*-(1*S*,2*S*,5*R*,6*R*)-2-(1-*tert*-butyl-1,1-dimethylsilyl)oxymethyl-5,6-dimethyl-1,2,5,6-tetrahydrophthalic anhydride (**408**) (218mg, 0.672mmol) in dichloromethane (2.5mL) at 0°C under argon was added trifluoroacetic acid (514μL, 6.72mmol, 10eq). On completion of the addition the solution was warmed to RT and stirring was continued for 2h. Evaporation of the solvent gave the crude product (168mg) as a yellow oil. Chromatography of this material on silica (10g) with hexane:ethyl acetate:methanol:acetic acid (50:10:0.3:0.3, 60:30:0.45:0.45 then 50:50:0.5:0.5) gave the **title compound (40c)** (132mg, 0.628mmol, 94%) as a crystalline solid: mp 171-174°C (from *tert*-butyl methyl ether) [lit.[98] 168-170°C]; R_f = 0.25 (hexane:ethyl acetate:methanol:acetic acid (60:30:0.45:0.45)); (Found: M^+, 210.0896. $C_{11}H_{14}O_4$ requires *M*, 210.0892); ν_{max} (KBr disc) 3393, 3018, 2979, 2935, 2891, 1766, 1758, 1707, 1694 and 1452cm^{-1}; δ_H (270MHz, $CDCl_3/CD_3OD$) 1.15 (3H, d, *J* 7.3Hz, C5-C*H*$_3$), 1.44 (3H, s, C4-C*H*$_3$), 2.23-2.37 (1H, m, C5-*H*), 2.97 (1H, d, *J* 9.4Hz, C3a-*H*), 3.07-3.20 (1H, m, C7a-*H*), 4.10 (1H, dd, *J* 4.2, 8.6Hz, C1-*H*), 4.36 (1H, dd, *J* 7.7, 8.6Hz, C1-*H'*), 5.48 (1H, dt, *J* 10.1, 2.3Hz, C7-*H*) and 5.72 (1H, ddd, *J* 2.4, 4.2, 10.1Hz, C6-*H*); δ_C (68.1MHz, $CDCl_3/CD_3OD$) 17.4, 26.4, 35.2, 37.6, 44.3, 45.6, 71.0, 123.1, 134.1, 176.6 and 179.2; *m/z* (EI, 40eV) 210 (20%), 192 (26), 164 (48), 121 (51), 107 (100), 97 (64), 91 (68) and 80 (72).

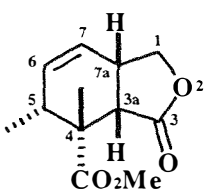
rel-(3a_S_, 4_R_, 5_R_, 7a_S_)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (40d)



40d

To a stirred solution of *rel*-(1*S*,2*S*,5*R*,6*R*)-2-(1-*tert*-butyl-1,1-dimethylsilyl)oxymethyl-1,5-dimethyl-1,2,5,6-tetrahydrophthalic anhydride (**409**) (21.6mg, 0.0666mmol) in dichloromethane (2.5mL) at 0°C under argon was added trifluoroacetic acid (51.0μL, 0.666mmol, 10eq). On completion of the addition the solution was warmed to RT and stirring was continued for 2h. Evaporation of the solvent gave the crude product (16.7mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate:methanol:acetic acid (50:10:0.3:0.3, 60:30:0.45:0.45 then 50:50:0.5:0.5) gave the **title compound (40d)** (10.6mg, 0.0504mmol, 76%) as a crystalline solid: mp 112-114°C (from *tert*-butyl methyl ether); R_f = 0.54 (hexane:ethyl acetate:methanol:acetic acid (60:30:0.45:0.45)); Found: M^+, 210.0892. $C_{11}H_{14}O_4$ requires *M*, 210.0892); ν_{max} (KBr disc) 3361, 3024, 2972, 2884, 1764 and 1707cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.16 (3H, d, *J* 7.5Hz, C5-C*H*$_3$), 1.50 (3H, s, C3a-C*H*$_3$), 2.70-2.84 (2H, m, C5-*H* and C7a-*H*), 2.98 (1H, d, *J* 6.2Hz, C4-*H*), 4.20 (1H, dd, *J* 4.6, 8.8Hz, C1-*H*), 4.56 (1H, dd, *J* 7.9, 8.8Hz, C1-*H'*), 5.59 (1H, dt, *J* 10.1, 2.4Hz, C6-*H*) and 5.74-5.88 (1H, m, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 17.5, 24.2, 30.4, 42.6, 43.0, 51.7, 71.7, 123.9, 133.0, 173.6 and 183.5; *m/z* (EI, 40eV) 210 (14%), 192 (12), 164 (25), 121 (67), 107 (100), 98 (35) and 91 (59).

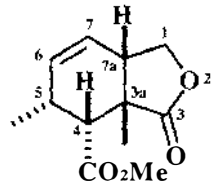
rel-methyl (3a_S_, 4_R_, 5_R_, 7a_S_)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (40a)



40a

To a stirred solution of *rel*-(3a*S*, 4*R*, 5*R*, 7a*S*)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (**40c**) (57.0mg, 0.271mmol) in diethyl ether (10mL) at -65° was added dropwise an ethereal solution of diazomethane[173] (**Section 6.6.3**). On completion of the addition the solvent was evaporated to give the crude product (62.0mg) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (10:1, 5:1 then 2:1) gave the **title compound** (**40a**) (57.8mg, 0.258mmol, 95%) as a colourless oil: R_f = 0.13 (hexane:ethyl acetate (5:1)); (Found: M^+, 224.1050. $C_{12}H_{16}O_4$ requires *M*, 224.1049); ν_{max} (film) 2977, 2951, 2913, 2828, 1777, 1769, 1738, 1731, 1455 and 1377cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.14 (3H, d, *J* 7.5Hz, C5-C*H*$_3$), 1.44 (3H, s, C4-C*H*$_3$), 2.27-2.41 (1H, m, C5-*H*), 3.00 (1H, d, *J* 9.4Hz, C3a-*H*), 3.09-3.22 (1H, m, C7a-*H*), 3.71 (3H, s, -CO_2CH_3), 4.10 (1H, dd, *J* 4.4, 8.6Hz, C1-*H*), 4.38 (1H, dd, *J* 7.7, 8.6Hz, C1-*H'*), 5.51 (1H, dt, *J* 10.1, 2.2Hz, C7-*H*) and 5.72 (1H, ddd, *J* 2.4, 4.2, 10.1Hz, C6-*H*); δ_C (68.1MHz, $CDCl_3$) 17.2, 25.8, 35.0, 37.6, 44.4, 45.5, 51.7, 70.7, 123.1, 133.7, 174.4 and 176.3; *m/z* (EI, 70eV) 224 (36%), 192 (29), 164 (49), 128 (54), 107 (69), 91 (47) and 80 (100).

rel-methyl (3a*S*, 4*R*, 5*R*, 7a*S*)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (410)



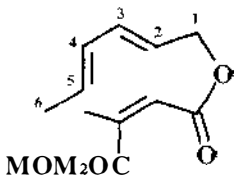
410

To a stirred solution of *rel*-(3a*S*, 4*R*, 5*R*, 7a*S*)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (**40d**) (23.2mg, 0.110mmol) in diethyl ether (10mL) at -65° was added dropwise an ethereal solution of diazomethane[173] (**Section 6.6.3**). On completion of the addition the solvent was evaporated to give the crude product (25.0mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate (10:1, 5:1 then 2:1) gave the **title compound** (**410**) (23.5mg, 0.105mmol, 95%) as a colourless oil: R_f = 0.10 (hexane:ethyl acetate (5:1)); (Found: M^+, 224.1049. $C_{12}H_{16}O_4$ requires *M*, 224.1049); ν_{max} (film) 3025, 2971, 1878, 1768, 1731 and 1454cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.14 (3H, d, *J* 7.5Hz, C5-C*H*$_3$), 1.41 (3H, s, C3a-C*H*$_3$), 2.59-2.72 (1H, m, C5-*H*), 2.73-2.85 (1H, m, C7a-*H*), 2.81 (1H, d, *J* 5.7Hz, C4-*H*), 3.63 (3H, s, -CO_2CH_3), 4.17 (1H, dd, *J* 8.1, 9.9Hz, C1-*H*), 4.56 (1H, dd, *J* 7.9, 9.9Hz, C1-*H'*), 5.57 (1H, dt, *J* 9.9, 2.0Hz, C6-*H*) and 5.70 (1H, dt, *J* 9.9, 3.1Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 18.5, 26.5, 28.2, 41.2, 43.0, 50.3, 51.6, 69.9,

123.9, 129.9, 172.3 and 180.5; *m/z* (EI, 70eV) 224 (26%), 193 (25), 164 (59), 120 (49), 107 (100) and 91 (42).

6.4.3 Preparation of *exo* adducts

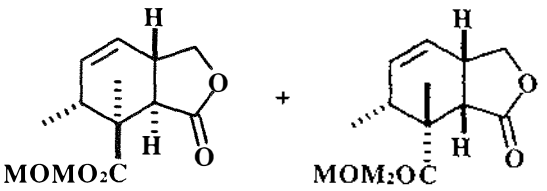
1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-methoxymethyl (2*Z*)-3-methyl-2-butenedioate (411)



411

To a stirred solution of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (**38c**) (57.4mg, 0.273mmol) in dichloromethane (1mL) at RT under argon was added triethylamine (189μL, 1.37mmol, 5eq) and chloromethyl methyl ether (51.9μL, 0.683mmol, 2.5eq). Stirring was continued for 10min then the reaction mixture was diluted with dichloromethane (10mL) and partitioned against saturated aqueous sodium bicarbonate (10mL), water (10mL), 10% aqueous hydrochloric acid (10mL), water (10mL) and brine (10mL) then dried, filtered and evaporated to give the crude product (61.9mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate (10:1, 5:1 then 2:1) gave the **title compound (411)** (40.8mg, 0.160mmol, 59%) as a colourless oil: R_f = 0.43 (hexane:ethyl acetate (5:1)); (Found: M^+, 254.1160. $C_{13}H_{18}O_5$ requires *M*, 254.1154); ν_{max} (film) 3000, 2956, 2852, 1724, 1654, 1445, 1350 and 1266cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.76 (3H, d, *J* 6.8Hz, C6-*H*), 2.08 (3H, d, *J* 1.8Hz, -CH=CCH_3-), 3.51 (3H, s, -CH_2OCH_3), 4.62 (2H, d, *J* 6.8Hz, C1-*H*), 5.36 (2H, s, -CH_2OCH_3), 5.61 (1H, dt, *J* 14.9, 6.8Hz, C2-*H*), 5.75 (1H, dq, *J* 14.9, 6.8Hz, C5-*H*), 5.88 (1H, q, *J* 1.8Hz, -C*H*=CCH_3-), 5.97-6.10 (1H, m, C4-*H*) and (1H, dd, *J* 10.3, 14.9Hz, C3-*H*); δ_C (68.1MHz, $CDCl_3$) 18.2, 20.5, 57.9, 65.3, 91.6, 120.8, 123.0, 130.2, 131.3, 135.1, 144.9, 164.4 and 168.2; *m/z* (EI, 40eV) 254 (1%), 158 (9), 141 (18), 113 (18), 97 (56), 79 (13) and 45 (100).

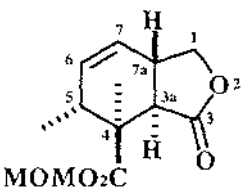
***rel*-methoxymethyl (3a*R*, 4*S*, 5*R*, 7a*S*)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (412)** and ***rel*-methoxymethyl (3a*S*, 4*R*, 5*R*, 7a*S*)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (413)**



412 **413**

To a stirred solution of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-methoxymethyl (2*Z*)-3-methyl-2-butenedioate (**411**) (35.4mg, 0.139mmol) in toluene (28.0mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (6.1mg, 0.014mmol, 0.1eq). The solution was warmed to reflux and heating was continued for 19h. Evaporation of the solvent gave the crude product (42.0mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate (10:1, 5:1 then 2:1) gave the **title compounds** (**412** and **413**) (34.0mg, 0.134mmol, 96%, **412:413** (88:12)), *vide infra*.

***rel*-methoxymethyl (3a*R*, 4*S*, 5*R*, 7a*S*)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (412)**

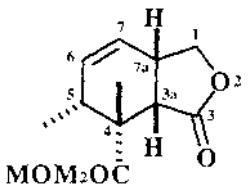


412

White needles; mp 89.4-90.5°C (from *tert*-butyl methyl ether); R_f = 0.44 (hexane:ethyl acetate (5:1)); (Found: M^+-H_2O, 236.1053. $C_{13}H_{16}O_4$ requires *M*, 236.1049); ν_{max} (KBr disc) 3023, 2974, 2909, 2837, 1774, 1742, 1477 and 1451cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.04 (3H, d, *J* 7.5Hz, C5-CH_3), 1.58 (3H, s, C4-CH_3), 2.17 (1H, d, *J* 13.6Hz, C3a-*H*), 2.96-3.16 (2H, m, C5-*H* and C7a-*H*), 3.45 (2H, s, -CH_2OCH$_3$), 3.80 (1H, dd, *J* 7.9, 11.4Hz, C1-*H*), 4.43 (1H, dd, *J* 6.8, 7.9Hz, C1-*H'*), 5.26 (3H, s, -CH$_2$OCH_3) and 5.65-5.75 (2H, m, C6-*H* and C7-*H*); δ_C (68.1MHz, $CDCl_3$) 16.9, 19.6, 37.8, 38.7,

44.6, 46.4, 57.8, 69.6, 90.8, 121.9, 136.1, 173.9 and 174.4; *m/z* (EI, 70eV) 236 (0.2%), 164 (15), 133 (11), 119 (19), 105 (14), 91 (10) and 45 (100).

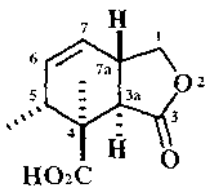
rel-methoxymethyl (3a*S*, 4*R*, 5*R*, 7a*S*)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (413)



413

Colourless oil; R_f = 0.34 (hexane:ethyl acetate (5:1)); (Found: M^+, 254.1148. $C_{13}H_{18}O_5$ requires *M*, 254.1154); ν_{max} (film) 2975, 2916, 2850, 1770, 1773, 1738, 1732, 1455 and 1375cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.21 (3H, d, *J* 7.5Hz, C5-C*H*$_3$), 1.51 (3H, s, C4-C*H*$_3$), 2.34-2.47 (1H, m, C5-*H*), 3.08 (1H, d, *J* 9.2Hz, C3a-*H*), 3.13-3.25 (1H, m, C7a-*H*), 3.50 (3H, s, -CH_2OCH_3), 4.16 (1H, dd, *J* 4.0, 8.8Hz, C1-*H*), 4.41 (1H, dd, *J* 7.5, 8.8Hz, C1-*H'*), 5.31 (1H, B of AB, J_{AB} 6.2Hz, -C*H*H'OCH3), 5.34 (1H, A of AB, J_{AB} 6.2Hz, -CH*H'*OCH3), 5.55 (1H, dt, *J* 10.1, 2.2Hz, C6-*H*) and (1H, ddd, *J* 2.4, 4.2, 10.1Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 17.3, 26.1, 35.1, 37.6, 44.4, 44.7, 58.0, 70.8, 91.1, 123.2, 134.0, 173.7 and 176.3; *m/z* (EI, 80eV) 254 (1%), 165 (9), 121 (15), 105 (17), 91 (15) and 45 (100).

rel-(3a*R*, 4*S*, 5*R*, 7a*S*)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (39c)

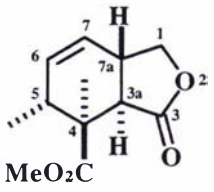


39c

To a stirred solution of *rel*-methoxymethyl (3a*R*, 4*S*, 5*R*, 7a*S*)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (**412**) (17.5mg, 0.0688mmol) in dichloromethane (3.0mL) at RT under argon was added trifluoroacetic acid (54.1µL, 0.688mmol, 10eq). Stirring was continued for 18h then the solvent was evaporated to give the crude product (20.0mg) as a yellow oil. Chromatography of this

material on silica (2g) with hexane:ethyl acetate (2:1) then hexane:ethyl acetate:methanol:acetic acid (60:30:0.45:0.45)) gave the **title compound** (**39c**) (13.9mg, 0.0661mmol, 96%) as a crystalline solid: mp 138-140°C (from *tert*-butyl methyl ether); R_f = 0.32 (hexane:ethyl acetate:methanol:acetic acid (60:30:0.45:0.45)); (Found: M^+-OH, 193.0865. $C_{11}H_{13}O_3$ requires *M*, 193.0865); ν_{max} (KBr disc) 3398, 2980, 2965, 2918, 1790, 1692 and 1467cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.05 (3H, d, *J* 7.3Hz, C5-C*H*$_3$), 1.59 (3H, s, C4-C*H*$_3$), 2.14 (1H, d, *J* 13.4Hz, C3a-*H*), 2.91-3.04 (1H, m, C5-*H*), 3.14-3.30 (1H, m, C7a-*H*), 3.81 (1H, dd, *J* 7.9, 11.4Hz, C1-*H*), 4.45 (1H, dd, *J* 7.0, 7.9Hz, C1-*H'*), 5.65-5.75 (2H, m, C6-*H* and C7-*H*); δ_C (68.1MHz, $CDCl_3$) 17.0, 20.0, 37.9, 38.4, 44.6, 45.9, 69.7, 122.2, 135.9, 174.0 and 181.3; *m/z* (EI, 40eV) 193 (0.5%), 164 (47), 121 (100), 105 (67), 91 (36), 79 (21) and 41 (18).

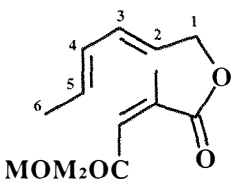
rel-methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (39a)



39a

To a stirred solution of *rel*-(3a*R*, 4*S*, 5*R*, 7a*S*)-4,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (**39c**) (9.2mg, 0.044mmol) in diethyl ether (5mL) at -65°C was added dropwise an ethereal solution of diazomethane[173] (**Section 6.6.3**). On completion of the addition the solvent was evaporated to give the crude product (9.5mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate (5:1 then 2:1) gave the **title compound** (**39a**) (6.2mg, 0.028mmol, 64%) as a crystalline solid; mp 108-109°C (from *tert*-butyl methyl ether) (lit.[98] 94-96°C); R_f = 0.55 (hexane:ethyl acetate (2:1)); (Found: M^+, 224.1058. $C_{12}H_{16}O_4$ requires *M*, 224.1049); ν_{max} (KBr disc) 3025, 2995, 2916, 2849, 1786, 1730, 1465 and 1369cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.03 (3H, d, *J* 7.5Hz, C5-C*H*$_3$), 1.54 (3H, s, C4-C*H*$_3$), 2.13 (1H, d, *J* 13.6Hz, C3a-*H*), 2.95-3.11 (2H, m, C5-*H* and C7a-*H*), 3.71 (3H, s, -CO_2C*H*$_3$), 3.79 (1H, dd, *J* 7.9, 11.4Hz, C1-*H*), 4.43 (1H, dd, *J* 7.3, 7.9Hz, C1-*H'*) and 5.62-5.75 (2H, m, C6-*H* and C7-*H*); δ_C (68.1MHz, $CDCl_3$) 16.9, 19.8, 38.0, 38.7, 44.9, 46.1, 52.3, 69.6, 122.0, 136.1, 173.9 and 175.4; *m/z* (EI, 70eV) 224 (2%), 193 (3), 178 (7), 164 (58), 119 (100), 105 (68), 91 (43), 79 (21) and 41 (20).

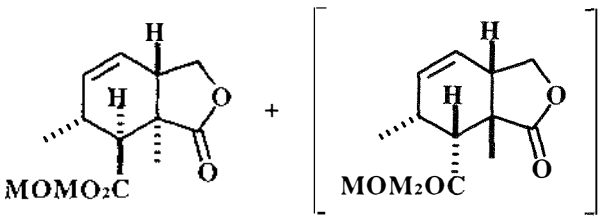
1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-methoxymethyl (2*Z*)-2-methyl-2-butenedioate (414)



414

To a stirred solution of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (**38d**) (34.8mg, 0.167mmol) in dichloromethane (1mL) at RT under argon was added triethylamine (57.4μL, 0.414mmol, 2.5eq) and chloromethyl methyl ether (15.1μL, 0.199mmol, 1.2eq). Stirring was continued for 5min then the reaction mixture was diluted with dichloromethane (10mL) and partitioned against saturated aqueous sodium bicarbonate (10mL), water (10mL), 10% aqueous hydrochloric acid (10mL), water (10mL) and brine (10mL) then dried, filtered and evaporated to give the crude product (46.8mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate (10:1 then 5:1) gave the **title compound** (**414**) (36.6mg, 0.144mmol, 86%) as a colourless oil: R_f = 0.43 (hexane:ethyl acetate (5:1)); (Found: M^+, 254.1159. $C_{13}H_{18}O_5$ requires M, 254.1154); ν_{max} (film) 3001, 2957, 2852, 1734, 1654, 1446, 1350 and 1265cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.76 (3H, d, J 6.8Hz, C6-*H*), 2.07 (3H, d, J 1.5Hz, -CH=CCH_3-), 3.44 (3H, s, -CH_2OCH_3), 3.72 (2H, d, J 6.8Hz, C1-*H*), 5.26 (2H, s, -CH_2OCH_3), 5.66 (1H, dt, J 15.2, 6.8Hz, C2-*H*), 5.77 (1H, dq, J 14.9, 6.8Hz, C5-*H*), 5.87 (1H, q, J 1.5Hz, -C*H*=CCH_3-), 5.99-6.12 (1H, m, C4-*H*) and 6.28 (1H, dd, J 10.3, 15.2Hz, C3-*H*); δ_C (68.1MHz, $CDCl_3$) 18.2, 20.6, 57.7, 66.0, 90.8, 120.3, 122.9, 130.2, 131.4, 135.4, 146.2, 164.0 and 168.3; *m/z* (EI, 40eV) 254 (1%), 158 (7), 141 (12), 113 (16), 97 (63), 81 (45) and 45 (100).

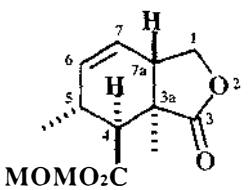
***rel*-methoxymethyl (3a*R*, 4*S*, 5*R*, 7a*S*)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (415)** and ***rel*-methoxymethyl (3a*S*, 4*R*, 5*R*, 7a*S*)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (416)**



415 **416**

To a stirred solution of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-methoxymethyl (2*Z*)-2-methyl-2-butenedioate (**414**) (34.9mg, 0.137mmol) in toluene (28.0mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (6.0mg, 0.027mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 22h. Evaporation of the solvent gave the crude product (36.6mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate (5:1 then 2:1) gave the **title compounds (415** and **416)** (34.5mg, 0.136mmol, 99%, **415:416** (93:7), *vide infra*. (Adduct **416** was unable to be isolated and characterised. The structure of this compound is speculative and based on limited proton NMR analysis of mixtures only.)

***rel*-methoxymethyl (3a*R*, 4*S*, 5*R*, 7a*S*)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (415)**

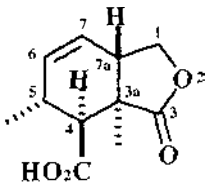


415

Colourless oil; R_f = 0.18 (hexane:ethyl acetate (5:1)); (Found: M^+, 254.1141. $C_{13}H_{18}O_5$ requires M, 254.1154); ν_{max} (film) 2969, 2935, 2878, 1778, 1731 and 1454cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.07 (3H, s, C3a-CH_3), 1.32 (3H, d, J 7.5Hz, C5-CH_3), 2.48 (1H, d, J 3.3Hz, C4-*H*), 2.49-2.62 (1H, m, C5-*H*), 3.48 (3H, s, -CH_2OCH_3), 3.51-3.63 (1H, m, C7a-*H*), 4.10 (1H, dd, J 8.3, 12.1Hz, C1-*H*), 4.46-4.54 (1H, m, C1-*H'*), 5.17 (1H, B of AB, J_{AB} 6.0Hz, -C*H*H'OCH3), 5.35 (1H, A of

AB, J_{AB} 6.0Hz, -CH*H*'OCH3), 5.67 (1H, ddd, *J* 2.4, 3.1, 9.7Hz, C7-*H*) and 5.81 (1H, dt, *J* 2.9, 9.7Hz, C6-*H*); δ_C (68.1MHz, $CDCl_3$) 17.2, 23.1, 34.5, 39.2, 43.9, 51.2, 57.8, 68.6, 90.7, 122.3, 133.9, 173.1 and 177.9; *m/z* (EI, 70eV) 224 (2%), 193 (5), 164 (6), 133 (20), 119 (24), 105 (16) and 45 (100).

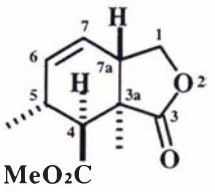
rel-(3a*R*, 4*S*, 5*R*, 7a*S*)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (39d)



39d

To a stirred solution of *rel*-methoxymethyl (3a*R*, 4*S*, 5*R*, 7a*S*)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (**415**) (29.3mg, 0.115mmol) in dichloromethane (5.0mL) at RT under argon was added trifluoroacetic acid (90.6µL, 1.15mmol, 10eq). Stirring was continued for 6h then the solvent was evaporated to give the crude product (35.0mg) as a yellow oil. Chromatography of this material on silica (3g) with hexane:ethyl acetate (10:1, 5:1 then 2:1:) then hexnae:ethyl acetate:methanol:acetic acid (50:50:0.5:0.5) gave the **title compound** (**39d**) (21.4mg, 0.102mmol, 89%) as a crystalline solid: mp 157-160°C (from *tert*-butyl methyl ether); R_f = 0.19 (hexane:ethyl acetate (2:1)); (Found: M^++H, 211.0978. $C_{11}H_{15}O_4$ requires *M*, 211.0970); ν_{max} (KBr disc) 2975, 2937, 2913, 2880, 1773, 1767, 1704, 1698 and 1435cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.06 (3H, s, C3a-CH_3), 1.33 (3H, d, *J* 7.7Hz, C5-CH_3), 2.48 (1H, d, *J* 3.1Hz, C4-*H*), 2.55-2.70 (1H, m, C5-*H*), 3.46-3.59 (1H, m, C7a-*H*), 4.09 (1H, dd, *J* 8.3, 11.9Hz, C1-*H*), 4.47-4.54 (1H, m, C1-*H*'), 5.68 (1H, ddd, *J* 2.4, 3.1, 9.9Hz, C7-*H*) and 5.80 (1H, dt, *J* 9.9, 3.1Hz, C6-*H*); δ_C (68.1MHz, $CDCl_3$) 17.1, 23.3, 34.6, 39.0, 43.7, 50.8, 68.7, 122.1, 134.1, 178.2 and 178.9; *m/z* (EI, 70eV) 211(1%), 164 (17), 121 (100), 105 (77), 91 (42), 77 (19) and 41 (18).

***rel*-methyl (3a*R*, 4*S*, 5*R*, 7a*S*)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate (417)**

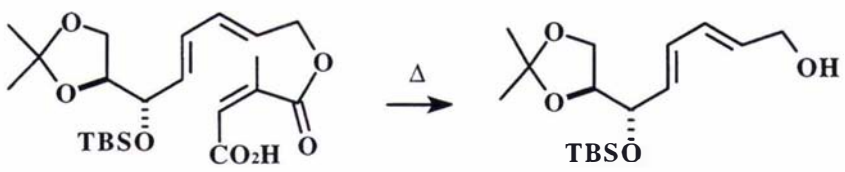


417

To a stirred solution of *rel*-(3a*R*, 4*S*, 5*R*, 7a*S*)-3a,5-dimethyl-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylic acid (**39d**) (8.9mg, 0.042mmol) in diethyl ether (5mL) at -65°C was added dropwise an ethereal solution of diazomethane[173] (**Section 6.6.3**). On completion of the addition the solvent was evaporated to give the crude product (9.7mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate (5:1 then 2:1) gave the **title compound** (**417**) (9.4mg, 0.042mmol, 100%) as a colourless oil: R_f = 0.15 (hexane:ethyl acetate (5:1)); (Found: M^+, 224.1046. $C_{12}H_{16}O_4$ requires *M*, 224.1049); ν_{max} (film) 3030, 2967, 2919, 2876, 2849, 1779, 1731 and 1435cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.06 (3H, s, C3a-C*H*$_3$), 1.29 (3H, d, *J* 7.5Hz, C5-C*H*$_3$), 1.25 (1H, d, *J* 3.3Hz, C4-*H*), 2.47-02.59 (1H, m, C5-*H*), 3.52-3.65 (1H, m, C7a-*H*), 3.71 (3H, s, -CO_2CH_3), 4.09 (1H, dd, *J* 8.3, 12.1Hz, C1-*H*), 4.46-4.54 (1H, m, C1-*H'*), 5.67 (1H, dt, *J* 9.7, 2.9Hz, C6-*H*) and 5.80 (1H, dt, *J* 9.7, 2.9Hz, C7-*H*); δ_C (68.1MHz, $CDCl_3$) 17.3, 23.0, 34.5, 39.3, 44.0, 51.2, 52.0, 68.5, 122.2, 134.1, 174.0 and 178.0; *m/z* (EI, 70eV) 224 (4%), 193 (12), 164 (22), 121 (100), 105 (51) and 91 (30).

6.4.3 Attempted DA reactions

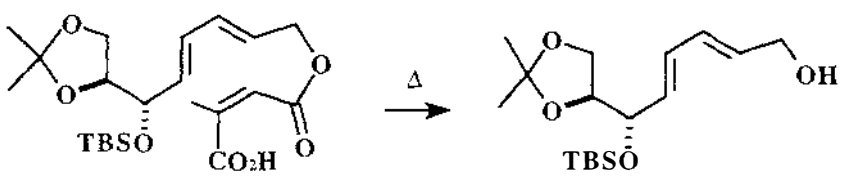
Attempted ETDA reaction of 1-((2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (401)



401 **228**

To a stirred solution of 1-((2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (**401**) (37.0mg, 0.0840mmol) in toluene (16.8mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (3.7mg, 0.017mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 12h. Evaporation of the solvent gave the crude product (40.7mg) as a yellow oil. Chromatography of this material on silica (5g) with hexane:ethyl acetate (5:1) gave **(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol** (**228**) (16.7mg, 0.0508mmol, 61%), *vide supra.*

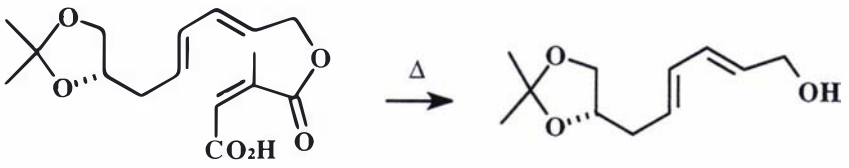
Attempted ETDA reaction of 1-((2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (402)



402 **228**

To a stirred solution of 1-((2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (**402**) (9.4mg, 0.021mmol) in toluene (4.2mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (0.9mg, 0.004mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 24h. Evaporation of the solvent gave the crude product (10.4mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate (2:1) gave **(2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)-oxy-4,6-octadien-1,2,8-triol** (**228**) (3.9mg, 0.012mmol, 57%), *vide supra.*

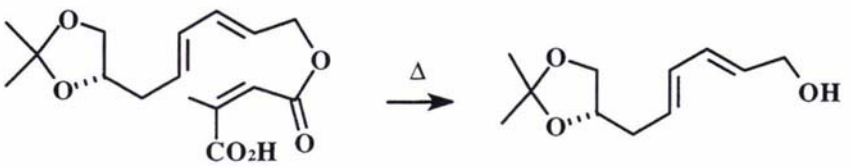
Attempted ETDA reaction of 1-((2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (403)



403 **235**

To a stirred solution of 1-((2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (**403**) (14.8mg, 0.0477mmol) in toluene (9.5mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (2.1mg, 0.0095mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 12h. Evaporation of the solvent gave the crude product (17.0mg) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (2:1) gave **(2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-4,6-octdadiene-1,2,8-triol** (**235**) (5.9mg, 0.030mmol, 63%), *vide supra.*

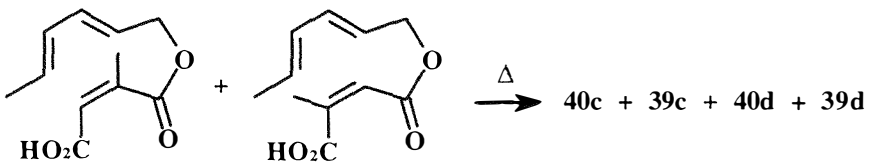
Attempted ETDA reaction of 1-((2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (404)



404 **235**

To a stirred solution of 1-((2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2-dihydroxy-4,6-octadien-8-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (**404**) (7.4mg, 0.024mmol) in toluene (4.7mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (1.0mg, 0.0045mmol, 0.2eq). The solution was warmed to reflux and was heating continued for 5h. Evaporation of the solvent gave the crude product (8.5mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate (2:1) gave **(2*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-4,6-octdadiene-1,2,8-triol** (**235**) (2.6mg, 0.013mmol, 54%), *vide supra.*

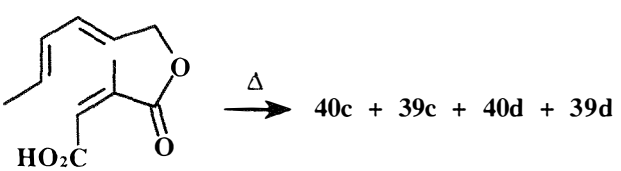
Attempted ETDA reaction of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (38d) and 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (38c) (64:65, 1:1)



38d **38c**

A stirred solution of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (**38d**) and 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (**38c**) (**38d:38c** (50:50)) (96.3mg, 0.458mmol) in xylene (3.98mL) was warmed to reflux under argon and heating was continued for 15h.[98] The solvent was evaporated, the residue was redissolved in $CDCl_3$ and proton NMR analysis was carried out. The crude material contained **compounds 40c**, **39c**, **40d** and **39d** (**40c**:**39c**:**40d**:**39d** (51:16:27:6)) (mass balance = 90.6mg, 94%) as a yellow oil. To a stirred solution of the crude material in dichloromethane (8.3mL) at RT under argon was added trifluoroacetic acid (155μL, 1.97mmol, *ca.* 5eq). Stirring was continued for 24h and then the solvent and trifluoroacetic acid were evaporated. The residue was redissolved in $CDCl_3$ and proton NMR analysis was carried out. The crude material contained **compounds 40c**, **39c**, **40d** and **39d** (**40c**:**39c**:**40d**:**39d** (50:14:28:8)) (mass balance = 83.0mg, 89%) as a yellow oil.

Attempted ETDA reaction of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (38d)

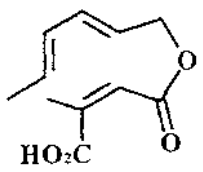


38d

A stirred solution of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (**38d**) (16.7mg, 0.0794mmol) in xylene (0.69mL) was warmed to reflux under argon and heating was continued for 15h.[98] The solvent was evaporated, the residue was redissolved in $CDCl_3$ and proton NMR analysis was carried out. The crude material contained **compounds 40c**, **39c**, **40d** and **39d** (**40c**:**39c**:**40d**:**39d**

(55:7:28:10)) as a yellow oil. To a stirred solution of the crude material in dichloromethane (1.7mL) at RT under argon was added trifluoroacetic acid (31μL, 0.39mmol, *ca.* 5eq). Stirring was continued for 24h and then the solvent and trifluoroacetic acid were evaporated. The residue was redissolved in $CDCl_3$ and proton NMR analysis was carried out. The crude material contained **compounds 40c**, **39c**, **40d** and **39d** (**40c**:**39c**:**40d**:**39d** (53:11:29:7)) (mass balance = 15.2mg, 91%) as a yellow oil.

Attempted ETDA reaction of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (38c)

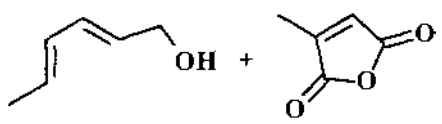


Δ → **40c + 39c + 40d + 39d**

38c

A stirred solution 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (**38c**) (69.6mg, 0.331mmol) in xylene (2.90mL) was warmed to reflux under argon and heating was continued for 15h.[98] The solvent was evaporated, the residue was redissolved in $CDCl_3$ and proton NMR analysis was carried out. The crude material contained **compounds 40c**, **39c**, **40d** and **39d** (**40c**:**39c**:**40d**:**39d** (54:11:24:11)) as a yellow oil. To a stirred solution of the crude material in dichloromethane (7.0mL) at RT under argon was added trifluoroacetic acid (129μL, 1.64mmol, *ca.* 5eq). Stirring was continued for 24h and then the solvent and trifluoroacetic acid were evaporated. The residue was redissolved in $CDCl_3$ and proton NMR analysis was carried out. The crude material contained **compounds 40c**, **39c**, **40d** and **39d** (**40c**:**39c**:**40d**:**39d** (52:12:29:7)) (mass balance = 62.5mg, 90%) as a yellow oil.

Attempted BDA reaction of (2*E*,4*E*)-2,4-hexadien-1-ol (301) and citraconic anhydride (406)

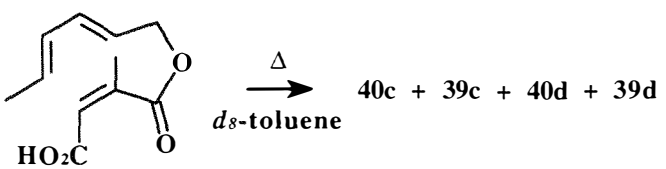


Δ → **40c + 39c + 40d + 39d**

301 **406**

A stirred solution (2*E*,4*E*)-2,4-hexadi-1-ol (**301**) (50.7mg, 0.517mmol) and citraconic anhydride (**406**) (46.3μL, 517mmol, 1eq) in xylene (4.50mL) was warmed to reflux under argon and heating was continued for 15h.[98] The solvent was evaporated, the residue was redissolved in $CDCl_3$ and proton NMR analysis was carried out. The crude material contained **compounds 40c**, **39c**, **40d** and **39d** (**40c:39c:40d:39d** (57:7:30:6)) as a yellow oil. To a stirred solution of the crude material in dichloromethane (10.9mL) at RT under argon was added trifluoroacetic acid (202μL, 2.57mmol, *ca.* 5eq). Stirring was continued for 24h and then the solvent and trifluoroacetic acid were evaporated. The residue was redissolved in $CDCl_3$ and proton NMR analysis was carried out. The crude material contained **compounds 40c**, **39c**, **40d** and **39d** (**40c:39c:40d:39d** (58:7:29:7)) (mass balance = 108.7mg, 95%) as a yellow oil.

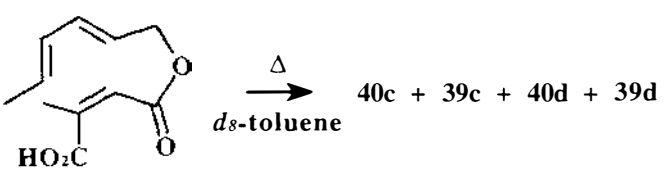
Proton NMR experiment on 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (38d)



38d

To 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-2-methyl-2-butenedioate (**38d**) (20.2mg, 0.0961mmol) was added d_8-toluene (835μL) under argon at RT. The resulting solution was transferred to an NMR tube and this was heated to 110°C. At specific time intervals (0min, 15min, 30min, 45min, 60min, 90min, 2h, 4h, 8h, 16h, 24h, 48h, 70h, 93h and 140h), the reaction mixture was quenched in ice water and a proton NMR spectrum was recorded. Stack plots of these spectra are illustrated in **Figures 4.11** and **4.12** (**Section 4.5.2**).

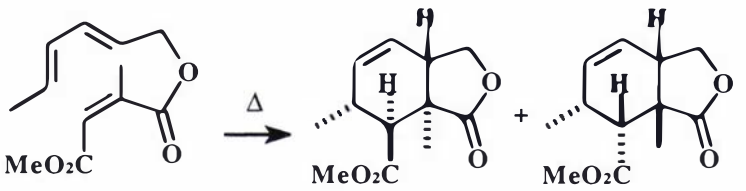
Proton NMR experiment on 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (38c)



38c

To 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-hydrogen (2*Z*)-3-methyl-2-butenedioate (**38c**) (18.8mg, 0.0894mmol) was added d_8-toluene (777µL) under argon at RT. The resulting solution was transferred to an NMR tube and this was heated to 110°C. At specific time intervals (0min, 15min, 30min, 45min, 60min, 90min, 2h, 4h, 8h, 16h, 24h, 48h, 70h, 93h and 140h), the reaction mixture was quenched in ice water and a proton NMR spectrum was recorded. Stack plots of these spectra are illustrated in **Figures 4.13** and **4.14 (Section 4.5.2)**.

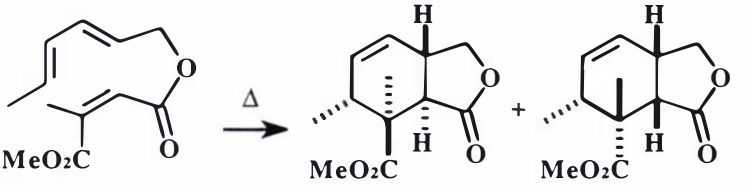
ETDA reaction of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-methyl (2*Z*)-2-methyl-2-butenedioate (405)



405 **417** **410**

To a stirred solution of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-methyl (2*Z*)-2-methyl-2-butenedioate (**405**) (50.0mg, 0.223mmol) in toluene (45mL) at RT under argon was added 2,6-di-*tert*-butyl-4-methylphenol (9.8mg, 0.44mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 24h. Evaporation of the solvent gave the crude product (60.0mg) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (5:1 then 2:1) gave **recovered starting material (405)** (2.8mg, 0.012mmol, 5%) followed by the **ETDA adducts (417** and **410)** (33.4mg, 0.149mmol, 71% (at 95% conversion), **417:410** (93:7)), *vide supra.*

ETDA reaction of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-methyl (2*Z*)-3-methyl-2-butenedioate (38a)



38a **39a** **40a**

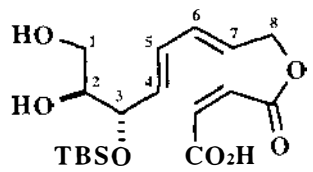
To a stirred solution of 1-((2*E*,4*E*)-2,4-hexadien-1-yl) 4-methyl (2*Z*)-3-methyl-2-butenedioate (**38a**) (45.0mg, 0.201mmol) in toluene (40.1mL) at RT under argon was

added 2,6-di-*tert*-butyl-4-methylphenol (8.8mg, 0.040mmol, 0.2eq). The solution was warmed to reflux and heating was continued for 24h. Evaporation of the solvent gave the crude product (53.9mg) as a yellow oil. Chromatography of this material on silica (4g) with hexane:ethyl acetate (10:1 then 5:1) gave the **ETDA adducts** (**39a** and **40a**) (29.2mg, 0.130mmol, 65%, **39a:40a** (84:16)), *vide supra.*

6.5 Experimental for Chapter Five

6.5.1 Preparation of precursors

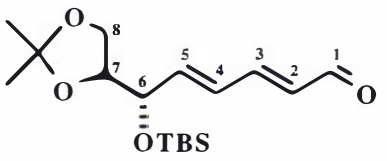
(2*S*,3*S*,4*E*,6*E*)-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,5-octadien-8-yl hydrogen maleate (515)



515

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6-octadien-8-yl hydrogen maleate (**236**) (26.1mg, 0.0615mmol) in dichloromethane (5mL) at 0°C under argon was added dropwise trifluoracetic acid (50μL, 0.62mmol, 10eq). On completion of the addition the solution was warmed to RT and stirring was continued for 20min. The solvent was evaporated to give the crude product (25.0mg) as a yellow oil. Chromatography of this material on silica (2g) with hexane:ethyl acetate:methanol:acetic acid (50:50:0.5:0.5) gave the **title compound** (**515**) (13.9mg, 0.0360mmol, 59%) as a colourless oil: $[\alpha]_D^{19.5}$ = -0.70° (c = 0.42, dichloromethane); R_f = 0.11 (hexane:ethyl acetate:methanol:acetic acid (50:50:0.5:0.5); (Found: M^+-(H_20+C_4H_9), 311.0955. $C_{14}H_{19}O_6Si$ requires *M*, 311.0951); ν_{max} (film) 3431, 2953, 2925, 2887, 2857, 1729, 1644, 1472 and 1462cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.055 and 0.095 (6H, 2 x s, -Si(CH_3)$_2$-), 0.915 (9H, s, -C(CH_3)$_3$), 3.50-3.75 (3H, m, C1-*H* and C2-*H*), 4.22 (1H, t, *J* 6.3Hz, C3-*H*), 4.80 (2H, d, *J* 7.0Hz, C8-*H*), 5.72-5.87 (2H, m, C4-*H* and C7-*H*), 6.18-6.46 (2H, m, C5-*H* and C6-*H*) and 6.37 and 6.46 (2H, 2 x d, B and A of AB, J_{AB} 13.0Hz, -*CH*=*CH*CO_2H); δ_C (68.1MHz, $CDCl_3$) -4.78, -3.96, 18.2, 25.9, 62.9, 66.7, 73.7, 74.8, 125.2, 128.9, 130.6, 134.8 (2 x C), 135.8, 164.7 and 167.1; *m/z* (EI, 70eV) 386 (0.2%), 311 (0.2), 281 (4), 227 (19), 117 (17), 95 (20), 75 (100), 59 (82) and 41 (65).

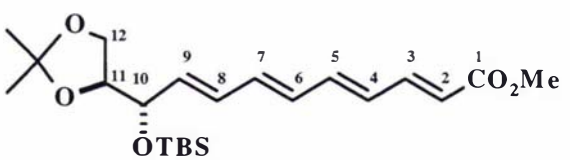
(2*E*,4*E*,6S,7*S*)-7,8-*O*-isopropylidene-6-(1-*tert*-butyl-1,1-dimethylsilyl) oxy-7,8-dihydroxy-2,4-octadienal (518)



518

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-4,6-octadien-1,2,8-triol (**228**) (1.015g, 3.09mmol) in dichloromethane (20mL) at RT under argon was added Dess-Martin periodinane[167] (**Section 6.6.1**) (1.442g, 3.40mmol, 1.1eq). Stirring was continued for 30min then saturated aqueous sodium bicarbonate (10mL) and saturated aqueous sodium thiosulphate (5mL) were added. The orgainic phase was partitioned against saturated aqueous sodium bicarbonate (10mL), water (10mL) and brine (10mL) then dried, filtered and evaporated to give the crude product (1.091g) as a yellow oil. Chromatography of this material on silica (30g) with hexane:ethyl acetate (5:1) gave the **title compound** (**518**) (0.833g, 2.55mmol, 83%) as a yellow oil: $[\alpha]_D^{21} = -30.4°$ (c = 0.70, dichloromethane); R_f = 0.34 (hexane:ethyl acetate (5:1)); (Found: M^+-CH_3, 311.1675. $C_{16}H_{27}O_4Si$ requires *M*, 311.1679); ν_{max} (film) 2986, 2955, 2931, 2887, 2858, 1730, 1693, 1682, 1644, 1472, 1462, 1381, 1371 and 1255cm^{-1}; δ_H (270MHz, $CDCl_3$) 0.061 and 0.085 (6H, 2 x s, -Si(CH_3)$_2$-), 0.904 (9H, s, -C(CH_3)$_3$), 1.33 and 1.40 (6H, 2 x s, -C(CH_3)$_2$-), 3.80 (1H, dd, *J* 5.8, 8.7Hz, C8-*H*), 3.97 (1H, dd, *J* 6.7, 8.7Hz, C8-*H'*), 4.11-4.19 (1H, m, C7-*H*), 4.44 (1H, td, *J* 5.1, 1.3Hz, C6-*H*), 6.16 (1H, dd, *J* 8.0, 15.3Hz, C2-*H*), 6.29 (1H, dd, *J* 5.1, 15.2Hz, C5-*H*), 6.56 (1H, ddd, *J* 1.3, 10.9, 15.2Hz, C4-*H*), 7.13 (1H, dd, *J* 10.9, 15.3Hz, C3-*H*) and 9.58 (1H, d, *J* 8.0Hz, C1-*H*); δ_C (68.1MHz, $CDCl_3$) -4.79, -4.64, 18.3, 25.0, 25.8, 26.3, 65.0, 72.6, 78.0, 109.5, 129.0, 131.7, 142.9, 150.9 and 193.5; *m/z* (EI, 80eV) 311 (4%), 269 (25), 226 (100), 211 (33), 129 (21), 101 (95), 73 (74), and 43 (35).

methyl (2*E*,4*E*,6*E*,8*E*,10*S*,11*S*)-11,12-*O*-isopropylidene-10-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-11,12-dihydroxy-2,4,6,8-dodecateraenoate (519)



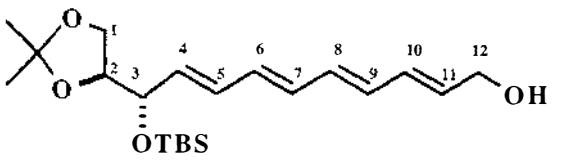
519

To a stirred solution of (2*E*,4*E*,6S,7*S*)-7,8-*O*-isopropylidene-6-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-7,8-dihydroxy-2,4-octadienal (**518**) (2.435g, 7.46mmol) in dichloromethane (20mL) at RT under argon was added methyl 4-(triphenylphosphoranylidene)-(2*E*)-2-butenoate[168, 169] (**Section 6.6.2**) (4.03g, 11.2mmol, 1.5eq). On completion of the addition the solution was warmed to reflux and stirring was continued for 3h. The reaction mixture was diluted with hexane (80mL) and passed through a silica plug (4cm diameter x 14cm deep) which was saturated with hexane. The silica was then eluted with hexane:ethyl acetate (3:1) to give the crude product (2.826g) as a yellow oil. Chromatography of this material on silica (60g) with hexane:ethyl acetate (19.5:1 then 9:1) gave compound **519** as a mixture of *Z*- and *E*-stereoisomers (1.406g, 3.44mmol, 46%).

Isomerisation.

To a stirred solution of the *Z*- and *E*-stereoisomers of compound **519** (1.406g, 3.44mmol) in dichloromethane (60mL) at room temperature under argon was added a solution of iodone (25.0mmol/L in dichloromethane, 1.52mL, 0.0380, 0.011eq). On completion of the addition the reaction mixture was place in the dark for 2h then in direct sunlight for 1h. Two further aliquots of iodine solution (0.250mol/L in dichloromethane, 1.52mL, 0.380mmol, 0.11eq) were added at 1h intervals. The reaction mixture was partitioned against saturated aqueous sodium thiosulphate (50mL), water (50mL), brine (50mL) then dried, filtered and evaporated to give the crude product (1.604g) as a yellow oil. Chromatography of this material on silica (48g) with hexane:ethyl acetate (19.5:1 then 9:1) gave the **title compound** (**519**) (0.8340g, 2.04mmol, 59%) as a yellow oil: $[\alpha]_D^{20}$ = -45.1° (c = 1.97, dichloromethane); R_f = 0.36 (hexane:ethyl acetate (9:1)); (Found: M^+, 408.2333. $C_{22}H_{36}O_5Si$ requires M, 408.2333); ν_{max} (film) 2987, 2953, 2991, 2886, 2857, 1714, 1620, 1598, 1472, 1462, 1379, 1380 and 1260cm^{-1}; λ_{max} (methanol)/nm 329 (ε/Lmol^{-1}cm^{-1} 5.22 x 10^4); δ_H (270MHz, $CDCl_3$) 0.050 and 0.070 (6H, 2 x s, -Si(C*H*$_3$)$_2$-), 0.896 (9H, s, -C(C*H*$_3$)$_3$), 1.325 and 1.383 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 3.74 (3H, s, -CO$_2$C*H*$_3$), 3.78 (1H, dd, *J* 6.2, 8.5Hz, C12-*H*), 3.94 (1H, dd, *J* 6.7, 8.5Hz, C12-*H'*), 4.05-4.13 (1H, m, C11-*H*), 4.29-4.35 (1H, m, C10-*H*), 5.82 (1H, dd, *J* 5.9, 14.2Hz, C9-*H*), 5.87 (1H, d, *J* 15.5Hz, C2-*H*), 6.21-6.64 (5H, m, C4-*H*, C5-*H*, C6-*H*, C7-*H* and C8-*H*) and 7.31 (1H, dd, *J* 11.3, 15.5Hz, C3-*H*); δ_C (68.1MHz, $CDCl_3$) -4.75, -4.53, 18.3, 25.2, 25.8, 26.4, 51.5, 65.2, 73.4, 78.6, 109.4, 120.2, 129.9, 131.2, 131.7, 134.6, 136.3, 140.4, 144.4 and 167.3; *m/z* (EI, 70eV) 408 (7%), 351 (9), 333 (9), 308 (43), 101 (100) and 73 (34).

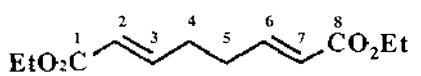
(2*S*,3*S*,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-ol (520)



520

To a stirred solution of methyl (2*E*,4*E*,6*E*,8*E*,10*S*,11*S*)-11,12-*O*-isopropylidene-10-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-11,12-dihydroxy-2,4,6,8-dodecateraenoate (**519**) (385.2mg, 0.943mmol) in dichloromethane (10mL) at -10°C under argon was added dropwise diisobutylaluminium hydride (1.5mol/L in toluene, 1.38mL, 2.07mmol, 2.2eq). On completion of the addition the reaction mixture was warmed to -80°C. Hexane (20mL) then ethyl acetate (4mL) was cautiously added then the reaction mixture was eluted through a silica plug (4cm diameter x 7cm deep) which was saturated with hexane. The silica was then eluted with hexane:ethyl acetate (2:1, 3 x 50mL) to give the crude product (399.0mg) as a yellow oil. Chromatography of this material on silica (20g) with hexane:ethyl acetate (5:1 then 2:1) gave the **title compound** (**520**) (317.5mg, 0.834mmol, 88%) as a colourless oil: $[\alpha]_D^{20.5}$ = -47.5° (c = 2.77, dichloromethane); R_f = 0.46 (hexane:ethyl acetate (2:1)); (Found: M^+, 380.2384. $C_{21}H_{36}O_4Si$ requires M, 380.2383); ν_{max} (film) 3415, 2986, 2954, 2929, 2885, 2856, 1645, 1609, 1471, 1462, 1380, 1370 and 1254cm^{-1}; λ_{max} (methanol)/nm 314 (ε/Lmol^{-1}cm^{-1} 5.19 x 10^4), 300 (5.95 x 10^4) and 288 (4.14 x 10^4); δ_H (270MHz, $CDCl_3$) 0.049 and 0.067 (6H, 2 x s, -Si(C*H*$_3$)$_2$-), 0.893 (9H, s, -C(C*H*$_3$)$_3$), 1.33 and 1.38 (6H, 2 x s, -C(C*H*$_3$)$_2$-), 1.81 (1H, s, -O*H*), 3.78 (1H, dd, *J* 6.2 ,8.5Hz, C1-*H*), 3.93 (1H, dd, *J* 6.7, 8.5Hz, C1-*H'*), 4.04-4.12 (1H, m, C2-*H*), 4.14-4.24 (2H, m, C12-*H*), 4.24-4.31 (1H, m, C3-*H*), 5.94-5.61 (2H, m, C4-*H* and C11-*H*) and 6.14-6.37 (6H, m, C5-*H*, C6-*H*, C7-*H*, C8-*H*, C9-*H* and C10-*H*); δ_C (68.1MHz, $CDCl_3$) -4.74, -4.49, 18.3, 25.3, 25.8, 26.4, 63.3, 65.3, 73.6, 78.7, 109.4, 131.3, 131.7, 132.0, 132.1, 132.3, 132.5, 132.6 and 132.9; *m/z* (EI, 70eV) 380 (9%), 323 (7), 305 (8), 279 (100), 101 (85) and 73 (55).

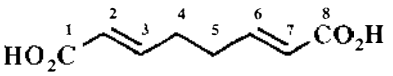
diethyl (2*E*,6*E*)-2,6-octadienedioate (523)



523

To a stirred solution of succinaldehyde[11] (**Section 6.6.4**) in dichlormethane (150mL, from the total volume (300mL)) at RT under argon was added ethyl (triphenylphosphoranylidene)ethanoate (26.4g, 0.0728mol). On completion of the addition the solution was warmed to reflux and stirring was continued for 64h. The solvent was evaporated and the crude product extracted from the solid material with pentane (3 x 200mL). Evaporation of the pentane gave the crude product (9.22g) as a yellow oil. Kugelrhor distillation of this material (200°C/0.05mmHg) gave the **title compound** (**523**) (7.22g, 0.0319mol, 88%) as a colourless oil: R_f = 0.36 (hexane:ethyl acetate (5:1)); (Found: M^+, 226.1212. $C_{12}H_{18}O_4$ requires M, 226.1205); ν_{max} (film) 2981, 2937, 2904, 1719, 1654, 1367 and 1269cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.29 (3H, t, J 7.1Hz, -$CO_2CH_2CH_3$), 2.34-2.42 (2H, m, C4-*H*), 4.12 (2H, q, J 7.1Hz, -$CO_2CH_2CH_3$), 5.86 (1H, J 15.6Hz, C2-*H*) and 6.88-6.99 (1H, m, C3-*H*); δ_C (68.1MHz, $CDCl_3$) 14.2, 30.4, 60.1, 122.2, 146.5 and 166.0; *m/z* (EI, 70eV) 226 (1%), 181 (96), 152 (77), 107 (41), 85 (100), 79 (82) and 68 (57).

(2*E*,6*E*)-2,6-octadienedioic acid (524)



524

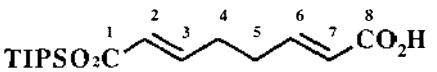
To a stirred solution of diethyl (2*E*,6*E*)-2,6-octadienedioate (**523**) (1.00g, 4.42mmol) in tetrahydrofuran (11mL) at RT was added aqueous potassium hydroxide solution (1.0mol/L, 44mL, 44mmol, 10eq). Stirring was continued for 2h then the reaction mixture was partitioned against diethyl ether (50mL). The aqueous layer was titrated with 10 % aqueous hydrochloric until it was pH 1, then it was filtered. The crude product was rinsed with acetone (3 x 50mL) and dried to constant mass on high vacuum to give the **title compound** (**524**) (0.514g, 3.02mmol, 68%) as a white powder: mp 255-259°C (dec.) (lit.[243] 250-252°C (dec.)); R_f = 0.08 (ethyl acetate:methanol:acetic acid (100:0.5:0.5)); (Found: M^++NH_4, 188.0918. $C_8H_{14}NO_4$ requires M, 188.0923); ν_{max} (KBr disc) 2921, 1685, 1636 and 1430cm^{-1}; δ_H (270MHz, d_6-DMSO/internal reference 2.50ppm) 2.27-2.41 (2H, m, C4-*H*), 5.80 (1H, d, J 15.6Hz, C2-*H*) and 6.71-6.85 (1H, m, C3-*H*); δ_C (68.1MHz, d_6-DMSO/internal reference 39.7ppm) 30.6, 123.3, 148.3 and 167.7; *m/z* (CI/NH_3, 70eV) 188(0.4%), 167 (6), 153 (12), 124 (100), 79 (56), 68 (41) and 39 (24).

triisopropylsilyl hydrogen (2*E*,6*E*)-2,6-octadienedioate (525) and *bis*-triisopropylsilyl (2*E*,6*E*)-2,6-octadienedioate (526)

525 **526**

To a stirred solution of (2*E*,6*E*)-2,6-octadienedioic acid (**524**) (0.502g, 2.95mmol) and triethylamine (430μL, 3.10mmol, 1.05eq) in tetrahydrofuran (200mL) at RT under argon was added triisopropylsilyl chloride (632μL, 2.95mmol, 1eq) *via* syringe pump over the course of 1h. On completion of the addition silica (6g) was added and the solvent evaporated. This material was loaded onto a silica column (30g) and eluted with hexane:ethyl acetate (5:1 then 1:1) then ethyl acetate:methanol:acetic acid (100:0.5:0.5) to give **title compounds 525** (0.445g, 1.36mmol, 44%) and **526** (0.314g, 0.650mmol, 22%), *vide infra*, followed by **recovered starting material (524)** (0.100g, 0.588mmol, 20%), *vide supra.*

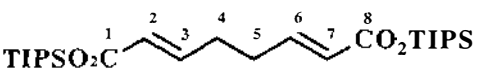
triisopropylsilyl hydrogen (2*E*,6*E*)-2,6-octadienedioate (525)



525

Crystalline solid: mp 74-75°C (from hexane/diethyl ether); R_f = 0.47 (hexane:ethyl acetate (1:1)); (Found: M^+-C_3H_7, 283.1361. $C_{14}H_{23}O_4Si$ requires *M*, 283.1366); ν_{max} (KBr disc) 3367, 3063, 2946, 2868, 2717, 1697, 1641, 1465, 1427 and 1321cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.09 (18H, d, *J* 7.3Hz, -Si(CH(C*H*$_3$)$_2$)$_3$), 1.24-1.42 (3H, m, -Si(C*H*(CH$_3$)$_2$)$_3$), 2.36-2.46 (4H, m, C4-*H* and C5-*H*), 5.87 (2H, d, *J* 15.6Hz, C2-*H* and C7-*H*) and 6.84-7.15 (2H, m, C3-*H* and C6-*H*); δ_C (68.1MHz, $CDCl_3$) 12.1, 17.9, 30.2, 30.7, 121.5, 123.9, 147.0, 149.7, 165.8 and 171.2; *m/z* (EI, 70eV) 283 (100%), 265 (8), 237 (28), 223 (25), 131 (24), 103 (29), 75 (35) and 61 (18).

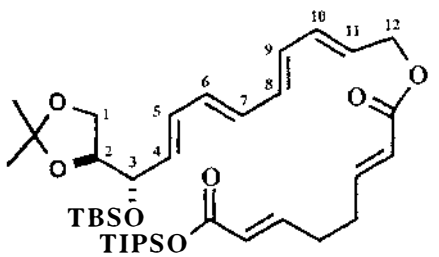
***bis*-triisopropylsilyl (2*E*,6*E*)-2,6-octadienedioate (526)**



526

Yellow oil: R_f = 0.95 (hexane:ethyl acetate (5:1)); (Found: M^+-C_3H_7, 439.2695. $C_{23}H_{43}O_4Si_2$ requires *M*, 439.2699); ν_{max} (film) 2945, 2892, 2867, 1698, 1650, 1464, 1384, 1368 and 1283cm^{-1}; δ_H (270MHz, $CDCl_3$) 1.09 (18H, d, *J* 7.3Hz, -Si(CH(C*H*$_3$)$_2$)$_3$), 1.22-1.42 (3H, m, -Si(C*H*(CH$_3$)$_2$)$_3$), 2.36-2.41 (2H, m, C4-*H*), 5.85 (1H, d, *J* 15.4Hz, C2-*H*) and 6.84-6.98 (1H, m, C3-*H*); δ_C (68.1MHz, $CDCl_3$) 12.1, 17.9, 30.4, 123.8, 147.2 and 165.7; *m/z* (EI, 70eV) 439 (100%), 198 (11), 157 (10), 115 (22), 87 (10) and 59 (13).

(2*S*,3S,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl (2*E*,6*E*)-2,6-octadienedioate (527)

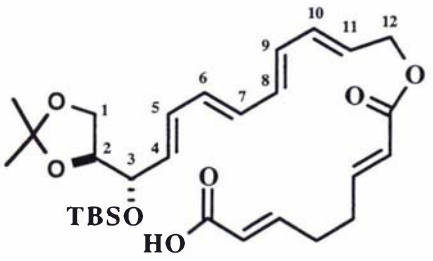


527

To a stirred solution of (2*S*,3*S*,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-ol (**520**) (0.255g, 0.670mmol) in dichloromethane (2.3mL) at 0°C under argon was added 2,6-di-*tert*-butyl-4-methylphenol (29.5mg, 0.134mmol, 0.2eq), triisopropylsilyl hydrogen (2*E*,6*E*)-2,6-octadienedioate (**525**) (0.273g, 0.836mmol, 1.25eq), dicyclohexylcarbodiimide (0.207g, 1.00mmol, 1.5eq) and N,N-dimethylaminopyridine (12.2mg, 0.100mmol, 0.15eq). Stirring was continued for 3h then the reaction mixture was diluted with hexane (10mL) and passed through a silica plug (4cm diameter x 5cm deep) which was then eluted with hexane:ethyl acetate (10:1, 5 x 50mL) then hexane:ethyl acetate (10:1, 3 x 50mL) and the solvent was evaporated to give the crude product (0.336g) as a yellow oil. Chromatography of this material on silica (15g) with hexane:ethyl aceatate (20:1, 10:1 and 5:1) gave the **title compound** (**527**) (0.157g, 0.228mmol, 34%) as a yellow oil: $[\alpha]_D^{21}$ = -25.1° (c = 0.89, dichloromethane); R_f = 0.58 (hexane:ethyl acetate (5:1)); (Found: M^+, 688.4205. $C_{38}H_{64}O_7Si_2$ requires *M*, 688.4191); ν_{max} (film) 2948, 2893, 2867, 1723, 1698, 1650, 1473, 1463, 1380, 1370 and 1283cm^{-1}; λ_{max} (methanol)/nm 316 (ε/Lmol^{-1}cm^{-1} 4.07 x 10^4), 302 (4.74 x 10^4), 289 (3.45 x 10^4) and 199 (1.47 x 10^5); δ_H (270MHz, $CDCl_3$) 0.057 and 0.076 (6H, 2 x s, -Si(C*H*$_3$)$_2$-), 0.902 (9H, s, -C(C*H*$_3$)$_3$), 1.09 (18H, d, *J* 7.3Hz, -Si(CH(C*H*$_3$)$_2$)$_3$), 1.18-1.45 (3H, m, -Si(C*H*(CH$_3$)$_2$)$_3$), 1.34 and 1.39 (3H, 2 x s, -C(CH$_3$)$_2$-), 2.36-2.42 (4H, m, -C*H*$_2$C*H*$_2$-),

3.79 (1H, dd, *J* 6.2, 8.5Hz, C1-*H*), 3.94 (1H, dd, *J* 6.7, 8.5Hz, C1-*H'*), 4.04-4.13 (1H, m, C2-*H*), 4.29 (1H, t, *J* 5.7Hz, C3-*H*), 4.68 (2H, d, *J* 6.5Hz, C12-*H*), 5.51-5.93 (2H, m, C4-*H* and C11-*H*), 5.88 and 5.86 (2H, 2 x dd, *J* 15.7Hz, 2 x -CH=C*H*-CO_2-), 6.08-6.44 (6H, m , C5-*H*, C6-*H*, C7-*H*, C8-*H*, C9-*H* and C10-*H*), and 6.82-7.04 (2H, m, 2 x -C*H*=CH-CO_2-); δ_C (68.1MHz, $CDCl_3$) -4.72, -4.49, 12.1, 17.8, 18.3, 25.3, 25.9, 26.4, 30.3, 30.6, 64.6, 65.3, 73.7, 78.7, 109.3, 122.0, 123.9, 126.6, 128.2, 131.6, 131.7, 132.4, 133.0, 133.9, 134.3, 147.1, 147.2, 165.7 and 165.8; *m/z* (EI, 70eV) 688 (2%), 613 (5), 587 (48), 283 (24), 262 (81), 101 (100) and 73 (49).

(2*S*,3*S*,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl hydrogen (2*E*,6*E*)-2,6-octadienedioate (529)



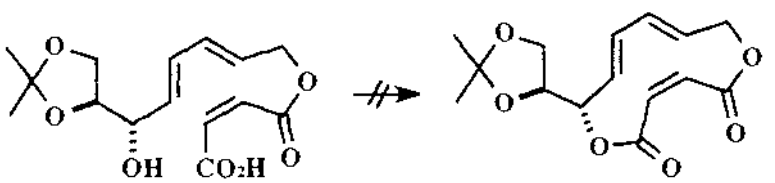
529

To a stirred solution of (2*S*,3S,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl (2*E*,6*E*)-2,6-octadienedioate (**527**) (63.6mg, 0.0923mmol) in methanol (25mL) at RT under argon was added anhydrous potassium carbonate (25.4mg, 0.184mmol, 2eq).[232] Stirring was continued for 10min then the reaction mixture was diluted with diethyl ether (100mL) and partitioned against saturated aqueous ammonioum chloride (50mL). The aqueous layer was extracted with diethyl ether (50 mL) and the combined extracts were washed with water (10mL) and brine (10mL) then dried, filtered and evaporated to give the crude product (70.4mg) as a yellow oil. Chromatography of this material on silica (3.5g) with hexane:ethyl acetate (2:1) then hexane:ethyl acetate:methanol:acetic acid (66:33:0.5:0.5 then 50:50:0.5:0.5) gave the **title compound** (**529**) (49.0mg, 0.0920mmol, 100%) as a yellow oil: $[\alpha]_D^{20}$ = -26.2° (c = 2.3, dichloromethane); R_f = 0.53 (hexane:ethyl acetate:methanol:acetic acid (50:50:0.5:0.5)); (Found: M^+, 532.2901. $C_{29}H_{44}O_7Si$ requires *M*, 532.2856); ν_{max} (film) 3164, 2985, 2856, 2953, 2930, 2886, 2856, 1721, 1697, 1651, 1472, 1462, 1422, 1380, 1370 and 1257cm^{-1}; λ_{max} (methanol)/nm 316 (ε/Lmol^{-1}cm^{-1} 8.92 x 10^4), 302 (1.02 x 10^5), 289 (7.32 x 10^4) and 197 (1.20 x 10^5); δ_H (270MHz, $CDCl_3$) 0.054 and 0.073 (6H, 2 x s, -Si(C*H*$_3$)$_2$-), 0.899

(9H, s, -C(CH_3)$_3$), 1.34 and 1.39 (6H, 2 x s, -C(CH_3)$_2$-), 3.79 (1H, dd, *J* 6.2, 8.5Hz, C1-*H*), 3.94 (1H, dd, *J* 6.6, 8.5Hz, C1-*H'*), 4.04-4.13 (1H, m, C2-*H*), 4.29 (1H, t, *J* 6.3Hz, C3-*H*), 4.68 (2H, d, *J* 6.3Hz, C12-*H*), 5.65-5.94 (2H, m, C4-*H* and C11-*H*), 5.87 and 5.89 (2H, 2 x d, *J* 15.7Hz, 2 x -CH=C*H*-CO_2-), 6.11-6.14 (6H, m, C5-*H*, C6-*H*, C7-*H*, C8-*H*, C9-*H*, C10-*H*) and 6.88-7.12 (2H, m, 2 x -CH=C*H*-CO_2-); δ_C (68.1MHz, $CDCl_3$) -4.69, -4.44, 18.3, 25.3, 25.9, 26.5, 30.4, 30.6, 64.7, 65.3, 73.7, 78.8, 109.4, 121.7, 122.1, 126.6, 131.6, 131.7, 132.4 (2 x C), 133.0, 133.9, 134.3, 147.0, 149.4, 165.8 and 170.7; *m/z* (EI, 70eV) 532 (0.5%), 431 (5), 262 (19), 101 (80), 75 (100), 57 (26) and 41 (42).

6.5.1 Attempted macrocyclisations, deprotections and TIMDA reactions

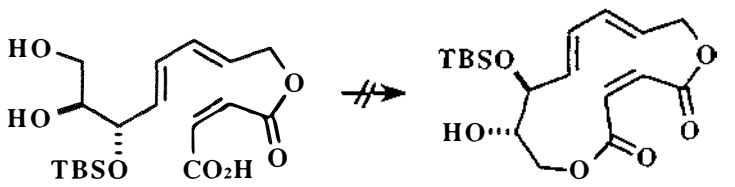
Attempted macrocyclisation of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl hydrogen maleate (237)



237 **513**

To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-1,2-*O*-isopropylidene-1,2,3-trihydroxy-4,6-octadien-8-yl hydrogen maleate (**237**) (57.7mg, 0.185mmol) in toluene (18mL) at RT under argon was added triethylamine (38.4μL, 0.277mmol, 1.5eq) and 2,4,6-trichlorobenzoyl chloride (31.8μL, 0.204mmol, 1.1eq). On completion of the addition the solution was stirred for 2h then N,N-dimethylaminopyridine (45.1mg, 0.370mmol, 2eq) was added and stirring continued for a further 10min.[223] The reaction mixture was diluted with diethyl ether (50mL), 2,6-di-*tert*-butyl-4-methylphenol (9.4mg, 0.040mmol, 0.2eq) was added and then it was partitioned against 10% aqueous hydrochloric acid (50mL), saturated aqueous sodium bicarbonate (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (61.3mg) as a yellow oil. Radial chromatography (1mm plate) was carried out on this material with hexane:ethyl acetate (1:1), but compound **513** could not be identified (by proton NMR analysis) in any of the fractions isolated .

Attempted macrocyclisation of (2*S*,3*S*,4*E*,6*E*)-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,5-octadien-8-yl hydrogen maleate (515)



515 **516**

Method A

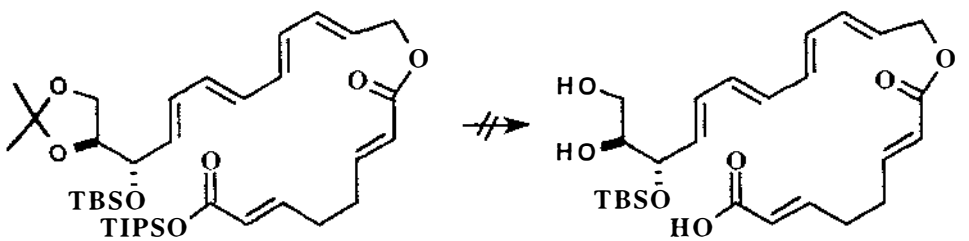
To a stirred solution of (2*S*,3*S*,4*E*,6*E*)-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,5-octadien-8-yl hydrogen maleate (**515**) (6.4mg, 0.017mol) in toluene (1.7mL) at RT under argon was added triethylamine (3.4μL, 0.025mol, 1.5eq) and 2,4,6-trichlorobenzoyl chloride (3.1μL, 0.020mmol, 1.2eq). On completion of the addition the solution was stirred for 18h then N,N-dimethylaminopyridine (45.1mg, 0.370mmol, 2eq) was added and stirring continued for a further 3h.[223] The reaction mixture was diluted with diethyl ether (50mL) and partitioned against 10% aqueous hydrochloric acid (50mL), saturated aqueous sodium bicarbonate (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (7.1mg) as a yellow oil. Mass spectral analysis of the crude material (EI, 70eV) recorded fragments with relative molecular masses greater than 700amu, indicating that polymerization may have occurred.

Method B

To a stirred solution of dicyclohexylcarbodiimde (235mg, 1.14mmol, 20eq), N,N-dimethylaminopyridine (348mg, 2.85mmol, 50eq) and trifluoromethanesulphonic acid (101μL, 1.14mmol, 20eq) in chloroform (19.1mL) at RT under argon was added a solution of (2*S*,3*S*,4*E*,6*E*)-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,5-octadien-8-yl hydrogen maleate (**515**) (22.0mg, 0.0569mmol) in chloroform (3.7mL) *via* syringe pump over 8h.[225] The reaction mixture was diluted with diethyl ether to precipitate urea and the filtrate was partitioned against 10% aqueous hydrochloric acid (50mL), water (50mL), saturated aqueous sodium bicarbonate (50mL), water (50mL) and brine (50mL) then dried, filtered and evaporated to give the crude product (150mg) as an amorphous solid. Chromatography was carried out on this material on silica (5g) with hexane:ethyl acetate (10:1 and 2:1) then hexane:ethyl acetate:methanol:acetic acid

(50:50:0.5:0.5), but compound **516** could not be identified (by proton NMR analysis) in any of the fractions isolated.

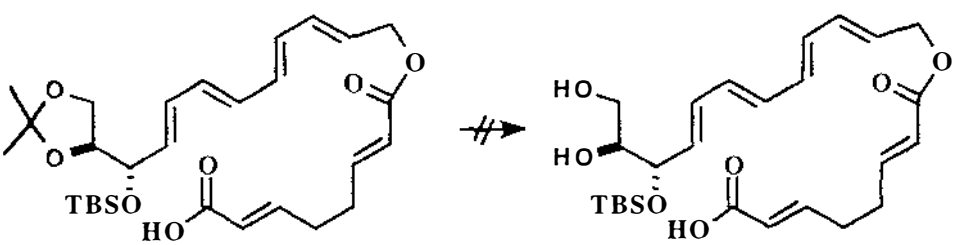
Attempted deprotection of (2*S*,3S,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl (2*E*,6*E*)-2,6-octadienedioate (527)



527 529

To a stirred solution of (2*S*,3S,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl (2*E*,6*E*)-2,6-octadienedioate (**527**) (14.3mg, 0.0208mmol) in dichloromethane (2.1mL) at 0°C under argon was added trifluoroacetic acid (16.5μL, 0.208mmol, 10eq). Stirring was continued for 30min and then the solvent was evaporated to give the crude product (8.1mg) as a yellow oil. Compound **529** could not be identified in the crude material by proton NMR analysis.

Attempted deprotection of (2*S*,3*S*,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl hydrogen (2*E*,6*E*)-2,6-octadienedioate (529)



528 529

Method A

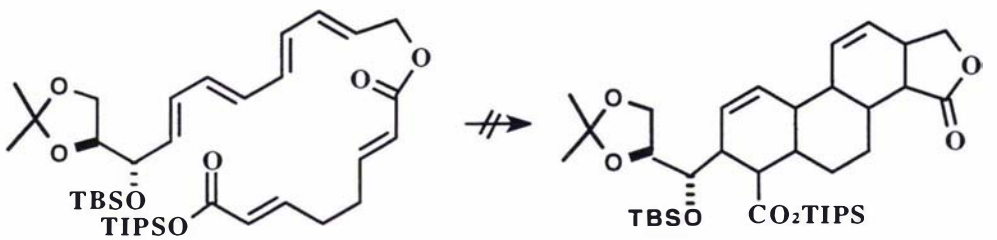
To a stirred solution of (2*S*,3*S*,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl hydrogen

(2*E*,6*E*)-2,6-octadienedioate (**529**) (5.0mg, 9.8μmol) in dichloromethane (0.9mL) at RT under argon was added trifluoroacetic acid (3.7μL, 47μmol, 5eq). Stirring was continued for 30min then the solvent was evaporated to give the crude product (4.0mg) as a yellow oil. Compound **529** could not be identified in the crude material by proton NMR analysis.

Method B

To a stirred solution of (2*S*,3*S*,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl hydrogen (2*E*,6*E*)-2,6-octadienedioate (**529**) (6.1mg, 7.7μmol) in tetrahydrofuran (1.0mL) at RT under argon was added acetic acid:water (3:1, 4mL).[234] Stirring was continued for 24h then toluene (2 x 20mL) was added sequentially and the solution was concentrated to remove the acetic acid. The crude product (3.8mg) was absorbed onto silica (200mg) then chromatography was carried out on silica (1g) with ethyl acetate, hexane:ethyl acetate:acetic acid:methanol (50:50:0.5:0.5) and ethyl acetate:acetic acid:methanol (100:0.5:0.5). Compound **529** could not be positively identified by proton NMR analysis in any of the fractions isolated.

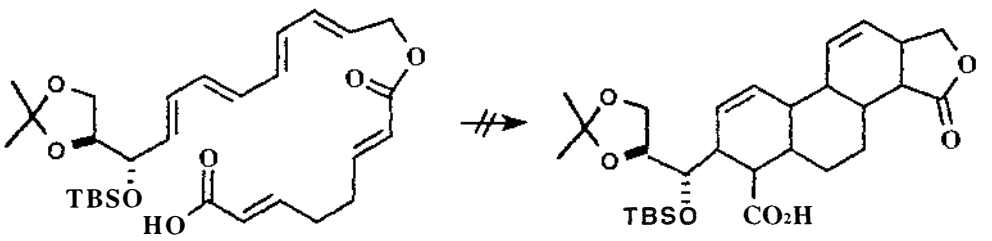
Attempted TIMDA reaction of (2*S*,3S,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl (2*E*,6*E*)-2,6-octadienedioate (527)



527 **535**

A solution of (2*S*,3S,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl triisopropylsilyl (2*E*,6*E*)-2,6-octadienedioate (**527**) (7.1mg, 0.010mmol) in d_6-DMSO (1.0mL) at RT under argon was transferred to an NMR tube and heated to 110°C for 11h. Destruction of the starting material was observed.

Attempted TIMDA reaction of (2*S*,3*S*,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl hydrogen (2*E*,6*E*)-2,6-octadienedioate (529)



528 536

To (2*S*,3*S*,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-isopropylidene-3-(1-*tert*-butyl-1,1-dimethylsilyl)oxy-1,2-dihydroxy-4,6,8,10-dodecateraen-12-yl hydrogen (2*E*,6*E*)-2,6-octadienedioate (**529**) (5.3mg, 9.9μmol) and 2,6-di-*tert*-butyl-4-methylphenol (0.412mg, 1.88μmol, 0.2eq) at RT under argon was added aqueous sodium bicarbonate solution (5.0mmol/L, 2.0mL, 0.010mol, 1eq). Sodium carbonate (7.6mg, 0.090mmol, 9.0 eq) was added to dissolve the starting material and the resulting solution was heated at reflux temperature for 5d. No reaction was observed.

6.6 Preparation of reagents

6.6.1 Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one)[167, 244, 245]

Part A[244]

To a vigorously stirred solution of 2-iodobenzoic acid (42.6g, 0.172mol) in dilute aqueous sulphuric acid (0.730mol/L, 365ml) at 55°C was added potassium bromate (38.0g, 0.228mol, 1.33eq) in twelve equal portions over 1h. On completion of the addition the solution was warmed to 70°C and stirring was continued for 3h. The reaction mixture was cooled on ice and the precipitate was filtered then rinsed with water (500mL), ethanol (3 x 25mL) and diethyl ether (3 x 25mL) and dried under vacuum to give **1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide** (41.0g, 0.146mol, 83%) as a crystalline white solid.

Part B[245]

To a stirred solution of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (41.0g, 0.146mol) in acetic anhydride (200mL, 2.12mol, 14.5eq) at RT under a calcium chloride drying tube was added *para*-toluenesulphonic acid monohydrate (0.250g, 1.31mmol, 8.97 x 10^{-3}eq). On completion of the addition the solution was warmed to 80°C and stirring was continued for 2h. The reaction mixture was cooled on ice then rapidly filtered. The precipitate was rinsed with diethyl ether (5 x 25mL) then dried under vacuum to give **1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one** (50.5g, 0.119mol, 82%) as a crystalline white solid.

6.6.2 Ethyl 4-(triphenylphosphoranylidene)-(2*E*)-2-butenoate[246, 168, 169]

Part A

To a stirred solution of ethyl (2*E*)-4-bromo-2-butenoate (20.0g, 0.104mol) in diethyl ether (200mL) at RT under argon was added triphenylphosphine (27.2g, 0.104mol, 1eq). On completion of the addition the solution was warmed to reflux and stirring was continued for 3d. The reaction mixture was cooled on ice and filtered, then the precipitate was rinsed with diethyl ether (3 x 50mL) to give **((2E)-4-ethoxycarbonyl-2-propenyl)triphenylphosphonium bromide** (31.7g, 0.0696mol, 67%) as a crystalline white solid.

Part B

To a stirred solution of ((2E)-4-ethoxycarbonyl-2-propenyl)triphenylphosphonium bromide (31.7g, 0.0696mol) in water (1L), cooled in ice, was added aqueous sodium hydroxide solution (2mol/L) until a sample tested basic with phenolphthalein indicator solution. The reaction mixture was filtered and the precipitate washed with water (4 x 50mL) then freeze dried for 4d to give the **title compound** as a yellow powder (22.7g, 0.609mol, 88%).

(A similar procedure was used to prepare **methyl 4-(triphenylphosphoranylidene)-(2*E*)-2-butenoate** from methyl (2*E*)-4-bromo-2-butenoate.)

6.6.3 Diazomethane[173]

To a stirred solution of potassium hydroxide (3.37g, 0.0600mol) in water (5mL) at RT was added aqueous ethanol (96%, 17mL). This solution was warmed to 65°C and a solution of N-methyl-N-nitroso-*para*-toluenesulphonamide (14.3g, 0.0667mol, 1.11eq) in diethyl ether (85mL) was added dropwise. The diazomethane and diethyl ether were distilled from the reaction mixture and condensed using a dry ice/acetone trap. Further diethyl ether (10mL) was added and distillation continued until the vapour produced was colourless. The solution was refrigerated and used as required.

6.6.4 Succinaldehyde[11]

To a stirred solution of 2,5-dimethoxytetrahydrofuran (10g, 0.0757mol) was added dilute aqueous hydrochloric acid (0.6mol/L, 50mL) at RT and stirring was continued for 45min. The solution was extracted with dichloromethane (3 x 15mL), then adjusted to pH 1 and extracted with further dichloromethane (15mL). The pH adjustment and extraction was repeated five times and then the combined dichloromethane fractions were dried, filtered and the volume made up to 300mL. Evaporation of the solvent was not carried out since neat succinaldehyde polymerizes on standing and it is volatile (bp 50-60°C/12mmHg[11]). The solution was refrigerated and used as required.

Appendix 1

1.1 Summary of two dimensional NMR experiments

1.1.1 COSY spectra

39a, 40a, 228, 238c, 241a:242a (66:34), 241b, 241c, 241d, 242b, 246, 247, 252, 270:271 (50:50), 305, 310, 314, 315, 320. 321, 408, 410 and 417.

1.1.2 NOESY spectra

39a, 40a, 238c, 241a:242a (66:34), 241b, 241c, 241d, 242b, 246, 247, 252, 310, 314, 315, 320. 321, 408, 410 and 417.

1.1.3 HETCOR spectra

38a, 228, 236, 238c, 241b, 241c, 241d, 305, 314 and 405.

1.1.4 HMQC spectra

39a, 40a, 240, 246, 247, 303, 306, 310, 315, 410 and 417.

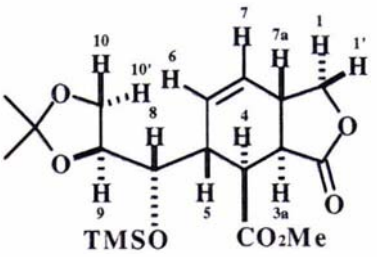
1.1.5 HSQC spectra

242b and 320.

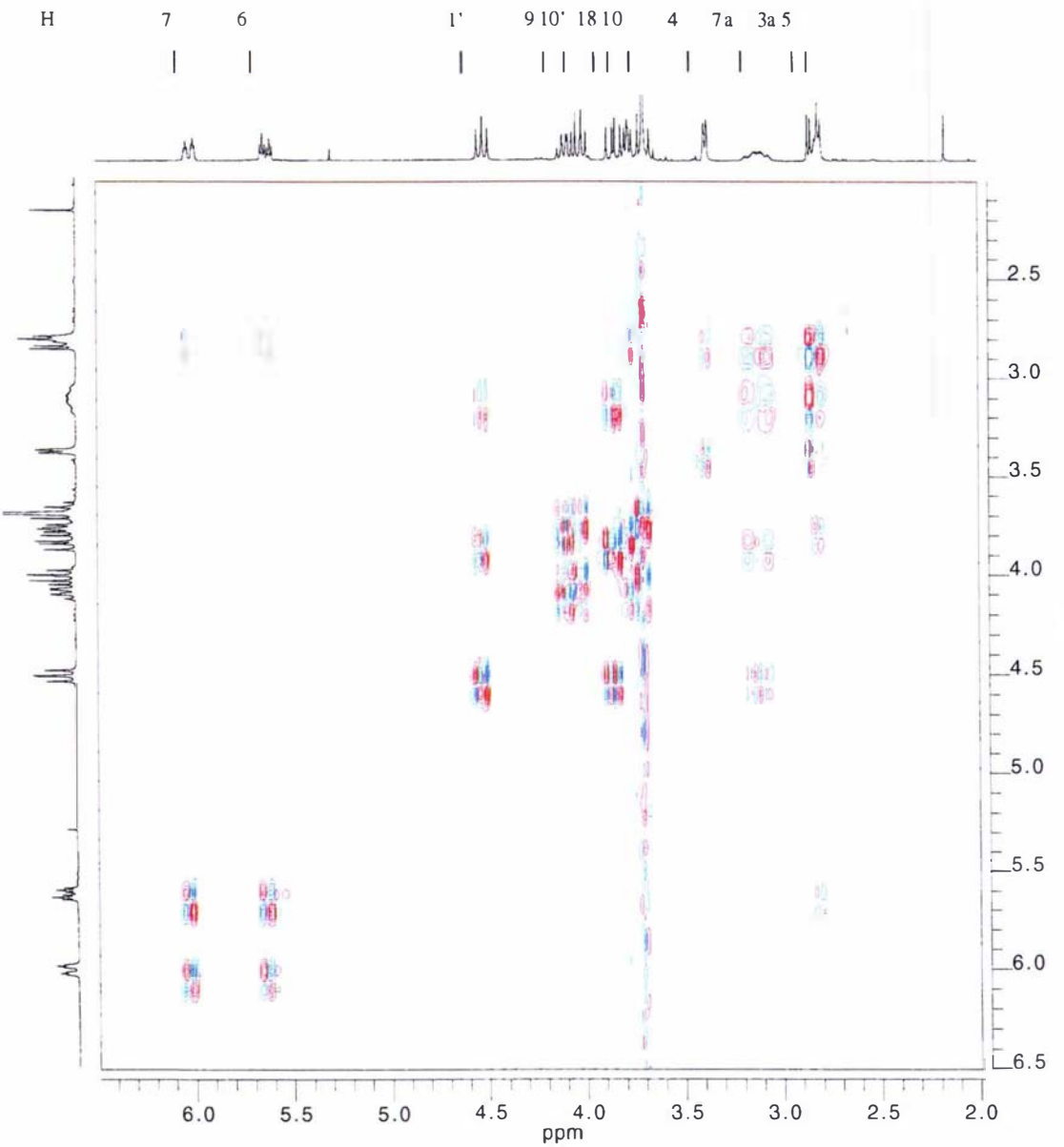
1.1.6 ROESY spectrum

321.

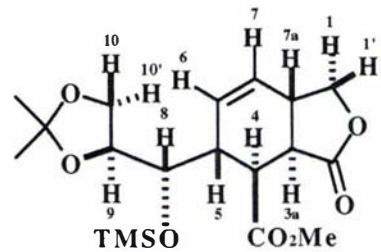
1.2C COSY spectrum of 241b



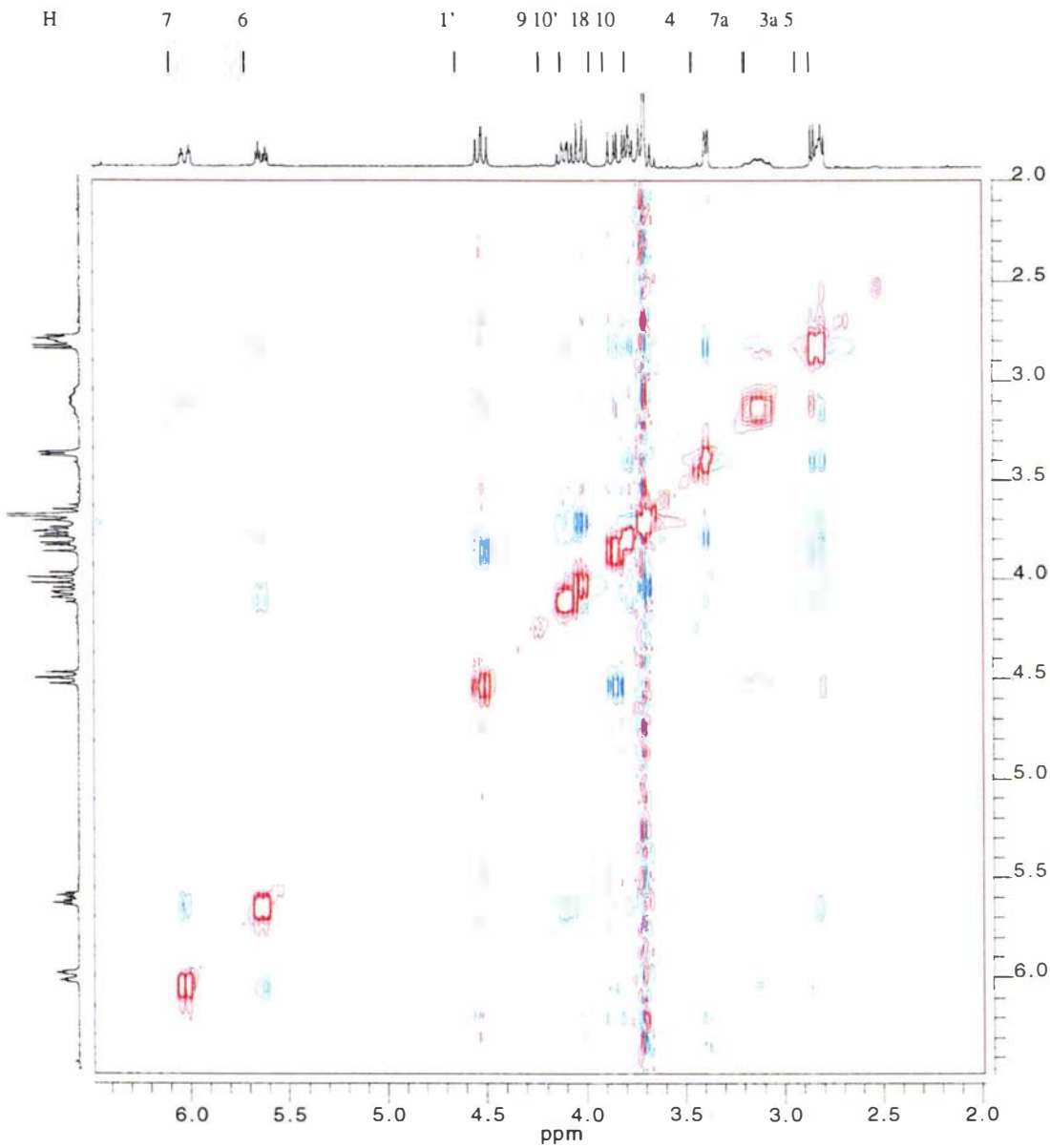
241b



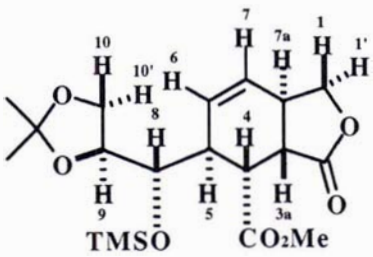
1.2N NOESY spectrum of 241b



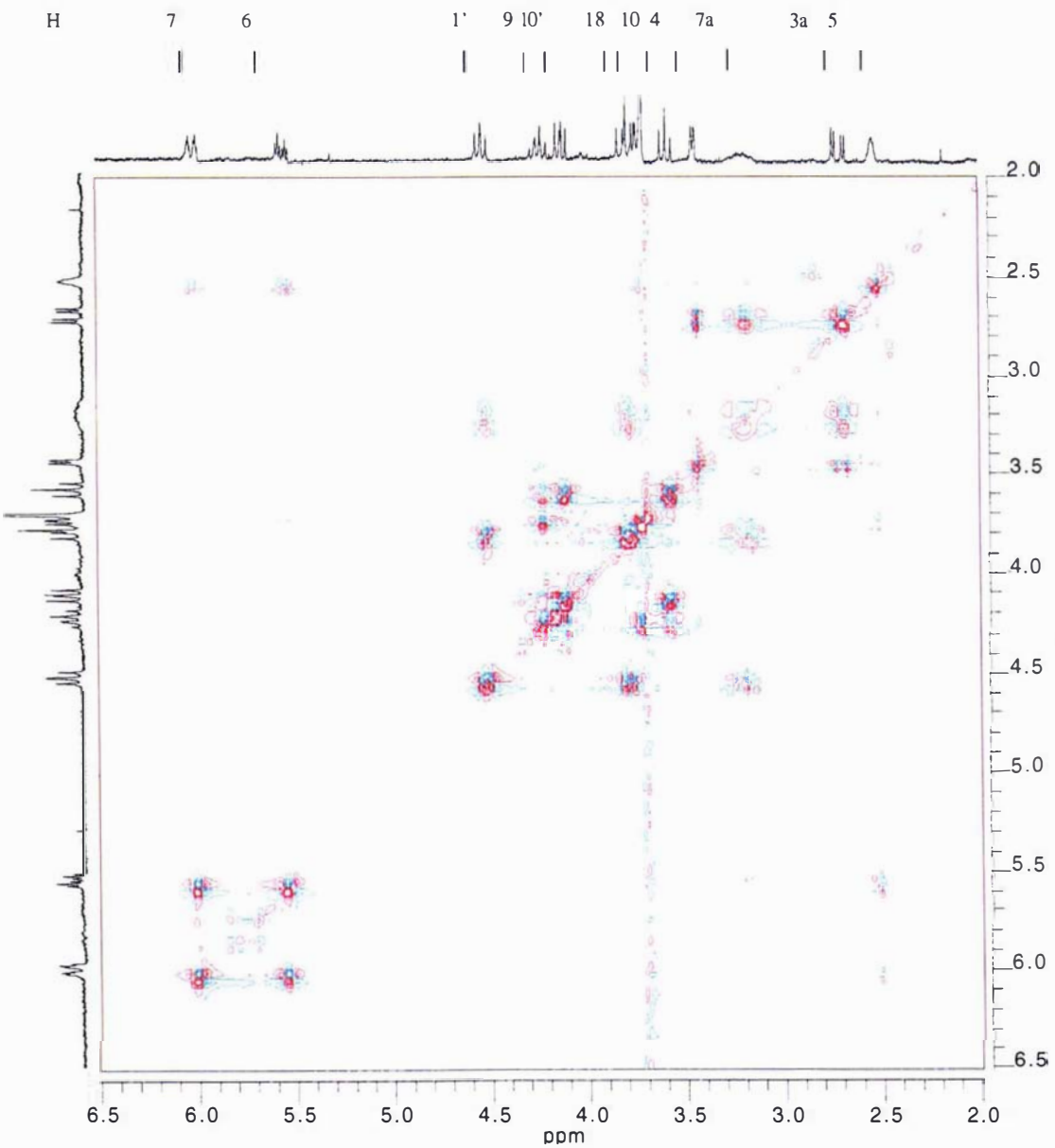
241b



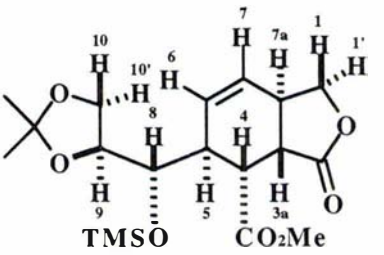
1.3C COSY spectrum of 242b



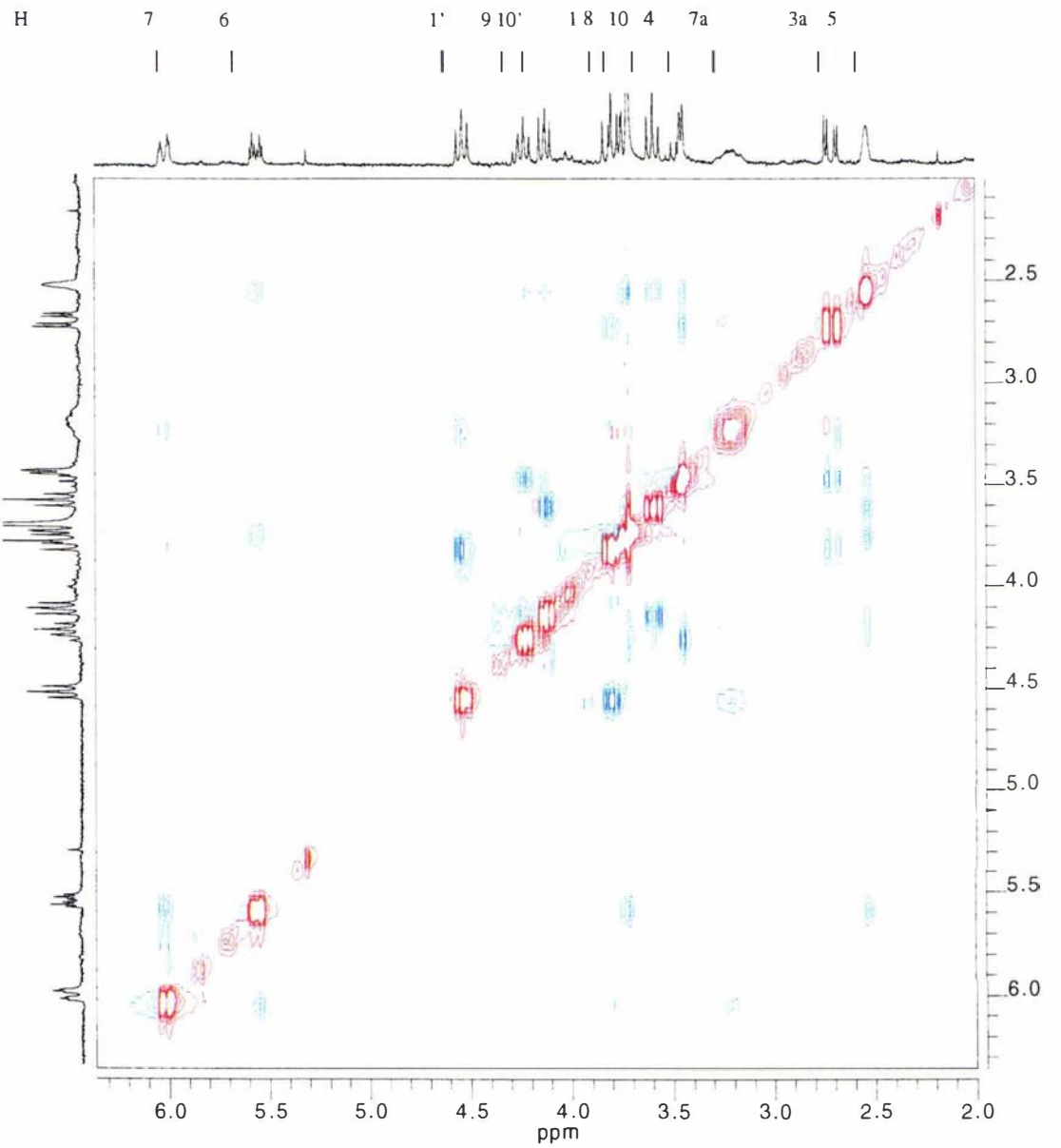
242b



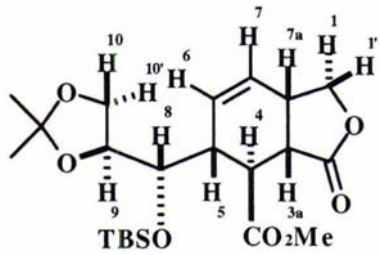
1.3N NOESY spectrum of 242b



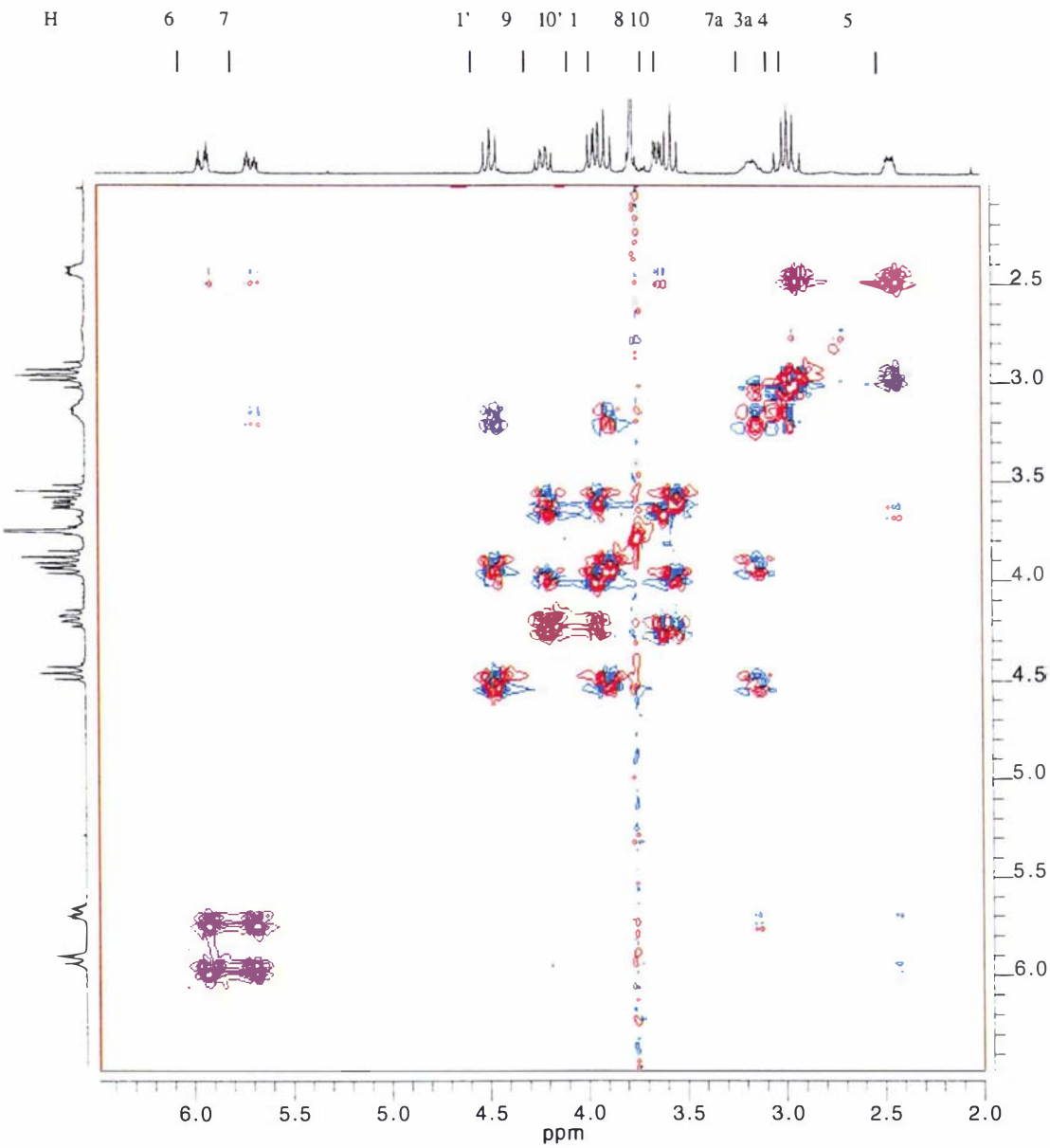
242b



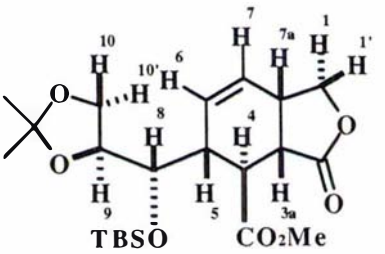
1.4C COSY spectrum of 314



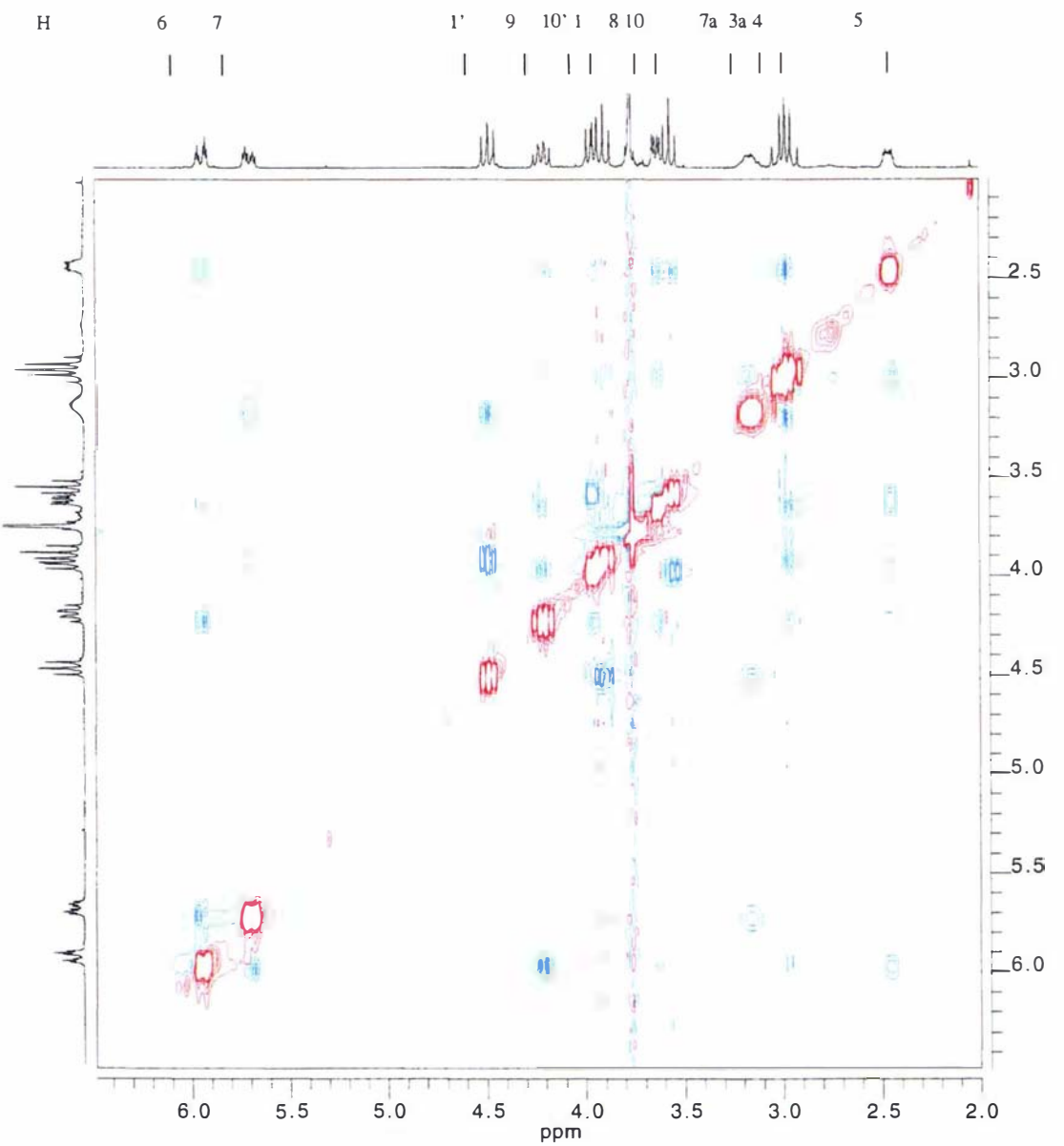
314



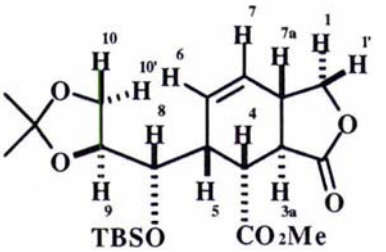
1.4N NOESY spectrum of 314



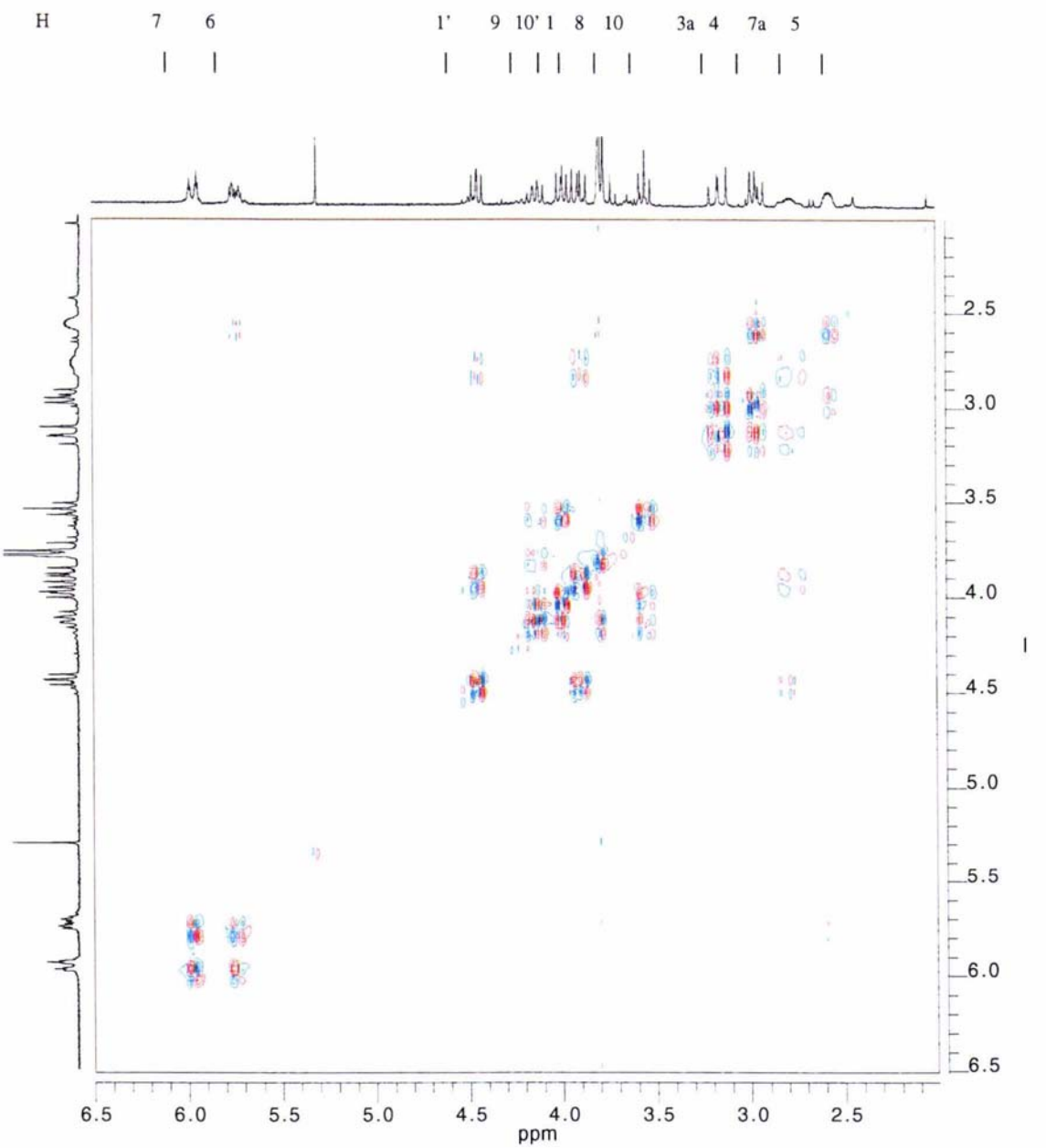
314



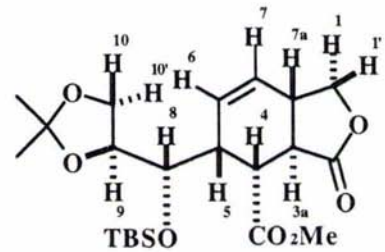
1.5C COSY spectrum of 315



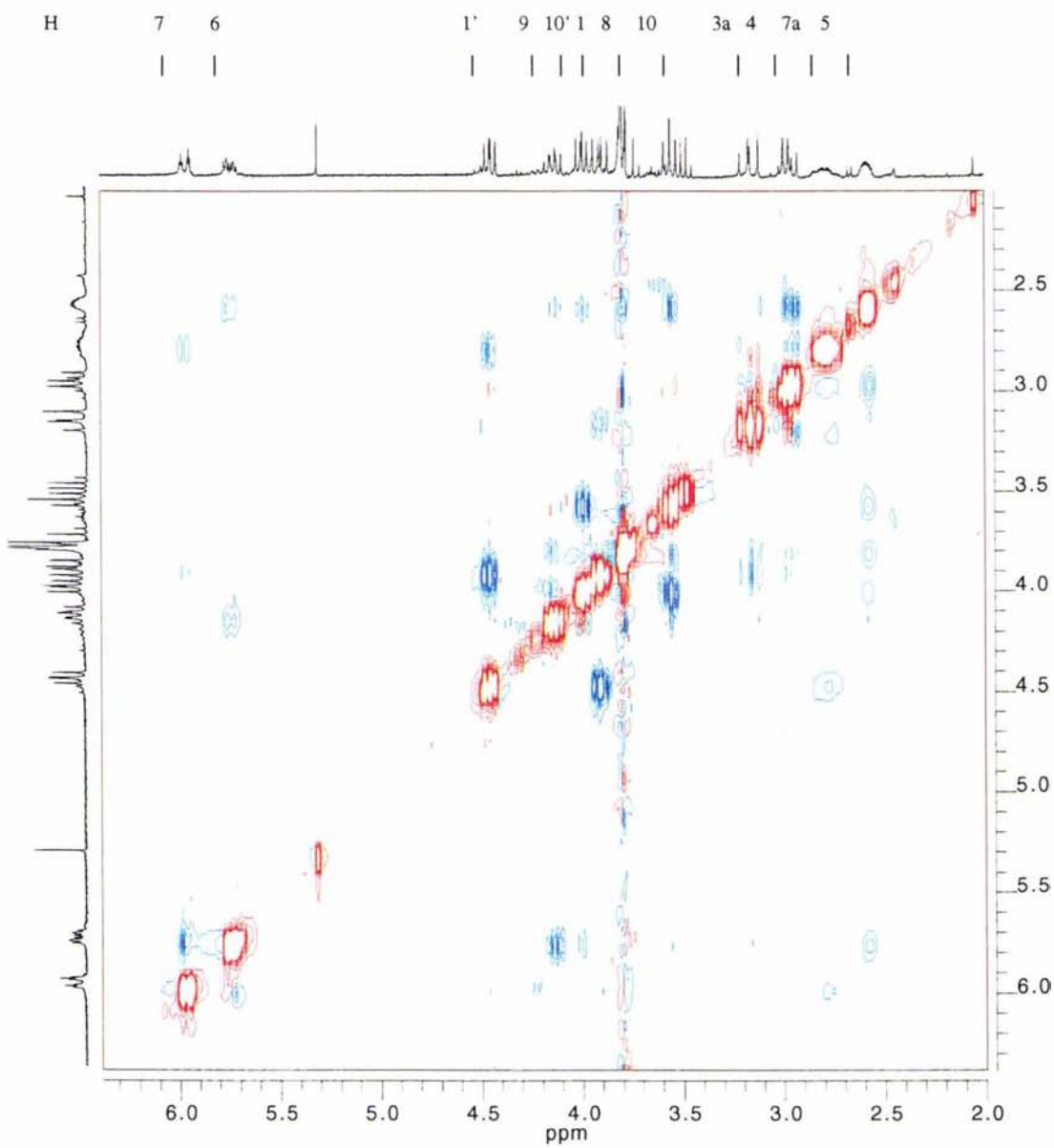
315



1.5N NOESY spectrum of 315



315



Appendix 2

2.1 Crystal data and structure refinement for compound 39a.

Empirical formula	$C_{12}H_{16}O_4$	
Formula weight	224.25	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.804(2) Å	α= 90°
	b = 13.331(3) Å	β= 95.17(3)°
	c = 8.068(2) Å	γ= 90°
Volume	1157.3(4) $Å^3$	
Z	4	
Density (calculated)	1.287 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	480	
Crystal size	.11 x .21 x .34 mm^3	
Theta range for data collection	1.89 to 25.00°	
Index ranges	-12<=h<=12, -15<=k<=15, 0<=l<=9	
Reflections collected	4275	
Independent reflections	2038 [R(int) = 0.0413]	
Completeness to theta = 25.00°	95.4 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2038 / 0 / 146	
Goodness-of-fit on F^2	1.015	
Final R indices [I>2sigma(I)]	R1 = 0.0387, wR2 = 0.1093	
R indices (all data)	R1 = 0.0806, wR2 = 0.1297	
Extinction coefficient	0.022(4)	
Largest diff. peak and hole	0.138 and -0.159 $e.Å^{-3}$	

2.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 39a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7459(3)	-1550(2)	3531(4)	93(1)
C(2)	8013(2)	-490(2)	3680(3)	62(1)
C(3)	7449(2)	32(2)	5078(3)	67(1)
C(4)	6652(2)	787(2)	4945(2)	63(1)
C(5)	6308(2)	1255(2)	3314(2)	52(1)
C(6)	4990(2)	1556(2)	2767(3)	66(1)
C(7)	5915(2)	1064(2)	446(3)	55(1)
C(8)	6547(2)	541(1)	1922(2)	47(1)
C(9)	7859(2)	127(1)	2046(2)	52(1)
C(10)	8118(2)	-500(2)	519(3)	83(1)
C(11)	8827(2)	956(2)	2153(2)	54(1)
C(12)	9318(2)	2583(2)	1297(4)	98(1)
O(1)	4999(1)	1643(1)	973(2)	65(1)
O(2)	6052(2)	1008(1)	-1002(2)	79(1)
O(3)	9827(1)	905(1)	2897(2)	83(1)
O(4)	8467(1)	1758(1)	1280(2)	76(1)

2.3 Bond lengths [Å] and angles [°] for 39a.

C(1)-C(2)	1.535(3)
C(2)-C(3)	1.500(3)
C(2)-C(9)	1.551(3)
C(3)-C(4)	1.322(3)
C(4)-C(5)	1.474(3)
C(5)-C(6)	1.507(3)
C(5)-C(8)	1.512(3)
C(6)-O(1)	1.453(3)
C(7)-O(2)	1.193(2)
C(7)-O(1)	1.353(2)
C(7)-C(8)	1.492(3)
C(8)-C(9)	1.515(2)
C(9)-C(11)	1.519(3)
C(9)-C(10)	1.535(3)
C(11)-O(3)	1.189(2)
C(11)-O(4)	1.319(2)
C(12)-O(4)	1.434(3)

C(3)-C(2)-C(1)	107.7(2)
C(3)-C(2)-C(9)	111.94(17)
C(1)-C(2)-C(9)	114.2(2)
C(4)-C(3)-C(2)	126.7(2)
C(3)-C(4)-C(5)	120.27(19)
C(4)-C(5)-C(6)	121.99(17)
C(4)-C(5)-C(8)	110.52(17)
C(6)-C(5)-C(8)	99.85(16)
O(1)-C(6)-C(5)	102.82(16)
O(2)-C(7)-O(1)	120.16(19)
O(2)-C(7)-C(8)	131.6(2)
O(1)-C(7)-C(8)	108.14(17)
C(7)-C(8)-C(5)	101.60(15)
C(7)-C(8)-C(9)	125.51(16)
C(5)-C(8)-C(9)	113.69(15)
C(8)-C(9)-C(11)	112.00(16)
C(8)-C(9)-C(10)	112.46(16)

C(11)-C(9)-C(10)	105.54(16)
C(8)-C(9)-C(2)	106.06(15)
C(11)-C(9)-C(2)	108.48(16)
C(10)-C(9)-C(2)	112.34(18)
O(3)-C(11)-O(4)	121.85(19)
O(3)-C(11)-C(9)	125.2(2)
O(4)-C(11)-C(9)	112.95(16)
C(7)-O(1)-C(6)	109.77(15)
C(11)-O(4)-C(12)	117.28(17)

2.4 Anisotropic displacement parameters ($Å^2$ x 10^3) for 39a. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	79(2)	57(1)	140(3)	19(2)	-8(2)	-1(1)
C(2)	50(1)	58(1)	76(1)	13(1)	-4(1)	2(1)
C(3)	61(1)	83(2)	55(1)	21(1)	-2(1)	-9(1)
C(4)	61(1)	85(2)	45(1)	3(1)	8(1)	-3(1)
C(5)	51(1)	56(1)	51(1)	-1(1)	7(1)	1(1)
C(6)	59(1)	74(1)	66(1)	3(1)	10(1)	12(1)
C(7)	51(1)	59(1)	53(1)	0(1)	-4(1)	-7(1)
C(8)	44(1)	47(1)	48(1)	-1(1)	0(1)	-4(1)
C(9)	45(1)	57(1)	54(1)	-5(1)	0(1)	3(1)
C(10)	74(2)	89(2)	84(2)	-30(1)	4(1)	16(1)
C(11)	45(1)	69(1)	47(1)	2(1)	6(1)	1(1)
C(12)	75(2)	95(2)	122(2)	39(2)	-3(2)	-28(1)
O(1)	57(1)	73(1)	64(1)	10(1)	-4(1)	11(1)
O(2)	84(1)	107(1)	45(1)	-1(1)	-7(1)	-1(1)
O(3)	51(1)	99(1)	96(1)	22(1)	-14(1)	-10(1)
O(4)	57(1)	81(1)	86(1)	27(1)	-6(1)	-16(1)

2.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 39a.

	x	y	z	U(eq)
H(1A)	7591	-1865	4603	112
H(1B)	6584	-1507	3208	112
H(1C)	7853	-1940	2727	112
H(2A)	8886	-566	3996	74
H(3A)	7706	-205	6179	80
H(4A)	6285	1036	5905	76
H(5A)	6842	1824	3225	63
H(6A)	4809	2197	3232	79
H(6B)	4389	1075	3071	79
H(8A)	6026	-27	2092	56
H(10A)	8953	-752	655	99
H(10B)	7545	-1052	429	99
H(10C)	8009	-100	-472	99
H(12A)	8934	3097	593	118
H(12B)	9476	2837	2410	118
H(12C)	10088	2386	886	118

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Errata

Page	Line	Amendment	
Abstract	12	the position allylic to	
Abstract	18	stereogenic centre	
i	13	**1.2.2.3 Enantioselective**	
iii	29	**6.4.4 Attempted DA**	
iv	1	**223**	
iv	3	**223**	
v	4	AcO	
v	-	c concentration (g/L)	
v	19	dicyclohexylcarbodiimide	
v	-	d.e. diastereomeric excess	
v	21	N,N-dimethylaminopyridine	
v	-	e.e. enantiomeric excess	
v	26	sulfoxide	
v	29	carbonyl close to diene	
v	35	carbonyl distant from diene	
vi	-	Ms mesyl	
vi	27	singlet	
1	8	observed[2].	
4	5	regiochemical	
10	10	is not	
18	-	**61** (*exo*)	**(Figure 1.22)**
22	8	(**81**)	
22	8	(**80**)	
26	3	refluxing xylene	
27	4	reactive propargylic dienophile	
31	6	two stereogenic centres responsible	
35	2	N-acyloxazolidinone	
36	-	Me_2AlCl	**(Figure 1.47)**
40	21	reaction was matched	
41	6	**Figure 1.53**	
41	-	Ms (for mesyl)	**(Figure 1.53)**
44	-	((-)-oblongolide)	**(Figure 1.58)**
60	14	74% yield	
66	3	number of	
66	21	was not	
70	5	to the present study are	
70	8	**256.**[188]	
70	16	**(256, Figure 2.14)**	
73	6	whereas the dienophile	
76	8	*Z*-stereoisomer	
77	19	(**252**)	
79	12	**236**	
79	13	**239**	
92	1	**236**	
92	2	**238c**	
96	3	**307**	
96	4	**306**	
97	2	to give rise	
115	-	ETDA	**(Figure 4.10)**
120	5	**405** and **38a**	
120	11	**38a**	
120	12	compound **405**	
120	13	of **39a** after	
120	14	adduct **40a**	
123	12	(**501**)	
123	14	(**502**)	
123	16	(**503**)	
123	18	(**504**)	
124	11	**507**	
127	32	the homologation increased	
128	10	**523**	
128	10	**524**	
130	-	remove Δ	**(Scheme 5.4)**
136	7	singlet	
148	20	**Preparation**	
156	17	δ_C (68.1MHz, $CDCl_3$) 0.458, 25.8, 26.4, 36.3, 39.2, 42.4, 42.9, 52.2, 66.1, 70.3, 76.3,109.6, 127.1, 128.1, 172.7 and 174.3;	
203	12	hexane	
212	25	dodecatetraenoate	
214	4	dodecatetraenoate	
215	1	dichloromethane	

Experimental (pages 135-225)

The first letter of each of the compound names should be capitalised, except where the name forms part of a sentence.

The TBS group in compounds **224-228, 236, 238c, 241c, 242c, 304-307, 310, 311, 314, 315, 320, 321, 401, 402, 407-409, 515, 518-520, 527** and **529** should be referred to as *tert*-butyldimethylsilyloxy instead of 1-*tert*-butyl-1,1-dimethylsilyloxy.

The side chain numbering in compounds **241b, 242b, 241c, 242c, 241d, 242d, 246-249, 251, 270, 271, 310, 311, 314, 315, 320** and **321** should begin with the carbon attached to the bicyclic ring system. Propanyl should be replaced with propyl.

The side chain numbering in compounds **236, 237, 238a-d, 239, 240, 304-307, 401-404, 515, 527** and **529** should begin with the carbon attached to the bridging oxygen of the ester.