Stereocontrol Of Intramolecular Diels-Alder Reactions

A thesis presented in partial fulfilment of the requirements for the degree

of

Doctor of Philosophy

in

Chemistry

at

Massey University

Rachel Marie Williamson

July 1999

ABSTRACT

The use of the intramolecular Diels-Alder (IMDA) reaction in target synthesis has prompted investigation into methods of controlling the stereochemistry of this versatile cycloaddition. Linking the diene and dienophile *via* an ester-tether is a synthetically facile method of generating a range of precursors for the IMDA reaction and allows rapid access to the hydroisobenzofuranone skeleton. This bicyclic[4.3.0]nonane ring system is common to many natural products, including spongians and several novel steroids. Many of the previous examples of ester-tethered IMDA reactions exhibited a lack of stereoselectivity or were performed on racemic mixtures of starting materials. This thesis describes the synthesis of chiral dienols and tetraenols in enantiomerically pure form from monosaccharides. The esters derived from these alcohols possessed a sterically demanding substituent in the ester tether, and the influence of this bulky dioxolane substituent upon the stereochemical outcome of the IMDA reaction was the subject of this study. The purpose of these investigations was to gain information on stereocontrol in the ester-tethered IMDA reaction and, thus, provide a foundation for the tandem IMDA (TIMDA) reaction.

A chiral dienol was synthesised in an enantiomerically pure form from D-glucose and used to prepare *Z*-methyl, *E*-methyl and propynoate esters with a dioxolane substituent on the ester tether. The IMDA reactions of these substrates were studied and found to exhibit high levels of diastereoselectivity. In particular, the IMDA reaction of the *Z*-methyl ester had both extremely high *exo/endo* selectivity (86:14) and complete π-diastereofacial selectivity. The IMDA reaction of the *E*-methyl ester was less selective. The diastereoselectivities of the IMDA reactions were explained by the minimised $A^{1,3}$-strain in the favoured transition state.

It has been long contended in the literature that the IMDA reactions of maleate half-esters (carboxylic acids) produced *endo* adducts whereas the corresponding *Z*-methyl esters (of the maleate half-esters) produced *exo* adducts. Comparison of the IMDA reaction of the *Z*-methyl ester described above with that of its maleate half-ester, disputed this theory. The IMDA reactions of the acid and of the methyl ester exhibited the same diastereoselectivity, with the same ratio of *exo:endo* adduct in each case. This result prompted an investigation into previous research in this area. It was discovered that the previously made assumptions as to the mechanism of reaction between dienols and maleic anhydride (MA) were suspect.

With the purpose of studying the differences in diastereoselectivity and relative rate caused by altering one of two adjacent stereocentres, the results of the model study on the chiral dienol were extended to two diastereomeric tetraenol systems. Both diastereomeric tetraene substrates were synthesised from monosaccharide starting materials; D-glucose and D-galactose. The D-glucose-derived esters were found to undergo IMDA reactions with higher levels of diastereoselectivity than those of the D-galactose-derived esters. In the case of the IMDA reactions of the D-galactose-derived esters, all four of the possible diastereoisomers were produced. In addition to the decreased diastereoselectivity, an increase in the rate of IMDA reaction of the D-galactose-derived substrates was observed when compared to the D-glucose-derived esters. Notably, as with the dienol series, the D-glucose-derived *Z*-methyl ester exhibited extremely high levels of diastereoselectivity.

A disconnection analysis of the cyclopentano perhydroanthrene skeleton of the steroids reveals that a TIMDA reaction would be an elegant method of synthesis. Towards this end, and utilising the information garnered from the model studies on dienol and tetraenol-derived substrates, the ester-tethered TIMDA reaction was investigated. A range of TIMDA precursors, in which a *bis*-diene (tetraene moiety) and *bis*-dienophile were linked *via* an ester tether, were assembled and TIMDA reactions of these substrates were attempted. The most promising area of investigation proved to be a diketone intermediate and future work remains to be performed in this area.

ACKNOWLEDGEMENTS

I would like to thank my supervisors; Mick Sherburn, for providing me with a challenging area for research, and Dave Harding for his support and help during the latter stages of this thesis. I am grateful to everyone, staff and students, who made my time at Massey fun and interesting. In particular, I would like to thank David Officer and Tony Burrell for 'adopting' me into the porphyrin group. I would also like to thank all past and present members of the Massey 'Sherburnite' research group.

I am indebted to Pat Edwards and his NMR expertise, which was vital to the completion of this research. I would also like to acknowledge Craig Turner at Sydney University for his work in subjecting several recalcitrant samples to HPLC and high field NMR.

Lots and lots of thanks to Bob, Geedha and Sophie Reid, who have provided me with numerous cups of tea, biscuits, advice and morale-boosting when needed.

I would like to thank my Mum and Dad for their love, support and words of wisdom (here it is Dad, **D**!). My sister, Kiri, has been great - the packages of chocolate goodies were most appreciated! Special thanks to Gavin Collis for both his friendship and his help in realising what had to be done.

CONTENTS

ABBREVIATIONS

Δ	reflux
Ac	acetyl
AcOH	acetic acid
AIBN	2,2′-azo-*bis*-isobutyronitrile
aq.	aqueous
Ar	aryl
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Bz	benzoyl
CSA	camphorsulfonic acid
COSY	correlated specroscopy
CH_2Cl_2	dichloromethane
d	day(s) or doublet
DA	Diels-Alder
o-DCB	*ortho*-dichlorobenzene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DEPT	distortionless enhancement by polarisation transfer
DIBAL-H	diisobutylaluminium hydride
DMAP	*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	dimethoxypropane
DMSO	dimethylsulfoxide
dppb	1,4-*bis*(diphenylphosphino)butane
EDG	electron donating group
EI	electron impact
eq	molar equivalents
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
Et_3N	triethylamine
eV	electron Volts
EWG	electron withdrawing group
FMO	frontier molecular orbital
FT	Fourier transform

h	hour(s)
H_2O	water
HETCOR	heteronuclear COSY
Hex	hexane
HOMO	highest occupied molecular orbital
Hz	Hertz
Im	imidazole
IR	infra-red
IMDA	intramolecular Diels-Alder reaction
^{i}Pr	*iso*-propyl
LUMO	lowest unoccupied molecular orbital
M	mol L^{-1}
MA	maleic anhydride
Me	methyl
MeOH	methanol
min	minute
MOM	methoxymethyl
MP	melting point
n-BuLi	*n*-butyl lithium
NMM	*N*-methylmaleiimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
Ph	phenyl
PhMe	toluene
PhH	benzene
ppm	parts per million
py	pyridine
q	quartet
R_f	retention factor
RT	room temperature
s	singlet
S.M.	starting material
t	time or triplet
^{t}Bu	*tert*-butyl
T	temperature
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran

TIMDA	tandem intramolecular Diels-Alder
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet-visible

1. INTRODUCTION

Many natural products have significant biological activity and great potential in medicine. Unfortunately these extremely useful compounds are often difficult to synthesise due to their complicated polycyclic structures, abundance of functional groups, connectivity and specific stereochemistry. A seemingly minor difference in absolute stereochemistry can have a major effect on the biological activity. A tragic example of this is the drug thalidomide used in the 1970's as a drug for the morning sickness which occurs in pregnancy. Produced as a racemic mixture of two enantiomers, it was discovered that whilst R-(+)-thalidomide was a powerful anti-nausea agent, S-(–)-thalidomide was transformed *in vivo* into metabolites which were both embryotoxic and teratogenic.[1] Many drugs in clinical practise are racemates as resolution is difficult, costly or impractical.[1] Often only one of the enantiomers is truly active. Hence, for reasons of safety and efficiency, there is an obvious need for enantioselective synthesis in the production of such compounds. The Diels-Alder (DA) reaction has proved to be a powerful method of construction of the bicyclic ring systems present in many natural products

1.1 The Diels-Alder Reaction

The 1,4-addition of an alkene (dienophile) to a 1,3-diene to form a cyclohexene ring (**Figure 1.1**) was first identified in 1928 by Otto Diels and Kurt Alder.[2] Specific examples of such reactions had appeared in the literature before this but the researchers had remained unaware of the significance and general applicability of the reaction.[3] Hence, Diels and Alder were credited with the discovery of the "diene synthesis" which is now known as the Diels-Alder reaction and is one of the most frequently used methods to construct the six-membered ring systems common in naturally occurring, bioactive natural products.[4]

The DA reaction generates two carbon-carbon bonds and up to four new stereogenic centres simultaneously with potentially high levels of regio-, diastereo- and enantioselectivity. The diene must be in the *cisoid* conformation in order for a reaction to take place, the *transoid* form will not undergo a DA reaction. There are three postulated mechanisms for the DA reaction: a concerted mechanism with no intermediate, a two step ionic mechanism and a two step radical mechanism. The majority of DA reactions take place *via* the concerted mechanism with the simultaneous closure of the two new σ-bonds between diene and dienophile giving rise to retention of the stereochemistry of the starting

materials and, hence, the largely predictable relative stereoselectivity associated with the DA reaction.

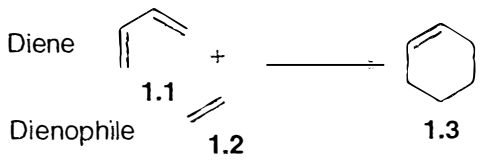


Figure 1.1

The intermolecular DA reaction between an unsymmetrically-substituted diene and dienophile can, in theory, produce mixtures of two regioisomers (**Figure 1.2**). In practice, one regioisomer often predominates, usually the "ortho" or "para" product. This preference for *ortho* and *para* regioisomers has been explained by frontier molecular orbital (FMO) theory and depends on the pattern and nature of substitution.[5]

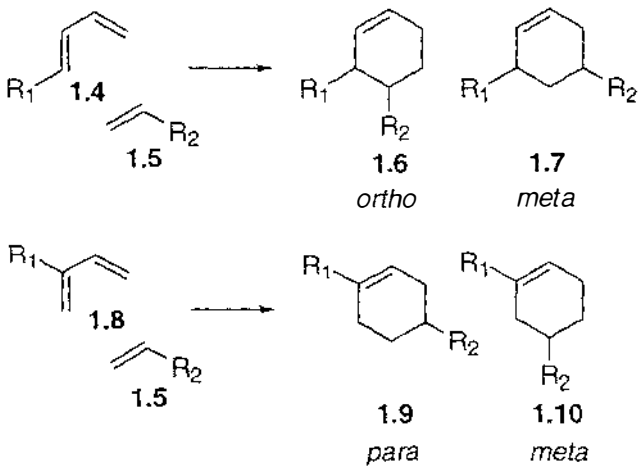


Figure 1.2

The presence of an electron-donating substituents on the diene and electron-withdrawing groups on the dienophile accelerate the rate of the DA reaction.[5] This is due to the energy of the LUMO of the dienophile being lowered and that of the HOMO of the diene being raised, resulting in an increase in the overlap of these orbitals. In the case of the less common reverse electron-demand DA reaction, the diene is substituted with an electron-withdrawing group whilst an electron-donating substituent is attached to the dienophile. In this case the interaction is between the HOMO of the dienophile and the LUMO of the diene.[5]

In the DA reaction of a cyclic diene there are two possible modes of addition illustrated by the reaction between cyclopentadiene and maleic anhydride (**Figure 1.3**). The *endo* mode, in which the more bulky part of the dienophile (containing the carbonyl groups of the electron-withdrawing group) are under the diene (**1.11**), is favoured over the *exo* mode, in which the less bulky part of the dienophile is under the diene (**1.13**). This preference for the *endo* adduct (**1.12**) is known as the "*endo* rule" and is explained by FMO theory.[5] Secondary orbital overlap between the carbonyl groups and the diene lowers the energy of the *endo* transition state relative to that of the *exo* transition state.

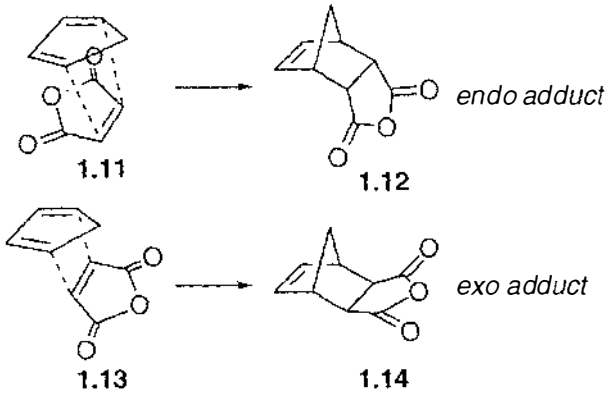


Figure 1.3

The DA reaction is not only confined to the formation of carbon-carbon bonds. Dienophiles consisting of N≡C-, -N=C, -N=N-, O=N- and -C=O moieties can react with dienes to form heterocyclic compounds. In addition, some heterodienes including -C=C-C=O, O=C-C=O and N=C-C=N undergo the DA reaction.[6]

1.2 Increasing The Rate And Regioselectivity Of The DA Reaction

The continuing use of the DA reaction in the synthesis of natural products has led to increased research into improving both the rate and selectivity of the reaction. The role of substituents on the rate of the DA reaction is well known. In addition to careful choice of reactants, there are physical and catalytic methods for increasing the rate of the DA reaction.[4]

Intermolecular DA reactions have large negative activation volumes and large negative volumes of reactions. This has led to the wide-spread use of high pressures as a method to induce [4 + 2] cycloaddition in less reactive and heat-sensitive substrates. Other

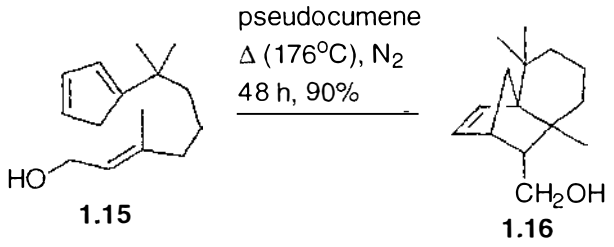
physical methods of inducing cyclisation in reluctant reactants include the use of ultrasonic radiation, microwave ovens and aqueous solvents.[4]

Biocatalysts such as antibody and enzymatic catalysts have been used successfully to increase both the rate and stereoselectivity of the DA reaction. Work is on-going in the area of tailored "Diels-Alderase" antibody enzymes.[4,7,8] Many DA reactions are catalysed by BrØnsted or Lewis acids *via* protonation or complexation of the dienophile. The use of Lewis acid catalysts in the DA reaction has been of growing interest due to, not only an acceleration in the rate of the DA reaction, but also an increased regio- and stereoselectivity.[4] It is believed that this is a result of donor-acceptor interactions between the electron-withdrawing group of the dienophile (Lewis base) and the catalyst (Lewis acid) lowering the energy of the FMOs of the dienophile. This results in a stabilisation of the transition state in the case of a normal electron-demand DA reaction.[5]

Another method of increasing the regioselectivity and rate of the DA reaction is to covalently link the diene and dienophile so as to secure an intramolecular DA (IMDA) reaction. This is the area of investigation of this thesis. The highly ordered transition state of the DA reaction means that if the diene and dienophile are linked, with the two reacting moieties part of the same molecule, then the activation entropy of the reaction is smaller and reaction rate would be expected to increase.[9,10] The constraints imposed on the transition state by the connecting chain (particularly chains with $n \leq 10$) result in excellent regioselectivity. This is discussed further in **Section 1.3**.

1.3 The IMDA Reaction

The DA reaction can be divided into two general types: the *inter*molecular DA reaction and the *intra*molecular DA reaction (IMDA). The intermolecular or bimolecular reaction has traditionally been useful in the construction of compounds containing cyclohexene rings, however increasing interest has been focused on the use of the IMDA reaction as an efficient way to synthesise complex bicyclic molecules. Although Alder and Schumacher proposed the idea of an intramolecular variant of the DA reaction in 1953,[11] it was some time before the advantages of this methodology were generally recognised with the IMDA reaction first used in natural product synthesis in the early 1960s[12,13] and the first review on the IMDA reaction published a decade later in 1974.[14] One of the earliest examples of deliberate application of the IMDA reaction was in an attempted synthesis of longifolene by Brieger.[13] The IMDA reaction of precursor **1.15** required reasonably forcing conditions (pseudocumene at reflux), yet was high yielding, forming the product **1.16** in 90% yield (**Scheme 1.1**).



1.15 **1.16**

Scheme 1.1

1.3.1 Advantages Of The IMDA Reaction

To the synthetic chemist, the most appealing aspect of the IMDA reaction is its efficiency. Two new carbon-carbon (or carbon-heteroatom) bonds, up to four new stereogenic centres and a new bicyclic system are formed in a single chemical step. With the appropriate functionalisation, the potential exists for the synthesis of complex polycyclic systems *via* a minimal sequence of reactions.

Due to favourable entropy factors IMDA reactions are generally faster and take place under considerably milder conditions than the corresponding intermolecular cases.[15] The intermolecular DA reaction has a highly ordered transition state resulting in a large negative activation entropy. By linking the diene and dienophile together with a tether the degrees of freedom in the starting material is reduced which results in a less negative entropy term.[9] However, the length of the chain connecting diene and dienophile has a pronounced effect on the rate of reaction with any entropic advantage diminishing in substrates with five or more atom chains *e.g.* formation of bicyclo[*n*.4.0] skeletons (this can be overcome, however, by reducing the degrees of freedom in the linking chain).[9] The nature of the connecting tether is also important in influencing the rate of reaction.

1.3.2 Regiochemistry Of The IMDA Reaction

IMDA reactions may be divided into two main classes based upon the mode of connection of the diene to the dienophile (**Figure 1.4**).[10] *Type 1* reactions are those in which the diene is attached to the dienophile by a tether from its terminus (*e.g.* triene **1.17**) while in *Type 2* reactions, the tether is attached to an internal diene position (*e.g.* triene **1.18**). It has been shown that, in general, both *Type 1* and *Type 2* IMDA reactions only occur if the tether contains three or more atoms.[10] This is due to the high level of strain involved

in the transition states of reactions of precursors with one or two atoms in the connecting chain. The majority of exceptions are mostly cyclic *Z*-dienes.

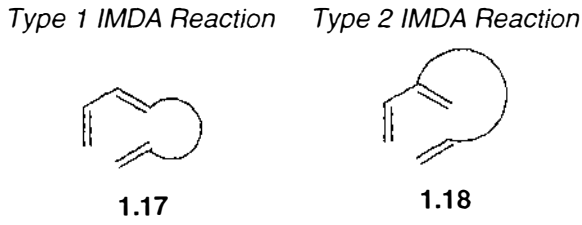


Figure 1.4

Regioselectivity is higher than in the *inter*molecular reaction due to the constraints imposed by the tether. Although the possibility of two regioisomers does exist for *Type 1* IMDA reactions, the majority of cases give the fused isomer exclusively, irrespective of substituent effects, due to the higher degree of strain in the transition state leading to the bridged product (**Figure 1.5**). Bridged products become more likely when the length of the tether is ten or more atoms.[10]

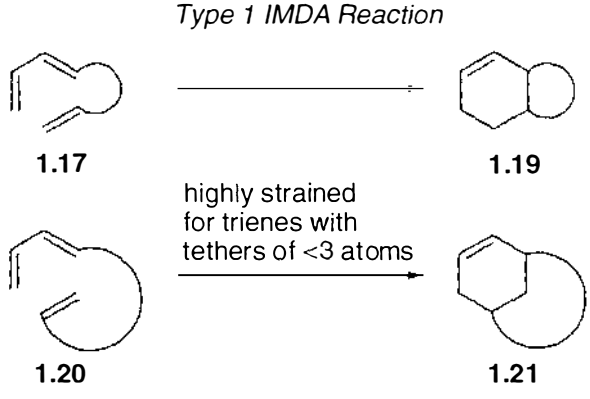


Figure 1.5

Type 2 IMDA reactions can only form bridged products, as shown in **Figure 1.6**. Again, the possibility of two regioisomers exists but tethers containing fewer than five members produce *meta*-bridged cycloadducts exclusively.[9]

Type 2 IMDA Reaction

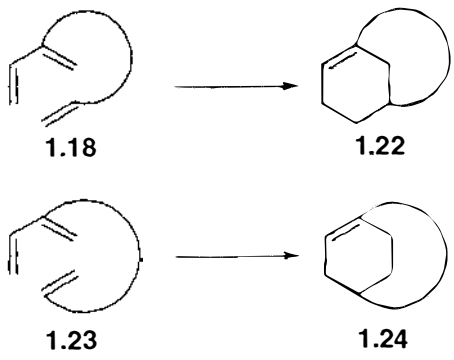


Figure 1.6

The focus of this thesis is on **Type 1** IMDA reactions, thus **Type 2** reactions will not be discussed further.

1.4 Stereochemical Aspects Of The IMDA Reaction

During the IMDA reaction, up to four new stereogenic centres can be generated with the result that up to eight stereoisomers are possible from the cycloaddition. The ability to control the stereoselectivity of the IMDA reaction is crucial to its successful application in the synthesis of medicinal products because of the dependence of biological activity upon stereochemistry. The stereochemical outcome of the IMDA reaction is determined by two factors; 1) the geometries of the diene and dienophile, and 2) the nature of the transition state.[16]

Due to the concerted nature of the mechanism, the geometries of the diene and dienophile are preserved in the DA reaction. The exceptions to this rule involve cases where reaction conditions have resulted in an isomerisation occurring before[16] or after cyclisation.[17] The increased reactivity of *E*-dienes compared to that of *Z*-dienes has resulted in the widespread use of *E*-dienes in the IMDA reaction.[9,16]

The nature of the transition state determines whether the newly formed ring junction is *cis*-fused or *trans*-fused (**Figure 1.7**). The "*endo* rule", applicable to the intermolecular DA reaction, cannot be relied upon to predict the stereochemical outcome of the IMDA reaction.

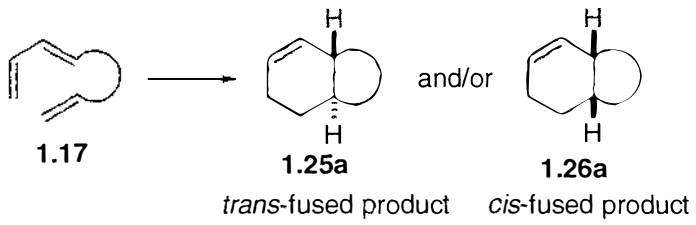
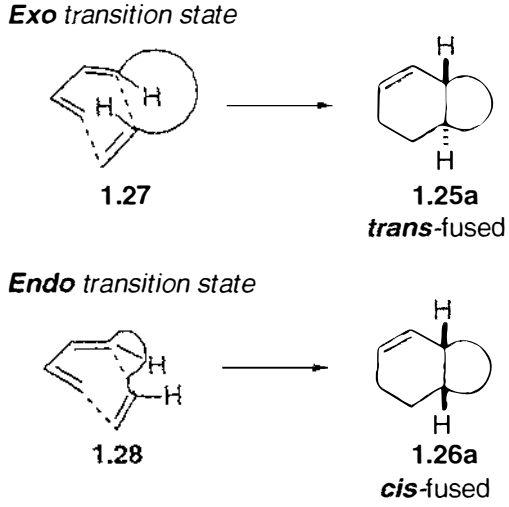


Figure 1.7

The IMDA reaction of *Z*- and *E*-dienes can give either *trans*- or *cis*-fused products depending on the orientation of the diene relative to the dienophile in the transition state (*i.e.* whether addition is *via* an *exo* or *endo* mode).[9] In this thesis, the terms *exo* and *endo* refer to the spatial position of the tether group. When the bulk of the tether group is towards the forming cyclohexene ring, this is referred to as an *endo* transition state. When the bulk of the tether is facing away from the forming cyclohexene this is an *exo* transition state. **Figure 1.8** and **Figure 1.9** show the *exo* and *endo* transition states for both a *Z*- and *E*-diene.

The terms *Z*- diene and *E*-diene are used to denote the stereochemistry of the double bond immediately attached to the tether.[9] An *E*-diene will give a *trans*-fused ring junction from an *exo* transition state and a *cis*-fused ring junction from an endo transition state (**Figure 1.8**).



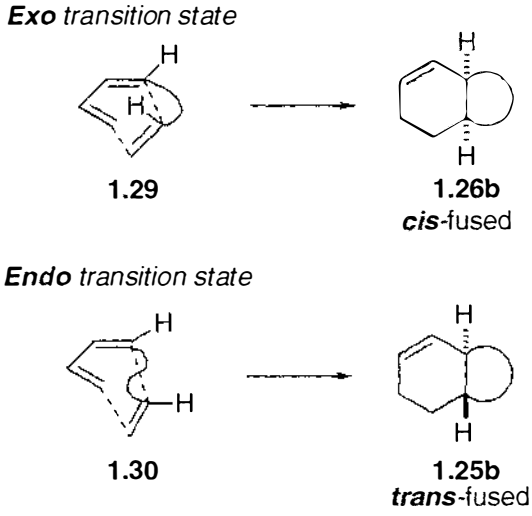
Transition states of an E-diene leading to trans and cis-fused bicyclic adducts.

Figure 1.8

Conversely, the *exo* transition state of a *Z*-diene produces a *cis*-fused ring junction and the *endo* transition state results in a *trans*-fused product (**Figure 1.9**). *Z*-dienes with

three or four atom tethers produce only *cis*-fused adducts as the *endo* transition state leading to the *trans*-fused product is highly strained.[10]

The most frequent class of IMDA precursors are those containing a *E*-diene due to the higher reactivity of such substrates compared to those containing a *Z*-diene.



Transition states of a Z-diene leading to cis and trans-fused bicyclic adducts.

Figure 1.9

Another aspect of stereochemistry to consider is the π-facial selectivity of the IMDA reaction. There are two *exo* and two *endo* modes of addition, as the dienophile can approach the diene from below or from above. The two different approaches of dienophile to diene are illustrated below by the *exo* transition states of an *E*-diene (**Figure 1.10**).

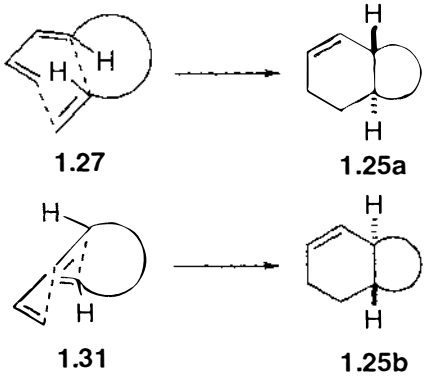
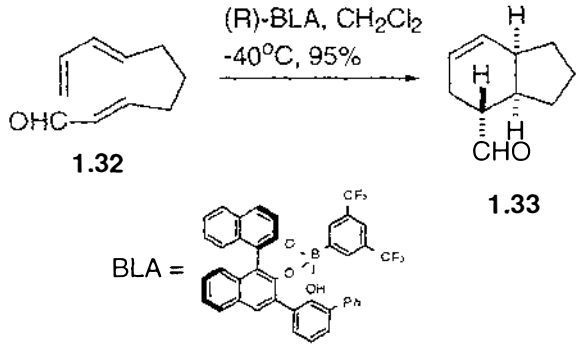


Figure 1.10

1.4.1 Methods Of Controlling Stereochemistry In The IMDA Reaction

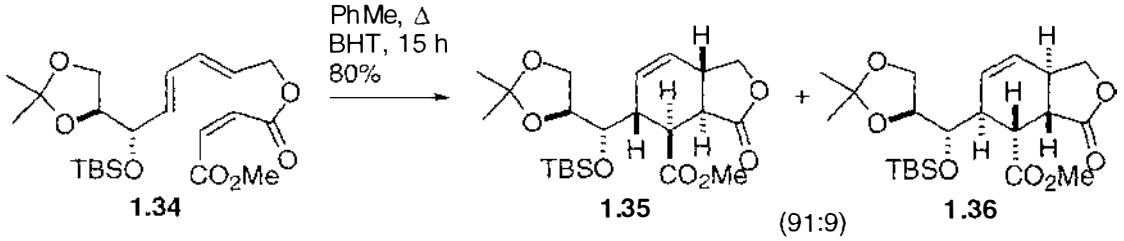
If the reacting substrate is chiral *i.e.* it contains an existing stereogenic centre, mixtures of diastereoisomers can result from the IMDA reaction. In order for the IMDA reaction to be of practical use in natural product (and other) syntheses, controlling the stereochemistry of the IMDA reaction is of paramount importance. Diastereomeric control can be achieved by π-facial differentiation in the developing transition state of the IMDA reaction. Methods of achieving this in the DA reaction include; the use of a chiral catalyst, the use of a stereogenic centre attached to the diene and the use of a stereogenic centre attached to the dienophile.[18] These methods can be applied to the IMDA reaction with the additional variation of the use of a stereogenic centre on the tether. The following selected examples demonstrate the levels of stereoselectivity which can be achieved in the IMDA reaction.

The use of chiral catalysts can result in high stereoselectivities as evidenced by work performed by Yamamoto *et al.*[19] A BrØnsted acid-assisted chiral Lewis acid (BLA) catalyst was designed and applied to the IMDA reaction of decatrienal **1.32**, producing only the *endo* adduct **1.33** in 95% yield (**Scheme 1.2**).



Scheme 1.2

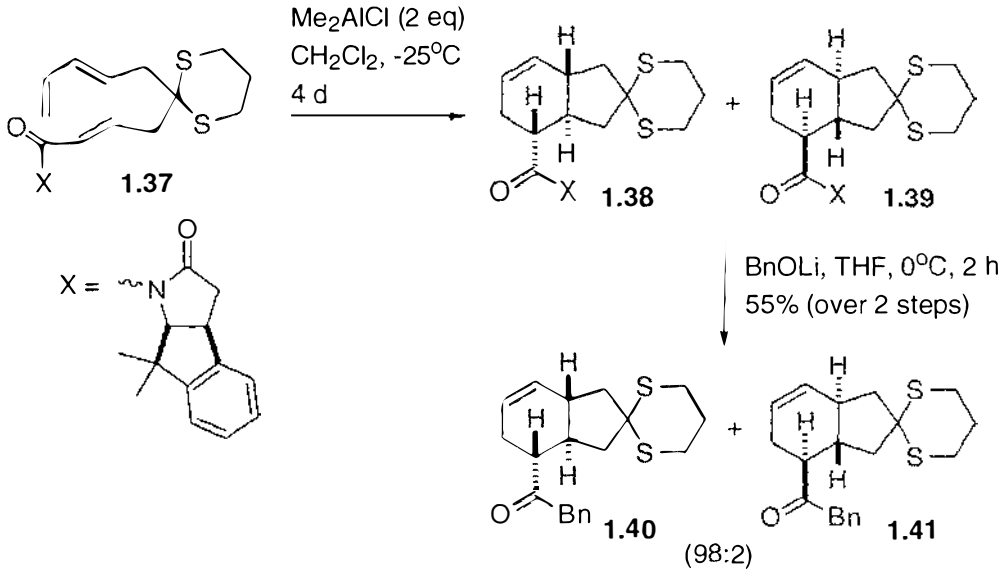
Lilly and Sherburn studied the IMDA reaction of diene ester **1.34**, containing a stereogenic centre allylic to the diene.



Scheme 1.3

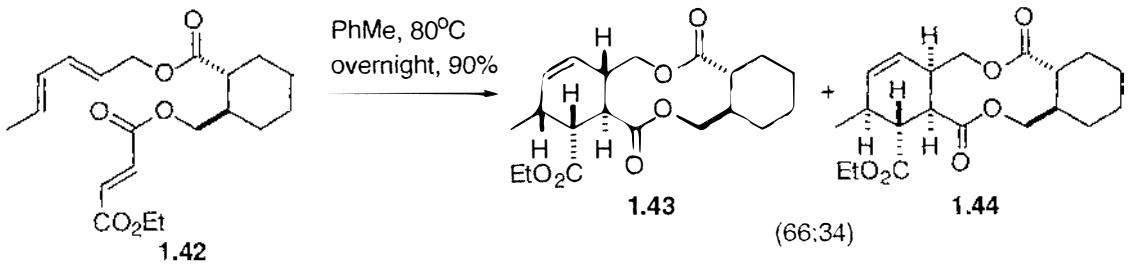
Excellent levels of both *exo/endo* (100:0) and π-diastereofacial (91:9) selectivity were achieved in this high yielding reaction (**Scheme 1.3**).[20]

Alternatively, as opposed to attaching a stereogenic centre to the diene, the dienophile can be substituted with a chiral element as in the study performed by Hoshino *et al.*[21] The Lewis acid-mediated IMDA reaction of triene **1.37** produced a mixture of two inseparable diastereoisomers **1.38** and **1.39** (**Scheme 1.4**). Removal of the chiral auxiliary and concomitant formation of the corresponding benzyl esters **1.40** and **1.41** allowed determination of the diastereoselectivity of the IMDA reaction. This IMDA reaction produced only the two *exo* diastereoisomers and exhibited a very high π-diastereofacial selectivity (98:2), albeit in moderate yield (55%).



Scheme 1.4

The stereoselectivity of the IMDA reaction can also be controlled including stereogenic elements on the ester tether. This is an option not available in the case of the intermolecular DA reaction. Craig and Gordon heated the triene ester **1.42** in toluene at 80°C, to give a mixture of diastereoisomers in high yield (**Scheme 1.5**).[22] Only two of the possible four diastereoisomers were produced from this reaction with a moderate level of selectivity shown towards the *exo* isomer **1.43** (66:34, *exo*:*endo*).



Scheme 1.5

1.5 Types Of Tethers Used In The IMDA Reaction

The connecting chain linking the diene and dienophile can have a profound effect on the rate and stereochemical outcome of the IMDA reaction. Properties of the tether such as the type of linking atoms, flexibility, ring strain, steric buttressing and electronic effects can all influence the rate and selectivity of the reaction.[16]

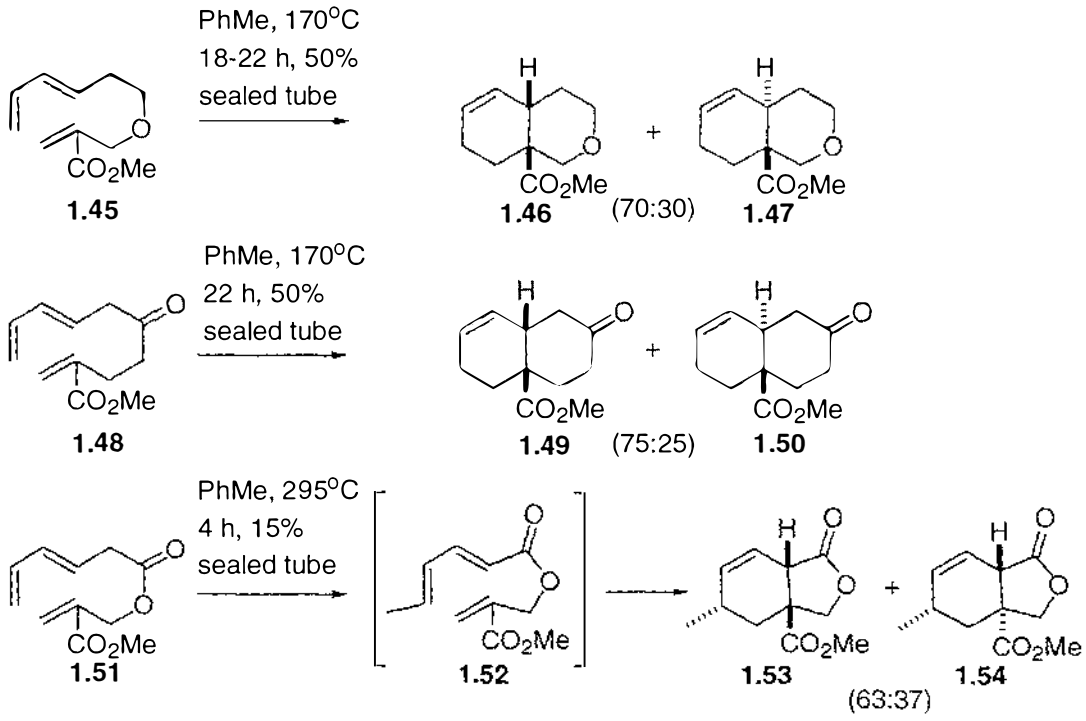
IMDA reactions carried out on substrates with acyclic all-carbon chains often give mixtures of *cis*- and *trans*-fused products, with a minimal selectivity towards the *trans*-fused cycloadduct. This is due to the high reaction temperatures needed for reaction of these non-activated systems.[9] The inclusion of a heteroatom in the tether has been found to influence both the rate and selectivity of the IMDA reaction. Examples of functional groups present in linking chains include amines, thioethers, ethers, amides and esters.

Replacing a methylene group in the tether of a simple triene system with an amine, ether or thioether has been shown to have little effect upon the rate and stereoselectivity of the IMDA reaction whilst replacement with an amide gives a significant differences.[10,16] These effects are due to the conformational preferences of the amide group. Nonatrienes with amide linkages show a preference for the *cis*-fused product as long as a terminal activating group is not present.[10] One of the simplest ways to link a diene and dienophile is with an ester group. Reactions to form esters are fast, facile and high yielding. However, the presence of an ester functionality in the tether often introduces reactivity problems which are discussed fully in the next section.

1.6 Ester-tethered IMDA Reactions

1.6.1 Problems Associated With The Use Of An Ester Tether

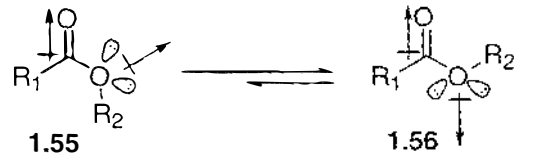
The utilisation of an ester linkage between diene and dienophile often has an adverse effect on the rate of the IMDA reaction with either a failure to cyclise or high temperatures needed for a successful reaction. Boeckman and Demko demonstrated that this lack of reactivity was due to the ester functionality rather than to the presence of an ether oxygen or a carbonyl group.[23] This was investigated in the series of IMDA reactions shown below (**Scheme 1.6**). Whereas ether-linked triene **1.45** and ketone-linked triene **1.48** both undergo IMDA reactions when heated in toluene at 170°C in sealed tubes to form the desired bicyclo[4.4.0] ring systems, triene ester **1.51** does not. Heating the ester-linked triene **1.51** in toluene in a sealed tube to 295°C results in an isomerisation to form the conjugated diene ester **1.52** which then cyclises to give the bicyclo[4.4.0]nonenes **1.53** and **1.54** in 15% yield.[23]



Scheme 1.6

The reduced reactivity of trienes with an ester tether in contrast to those with ether or ketone tethers could be partly due to the conformational requirements of the ester group in the transition state. Esters can adopt either an *s-cis* or *s-trans* conformation with the

s-trans conformer **1.56** being favoured for the great majority of esters (**Figure 1.11**).[24,25] Esters are more stable in the *s-trans* conformation **1.56** due, in large part, to a minimisation of dipole effects: the *s-cis* conformer **1.55** has the dipoles aligned and hence is the higher energy isomer.[24]

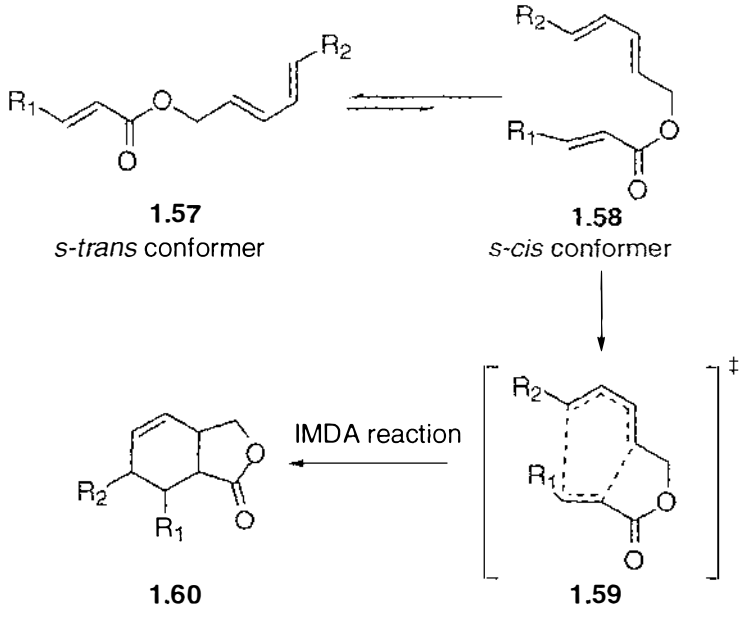


1.55 *s-cis* conformer

1.56 *s-trans* conformer

Figure 1.11

In order to achieve the necessary transition state for cyclisation, there must be a rotation about the ester bond to give the less favourable *s-cis* conformer **1.58** (the diene also needs to be in the *s-cis* conformation) (**Figure 1.12**).



1.57 *s-trans* conformer

1.58 *s-cis* conformer

1.60

1.59

Figure 1.12

Both experimental results and *ab initio* calculations show the barrier to rotation about the ester C-O bond to be 10-13 kcal mol^{-1} and the *s-trans* isomer to be more stable than the *s-cis* by 5-6 kcal mol^{-1}.[25] This energy difference ($\Delta H = \approx 5$-6 kcal mol^{-1}) means that at 25°C only 0.01% of triene **1.51** is in the conformation necessary for an IMDA reaction to occur. When the temperature is raised to 295°C, the percentage of reactive conformer is

still only 0.8%.* Obviously, the exact energy difference between the *s-trans* and *s-cis* conformers of any particular substrate is dependent on substitution, however, this significant energy difference between ester rotamers may explain the lack of reactivity of many ester-tethered trienes. The rate-reducing effect of an ester group is less pronounced when the ester group is placed such that it activates the dienophile. Singly activated trienes in which the carbonyl group of the ester tether is in conjugation with the dienophile will undergo an IMDA reaction if reasonably forcing conditions are used, *e.g.* the use of pressure and high temperature.[26,27]

Although the ester tether has been associated with a lack of reactivity (**Section 1.6.1**), there are a variety of examples of successful ester-linked IMDA reactions in the literature. Previous examples of IMDA reactions resulting in bicyclo[4.3.0]nonene systems are surveyed here. The defining features of these reactions include the following:

- They are Type 1 IMDA reactions (**Section 1.3.2**)
- The tethers linking the diene and dienophile consist of three atoms
- The carbonyl of the ester tether is in conjugation with the dienophile
- The diene is either acyclic or semicyclic with the ring remote from the tether

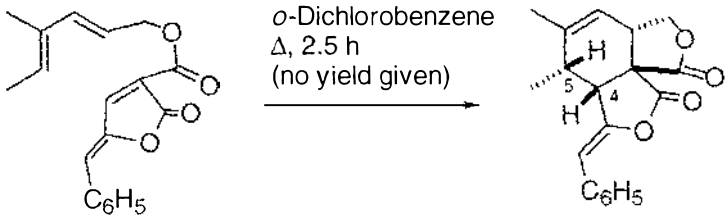
The focus of the following review is on the stereoselectivity of the ester-tethered IMDA reaction and on general features leading to increased reactivity. There is a detailed discussion of examples exhibiting π-diastereofacial selectivity in **Chapter 2**.

1.6.2 Examples With A Cyclic Dienophile

Weinreb and Auerbach constructed the isoindolane skeleton of the cytochalasins *via* an IMDA reaction.[28] The cytochalasins are microbial metabolites with unusual biological effects upon living cells. The stable crystalline ester **1.61** was heated in refluxing *o*-dichlorobenzene producing a crystalline tricyclic dilactone **1.62** (**Scheme 1.7**). The H4-H5 proton coupling constant (J = 7 Hz) supported a *cis* relationship between these protons. The stereochemistry of the cycloadduct, therefore, corresponds to an *endo* transition state. The dienophile is activated by conjugation with two carbonyl groups and conjugation to the styrene.

---

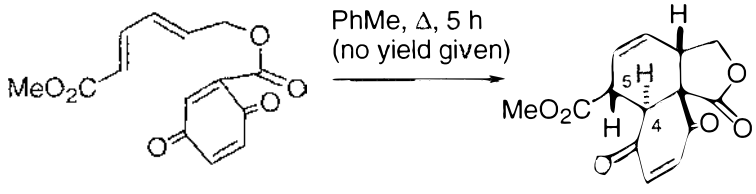
* Percentage of triene ester in the reactive conformer was calculated using the equation $K = e^{-(\Delta E/RT)}$, where K is the equilibrium constant between isomers; e = 2.718; ΔE = energy difference between isomers (cal); T = absolute temperature (Kelvin) and R = 1.986 cal/mol.K (the gas constant).



1.61 **1.62**

Scheme 1.7

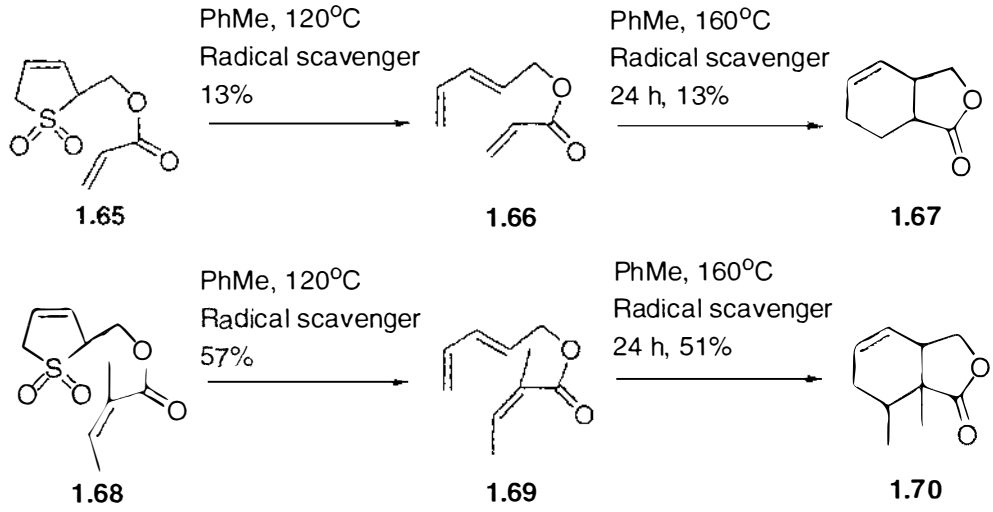
The IMDA reaction was used in model studies towards the total synthesis of myrocin C, an isolate from the soil fungus *Myrothecium verrucaria* exhibiting broad spectrum anti-microbial activity.[29] Danishefsky *et al.* heated quinone **1.63** in refluxing toluene for 5 h to produce cycloadduct **1.64** (**Scheme 1.8**). The coupling constant between the H4 and H5 protons of **1.64** (J = 10.8 Hz) indicated that, in contrast to the IMDA reaction of the related system studied by Weinreb and Auerbach, the quinone dienophile approaches the diene in an *exo* manner in the transition state of the intramolecular cycloaddition. In comparison to the system studied by Weinreb *et al.*, the dienophile of quinone **1.63** had both internal and peripheral activation, whilst the diene was substituted with an electon-withdrawing group.



1.63 **1.64**

Scheme 1.8

3-Sulfolenes were used as synthetic equivalents of 1,3-dienes in IMDA reactions by Lee *et al.*[30] Sulfolenyl esters **1.65** and **1.68** were heated to 120°C in toluene in sealed tubes, in the presence of 3-*t*-butyl-4-hydroxy-5-methylphenylsulfide, resulting in the cheleotropic elimination of SO_2 (**Scheme 1.9**). Subsequent IMDA reaction at 160°C gave **1.67** and **1.70** respectively. Unfortunately, no stereochemical information was provided in this paper.



Scheme 1.9

1.6.3 The Preference For *Trans*-fused Cycloadducts

Several research groups have found that *E*-dienes with three carbon atoms in the tether linking the diene and dienophile and an ester substitutent on the terminal carbon atom of the dienophile **1.71** cyclise preferentially *via* an *exo* transition state to yield *trans*-fused cycloadducts **1.72** (**Figure 1.13**). The reasons proposed for this preference for *trans*-fused cycloadducts are discussed later (**Section 2.6.1**).

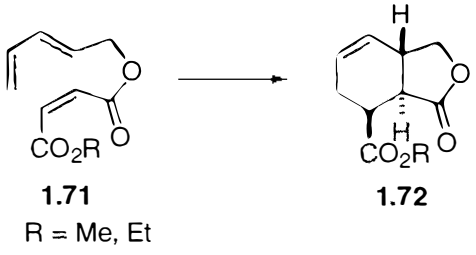
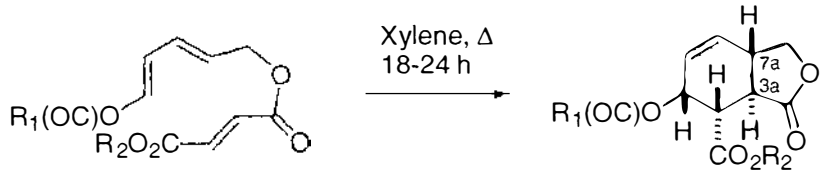


Figure 1.13

Becher and co-workers studied the series of esters **1.73-1.75**, which underwent cyclisation when heated to reflux in xylene (**Scheme 1.10**) producing only the corresponding *trans*-fused cycloadduct in each reaction.[31,32] In each case, the value of the coupling constant between the ring-junction protons (H3a-H7a) was 13 Hz. This large coupling constant is indicative of a *trans* ring junction.

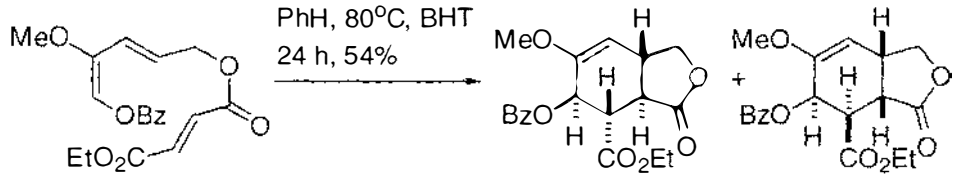


1.73 R_1 = Ph, R_2 = Et
1.74 R_1 = PhCH=CH, R_2 = Et
1.75 R_1 = Ph, R_2 = Me

1.76 R_1 = Ph, R_2 = Et 74%
1.77 R_1 = PhCH=CH, R_2 = Et 13%
1.78 R_1 = Ph, R_2 = Me 88%

Scheme 1.10

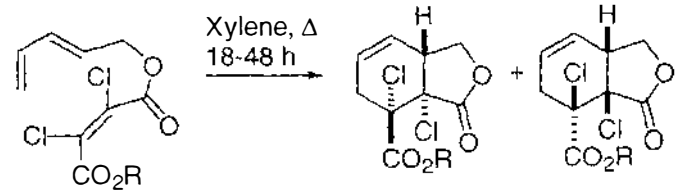
Similarly, the unstable triene **1.79** also showed a preference for the *trans*-fused product, with heating in benzene at 80°C for 24 h giving two cycloadducts **1.80** and **1.81** in 54% overall yield and a 70:30 *trans:cis*-fused ratio (**Scheme 1.11**).[33] The presence of the methoxy substituent was found to result in enhanced dienophile reactivity. It is unclear whether the formation of the *cis*-fused product in this case is due to the presence of the extra methoxy group on the diene or the alternative orientation of the benzoyloxy substituent.



1.79 **1.80** (70:30) **1.81**

Scheme 1.11

A preference towards *trans*-fused cycloadducts was shown in the IMDA reactions of the series of dichloromaleates investigated by Batchelor and Mellor (**Scheme 1.12**).[34,35]



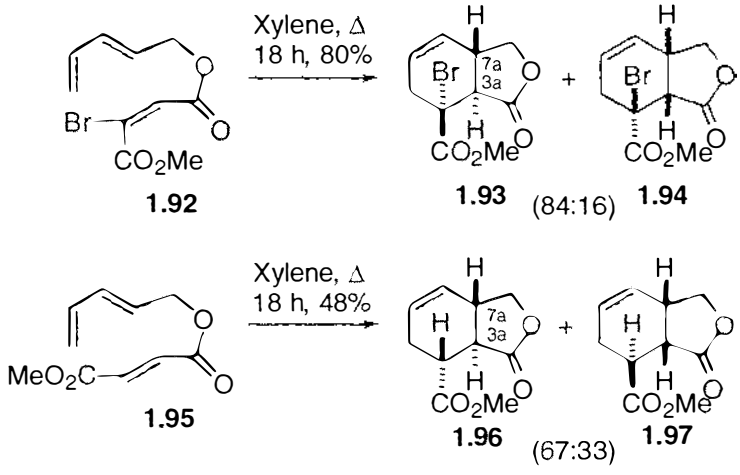
1.82 R = Me
1.83 R = CH_2Ph
1.84 R = CH_2CH_2TMS
1.85 R =

1.86 68%
1.87 51% **1.88** 6%
1.89 38% **1.90** 25%
1.91 33%

Scheme 1.12

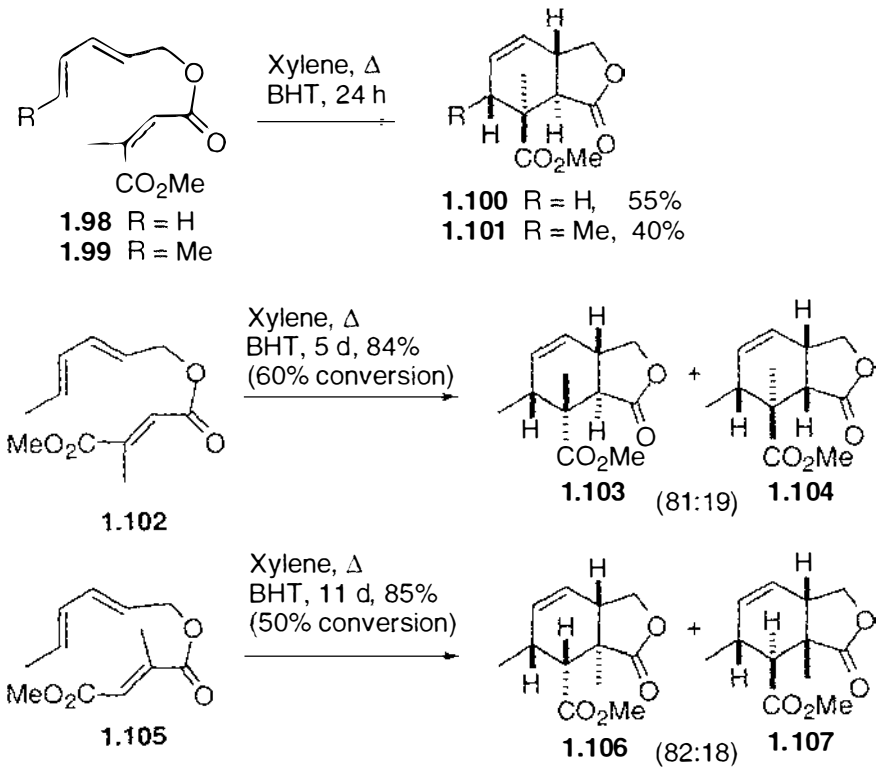
The greatest selectivity towards the *exo* transition state occurred in the cyclisations of **1.82** and **1.85**, R = Me and R = 3,4-methylenedioxybenzyl, with only a single adduct isolated in each case. The esters **1.83** and **1.84** also gave mainly the *trans*-fused products, however, in these two cases the *cis*-fused adducts were also formed as minor products.

Bromo ester **1.92** gave predominantly (84:16) the *trans*-fused product with heating to reflux in xylene for 18 h, producing lactones **1.93** and **1.94** in 80% yield (**Scheme 1.13**).[35] The IMDA reaction of the fumarate **1.95** was slightly less *trans* selective (67:33) and lower yielding (48% yield). The *trans*-fused adducts **1.96** and **1.97** showed a characteristic ring junction coupling constant of J = 13.5 Hz for protons H3a and H7a, whilst the *cis*-fused cycloadducts showed a much smaller coupling constant ($J_{H3a\text{-}H7a}$ = 7.0 Hz).



Scheme 1.13

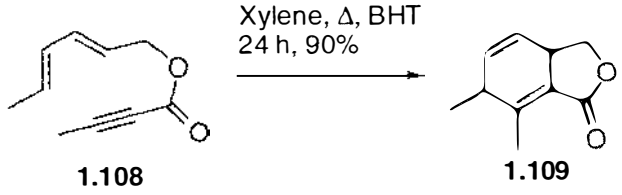
The triene esters **1.98** and **1.99** were heated to reflux in xylene for 24 h producing only the *trans*-fused product **1.100** and **1.101** in 55% and 40% yield respectively (**Scheme 1.14**).[36,37] Less selective were the IMDA reactions of triene esters **1.102** and **1.105**.[37] Both **1.102** and **1.105** proved considerably less reactive than **1.98** and **1.99**, presumably due to steric effects, with lengthy reaction times (5 days for **1.102** and 11 days for **1.105**) resulting in only partial conversion. The ratio of *trans*-fused:*cis*-fused adduct for the IMDA reaction of **1.102** (81:19) was comparable to that of **1.105** (82:18), showing that the placement of the methyl group on either carbon of the fumarate residue provides the same level of *endo/exo* stereoselectivity.



Scheme 1.14

1.6.4 Increased Reactivity Of Acetylenic Dienophiles

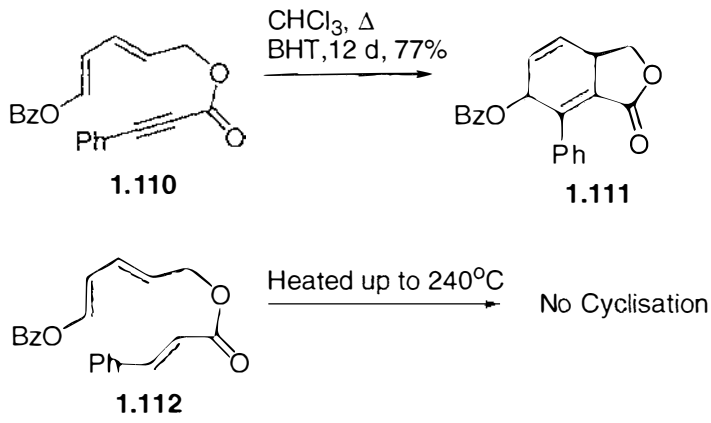
In comparison to the work described above (**Scheme 1.14**), an increased reactivity was seen in the IMDA reaction of the acetylenic substrate **1.108**.[37] Refluxing **1.108** in xylene for 24 h (a considerably shorter reaction time than that of the related alkenic examples) resulted in a 90% yield of cycloadduct **1.109** (**Scheme 1.15**).



Scheme 1.15

Becher *et al.* also investigated the effect of modifying the dienophile IMDA reactivity, comparing the IMDA reaction of *trans*-cinnamate **1.112** with that of the analogous acetylene **1.110** (**Scheme 1.16**).[31] The triene ester **1.112** failed to cyclise even when heated to 240°C. In contrast, the acetylene substrate **1.110** underwent cyclisation after

12 days in refluxing chloroform. This result emphasises the increased reactivity of an acetylenic dienophile over the *E*-alkene.

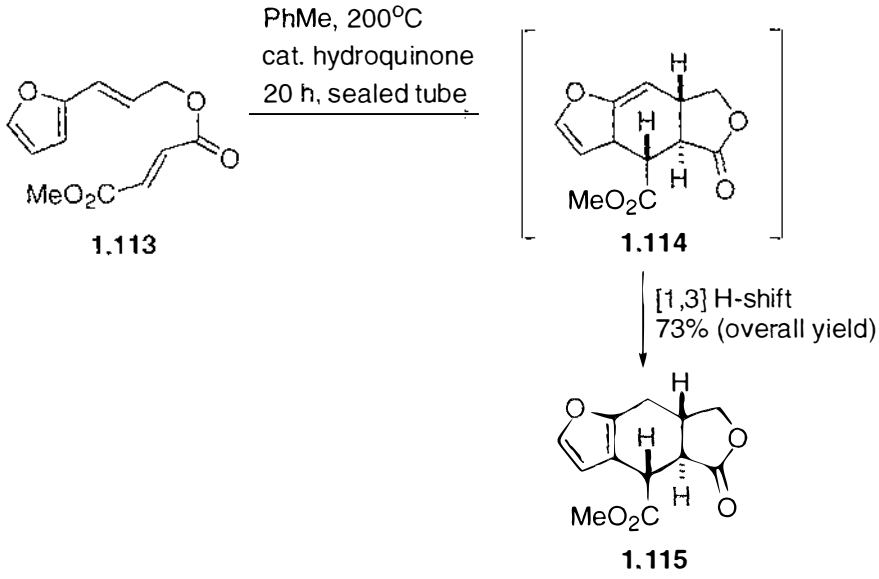


Scheme 1.16

1.6.5 Examples With Semi-Cyclic Dienes

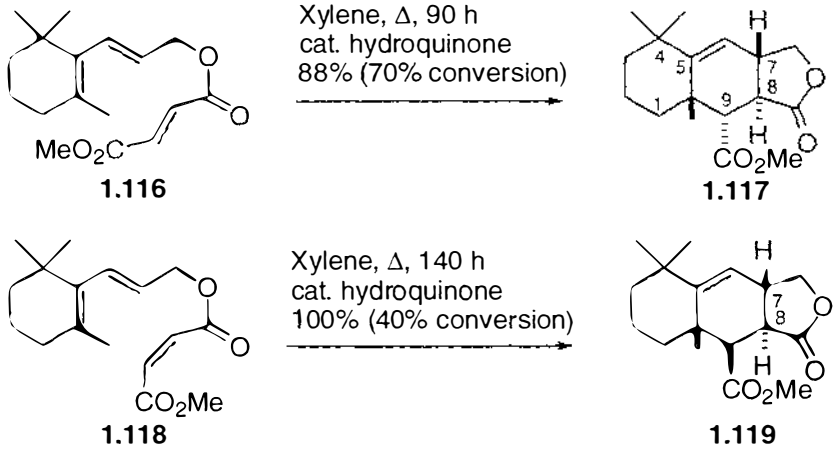
There are examples in the literature of ester-tethered IMDA reactions involving semi-cyclic dienes. The following examples have been included in this survey as the rings of the semi-cyclic dienes are remote to the tether and therefore should not restrict the conformation of the transition state.

A system with part of the diene moiety included in a furan ring was studied by Kotsuki *et al.* in an approach to benzofurans.[38] The acrylate precursors were unreactive,[38,39] however, fumarate precursors formed IMDA adducts in reasonable yield (**Scheme 1.17**). A coupling constant of J = 13.6 Hz for the lactone ring-junction hydrogens indicated a *trans* ring-junction geometry in the IMDA adducts.



Scheme 1.17

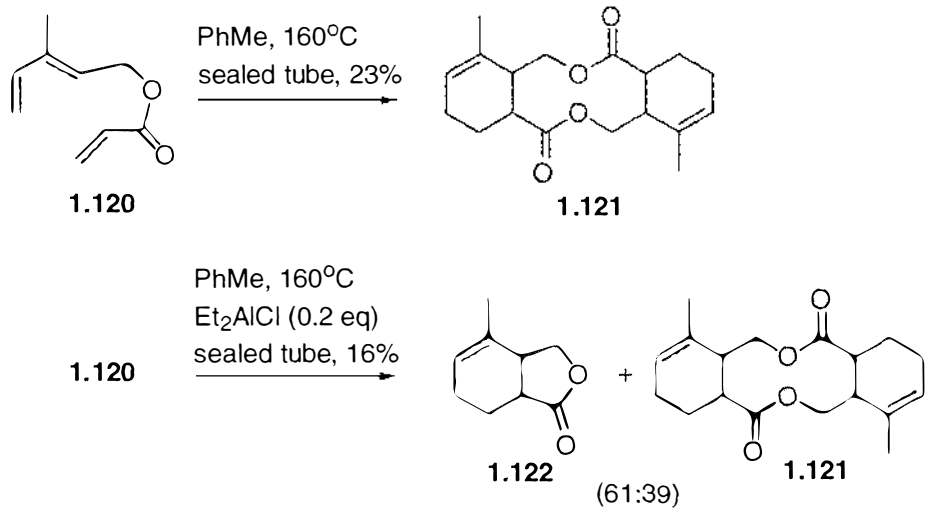
Attempts to cyclise **1.116** using acid catalysts such as zinc chloride, aluminium chloride and trifluoroacetic acid were unsuccessful, with no reaction taking place.[40] Heating the starting material in a sealed tube at 150°C was also unproductive, resulting in a messy reaction with a very low yield. However, heating both the β-ionone derived esters **1.116** and **1.118** to reflux in xylene with a catalytic quantity of hydroquinone yielded the adducts **1.117** and **1.119** respectively in good yield (**Scheme 1.18**). In line with the results of Kotsuki and co-workers,[38] a *trans* ring junction, and hence an *exo* transition state, was found to be formed exclusively in the IMDA reactions performed by Wu and He.[40] (The *trans* ring-junction was indicated by a coupling constant of J = 13.2 Hz between H7 and H8).



Scheme 1.18

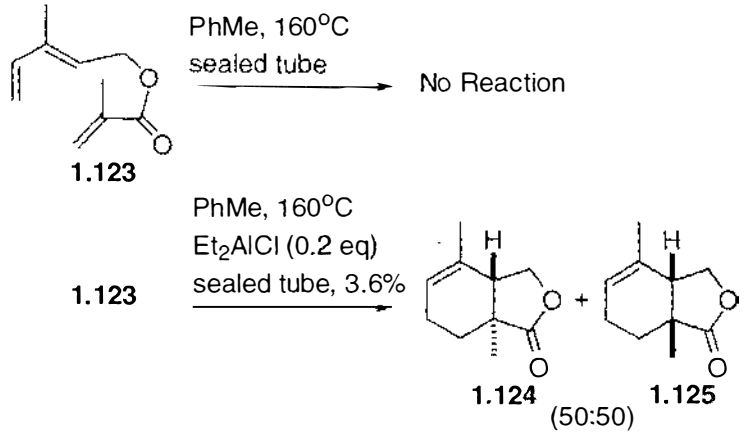
1.6.6 Lewis Acid Catalysis

The use of Lewis acid catalysts is prescribed for increasing both the rate and stereoselectivity of the DA reaction,[4] and research has been carried out regarding the applicability of Lewis acid catalysis to the ester-tethered IMDA reaction.[41] Heating a dilute solution of the unactivated triene ester **1.120** in toluene at 160°C resulted in the dimeric lactone **1.121** in 23% yield (**Scheme 1.19**).[41] When the reaction was repeated in the presence of a Lewis acid (Et_2AlCl), a 61:39 mixture of the *bis*-lactone **1.121** and the expected IMDA adduct **1.122** (no stereochemical information reported) resulted, albeit in low yield (16.4%).



Scheme 1.19

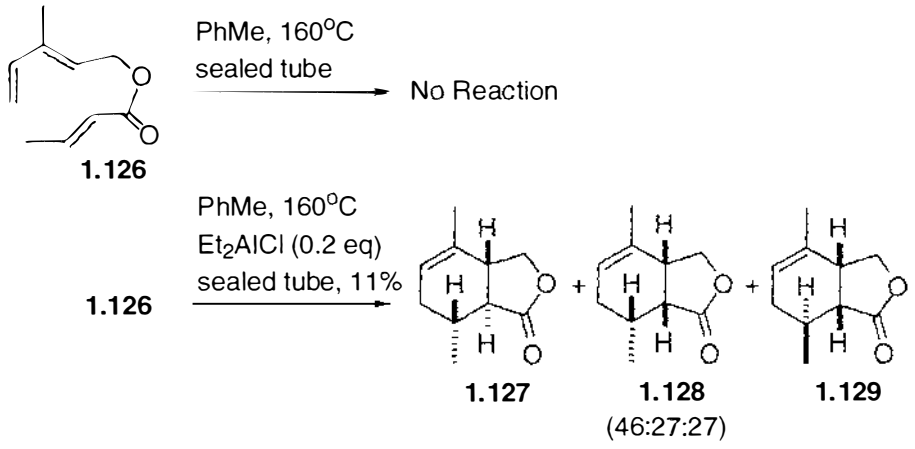
The more highly substituted ester **1.123** did not undergo reaction in toluene at 160°C (**Scheme 1.20**).



Scheme 1.20

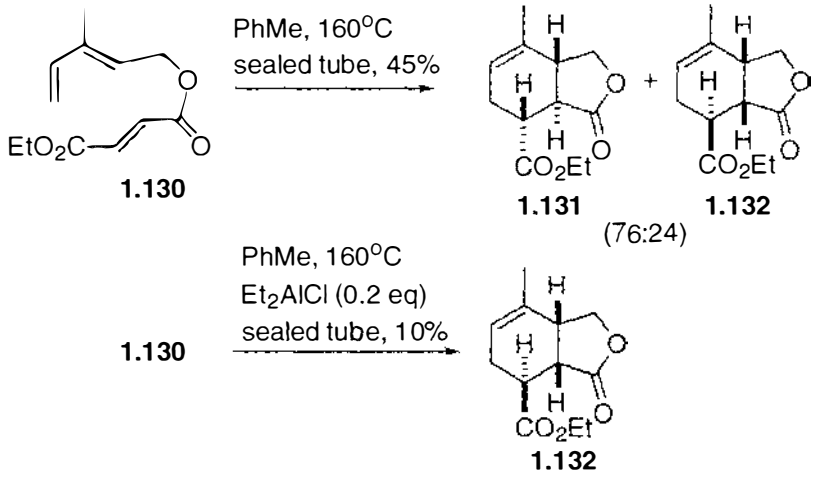
The addition of Lewis acid (Et_2AlCl) was necessary in order for cyclisation to occur, although the reaction was very low yielding.[41] The IMDA reaction of **1.123** produced a 50:50 mixture of *cis/trans*-fused cycloadducts **1.124** and **1.125**.

Triene ester **1.126** showed the same pattern of reactivity, with no reaction occurring in the absence of the Lewis acid and a low yielding IMDA reaction occurring in the presence of a Lewis acid (**Scheme 1.21**). The IMDA reaction of **1.126** showed a preference for the *trans*-fused adduct **1.127**.



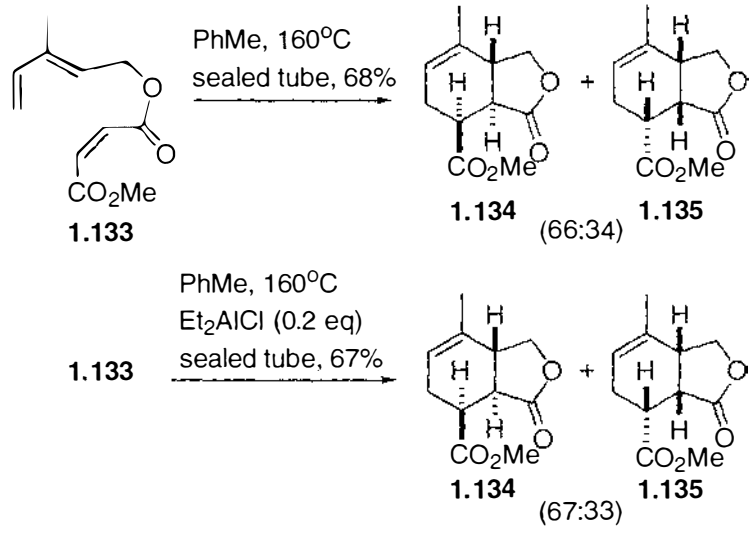
Scheme 1.21

It is interesting to note the increase in reactivity with the use of a terminal ester group. Fumarate derived ester **1.130** was heated in toluene at 160°C to yield a mixture of cycloadducts in 45% yield (**Scheme 1.22**).[41] The *trans*-fused adduct **1.131** was the major isomer (76:24). When the reaction was repeated in the presence of Et_2AlCl, only the *cis*-fused product **1.132** was formed and the yield was significantly lower (10%).



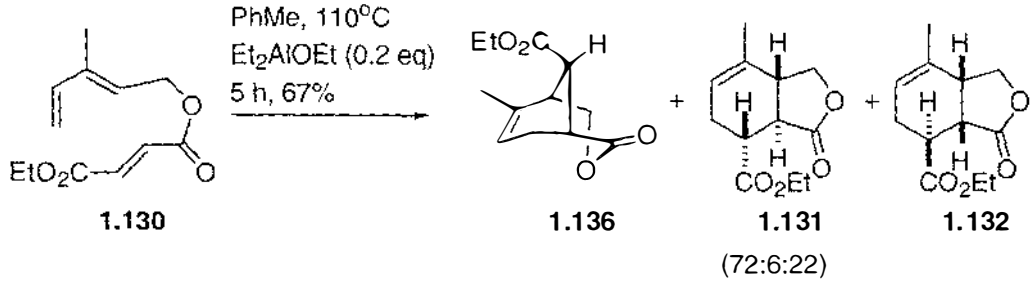
Scheme 1.22

Similarly, the maleate ester **1.133** showed an increased reactivity compared to the corresponding unactivated triene esters.[41] Maleate **1.133** was heated in toluene at 160°C resulting in a 66:34 mixture of *trans:cis*-fused cycloadducts **1.134** and **1.135** in 68% yield (**Scheme 1.23**). The use of Lewis acid (diethylaluminium chloride) appeared to have an insignificant effect on either the rate or the selectivity of the IMDA reaction.



Scheme 1.23

Changing the Lewis acid from diethylaluminium chloride to diethylaluminium ethoxide resulted in the formation of a cycloaddition-rearrangement product.[42] Heating the fumarate ester **1.130** in toluene at 110°C in the presence of diethylaluminium ethoxide for 5 h resulted in a mixture of IMDA adducts **1.131** and **1.132** and the major product, oxabicyclo[3.3.1]nonene **1.136** (**Scheme 1.24**). Fukumoto *et al.* proposed that the Lewis acid co-ordinated to the *trans*-fused IMDA adduct **1.131** with a subsequent cationic rearrangement giving the oxabicyclononene **1.136**.



Scheme 1.24

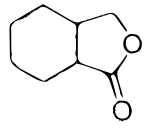
As the preceding examples attest, the use of Lewis acid catalysts in ester-linked IMDA reactions appears to be of little benefit to either the selectivity or the rate. In fact, in

general, higher yields were observed in the reactions performed in the absence of a Lewis acid.

1.6.7 Summary Of Previous Work

The examples above indicate the viability and scope of the ester-tethered IMDA reaction. Several trends can be delineated: an increase in rate when the dienophile is activated by terminal ester substitution, the preference for the *trans*-fused cycloadduct when the dienophile is terminally substituted with an ester functional group and the increased rate of cycloaddition of acetylenic dienophiles compared to the analogous alkenes.

1.7 Natural Products With The Hydroisobenzofuranone Nucleus

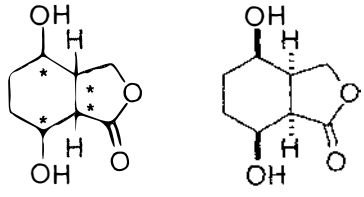


1.137

Figure 1.14

The bicyclo[4.3.0]nonane **1.137** (**Figure 1.14**) is a common component of many natural products with interesting biological activity. Selected examples containing this 6,5-ring system are included in this section with the examples being examined in order of increasing structural complexity.

Over fifty years ago, a lactone named garlicin was isolated from steam distillation residues of an aqueous garlic broth.[43] Garlicin was found to exhibit high anti-microbial activity against Lactobacillus and *Escherichia coli.* Zwergal proposed **1.138** as the structure of garlicin (**Figure 1.15**).



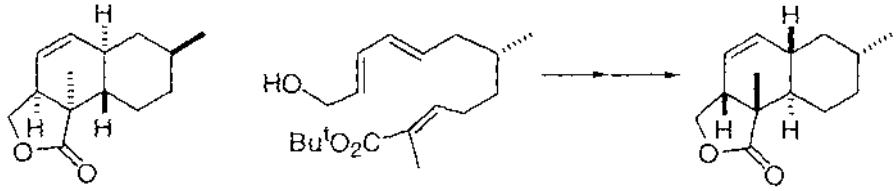
1.138
Garlicin

1.139

Figure 1.15

However, the stereochemistry of garlicin was not assigned and the four stereogenic centres in the molecule meant that the actual structure could have been one of eight possible diastereoisomers. Recently, a synthesis of garlicin was reported in which one of the eight possible diastereomers was synthesised using an intermolecular DA reaction as a key step in the synthetic sequence.[44] This compound **1.139** differed markedly in physical properties, *e.g.* solubility and melting point, to those reported previously for garlicin by Zwergal.

The structure of oblongolide, isolated from *Phomopsis oblonga* in low yield, has been determined to be the tricyclic lactone **1.140** (Scheme 1.25).[45] *P. oblonga* is a fungus frequently found in the outer bark of healthy elm trees with research showing that oblongolide is an effective deterrent for the elm bark beetle, which rejects trees treated with extracts from *P. oblonga.* A recent synthesis of oblongolide involved an IMDA reaction as a key reaction step.[46] The enantiomer of natural oblongolide was synthesised, allowing confirmation of the absolute stereochemistry of the natural isomer **1.142**.



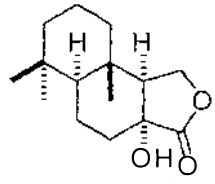
1.140
Oblongolide

1.141

1.142

Scheme 1.25

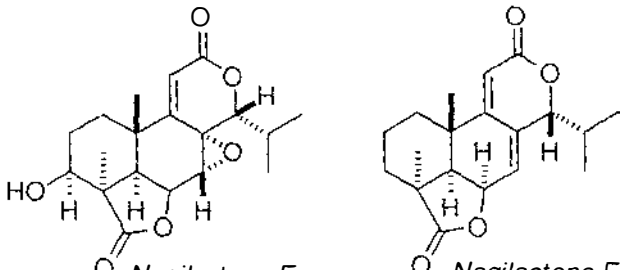
Another tricyclic lactone showing interesting biological activity is peniopholide **1.143**, the active compound from the fungus *Peniophora polygonia* (**Figure 1.16**).[47] *P. polygonia* is a wood staining fungus found on aspen trees which has shown an antagonism towards *Phellinus tremulae*, a fungus which causes tree rot in aspens. Peniopholide has been isolated and its structure assigned.



Peniopholide
1.143

Figure 1.16

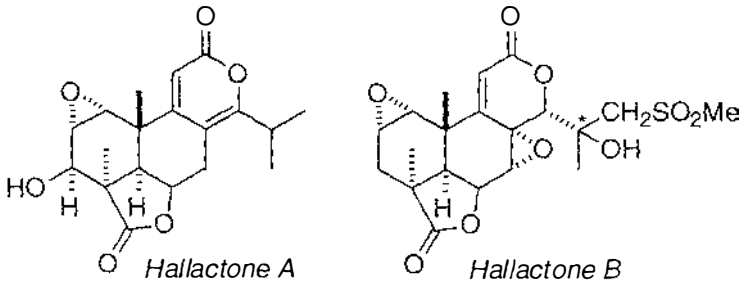
More complex polycyclic systems showing biological activity are the nagilactones, a group of nor- and bisnorditerpenoid dilactones which have been isolated from several Podocarpus species. Shown in **Figure 1.17** are nagilactones E **1.144** and F **1.145**. Both nagilactone E and F have shown inhibitory action as plant growth regulators.[48] In addition, nagilactone E has shown moderate antifungal activity against *Candida albicans*, *Saccharomyces cerevisiae* and *Pityrosporum ovale*.[48]



Nagilactone E **1.144** *Nagilactone F* **1.145**

Figure 1.17

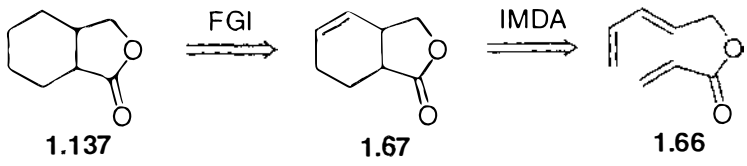
Hallactone A **1.146** and hallactone B **1.147** (**Figure 1.18**) were isolated from the leaves of *Podocarpus hallii* and their structures identified (the stereochemistry at the C* position was not assigned). Both have proved toxic to housefly larvae.[49]



Hallactone A **1.146** *Hallactone B* **1.147**

Figure 1.18

This small sample of natural products with interesting biological properties shows the wide variety of possible targets with a bicyclo[4.3.0]nonane functionality. An examination of the structure reveals, that after a functional group interconversion, an obvious route to these compounds is *via* an ester-tethered IMDA reaction (**Scheme 1.26**).



Scheme 1.26

The more complex tricyclic and tetracyclic examples require a more detailed and involved synthesis than merely a single IMDA reaction. One way of constructing such elaborate polycyclic systems in a quick, efficient manner would be to use two DA reactions in sequence, *i.e.* a tandem intramolecular DA (TIMDA) reaction. Attempts towards applying this methodology to the steroid framework are discussed in **Chapter 5**.

1.8 The Tandem DA Reaction

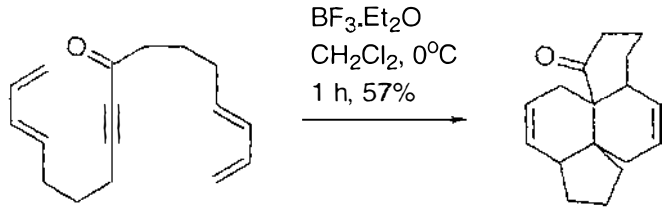
1.8.1 Introduction and Definitions

The goal of a synthetic chemist is to develop the ideal synthesis of a target compound. In a recent article, Wender stated that "Ideally, one would seek to design a synthesis in which the target molecule is made from readily available starting materials in one simple, safe, environmentally acceptable and resource-effective operation that proceeds quickly and in quantitative yield".[50] It can be argued that efficiency is one of the most important considerations when designing a synthesis. One method of increasing efficiency which is gaining in popularity is the use of "one pot" procedures. The more reaction steps a synthesis has, the more wasteful in terms of reagents and energy it is. Target molecules are usually made after a convoluted chain of chemical reactions which can use large amounts of solvents and raw materials whilst generating significant quantities of waste materials. In a one pot procedure, the reaction sequence is such that the first step creates the conditions necessary to trigger the next reaction *i.e.* there is no extraction and purification of the intermediate product. One pot procedures are gaining in prominence as a way of creating efficient syntheses.[50-53]

There are three subsets of the "one pot procedure". These have been referred to as tandem cascade, tandem consecutive and sequential reactions.[54]

- A *tandem cascade* reaction is defined as a process which involves two or more reactions in which the subsequent reaction occurs as a result of the functionality formed in the previous reaction with everything necessary for both reactions incorporated in the starting materials. The intermediate is not isolated as the reactions

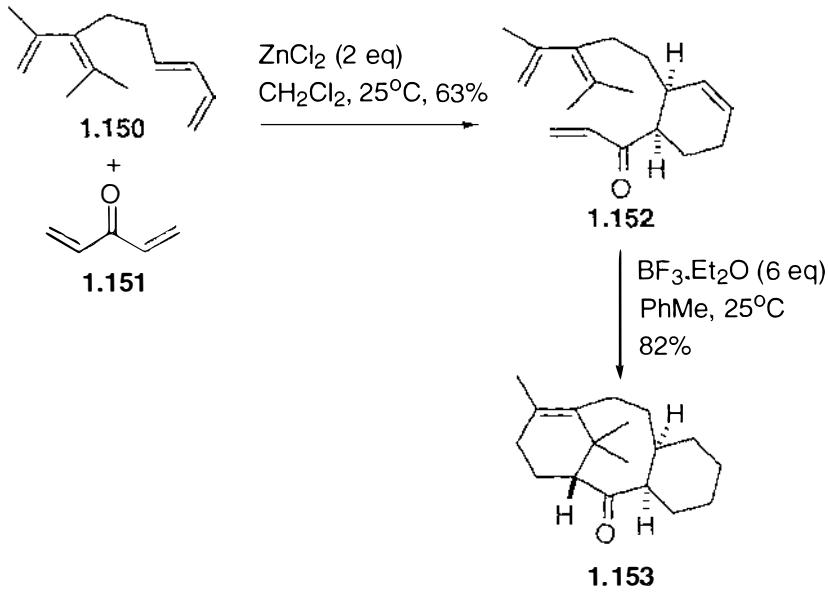
have similar rates. No additional components, reagents or changes in reaction conditions are necessary. The work of Giguerre *et al.* provides a good example of a tandem cascade DA reaction (**Scheme 1.27**).[55] The cascade reaction shown is stereoselective, producing only two of the four possible diastereoisomers (the sterochemistry of the products is not defined), and occurs under Lewis acid mediated conditions to give the tetracycle **1.149** in 57% yield.



1.148 **1.149**

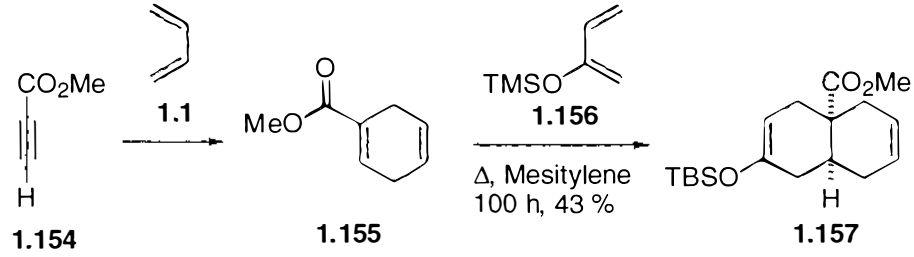
Scheme 1.27

- In a *tandem consecutive* reaction the intermediate can be isolated. The rates of the reactions are not comparable, with the rate of the second process being significantly slower than that of the first reaction. An additional reagent, catalyst or additional energy is required to effect the second reaction. An example of a consecutive reaction is work by Winkler *et al.* (**Scheme 1.28**).[56] The *bis*-diene **1.150** underwent an intermolecular reaction with *bis*-dienophile **1.151**. This DA reaction was mediated by zinc chloride and was highly regioselective due to the difference in reactivity of the mono- and tetra-substituted dienes. An IMDA reaction then occurred, in the presence of borontrifluoride etherate, to give the tricyclic product **1.153** as a single diastereisomer in 82% yield. This work represents the efficient synthesis of the taxane nucleus from two acyclic precursors in two steps with high relative stereocontrol. After the first DA reaction has occurred, the functionality is in place for the second IMDA reaction. Neither of the Lewis acids are capable of promoting both reactions.



Scheme 1.28

- *Sequential* reactions are those in which although the first reaction has created the required functionality, an additional reactant is required for the second reaction. An example of this is the work by Danishefsky *et al.* towards *dl*-vernolepin (**Scheme 1.29**).[57] The second DA reaction proceeds only after addition of the second diene **1.156**. Cycloaddition of 1,3-butadiene **1.1** with methyl propiolate **1.154** gave adduct **1.155**. This dienophile then reacted with diene **1.156** in refluxing mesitylene for 100 h to give **1.157** in 43% yield. Diene **1.156** is highly reactive and has given cycloadducts with dieneophiles previously considered poorly reactive.



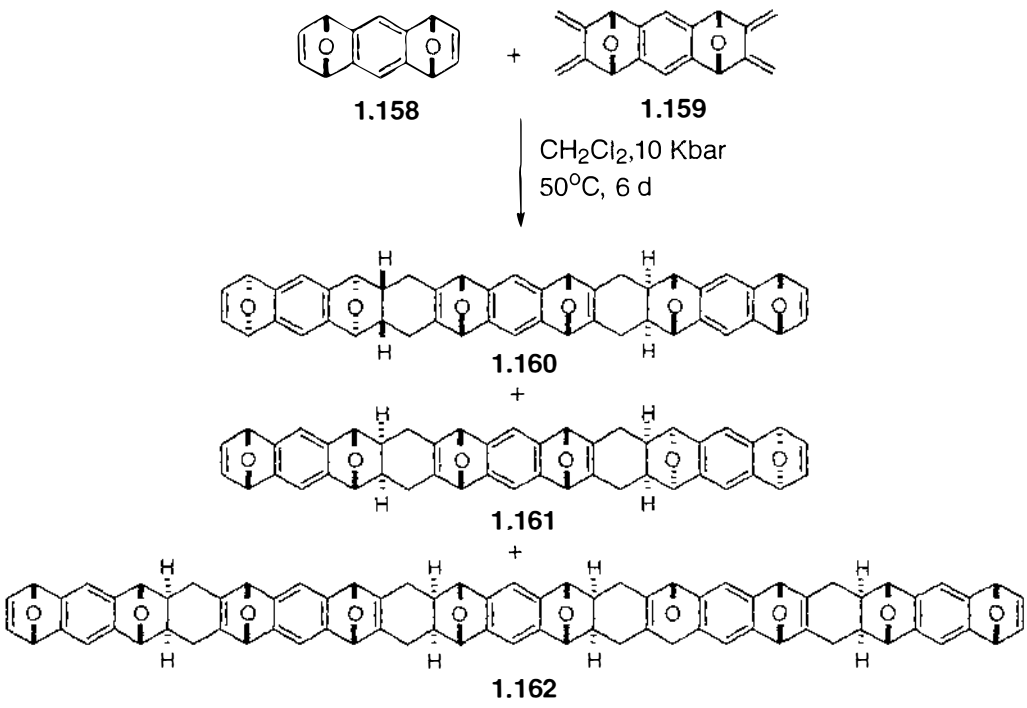
Scheme 1.29

The main foci of this review are the tandem cascade and tandem consecutive DA reactions. The following examples will illustrate sequences in which both reactions are intermolecular, those combining both intermolecular/intramolecular reactions and tandem intramolecular reactions.

1.8.2 Tandem Intermolecular DA Reactions

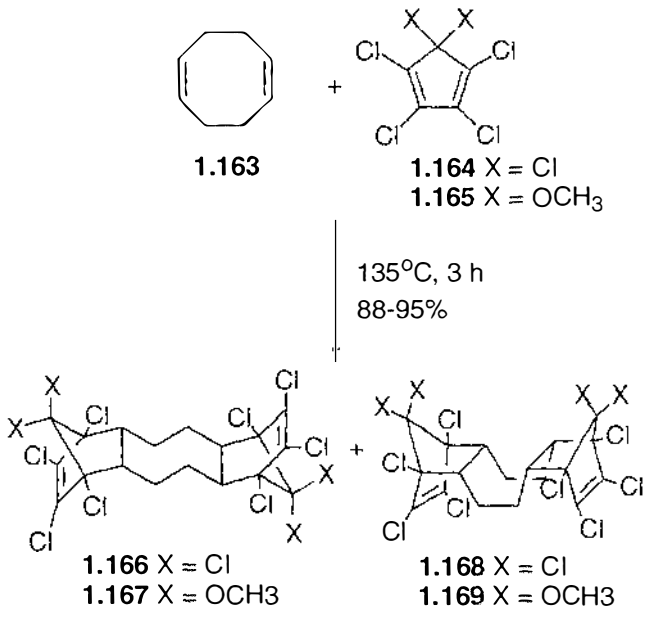
The following examples are of tandem DA reactions in which both of the DA reactions are intermolecular reactions.

An example of a tandem cascade reaction is that performed by Stoddart and co-workers in their investigations towards linear polyacenes (**Scheme 1.30**).[58] Two mole equivalents of the *bis*-dienophile **1.158** were reacted with the *bis*-diene **1.159** in CH_2Cl_2. After six days at 50°C and high pressure (10 Kbar) the major adducts **1.160**, **1.161** were produced along with **1.162** in trace amount.



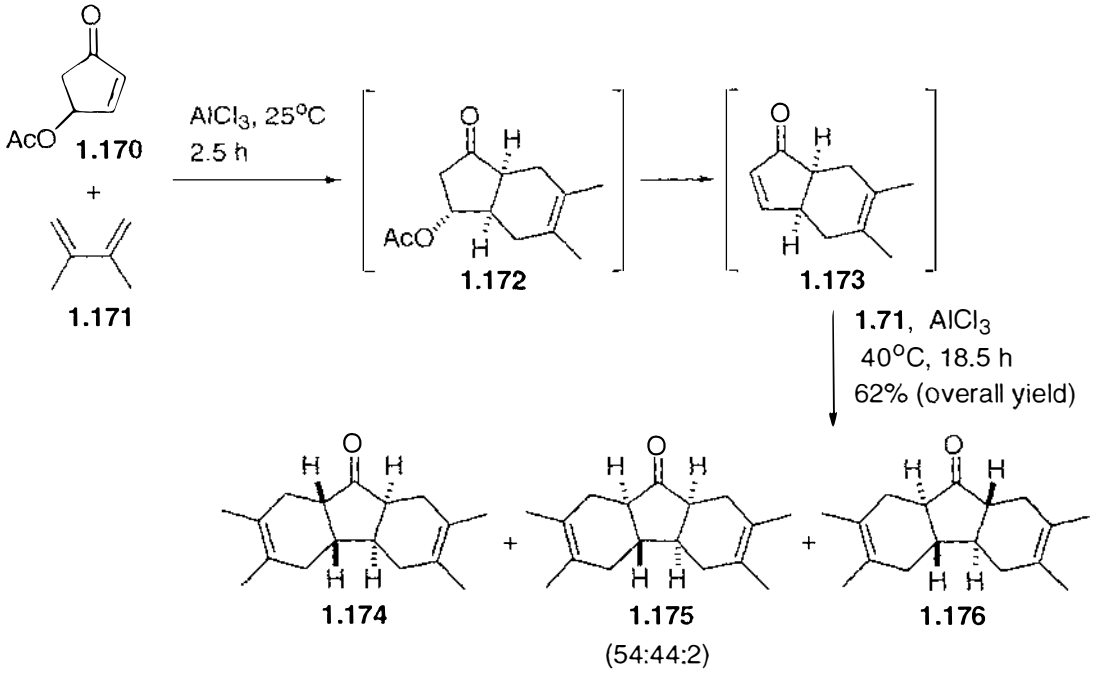
Scheme 1.30

Garcia *et al.* studied tandem cascade DA reactions of 1,5-cyclooctadiene **1.163** in order to investigate the stereochemical outcome.[59] Reaction of 1,5-cyclooctadiene **1.163** with excess hexachlorocyclopentadiene **1.164** or dimethoxytetrachlorocyclopentadiene **1.165** resulted in adducts **1.166**, **1.168** or **1.167**, **1.169** respectively (**Scheme 1.31**). The reactions were performed neat in **1.164** or **1.165** at 135°C and gave yields of 95% and 88% respectively. Only the *endo, endo*-DA *bis*-adducts were produced in this tandem cascade reaction.



Scheme 1.31

In their studies of a rapid approach to tricyclic molecules, Taticchi *et al.* studied the tandem sequential reactions of compounds such as **1.170** (**Scheme 1.32**).[60]

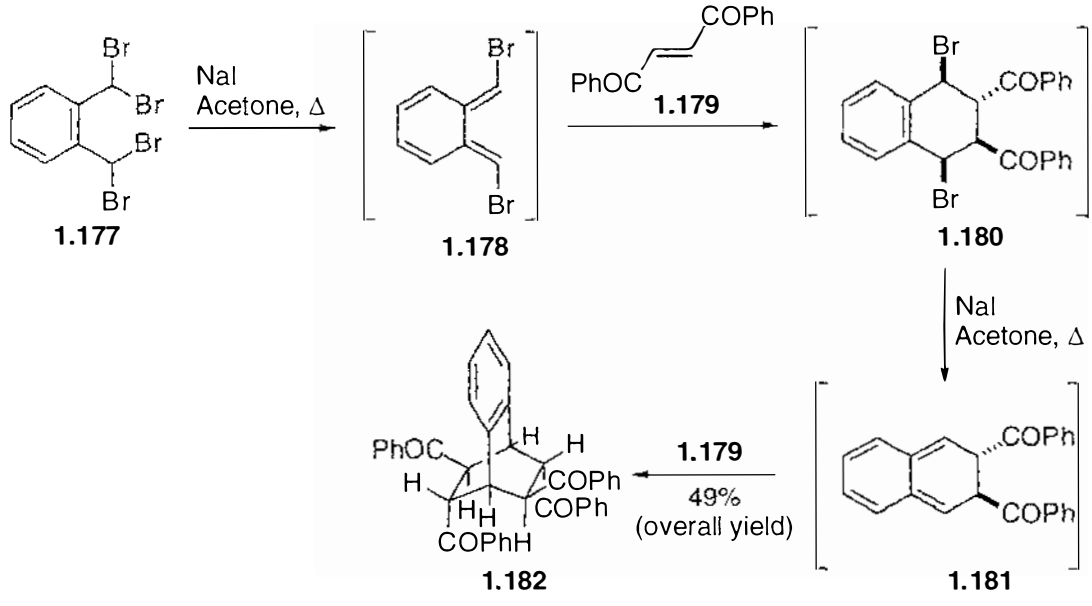


Scheme 1.32

4-Oxo-2-cyclopentenyl acetate **1.170**, 2,3-dimethyl-1,3-butadiene **1.171** and aluminium chloride were reacted at RT for 2.5 h to produce acetate **1.172**. Under these reaction conditions, **1.172** immediately underwent $AlCl_3$-induced β-elimination of acetic acid to

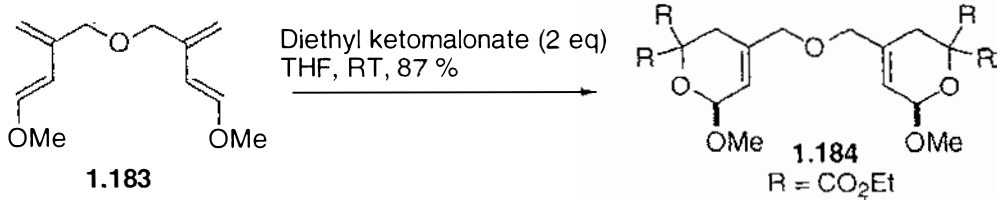
afford the dienophile **1.173** which then reacted with a second equivalent of 2,3-dimethyl-1,3-butadiene **1.171** at 40°C for 18.5 h to give a mixture of isomers **1.174**, **1.175** and **1.176** in a 54:44:2 ratio. Compounds **1.75** and **1.76** are epimers of **1.74**, the initial product of the tandem reaction.

When **1.177** was heated to reflux in acetone with excess 1,4-diphenyl-2-butene-1,4-dione **1.178** in the presence of excess sodium iodide, cycloadduct **1.182** was produced (**Scheme 1.33**).[61] Intermediate **1.178**, generated from **1.177**, underwent a DA reaction with the dienophile **1.179** to form an adduct **1.180** which then eliminated bromine to give the second intermediate **1.181**. This then readily underwent a second DA reaction with **1.179** to give the product **1.182**.



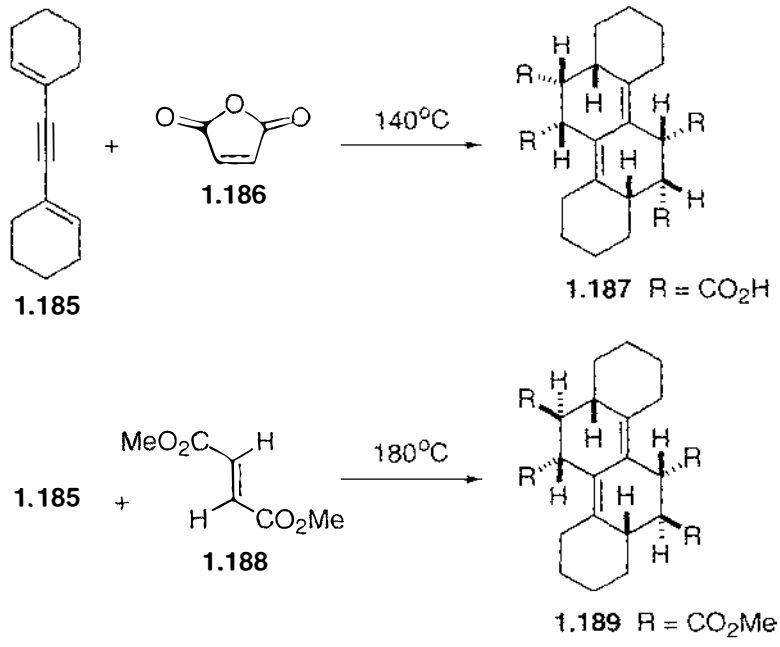
Scheme 1.33

The use of 1,4-dialkoxydienes as *bis*-dienes in tandem cascade reactions has been investigated by Duhamel *et al.*[62,63] An example of this work is the reaction between the highly reactive *bis*-diene **1.183** and diethyl ketomalonate to form the *bis*-heterocycle **1.184** (**Scheme 1.34**). Compounds such as **1.184** may have importance in a fast approach to pseudosaccharides, a class of biologically active compounds.



Scheme 1.34

Tandem intermolecular DA reaction of dienyne **1.185** with maleic anhydride **1.186** at 140°C, followed by hydrolysis of the anhydride functionality, gave the single tetracycle **1.187** (**Scheme 1.35**).[64] Reaction of **1.185** with dimethyl fumarate **1.188** at 180°C again gave a single adduct **1.189**. In both of these reactions, the dienophile approaches in an *endo* sense. The structures of both **1.187** and **1.189** were established by X-ray crystallography. The significance of these examples is that, in each case, six tetrahedral centres were formed stereoselectively during the tandem DA reactions.



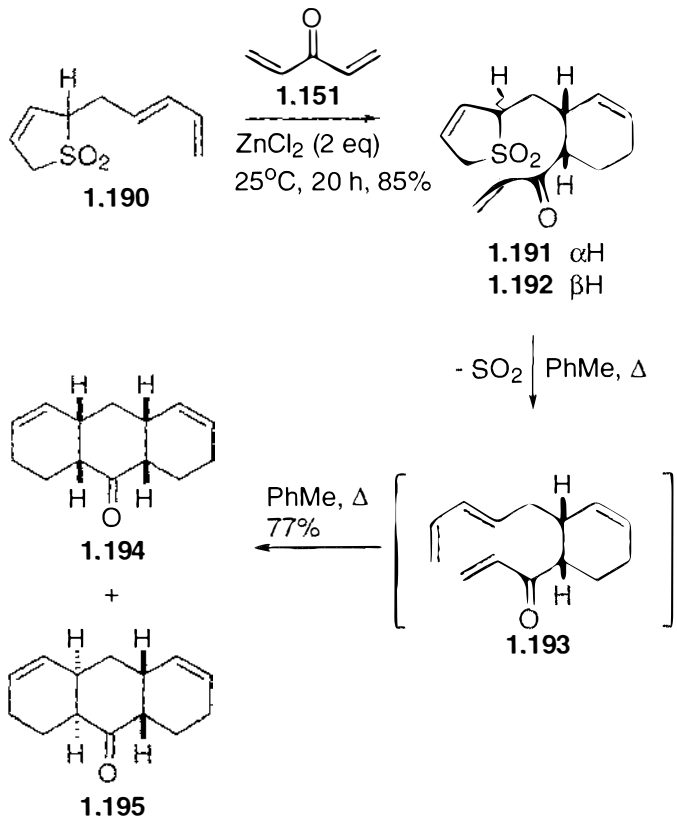
Scheme 1.35

1.8.3 Tandem Inter/Intramolecular DA Reactions

These are tandem reactions in which the first DA reaction is an *inter*molecular reaction, creating the functionality for the second *intra*molecular reaction.

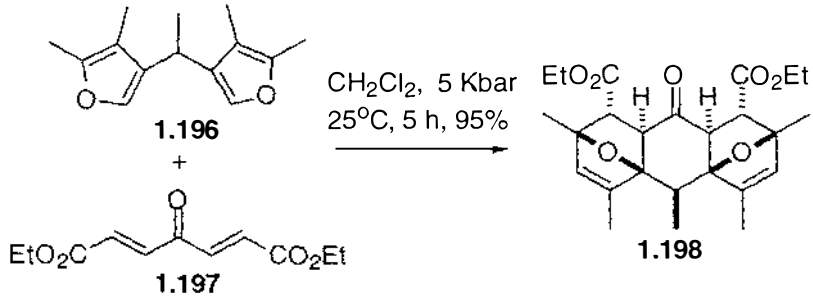
Winkler and co-workers synthesised a tricyclic ring system *via* a series of pericyclic reactions (**Scheme 1.36**).[65] An intermolecular reaction between diene **1.190** and *bis*-dienophile **1.151** gave the mono-Diels-Alder adducts **1.191** and **1.192** as a 48:52 mixture of diastereoisomers. The hydrogens at the ring-junction had a *cis* relationship in both diastereisomers due to an *endo* transition state during the DA reaction. Heating the mixture of adducts **1.191** and **1.192** in refluxing toluene resulted in the extrusion of sulfur dioxide and the subsequent IMDA of the unmasked diene with the internal dienophile. The IMDA reaction resulted in a 94:6 mixture of diastereomers **1.194** and

1.195 in 77% yield. A very similar reaction sequence, used to construct the tricyclic skeleton of the taxane nucleus, is described in **Section 1.8.1** (**Scheme 1.28**).[66]



Scheme 1.36

As part of their work towards a synthesis of the long-chain polypropionate fragments often found in natural products of biological interest, Vogel and Marchionni have investigated tandem cascade reactions.[67] An equimolar mixture of **1.196** and **1.197** was pressurised at 5 Kbar for 5 h (**Scheme 1.37**). This reaction was highly stereoselective with only a single product **1.198** being obtained in 95% yield.

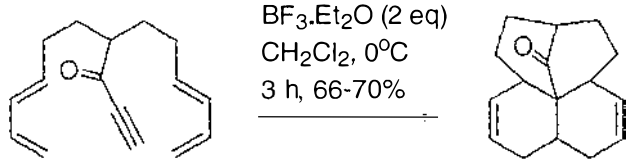


Scheme 1.37

1.8.4 Tandem Intramolecular DA (TIMDA) Reactions

There are very few examples of tandem DA reactions in which both reactions are intramolecular which is probably due to the synthetic effort required to build appropriate precursors.

In addition to the TIMDA reaction of the linear precursor **1.148** described previously (**Scheme 1.27**), Giguerre *et al.* investigated the reaction of the branched tetraalkene ketone **1.199** (**Scheme 1.38**).[55,68] A dilute solution (0.005 M) of the precursor **1.199** readily underwent a TIMDA reaction, mediated by borontrifluoride etherate, to give the tetracycle **1.200**. Two of the four possible diastereoisomers were produced, in equal amounts. Increased diastereoselectivity was observed at lower temperature.

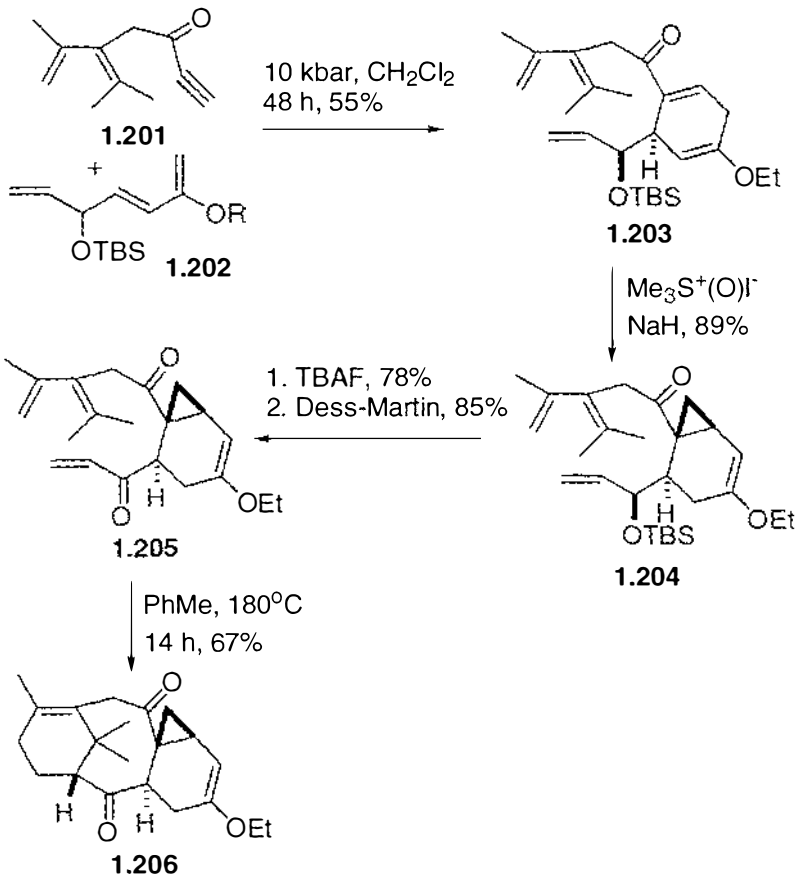


1.199 **1.200**

Scheme 1.38

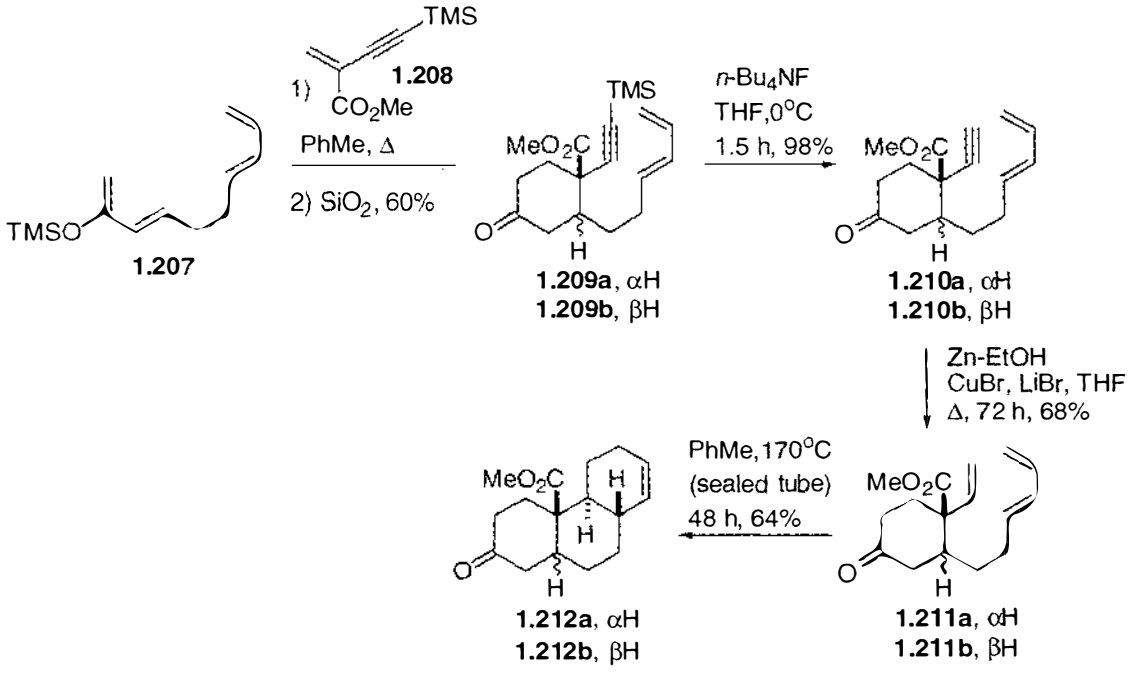
1.8.5 Tandem DA Strategies

As well as the tandem DA *reactions* described above, there are examples of tandem DA *strategies* in which the DA reactions are separated by one or more chemical transformations. Winkler *et al.* have used a tandem strategy to construct the taxane system (**Scheme 1.39**).[69] An intermolecular reaction between the acetylenic dienophile of **1.201** and triene **1.202** produces **1.203** as a 74:26 mixture of π-facial diastereoisomers. Reaction with dimethylsulfoxonium methylide gave the cyclopropane **1.204**. Desilylation and oxidation gave **1.205** which had sufficient reactivity to undergo an IMDA reaction in toluene at 180°C to yield adduct **1.206**. This example is best described as a tandem strategy rather than a tandem reaction as there are several individual chemical steps between the two DA reactions.



Scheme 1.39

Another example of a tandem DA strategy is the approach used by Spino and co-workers. towards the perhydrophenanthrene skeleton of steroids (**Scheme 1.40**).[70,71]



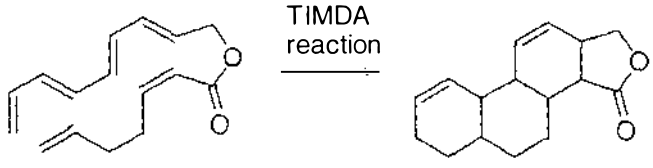
Scheme 1.40

In this example, the intermolecular DA reaction between tetraene **1.207** and *bis*-dienophile **1.208** was separated by several steps from the second IMDA reaction to form the product **1.212** (**Scheme 1.40**). The TMS group of **1.208** was intended to increase the *exo/endo* selectivity of the initial DA reaction and, in fact, both of the DA reactions in this synthesis showed a marked preference for the *trans*-fused isomers with the ratio of major:minor products being 5.8:1 (**1.212a**:**1.212b**).

1.9 Summary

There are many biologically active natural products with great potential for medicinal and other uses. In order to make these compounds available for testing and subsequent clinical use, efficient syntheses need to be designed. The DA reaction has long been used to construct the six-membered rings common to many natural products and now interest is focused upon the intramolecular variant of this reaction. The IMDA reaction has the potential to generate bicyclic ring systems in a single step and the ester-tethered IMDA reaction provides a method for the construction of the bicyclic lactone system common in many natural products.

Extension of the ester-tethered IMDA methodology would allow access to even more complex natural products. Linking two IMDA reactions together to create a TIMDA reaction could result in the formation of a tetracyclic system and up to 8 new stereogenic centres in a single reaction (**Scheme 1.41**). The utility of this methodology relies upon a thorough knowledge and understanding of the stereochemical factors of the IMDA reaction. This thesis is concerned with preliminary investigations towards the ester-tethered TIMDA reaction with the next chapter describing a model study of the stereochemical outcome of the ester-tethered IMDA reaction of a dienol.



1.213 **1.214**

Scheme 1.41

1.10 References

(1) *Stereoselectivity and Biological Activity of Drugs*; Ariens, E. J.; Soudijn, W.; Timmermanns, P. B. M. W. M., Eds.; Blackwell Scientific Publications, 1983.

(2) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

(3) Berson, J. A. *Tetrahedron* **1992**, *48*, 3-17.

(4) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741-761.

(5) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience, John Wiley and Sons: London, 1976.

(6) March, J. *Advanced Organic Chemistry*; 4th ed.; John Wiley and Sons Inc.: New York, 1992.

(7) Jäschke, A.; Frauendorf, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1378-1381.

(8) Eaton, B. E.; Tarasow, T. M.; Tarasow, S. L.; Tu, C.; Kellogg, E. *J. Am. Chem. Soc.* **1999**, *121*, 3614-3617.

(9) Ciganek, E. *Org. React.* **1984**, *32*, 1-374.

(10) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 513-550.

(11) Alder, K.; Schumacher, M. *Fortsch. Chem. Org. Naturst.* **1953**, *10*, 66-118.

(12) Klemm, L. H.; Gopinath, K. W. *Tetrahedron Lett.* **1963**, 1243-1245.

(13) Brieger, G. *J. Am. Chem. Soc.* **1963**, *85*, 3783-3784.

(14) Carlson, R. G. *Ann. Rep. Med. Chem.* **1974**, *9*, 270-279.

(15) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10-23.

(16) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene reactions*; Springer-Verlag: Berlin, 1984; Vol. 18.

(17) Magnus, P.; Walker, C. *Tetrahedron Lett.* **1986**, *27*, 651-654.

(18) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876-889.

(19) Yamamoto, H.; Ishihara, K.; Kurihara, H.; Matsumoto, M. *J. Am. Chem. Soc.* **1998**, *120*, 6920-6930.

(20) Lilly, M. J.; Sherburn, M. S. *Chem. Comm.* **1997**, 967-968.

(21) Hoshino, O.; Ishizaki, M.; Hara, Y.; Kojima, S. *Heterocycles* **1999**, *50*, 779-790.

(22) Craig, D.; Gordon, R. S. *Tetrahedron Lett.* **1998**, *39*, 8337-8340.

(23) Boeckman Jr., R. K.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789-1792.

(24) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley-Interscience, John Wiley and sons: New York, 1994, p 618-620.

(25) Bassindale, A. In *The Third Dimension in Organic Chemistry*; John Wiley and sons: 1984, p 72-78.

(26) White, J. D.; Nolen, E. G., Jr.; Miller, C. H. *J. Org. Chem.* **1986**, *51*, 1150-1152.

(27) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187-238.

(28) Weinreb, S. M.; Auerbach, J. *J. Org. Chem.* **1975**, *40*, 3311-3312.

(29) Danishefsky, S. J.; Chu-Moyer, M. Y.; Schule, G. K. *J. Am. Chem. Soc.* **1994**, *116*, 11213-11228.

(30) Lee, H. W.; Lee, W. B.; Lee, I.-Y. C. *Bulletin of the Korean Chemical Society* **1994**, *15*, 448-452.

(31) Becher, J.; Nielsen, H. C.; Jacobsen, J. P.; Simonsen, O.; Clausen, H. *J. Org. Chem.* **1988**, *53*, 1862-1871.

(32) Becher, J.; Ingendoh, A.; Clausen, H.; Nielsen, H. C. *Tetrahedron Lett.* **1985**, *26*, 1249-1252.

(33) Becher, J.; Jorgensen, T.; Nielsen, H. C.; Malhotra, N. *J. Heterocyl. Chem.* **1992**, *29*, 1841-1845.

(34) Batchelor, M. J.; Mellor, J. M. *Tetrahedron Lett.* **1985**, *26*, 5109-5112.

(35) Batchelor, M. J.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 985-995.

(36) White, J. D.; Sheldon, B. G.; Solheim, B. A.; Clardy, J. *Tetrahedron Lett.* **1978**, *52*, 5189-5192.

(37) White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273-2280.

(38) Kotsuki, H.; Kawamura, A.; Ochi, M.; Tokoroyama, T. *Chem. Lett.* **1981**, 917-920.

(39) Fraser-Reid, B.; Benko, Z.; Guiliano, R.; Sun, K. M.; Taylor, N. *J. Chem. Soc., Chem. Commun.* **1984**, 1029-1030.

(40) He, J.-F.; Wu, Y.-L. *Tetrahedron* **1988**, *44*, 1933-1940.

(41) Toyota, M.; Wada, Y.; Fukumoto, K. *Heterocycles* **1993**, *35*, 111-114.

(42) Toyota, M.; Wada, Y.; Nishikawa, Y.; Wada, T.; Fukumoto, K. *Heterocycles* **1994**, *38*, 1491-1496.

(43) Zwergal, A. *Die Pharmazie* **1948**, *7*, 245-256.

(44) Nour, R. A.; Schneider, K.; Urban, E. *Liebigs Annalen Chemie* **1992**, *56*, 383-386.

(45) Begley, M. J.; Grove, J. F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 861-863.

(46) Shing, T. K. M. *J. Chem. Soc., Chem. Commun.* **1996**, 49-50.

(47) Ayer, W. A.; Trifonov, L. S. *J. Nat. Prod.* **1992**, *55*, 1454-1461.

(48) Hayashi, Y.; Yokoi, J.; Watanabe, Y.; Sakan, T.; Masuda, Y.; Yamamoto, R. *Chem. Lett.* **1972**, 759-762.

(49) Russell, G. B.; Fenemore, P. G.; Singh, P. *J. Chem. Soc., Chem. Commun.* **1973**, 166-167.

(50) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, 765-769.

(51) Hall, N. *Science* **1994**, *266*, 32-34.

(52) Bradley, D. *Chem. Ind.* **1996**, 46.

(53) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3-30.

(54) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266-8277.

(55) Giguerre, R. J.; Hansen, J. A.; Goldberg, D. R. *Tetrahedron Lett.* **1993**, *34*, 8003-8006.

(56) Winkler, J. D.; Kim, H. S.; Kim, S.; Ando, K.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 2957-2962.

(57) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 6066-6075.

(58) Stoddart, J. F.; Ashton, P. R.; Isaacs, N. S.; Kohnke, F. H.; Mathias, J. P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1258-1261.

(59) Garcia, J. G.; Fronczek, F. R.; McLaughlin, M. L. *Tetrahedron Lett.* **1991**, *32*, 3289-3292.

(60) Taticchi, A.; Minuti, L.; Selvaggi, R. *Tetrahedron* **1993**, *49*, 1071-1078.

(61) Cava, M. P.; Parraka, J. P.; Sadanandam, E. V. *J. Org. Chem.* **1994**, *59*, 4308-4310.

(62) Duhamel, L.; Guillam, A.; Maddaluno, J. *Chem. Comm.* **1996**, 1295-1296.

(63) Duhamel, L.; Martin, C.; Maddaluno, J. *Tetrahedron Lett.* **1996**, *37*, 8169-8172.

(64) Miller, B.; Ionescu, D.; Silverton, J. V.; Dickinson, L. C. *Tetrahedron Lett.* **1996**, *37*, 1559-1562.

(65) Winkler, J. D.; Kim, S.; Condroski, K. R.; Asensio, A.; Houk, K. *J. Org. Chem.* **1994**, *59*, 6879-6881.

(66) Winkler, J. D.; Kim, H. S.; Kim, S. *Tetrahedron Lett.* **1995**, *36*, 687-690.

(67) Vogel, P.; Marchionni, C. *Tetrahedron Lett.* **1996**, *37*, 4149-4152.

(68) Giguerre, R. J.; Brodney, M. A.; O'Leary, J. P.; Hansen, J. A. *Synth. Comm.* **1995**, *25*, 521-531.

(69) Winkler, J. D.; Holland, J. M.; Peters, D. A. *J. Org. Chem.* **1996**, *61*, 9074-9075.

(70) Spino, C.; Crawford, J. *Tetrahedron Lett.* **1994**, *35*, 5559-5562.

(71) Spino, C.; Crawford, J.; Bishop, J. *J. Org. Chem.* **1995**, *60*, 844-851.

2. MODEL STUDIES ON A DIENOL

2.1 Introduction

As discussed in **Chapter 1**, many naturally occurring biologically active compounds contain the hydroisobenzofuranone framework (**Section 1.7**). A powerful method for constructing this bicyclic lactone is by utilising the IMDA reaction of an ester-linked triene **1.66** (**Figure 2.1**). In order for the method to be synthetically useful, the IMDA reaction must be stereoselective.

Figure 2.1

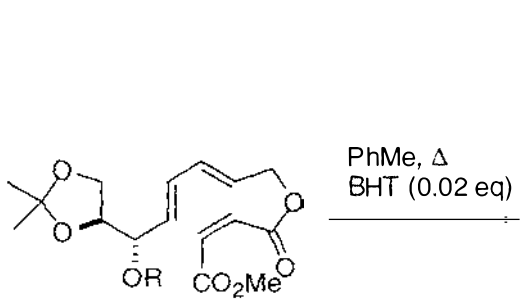
2.1.1 Previous Studies Of Stereocontrol In The Ester-Tethered IMDA Reaction

Methods of inducing stereoselectivity in the IMDA reaction have been described in **Section 1.4.1**. The main area of relevance to the research in this thesis is the incorporation of a stereogenic centre containing a sterically demanding group on the ester tether, although some examples of remote sterocontrol will also be discussed.

2.1.1.1 Ester-Tethered IMDA Reactions With Remote Stereocontrol

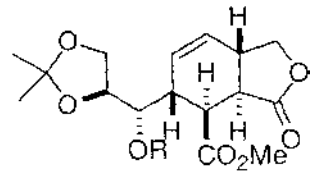
Placement of a stereogenic centre remote to the ester tether has been used to successfully induce stereocontrol in the IMDA reaction. The *trans*-fused isomer was the major adduct in each IMDA reaction in the maleate dienophile series studied by Lilly and Sherburn.[1] Enantiopure triene esters of the type **2.1** were heated to reflux in toluene to give mixtures of two *trans*-fused diastereoisomers **2.2** and **2.3** (**Scheme 2.1**). Stereocontrol was induced in the IMDA reaction by protecting the allylic secondary alcohol as silyl ethers of varying size. The free hydroxyl substrate exhibited only a modest diastereofacial preference (66:34), whereas the most sterically demanding protecting group, the triisopropyl ether, produced a very high level of stereocontrol (96:4). This work

demonstrates the high level of stereocontrol resulting from incorporation of a stereogenic centre on the diene remote to the diene-dienophile tether. It is important to note that, due to the starting materials being single enantiomers, the synthesis of the bicyclic lactone system is enantiodirected.



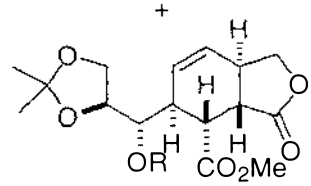
2.1

PhMe, Δ
BHT (0.02 eq)



Major diastereoisomer **2.2**

+

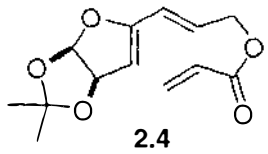


Minor diastereoisomer **2.3**

R	Yield	major:minor
H	86%	(66:34)
Me_3Si	67%	(82:18)
$^tBuMe_2Si$	80%	(91:9)
$^iPr_3Si$	68%	(96:4)

Scheme 2.1

Previously, Fraser-Reid *et al.* had investigated the feasibility of remote stereocontrol in the IMDA reactions of semi-cyclic dienol esters derived from diacetone glucose. The first substrate studied was acrylate **2.4** which, when heated in toluene, yielded only decomposed starting material with no evidence of a Diels-Alder adduct (**Scheme 2.2**).[2]

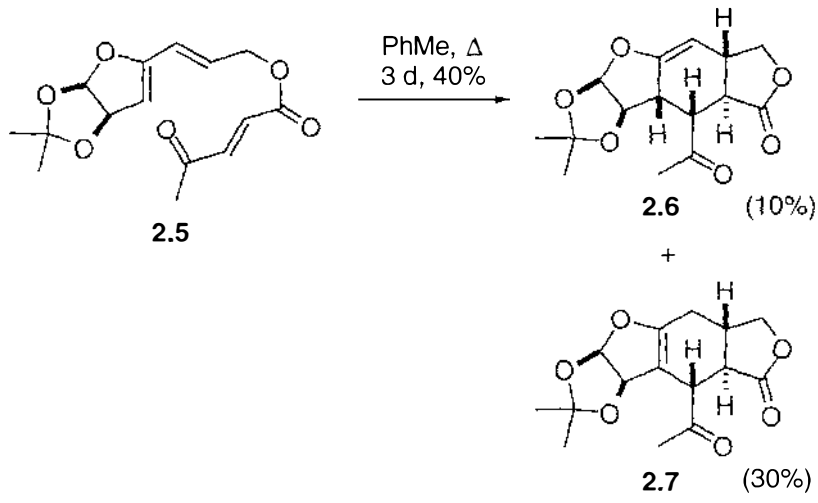


2.4

PhMe, Δ → Decomposition

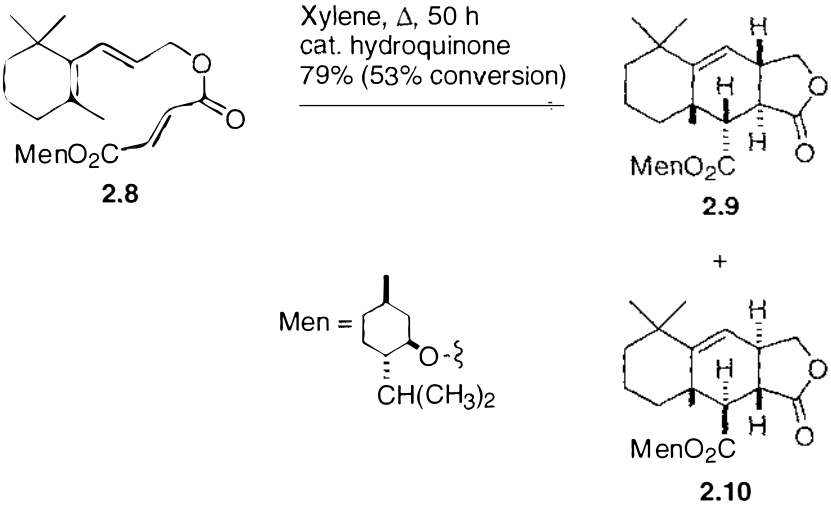
Scheme 2.2

Heating the more activated precursor **2.5** in toluene for three days gave a complex mixture containing the isomeric products **2.6** and **2.7** in 10% and 30% yields respectively (**Scheme 2.3**). The minor adduct **2.6** was produced diastereoselectively by the IMDA reaction and then isomerised, under the reaction conditions, to the major product **2.7**. The high π-facial selectivity was caused by the dioxolane group blocking dienophile approach from one face of the molecule.



Scheme 2.3

Wu and He introduced stereogenic centres at the dienophile terminus of β-ionone derived substrate **2.8** in order to effect asymmetric induction in the IMDA reaction.[3] Refluxing menthyl ester **2.8** in xylene containing a catalytic amount of hydroquinone gave two diastereoisomers **2.9** and **2.10** in 79% yield (**Scheme 2.4**). The ratio of **2.9** to **2.10** was 64:36, indicating that the chiral element on the dienophile imparted only a moderate degree of diastereoselectivity upon the IMDA reaction. The IMDA reaction proceeded exclusively *via exo* transition states, however, with both products possessing *trans*-fused ring junctions.

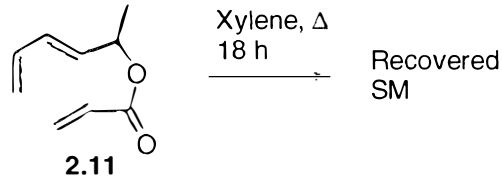


Scheme 2.4

2.1.1.2 The Use Of Tether Substituent-Directed Facial Stereocontrol In The Ester-Tethered IMDA Reaction

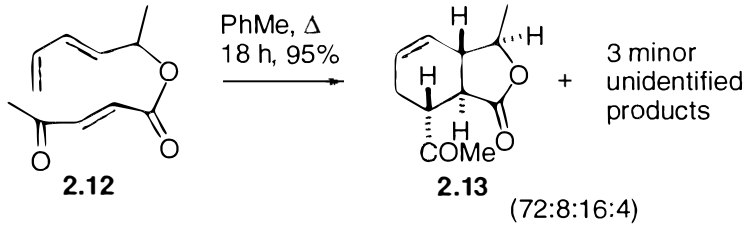
A major goal of the work described in this thesis is to control the stereochemical outcome of the IMDA reaction. The purpose of the model study detailed in this Chapter was to investigate methods of inducing stereocontrol in the IMDA reaction using a tether substituent. The following literature examples are those in which a degree of stereoselectivity has been imparted upon the IMDA reaction *via* a substituent on the ester tether linking the diene and dienophile.

Birtwhistle *et al.* investigated the stereoselectivity of the IMDA reactions of simple ester-linked diene and dienophile fragments in work directed towards the stereoselective synthesis of substituted cyclohexanes.[4] Attempts to cyclise the singly activated acrylate ester **2.11** in refluxing xylene proved unsuccessful, resulting only in the recovery of unreacted starting material (**Scheme 2.5**).



Scheme 2.5

This result (in line with Fraser-Reid's observations (**Scheme 2.2**)) led to an investigation into more reactive dienophilic components. Racemic ester **2.12**, containing a dienophile further activated by terminal ketone substitution, underwent an IMDA reaction after refluxing in toluene for 18 h to give four cycloadducts (72:16:8:4) with a mass balance of 95% (**Scheme 2.6**).

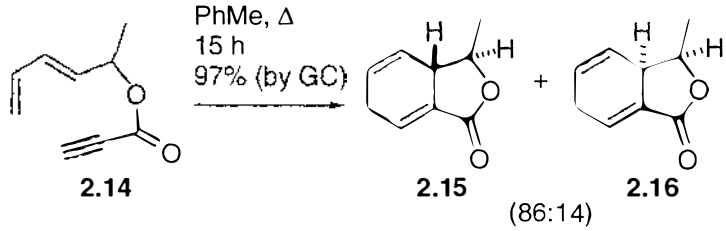


Scheme 2.6

The major component **2.13** was isolated by gas chromatography but no other pure

products were obtained, the workers noting that there were four diastereoisomeric cycloadducts from this reaction.

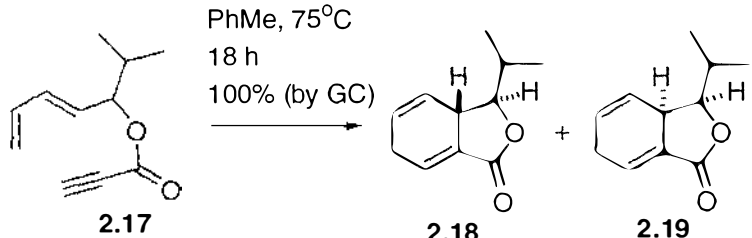
The enhanced reactivity of acetylenic dienophiles was emphasised by propynoate **2.14** undergoing an IMDA reaction in refluxing toluene (*c.f.* triene **2.11**). The racemic propynoate **2.14** gave an 86:14 mixture of bicyclic lactones **2.15** and **2.16** in 97% yield (**Scheme 2.7**). The 86:14 ratio of major to minor isomer shows that the methyl substituent imparted a good degree of facial selectivity upon the IMDA reaction. Interestingly, repeating the reaction at RT with increased pressure (19 kbar, 18 h) resulted in a loss of selectivity yielding a 75:25 mixture of **2.15** and **2.16** (100% yield by GC; not isolated).



2.14 **2.15** **2.16** (86:14)

Scheme 2.7

Increasing the steric bulk of the subsituent on the tether from a methyl to an isopropyl group was found to result in increased π-facial stereoselectivity, with thermal cyclisation of racemic propynoate ester **2.17** leading to a 97:3 mixture of **2.18** and **2.19** (**Scheme 2.8**).

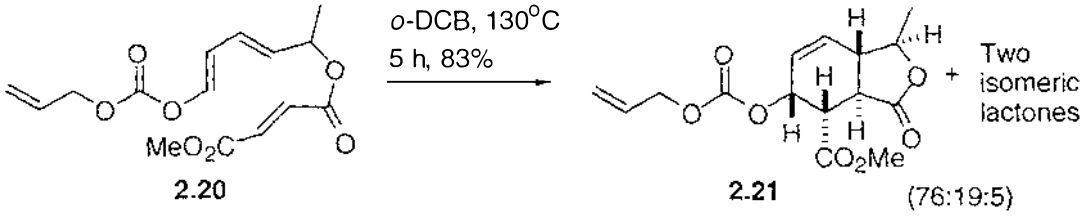


2.17 **2.18** **2.19** (97:3)

Scheme 2.8

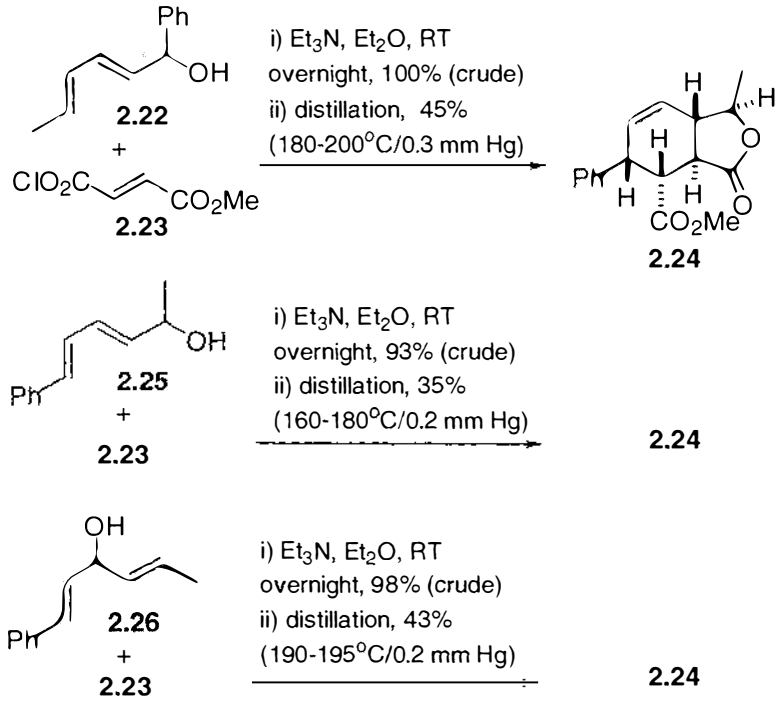
The authors concluded that acetylenic substrates were more reactive than their alkenic counterparts and that increased steric bulk of a tether substituent corresponded with increased π-facial selectivity in the IMDA reaction. In all three substrates studied, the IMDA reactions gave a major diastereoisomer resulting from cycloaddition to the same diastereofaces of the diene and dienophile.

Uguen *et al.* investigated the use of a stereocontrolling element on the ester tether in an approach to the brassinosteroids, a class of natural steroids with plant growth-regulating properties. The IMDA reaction of racemic fumarate **2.20**, in which a methyl substituent is present in the ester tether, resulted in a mixture of three isomers in a 76:19:5 ratio and 83% yield.[5] The major diastereoisomer **2.21** was formed *via* an *exo* transition state as evidenced by the *trans*-fused ring junction. The stereochemistries of the two minor cycloadducts were not elucidated, therefore π-facial and *endo/exo* selectivities cannot be quantified. It is clear that the stereoselectivity of this oxygenated diene is the same as that of the unsubstituted system (compare **Scheme 2.6** and **Scheme 2.9**).



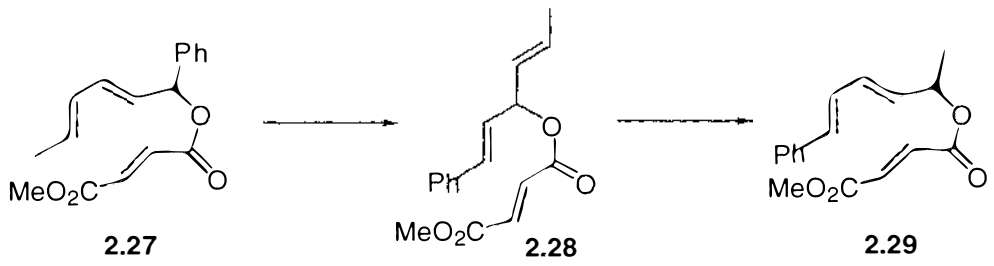
Scheme 2.9

Eberle and Weber esterified the isomeric phenylhexadienols **2.22**, **2.25** and **2.26** with the acid chloride of methyl hydrogen fumarate **2.23** to produce crude esters which, upon distillation in a Kugelrohr apparatus, gave the same cycloadduct **2.24** (**Scheme 2.10**).[6]



Scheme 2.10

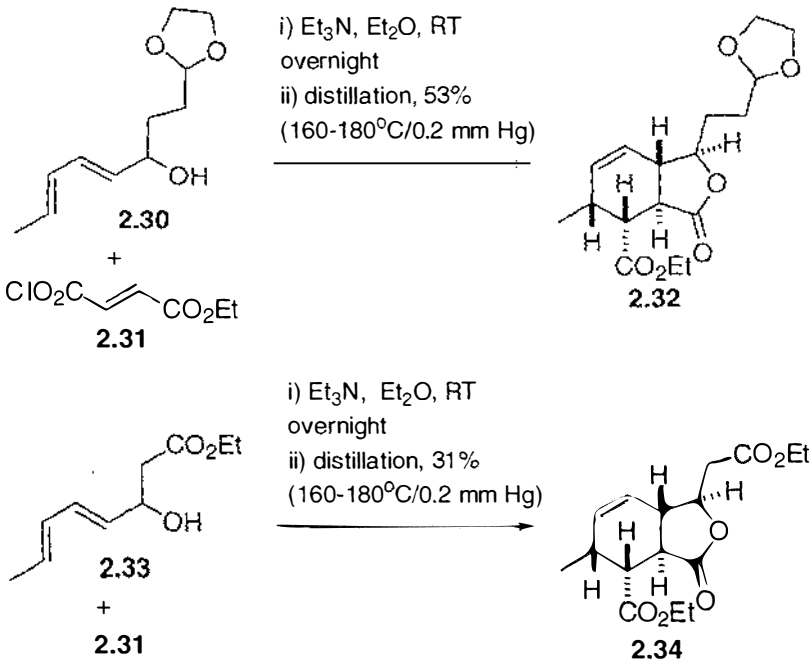
The intermediate non-cyclised triene esters were not isolated, however Eberle and Weber concluded that the isomeric esters **2.27** and **2.28** rearranged, *via* [3,3] sigmatropic shifts, to give ester **2.29** before cyclising (**Scheme 2.11**).



Scheme 2.11

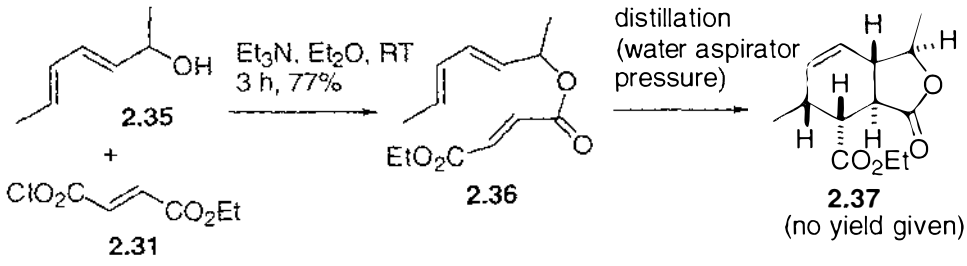
The methyl substituent in the ester linkage of **2.29** provided facial-stereocontrol in the IMDA reaction. While the stereochemistry of the product obtained by Eberle is the same as the major product obtained by Birtwhistle, the isolation of only one stereoisomer from this IMDA reaction does not appear to be consistent with the work of Birtwhistle.

Other substituents also resulted in stereocontrolled IMDA reactions. Alcohols **2.30**, **2.33** and **2.35** were esterified and then subjected to distillation, producing a single *trans*-fused isomer in each case (**Scheme 2.12**). The starting materials were racemic with the resultant cycloadducts existing as enantiomeric mixtures.



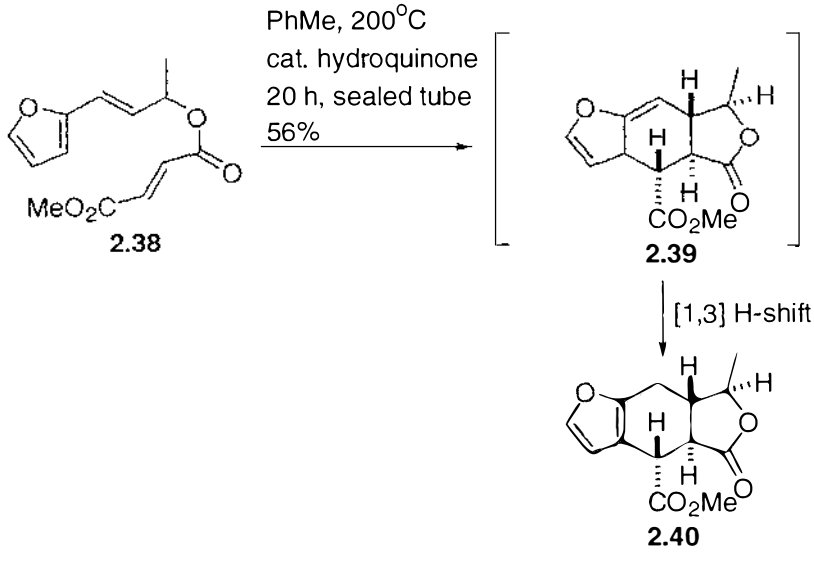
Scheme 2.12

The authors noted, interestingly, that triene **2.36** distills without IMDA reaction at 110-120°C under high vacuum (**Scheme 2.13**).



Scheme 2.13

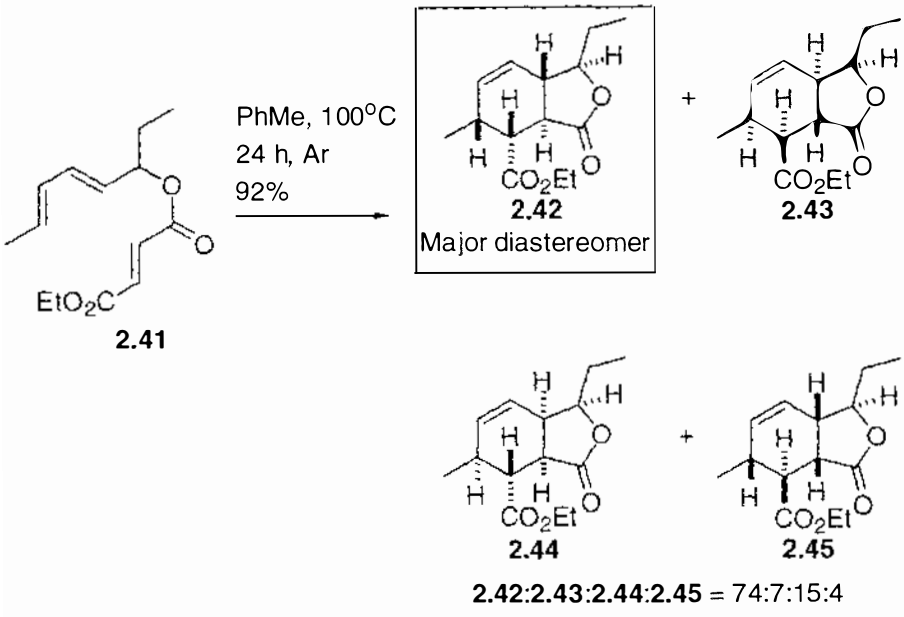
Kotsuki and co-workers investigated IMDA reactions involving a vinyl furan diene.[7] The racemic fumarate ester **2.38** was heated in toluene in a sealed tube to yield the tricyclic product **2.40**, the result of an IMDA reaction to form **2.39** followed by a [1,3] hydrogen shift (**Scheme 2.14**). Once again, the IMDA reaction occurred *via* the *exo* transition state and showed π-facial selectivity. In line with the observations of other groups, the corresponding acrylate ester was unreactive.



Scheme 2.14

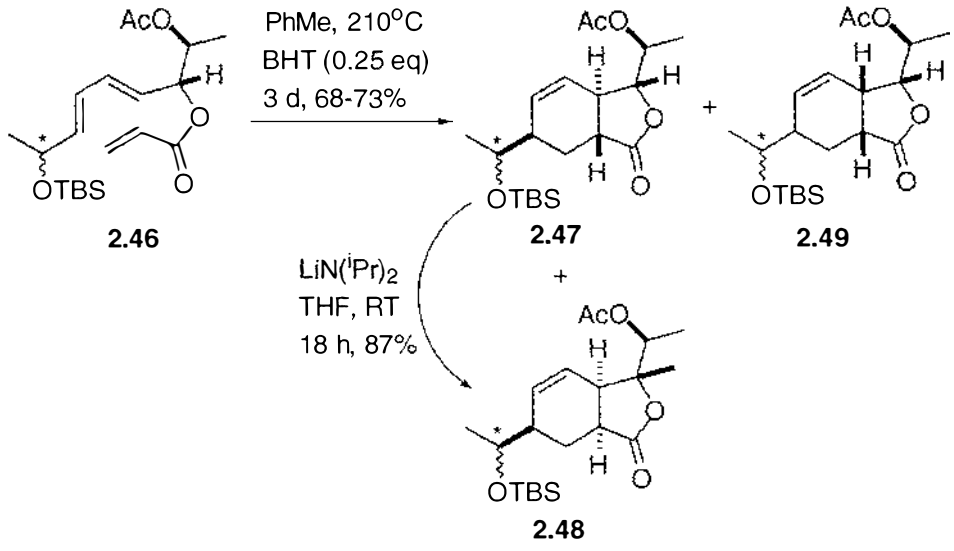
Arseniyadis *et al.* used an IMDA reaction in an efficient and stereoselective approach to the B-ring subunit of A-seco mevinic acid.[8,9] The ethyl substituent on the ester tether of (*E*,*E*,*E*)-undeca-2,7,9-trienoate **2.41** was intended to act as a stereocontrolling element to selectively produce the desired diastereoisomer **2.42**. The dienophile was activated by conjugation with the ester tether and by terminal substitution with an ethyl ester. Racemic trienoate **2.41** was heated in toluene (0.03 M solution) at 100°C for 24 h under argon to

afford a 74:7:15:4 mixture of four racemic cycloadducts in 92% yield (major adduct **2.42**) (**Scheme 2.15**). In this thorough investigation, all four stereoisomeric IMDA adducts were separated and characterised by nOe experiments. The close similarity in product distribution obtained by the independent studies of Arseniyadis (**Scheme 2.15**) and Birtwhistle (**Scheme 2.6**) seems to indicate that the stereocontrolling effects of the methyl and ethyl substituents on the tether are very similar, although the differences in substitution at the diene and dienophile termini may also influence the stereochemistry.



Scheme 2.15

The tetracyclic nucleus of (+)-pillaromycinone, the aglycone of the anthracycline antibiotic (-)-pillaromycin A, was synthesised in enantiopure form by White *et al.* using an IMDA reaction as a key step.[19] The IMDA reaction of L-(+)-rhamnose derived acrylate ester **2.46** (epimeric mixture at C*) produced a mixture of three diastereoisomers **2.47**, **2.49** and **2.48** in a 42:42:16 ratio and 68-73% yield (**Scheme 2.16**). This result showed that the bulky stereocontrolling element on the ester tether had imparted high π-facial stereoselectivity on the reaction (*ca.* 80:20), although the *exo/endo* selectivity of this IMDA reaction was poor (*ca.* 40:60).



Scheme 2.16

The *trans*-fused lactone **2.47** was later isomerised to the desired (more stable) *cis*-fused lactone **2.49** by treatment with lithium diisopropylamide. The C* epimers were converged later in the synthesis by deprotection of the silyl ether and oxidation to the ketone. This work represents the only reported example of a successful IMDA reaction of an acrylate ester of a 2,4-dien-1-ol.[†] The lack of *endo/exo* selectivity in this case is clearly due to the absence an activating group on the terminus of the dienophile.

2.1.2 Summary Of Previous Results And Aims Of This Study

In order to delineate the factors responsible for high *endo/exo-* and π-diastereofacial selectivities in IMDA reactions of this type, the reported stereoselectivities from the work performed by the research groups of Birtwhistle, Uguen, Arseniyadis and White are presented in **Table 2.1**.[‡]

From the results presented in **Table 2.1**, it is obvious that for synthetically useful levels of *exo/endo*-selectivity (*ca.* 80:20) a second activating group at the dienophile terminus is required. Of course, this is not a consideration with acrylate dienophiles.

[†] As we have seen (*vide supra*), several other groups have reported that such systems are unreactive towards IMDA cycloadditions.

[‡] Results from work performed by Eberle and Kotsuki's research groups are not included here since these workers report single stereoisomeric products, a outcome inconsistent with the wealth of papers in this area.

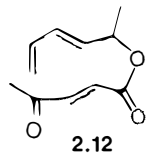
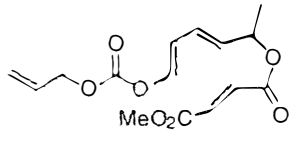
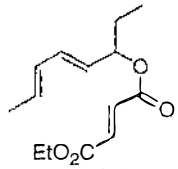
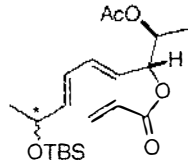
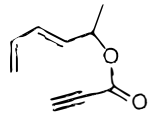
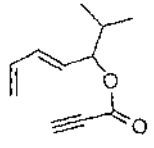
	Substrate	T (°C)	*Exo/Endo* Selectivity	π-facial Selectivity
Birtwhistle	 2.12	110°C	≥76:≤24	≥76:≤24
Uguen	 2.20	130°C	≥81:≤19	≥81:≤19
Arseniyadis	 2.41	100°C	81:19	78:22
White	 2.46	210°C	42:58	84:16
Birtwhistle	 2.14	110°C	-	86:14
Birtwhistle	 2.17	75°C	-	97:3

Table 2.1

The presence of a tether substituent results in IMDA reactions which favour the same H1-H7a *anti*-arrangement (**Figure 2.2**). This results from a minimisation of $A^{1,3}$-strain in the developing cycloaddition transition states (*vide infra*). It would be expected that increasing the size of R_1 would incur a greater degree of strain in transition states to H1-H7a *syn*-diastereoisomers. This appears to be borne out with Birtwhistle's propynoate substrates, in which the π-facial selectivity increases from 86:14 with a methyl substituent to 97:3 with an isopropyl substituent. It must be noted, however, that different cyclisation temperatures were reported for these two cases.

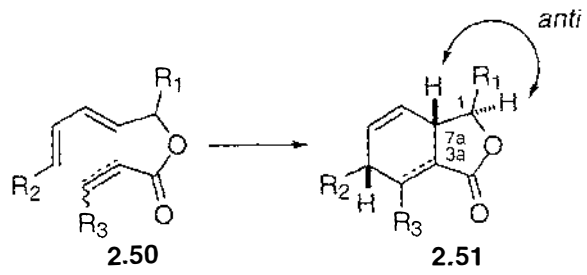


Figure 2.2

The presence of different substituents at the diene and dienophile termini of the remaining four examples prevent any further analysis of these results. Finally, it should be noted that none of these studies involve the incorporation of a *Z*-dienophile, and none compare the stereodirecting influence of a *Z*-dienophile versus the corresponding *E*-dienophile.

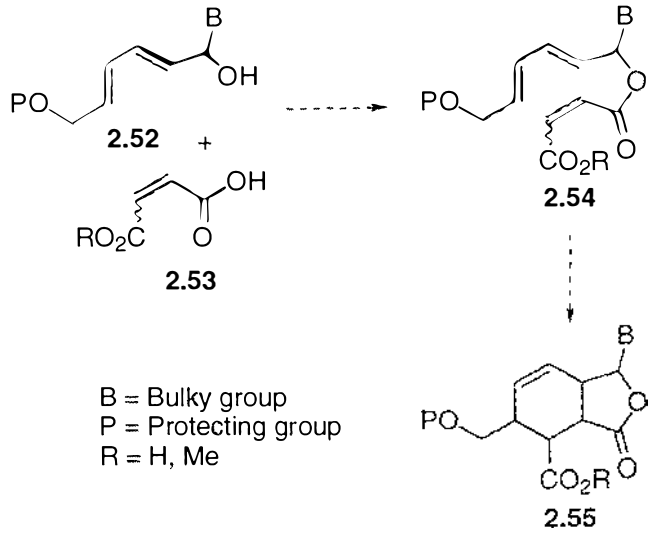
As is demonstrated by these previous results, π-facial stereoselectivity can be controlled to some extent by incorporating a subsituent at the allylic position of the ester tether. The majority of these examples consist of the IMDA reactions of racemates, producing mixtures of enantiomeric pairs. Enantioselective or enantiodirected syntheses in which a single enantiomerically pure product is produced are rare and more work needs to be performed in this area.

The aim of the present study is to optimise stereocontrol in IMDA reactions of this type. In order to achieve this goal, triene substituents with a very bulky dioxolane group were prepared. A CH_2OTBS group was appended at the dienophile terminus to allow further elaboration (see **Chapter 4** and **Chapter 5**). Three reactive dienophiles; maleate, fumarate and propynoate have been incorporated: the first two to maximise *exo* versus *endo* selectivity and the propynoate to further investigate the potential of π-facial stereocontrol.

2.1.3 Synthetic Strategy Towards The Hydroisobenzofuranone System.

The hydroisobenzofuranone nucleus **1.137** is a desirable target due to its prevalence in many biologically useful compounds found in nature. The purpose of the work presented in this **Chapter** was to investigate stereocontrol in the ester-tethered IMDA reaction and hence investigate the usefulness of this methodology for application in the synthesis of biologically active compounds with this common structural moiety.

The use of a bulky substituent (B) on the ester tether of IMDA precursor **2.54** (**Scheme 2.17**) was intended to act as a stereocontrolling element. As discussed previously (**Section 1.6**), a terminal ester substituent on the dienophile results in an increased rate of reaction and an increase in *exo* versus *endo* selectivity.



Scheme 2.17

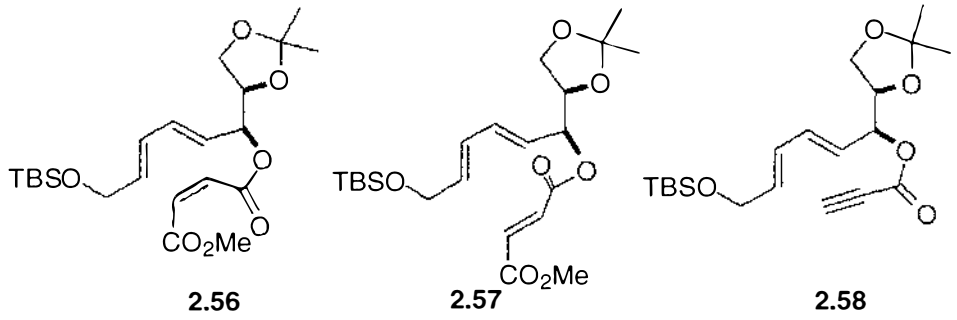
2.2 Model Studies On A Dienol System

2.2.1 Description Of The Model Study

In order to synthesise the bicyclic lactone system, and hence access a wide variety of important compounds, a model study was undertaken. The use of an ester group in the tether between diene and dienophile can prove problematic in the IMDA reaction (**Section 1.6**, **Chapter 1**) due to the reaction rate being significantly decreased, however, the creation of an ester tether is both synthetically facile and high yielding. The feasibility of a stereoselective ester-tethered IMDA reaction, producing enantiopure bicyclic lactones **1.67**, needed to be investigated both for its potential in affording expedient synthetic access to a wide range of natural products and for further application to a TIMDA reaction (**Chapter 5**).

The systems chosen for this model study were triene esters **2.56** and **2.57**, and propynoate **2.58** (**Figure 2.3**), containing an unactivated diene and an activated dienophile linked by an ester group. In two cases, the dienophile was activated both by conjugation with the ester tether and by terminal substitution with a methyl ester. It was

assumed, from literature precedent (**Section 1.6**, **Chapter 1**), that this terminal dienophile activation would help overcome the problems with decreased reactivity often associated with the use of an ester tether. The propynoate ester **2.58** was studied due to the rate increase seen previously with acetylenic dienophiles relative to alkenic dienophiles (**Section 1.6**, **Chapter 1**).[11] In order to influence the stereochemical outcome of the IMDA reaction, a substituent was placed at the allylic position of the linking chain between the diene and dienophile. Previous studies had shown that placing an isopropyl group as a substituent on the ester tether resulted in large π-facial diastereoselectivities.[4] Due to its similar size and synthetic accessibility, a dioxolane ring was chosen as a suitably sterically demanding substituent, presumed to be capable of exerting a comparable π-facial diastereofacial preference in the reaction. The diene systems shown were studied for two reasons. Firstly, they provided a convenient entry for the construction of the isobenzofuranoid system common in many biologically active compounds. In addition, they had the potential to serve as a model study for the initial IMDA reaction in a TIMDA reaction with the possibility existing of removing the silyl ether after cycloaddition and elaboration of the resultant alcohol to a diene which could participate in a second DA reaction.



2.56 **2.57** **2.58**

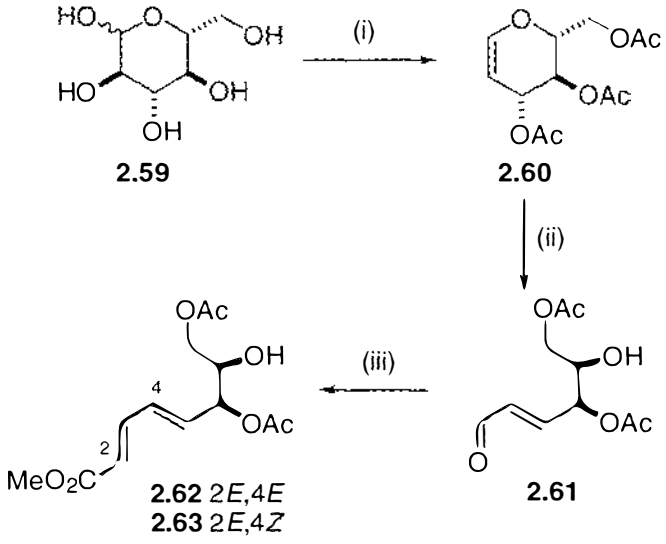
Figure 2.3

2.3 Synthesis Of The Chiral Dienol

The use of monosaccharides as starting materials is attractive due to their low cost and ready availability. In addition, they are available as enantiomerically pure compounds, thereby enabling large scale synthesis of enantiopure building blocks.[12] Using a sugar such as D-glucose as the starting material for the diene moiety ensures an enantiodirected synthesis. The production of tri-*O*-acetyl-D-glucal **2.60** on a 50 g scale from glucose **2.59** is a well documented process (**Scheme 2.18**).[13] The mercuric ion-assisted acid glycal ring opening (Perlin reaction) has been successfully performed on a wide variety of hexose, pentose and disaccharide derivatives and has proven to be a facile entry into

enantiopure, acyclic α,β-unsaturated aldehydes, logical precursors to chiral dienols. For these reasons, D-glucose was chosen as an ideal starting material for the synthesis. The choice of dienol for the model study was hence dictated by synthetic accessibility from glucose. Protection of the 1,2-diol residue of an acyclic glucose derivative as an acetonide was seen as a suitable method for creating the sterically demanding substituent needed for stereocontrol in the IMDA reaction. This dioxolane moiety was also envisioned as providing scope for further functionalisation of the IMDA adducts.

Treatment of triacetyl-D-glucal **2.60**, in dioxane, with mercuric sulfate and dilute aqueous sulfuric acid gave (2*E*,4S,5R)-4,6-diacetoxy-5-hydroxy-2-hexenal **2.61** in quantitative yield (**Scheme 2.18**).[13] Wittig reaction with the stabilised ylide, (carbomethoxymethylene)triphenylphosphorane, resulted in methyl 6,8-diacetoxy-7-hydroxy-2,4-octadienoate. Examination of ^{1}H and ^{13}C NMR spectra revealed the presence of a mixture of *E* and *Z* isomers **2.62** and **2.63**, at the newly formed carbon-carbon bond, in a 3:1 ratio. The formation of stereoisomeric mixtures of alkenes is not uncommon in Wittig reactions of α,β-unsaturated aldehydes.[14]

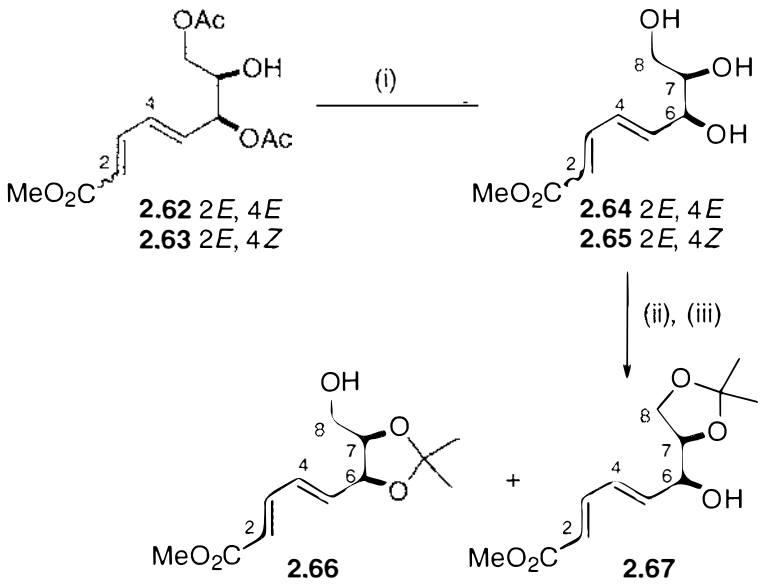


Reagents and Conditions: *(i) Ac_2O, Br_2/P, Zn/HOAc, 70%; (ii) $HgSO_4$ (0.03 eq), 5 mM H_2SO_4, 1,4-dioxane, RT, overnight, 100%; (iii) (carbomethoxymethylene)triphenylphosphorane (1.05 eq), Et_2O, Ar, RT, 4 h, 80%.*

Scheme 2.18

The acetyl groups were removed by mild hydrolysis with aqueous $KHCO_3$ in methanol to give a mixture of 6,7,8-triol compounds **2.64** and **2.65** (**Scheme 2.19**), the IR spectrum containing a typical, very broad absorption at 3389 cm^{-1} due to the presence of the three hydroxyl groups. In order to insert a bulky, stereocontrolling element, selective reprotection of the 7,8-diol (rather than the 6,7- or 6,8-diol moieties) with an isopropylidene group was necessary. Treatment with 2,2-dimethoxypropane in acetone

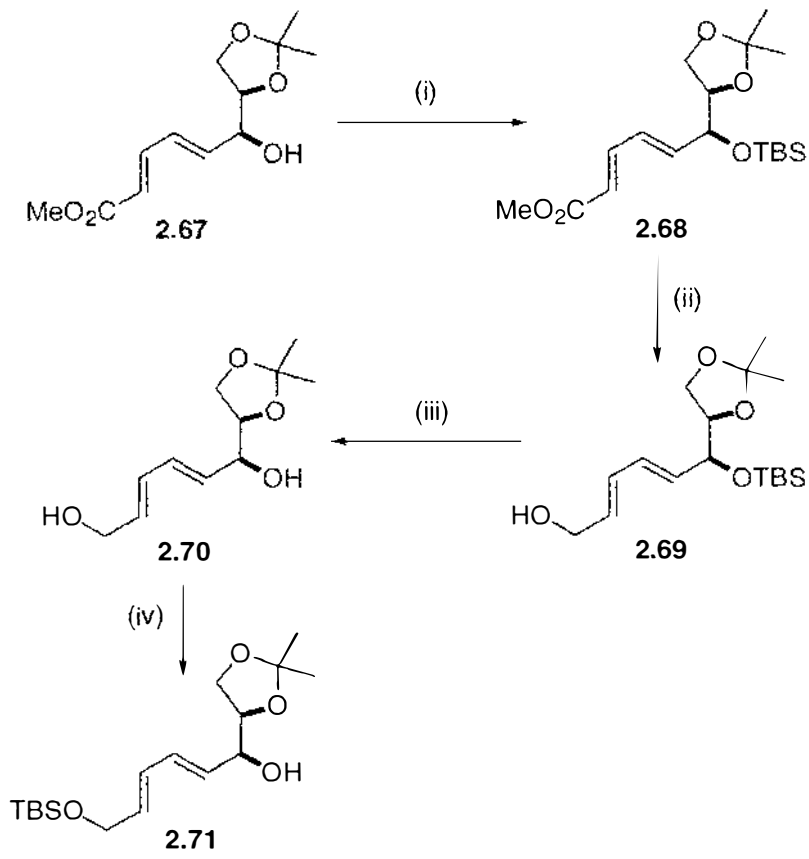
with a mild acid catalyst resulted in the formation of both the primary alcohol and the desired secondary alcohol (^{1}H and ^{13}C NMR spectra still indicating a mixture of *E* and *Z* isomers). In principle, the primary alcohol could be recycled by deprotection to the triol and subsequent reprotection with 2,2-dimethoxypropane, thus increasing the efficiency of the scheme. The mixture of primary and secondary alcohols was then equilibrated by radical isomerisation using thiophenol and AIBN to give the *E,E* dienes **2.66** and **2.67**. The desired product **2.67** was thus obtained in gram quantities, after chromatographic purification.



Reagents and Conditions: *(i) $KHCO_3$, H_2O/MeOH, RT, 4.5 h, 61%; (ii) 2,2-dimethoxypropane (8 eq), CSA (0.1 eq), acetone, 0°C, 3h; (iii) benzene, Ar, thiophenol (0.1 eq), AIBN (0.05 eq), hυ, 1 h then recharged with thiophenol (0.1 eq), AIBN (0.05 eq), hυ, 1 h, 82% over 2 steps, (**2.67**:**2.66** = 59:41)*

Scheme 2.19

The ester group of *E,E*-dienoate **2.67** could not be reduced directly to the corresponding alcohol, so the alcohol was first protected as the *tert*-butyldimethylsilyl ether **2.68**. Protection was accomplished using *tert*-butyldimethylsilyl chloride to give silyl ether **2.68** (**Scheme 2.20**). Reduction of the ester group of TBS ether **2.68** with DIBAL-H proceeded smoothly to give alcohol **2.69**. Deprotection of the silyl ether of the secondary alcohol of **2.69** with TBAF, followed by selective protection of the primary alcohol provided the desired chiral dienol **2.71** in high yield, the key intermediate for construction of a range of IMDA precursors.

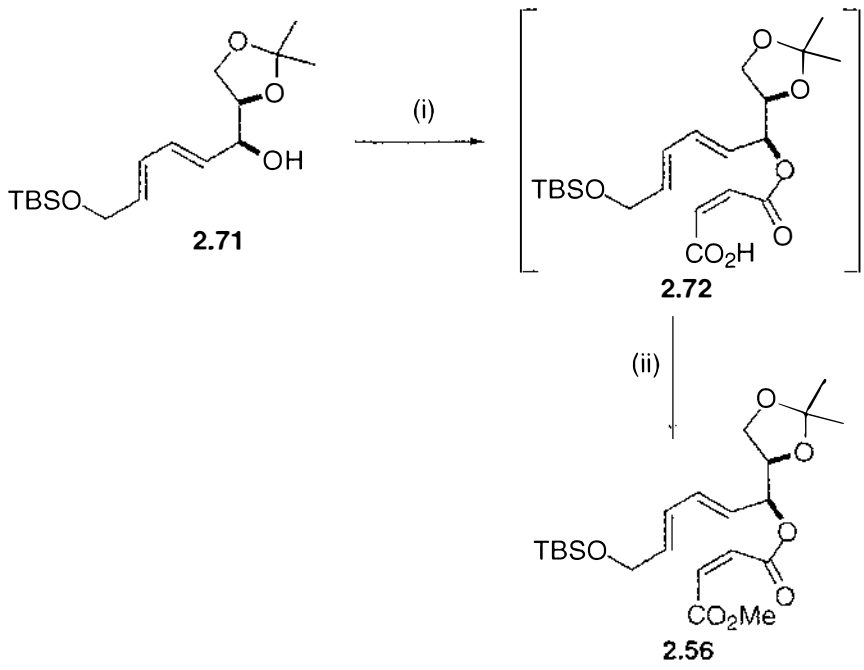


Reagents and Conditions: *(i) imidazole (2.5 eq), tert-butyldimethylsilyl chloride (1.2 eq), DMF, Ar, RT, 1.5 h, imidazole (1 eq), tert-butyldimethylsilyl chloride (0.5 eq), RT, 2 h, 98%; (ii) DIBAL-H (2.9 eq), Et_2O, -70°C, Ar, 15 min; (iii) TBAF (2.0 eq), THF, RT, Ar, 0.25 h, 87% over 2 steps; (iv) imidazole (2.5 eq), tert-butyldimethylsilylchloride (1.2 eq) (added in 2 portions), RT, Ar, 1 h, 99%.*

Scheme 2.20

2.4 Synthesis Of IMDA Precursors

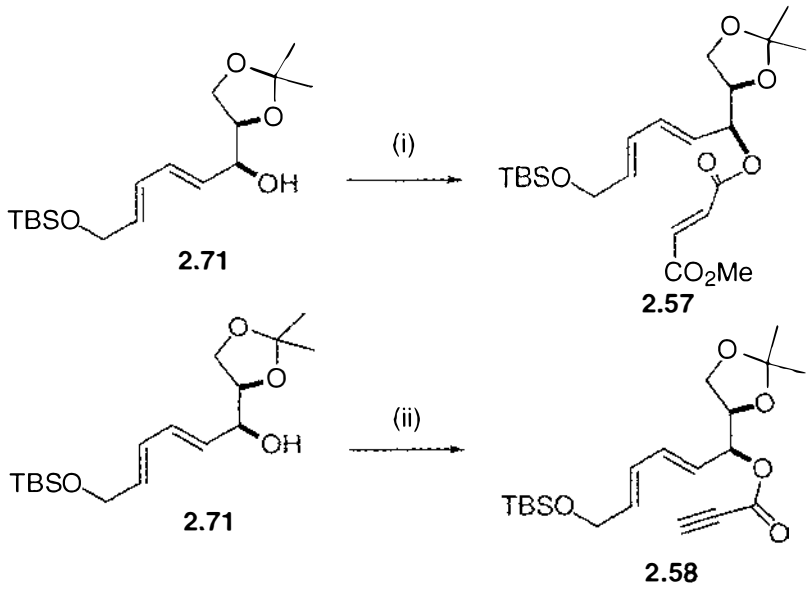
Dienol **2.71** was used to construct the IMDA precursors **2.56**, **2.57** and **2.58** (**Figure 2.3**). Reaction with maleic anhydride (MA) in the presence of triethylamine (Et_3N) and *N*,*N*-dimethylaminopyridine (DMAP) gave the maleate half-ester **2.72** , in a fast and facile transformation (**Scheme 2.21**). The acid **2.72** was unstable, undergoing IMDA reaction at RT (and upon attempted chromatographic purification), which made full characterisation of this compound difficult. Due to the propensity of the maleate half ester **2.73** to undergo cyclisation, it was converted immediately to the more stable *Z*-methyl ester **2.56** by *in situ* methylation with an ethereal solution of diazomethane.



Reagents and Conditions: *(i) Et_3N (1.6 eq), MA (2.2 eq), DMAP (0.1 eq), CH_2Cl_2, RT, Ar, 2 h; (ii) CH_2N_2, Et_2O, 72% over 2 steps.*

Scheme 2.21

The *E*-methyl ester **2.57** was made in a straightforward manner by esterifying dienol **2.71** with methyl hydrogen fumarate under DCC/DMAP-mediated conditions. The propynoate **2.58** was made in a similar way by the esterification of dienol **2.71** with propiolic acid (**Scheme 2.22**).



Reagents and Conditions: *(i) Methyl hydrogen fumarate (1.2 eq), DCC (1.3 eq), DMAP (0.1 eq), CH_2Cl_2, RT, Ar, 1 h, 88%, (ii) Propiolic acid (4.25 eq), DCC (4.6 eq), DMAP (0.3 eq), CH_2Cl_2, RT, Ar, overnight, 57%.*

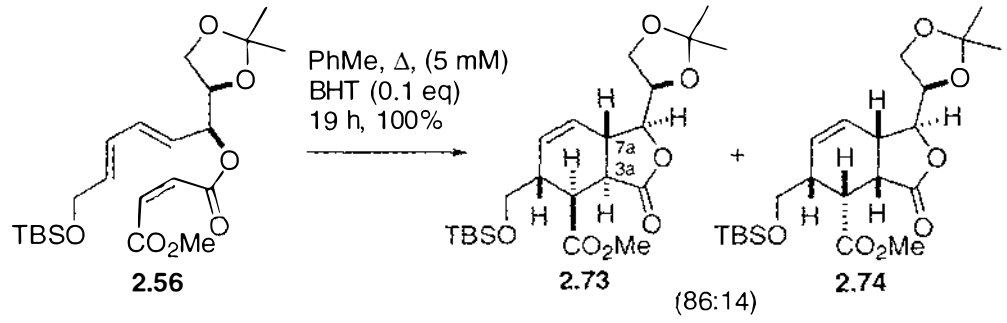
Scheme 2.22

2.5 The IMDA Reactions And Assignment Of Product Structures

IMDA reactions of the *Z*-methyl ester **2.56**, *E*-methyl ester **2.57** and propynoate **2.58** were carried out in dilute (5-10 mM) solution in refluxing toluene, under argon, in the presence of a small amount of the antioxidant BHT. Since the adducts of these IMDA reactions were obtained as oils, the stereochemistry of these compounds was elucidated by NMR, using COSY and NOESY experiments.

2.5.1 The IMDA Reaction Of The *Z*-Methyl Ester

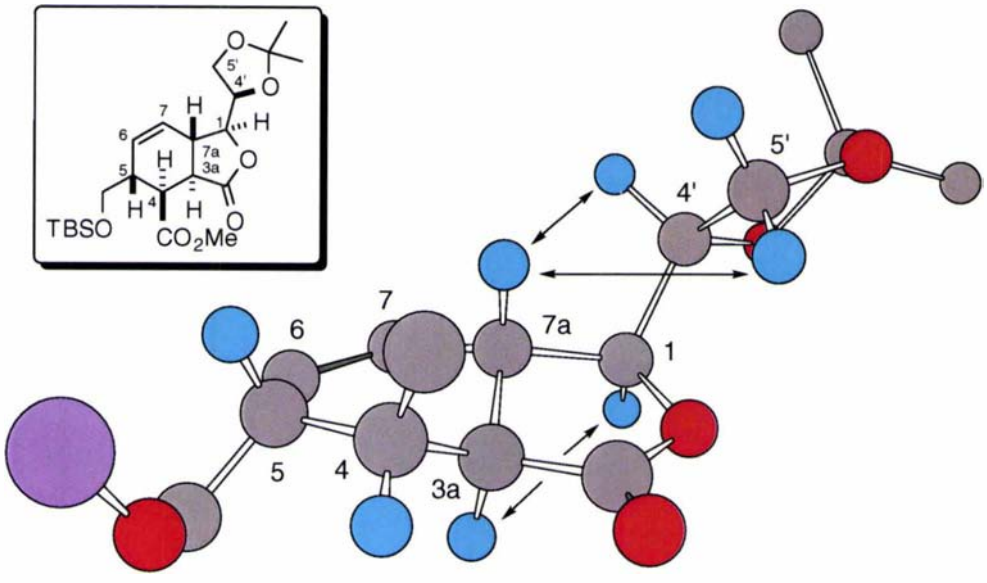
The *Z*-methyl ester **2.56** was heated to reflux in toluene for 19 h resulting in a very clean conversion into two chromatographically separable, diastereoisomeric cycloadducts **2.73** and **2.74** in quantitative yield.[§]



Scheme 2.23

The *trans*-ring fusion of the major product **2.73** (**Figure 2.4**), resulting from an *exo*-transition state, is clearly evident from the large 1,2-*trans* diaxial coupling constant between the protons attached to the ring junction ($J_{H3a\text{-}H7a}$ = 13.6 Hz). An nOe enhancement between H3a and H1 (**Figure 2.4**) indicated that H3a is on the α-face of the molecule (For Cosy and NOESY spectra of **2.73** see **Appendix**).

[§] The stereochemistry resulting from the IMDA reaction of the *Z*-methyl ester **2.56** compared to that of the *Z*-acid **2.72** was of interest as previous examples in the literature had reported different stereochemical results for the IMDA reactions of carboxylic acids versus methyl esters. This is discussed in **Chapter 3**.

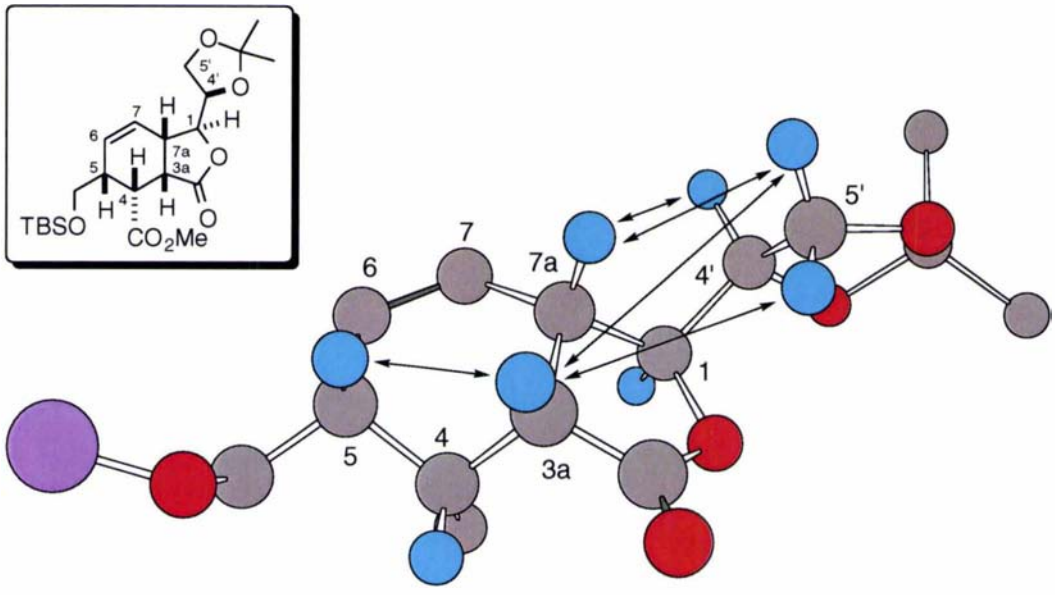


Chem 3D[15] *structure of 2.73 with pertinent nOe enhancements (some atoms removed for clarity).*

Figure 2.4

An nOe enhancement between H7a and *either* H4' or H5' (coincident signals in a variety of deuterated solvents) indicated that H7a is on the β-face of the molecule, a result which further supported the previous assignment of a *trans*-ring junction. The coupling constant between H7a and H1 also suggested an *anti* relationship ($J_{H1\text{-}H7a}$ = 10 Hz), although it has been previously noted that *J* values between such protons cannot be used to assign relative stereochemistry. The lack of coupling between the protons on C4 and C5 ($J_{H4\text{-}H5}$ = 0 Hz) indicated a dihedral angle of 90° and added further evidence to the assignment.

The ^{1}H NMR spectrum of the minor cycloadduct **2.74** did not exhibit as large a coupling constant between H3a and H7a ($J_{H3a\text{-}H7a}$ = 10.8 Hz) indicating the *cis*-ring junction geometry resulting from an *endo* transition state. The NOESY spectrum showed a through space interaction between H7a and H4' or H5' (coincident signals), indicating that H7a is on the β-face (**Figure 2.5**). An nOe enhancement between protons H3a and H4'/H5' indicated that H3a is also on the β-face of the molecule. Additional evidence for H3a being on the β-face was provided by an nOe enhancement between H3a and H5. Both of these nOe enhancements confirmed the *cis*-ring junction geometry. Seemingly in line with literature precedent, the H1-H7a coupling constant for **2.74** was significantly different to that of **2.73** (6.6 Hz versus 10.0 Hz).



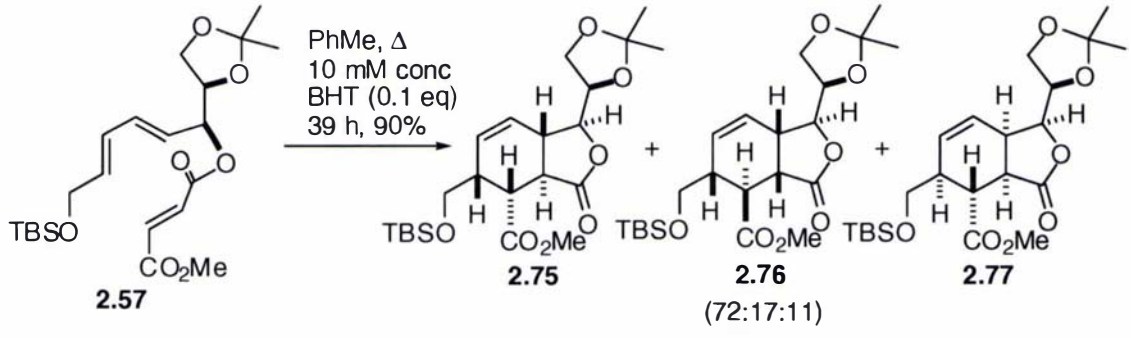
Chem 3D structure of 2.74 with pertinent nOe enhancements (some atoms removed for clarity).

Figure 2.5

Both the minor (*endo*) and major (*exo*) cycloadducts are the result of from dienophile approach from *below* the plane of the diene; in other words, this IMDA reaction exhibits *complete* π-diastereofacial selectivity.

2.5.2 The IMDA Reaction Of The *E*-Methyl Ester

Heating a solution of the *E*-methyl ester **2.57** in toluene for 39 h produced a 90% yield of a 72:17:11 mixture of three diastereoisomeric cycloadducts (**2.75**, **2.76** and **2.77**) separated by a combination of column chromatography and HPLC (**Scheme 2.24**). The IMDA reaction of the *E*-methyl ester proceeded more slowly than that of the *Z*-methyl ester and appeared to be less selective.

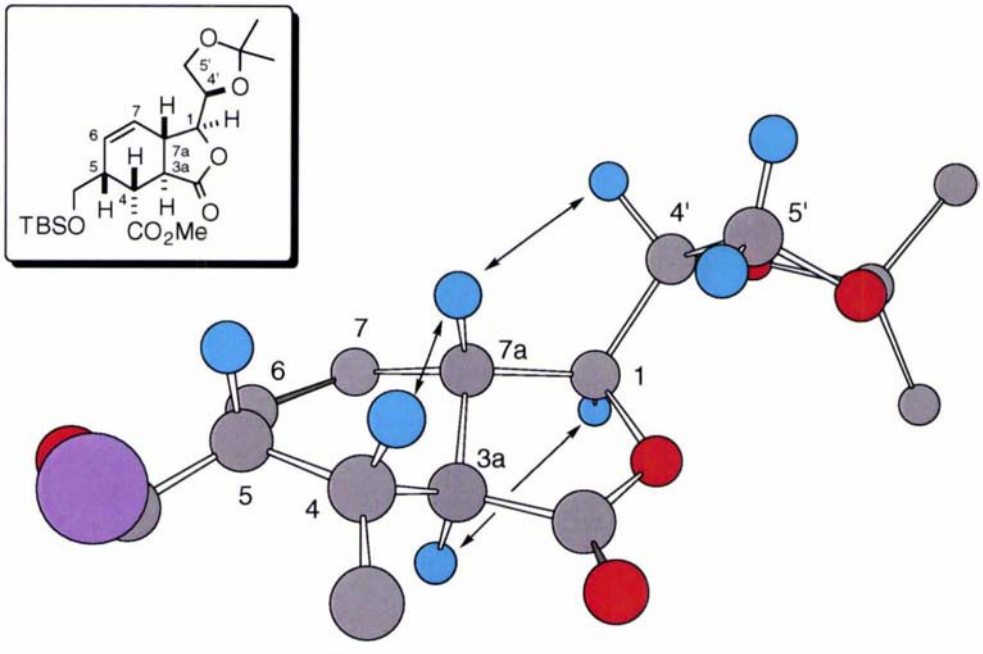


Scheme 2.24

The two minor diastereoisomers were difficult to separate and purify using preparative chromatography and required the use of HPLC techniques. In addition, it was necessary

to use high field strength NMR spectroscopy (400 and 600 MHz) to elucidate the structures of all three diastereoisomers.

The large coupling constant between the protons attached to the ring junction ($J_{H3a\text{-}H7a}$ = 13.0 Hz) indicated that the ring junction of the major product **2.75** is *trans*-fused and hence results from an *exo* transition state. The coupling constant between H7a and H1 suggested a *trans* relationship between these protons ($J_{H1\text{-}H7a}$ = 10.4 Hz) and was very similar to that observed for the major (*exo*) adduct of the *Z*-methyl ester, cycloadduct **2.73**. An nOe enhancement between H3a and H1 indicated that H3a is on the α-face of the molecule (**Figure 2.6**). An nOe enhancement between H7a and H4' implied that H7a is on the β-face of the molecule, a result which reinforces the previous assignment of a *trans*-ring junction.

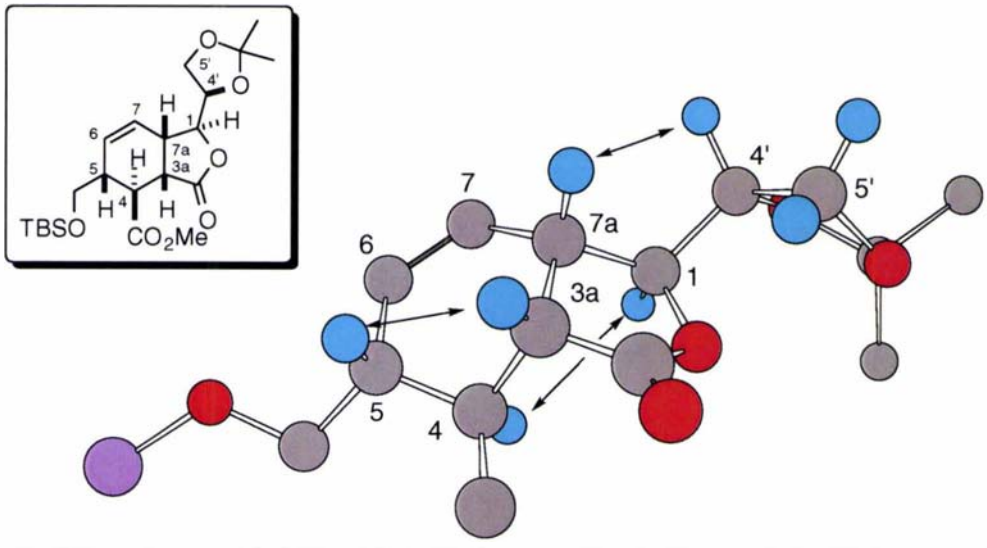


Chem 3D structure of 2.75 with pertinent nOe enhancements (some atoms removed for clarity).

Figure 2.6

Although the two minor diastereoisomers were present in nearly equivalent amounts, one (**2.76**) was slightly more abundant than the other (**2.77**). The structure of diastereoisomer **2.76** (**Figure 2.7**) was elucidated from NOESY and COSY experiments performed on a 400 MHz spectrometer. The coupling constant between the protons H3a and H7a ($J_{H3a\text{-}H7a}$ = 8.5 Hz) suggested a *cis*-fused ring junction resulting from an *endo* transition state. The nOe enhancement between protons H7a and H4' indicated that H7a is β to the plane of the molecule whilst an nOe enhancement between protons H4 and H1 implied that H4 is on the α-face of the molecule. The nOe enhancement between protons H3a and H5 meant that these two protons had to be on the same face of the molecule, a result which

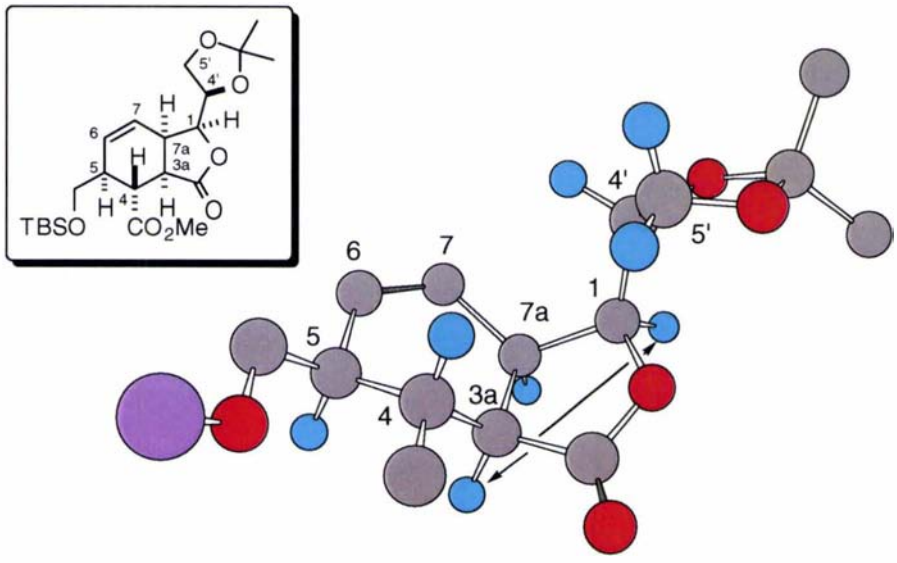
confirmed the *cis*-ring junction of the cycloadduct.



Chem 3D structure of 2.76 with pertinent nOe enhancements (some atoms removed for clarity).

Figure 2.7

The structure of the minor diastereoisomer **2.77**, was determined by NOESY and COSY NMR spectra obtained from a 600 MHz spectrometer. The ^{1}H NMR spectrum displayed a coupling constant between protons H3a and H7a which was typical of a *cis*-ring junction ($J_{H3a\text{-}H7a}$ = 8.2 Hz) which, in addition to an nOe enhancement between H3a and H1, identified its structure as that of the *endo* adduct arising from dienophile approach from above (**Figure 2.8**). The H3a-H7a ring junction coupling constant was very similar to that observed for previously identified *endo* adduct **2.76** ($J_{H3a\text{-}H7a}$ = 8.5 Hz).



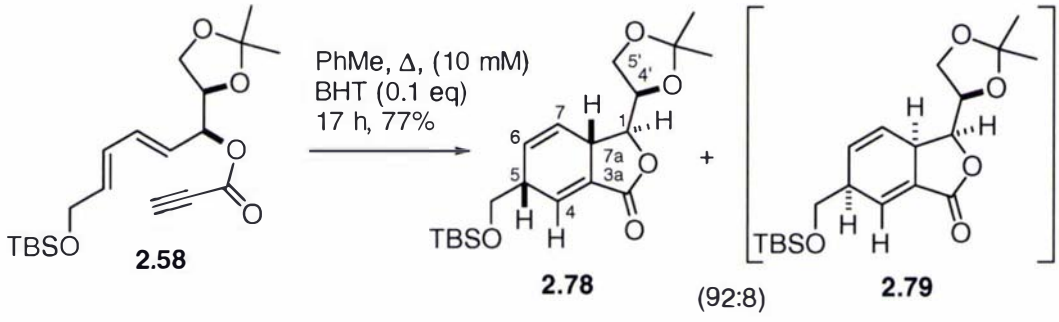
Chem 3D structure of 2.77 with pertinent nOe enhancement (some atoms removed for clarity).

Figure 2.8

The IMDA reaction of the *E*-methyl ester was less stereoselective than that of the *Z*-methyl ester; exhibiting a π-diastereofacial selectivity of 89:11 compared to the complete π-diastereofacial selectivity shown by the *Z*-methyl ester.

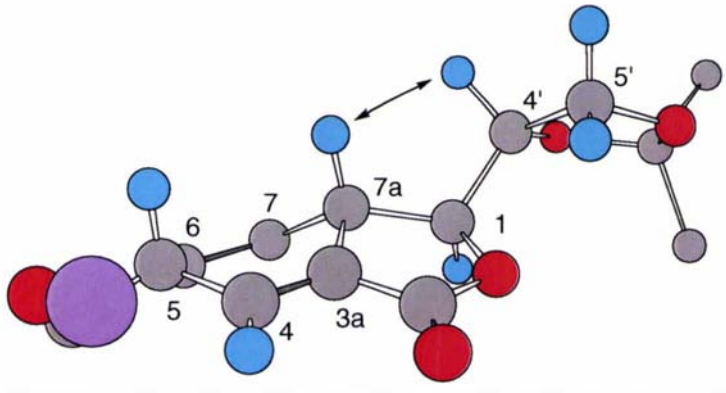
2.5.3 The IMDA Reaction Of The Propynoate Ester

The IMDA reaction of the propynoate **2.58** was both fast and highly stereoselective. Reaction was complete after 17 h in refluxing toluene with the formation of two diastereoisomers **2.78** and **2.79** in a 92:8 ratio and 77% isolated yield (after chromatography) (**Scheme 2.25**). The major and minor diastereoisomers could not be separated chromatographically, but structural elucidation of the major diastereoisomer **2.78** was possible due to the high proportion (92:8) of major to minor adduct.



Scheme 2.25

An nOe enhancement between H7a and H4' of the major diastereoisomer **2.78** indicated that H7a is on the β-face, as the molecule is represented (**Figure 2.9**).



Chem 3D structure of 2.78 with pertinent nOe enhancement (some atoms removed for clarity).

Figure 2.9

Once again, the major diastereoisomer is the result of approach of the dienophile to the lower face of the diene.

2.6 Stereoselectivity Of The IMDA Reactions

2.6.1 General Stereochemical Considerations

Four diastereoisomers are possible from the IMDA reaction of triene esters such as **2.80** (**Figure 2.10**) due to the presence of an existing stereogenic centre. This stereogenic centre causes the faces of the diene (and the dienophile) to be diastereotopic and this, in combination with the familiar *endo-/exo*-docking modes of diene and dienophile, ultimately leads to the possibility of two diastereomeric *exo* and two diastereomeric *endo* transition states. The stereochemistries of the four possible products are thus distinguished by the orientation of diene and dienophile in the transition state and can be separated into *endo/exo* and π-diastereofacial attributes.

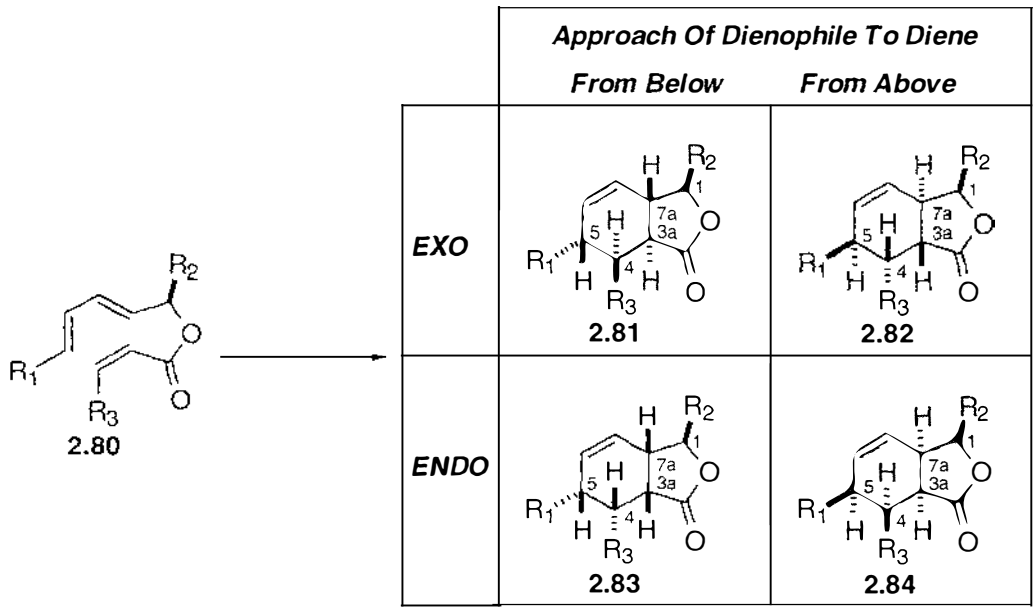


Figure 2.10

The relative stereochemistry between C1 and C7a is determined by the π-diastereofacial selectivity of the cycloaddition. The pre-existing allylic stereogenic centre of the IMDA precursor results in the two faces of the diene being diastereotopic, with the dienophile either approaching preferentially from below or above the plane of the diene (as **2.80** is represented). The sterically bulky R_2 substituent on the ester tether acts as a stereocontrolling element by introducing the issue of $A^{1,3}$-strain in the developing cycloaddition transition states.

The relative stereochemistry between C7a and C3a (as well as that between C4 and C3) is dictated by a preference for either an *exo* or an *endo* transition state. The terms *exo* and *endo* are used to indicate the position of the ester tether carbonyl group in the cycloaddition transition state. It has been demonstrated by White *et al.* that ester-linked IMDA precursors such as *Z*-methyl ester **2.56**, *E*-methyl ester **2.57** and propynoate **2.58** undergo IMDA reaction predominantly *via* a geometry in which the tether connecting diene and dienophile is *exo*.[16] The geometry of the diene (*E* or *Z*) has little effect on the *endo/exo* preference yet does affect the rate of the IMDA reaction, with k_Z being greater than k_E. The preference for *exo* addition can be explained by a non-synchronous transition state *i.e.* the formation of one σ-bond more rapidly than the other. The conformation preferentially adopted (for cycloaddition) is that in which the newly forming five-membered lactone is closed first (**2.86**) *rather* than that leading to a nine-membered ring (**2.87**), *i.e.* the C3a-C7a bond is formed before the C4-C5 bond (**Figure 2.11**). This results in steric effects associated with the developing C3a-C7a σ-bond being dominant in the transition state. The stereochemical preference for *trans*-oriented side chains on the γ-lactone prevails, resulting in a *trans*-fused cycloadduct and hence *exo* addition.

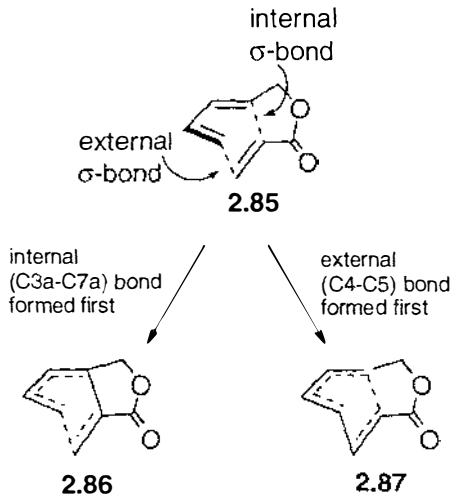


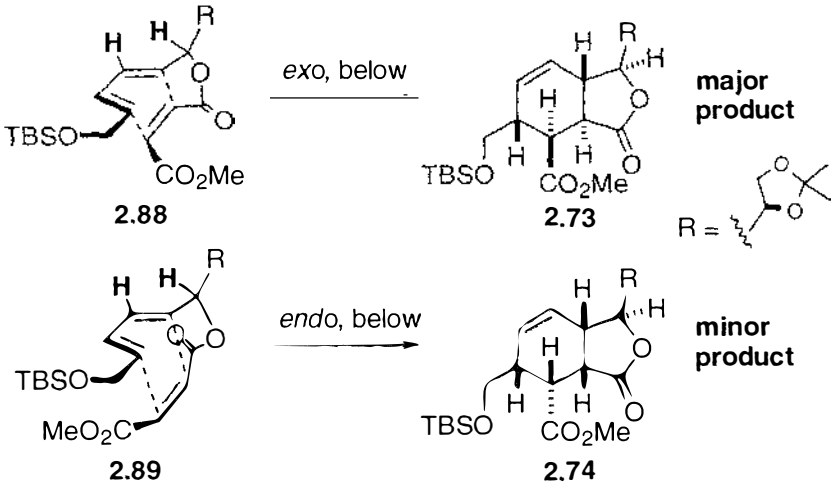
Figure 2.11

The geometry of the starting diene controls the relative stereochemistry between C7a and C5. An *E,E*-diene furnishes a C7a-C5 *syn* relationship. Likewise, the relative stereochemistry between C3a and C4 reflects the geometry of the dienophile. A *Z*-dienophile will result in a cycloadduct with the C3a and C4 hydrogens on the same side of the molecule whereas an *E*-dienophile results in a cycloadduct with the hydrogens on different faces. This conservation of diene and dienophile geometries is as a result of the concerted, suprafacial nature of the Diels-Alder reaction.

Finally, it should be noted that in the reactions described in this model study, the control of absolute stereochemistry (*i.e.* the configuration of the allylic stereogenic centre in **2.56** **2.57**, **2.58**) is effected by the use of α-D-glucose as an enantiomerically pure starting material.

2.6.2 Stereochemistry Of The *Z*-Methyl Ester IMDA Reaction

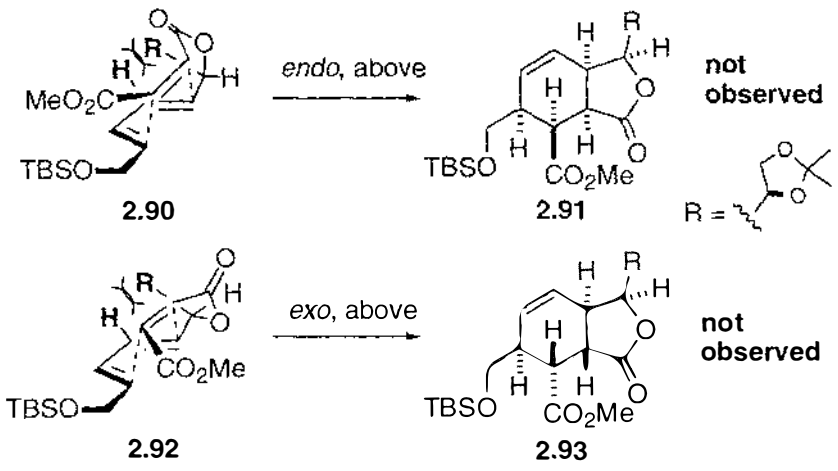
The IMDA reaction of the *Z*-methyl ester **2.56** resulted in a mixture of two cycloadducts **2.73** and **2.74** in 86:14 ratio (**Scheme 2.23**) showing good *exo/endo* selectivity (86:14) and complete π-facial selectivity (100:0). The major diastereoisomer was due to an *exo* mode of addition with the dienophile approaching from below the plane of the diene (as represented below in **Figure 2.12**). The minor diastereoisomer was due to an *endo* mode of addition with the dienophile again approaching from below. Examination of the transition states leading to both the minor and major cycloadducts shows that $A^{1,3}$-strain is minimised during the formation of both these products.



Transition states leading to the major and minor cycloadducts of the Z-methyl ester IMDA reaction.

Figure 2.12

The bulky dioxolane ring thus acts as a potent stereocontrolling element, by creating a situation in which approach of the dienophile from above the plane of the diene (in either *endo* or *exo* docking modes) is very unfavourable due to high $A^{1,3}$-strain. This is clearly seen in an examination of these unfavourable transition states (**Figure 2.13**).



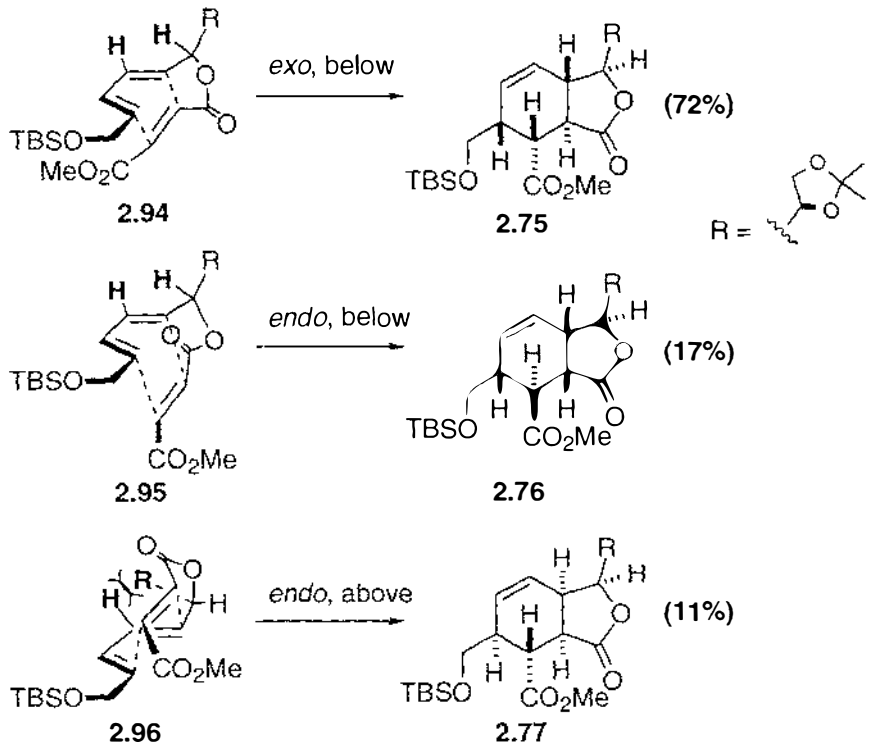
2.90 2.91 2.92 2.93

Transition states leading to the other possible cycloadducts of the Z-methyl ester IMDA reaction.

Figure 2.13

2.6.3 Stereochemistry Of The *E*-Methyl Ester IMDA Reaction

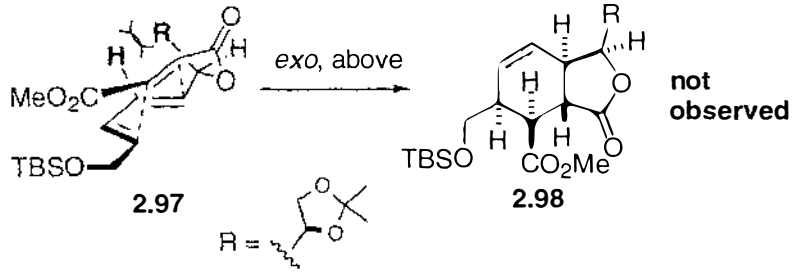
The IMDA reaction of the *E*-methyl ester **2.57** resulted in a mixture of three cycloadducts **2.75**, **2.76** and **2.77** in 72:17:11 ratio (**Scheme 2.24**) showing good *exo/endo* selectivity (72:28) and high π-diastereofacial selectivity (89:11). The major diastereoisomer **2.75** was due to an *exo* mode of addition with the dienophile approaching from below the plane of the diene (as represented below in **Figure 2.14**). The next most abundant (but still minor) diastereoisomer **2.76** was due to an *endo* mode of addition with the dienophile again approaching from below (**Figure 2.14**). Examination of the transition states leading to these cycloadducts shows that the $A^{1,3}$-strain is minimised in each case. The minor diastereoisomer **2.77** was formed from an *endo* transition state with the dienophile approaching the diene from above. Although this is very unfavourable in the *Z*-methyl ester case, the differing dienophile geometry of the *E*-methyl ester must have an effect on the stability of the transition state.



Transition states leading to the major and minor cycloadducts of the E-methyl ester IMDA reaction.

Figure 2.14

Examination of the transition state of the other possible cycloadduct (not produced in this reaction) shows an unfavourable $A^{1,3}$-strain due to the bulky dioxolane ring (**Figure 2.15**).

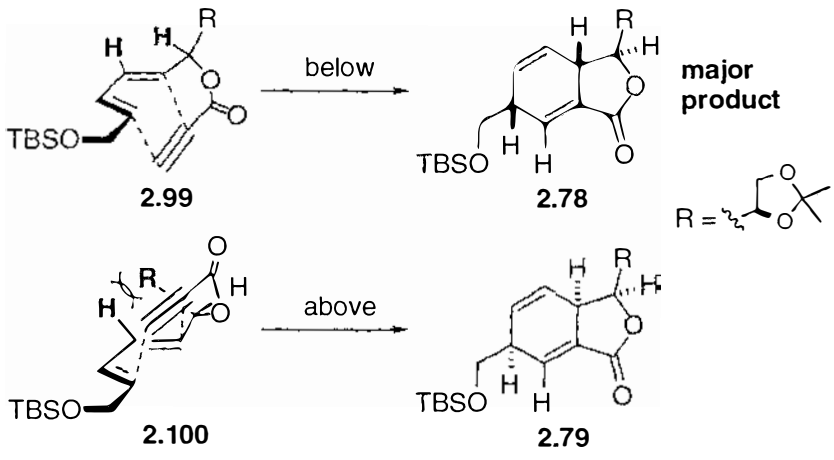


Transition state leading to the other possible cycloadduct of the E-methyl ester IMDA reaction.

Figure 2.15

2.6.4 Stereochemistry Of The Propynoate IMDA Reaction

The IMDA reaction of the propynoate ester **2.58** resulted in a mixture of two isomeric cycloadducts **2.78** and **2.79** exhibiting a high π-diastereofacial selectivity of 92:8. A consideration of *exo* and *endo* modes of addition is not applicable to the IMDA reaction of the propynoate ester as the products resulting from both modes of cycloaddition are identical. Once again, the transition state **2.99** of the major diastereoisomer shows a minimisation of $A^{1,3}$-strain compared to that of the transition state **2.100** leading to the minor isomer (**Figure 2.16**).



Transition states leading to the major and minor diastereoisomers of the propynoate IMDA reaction.

Figure 2.16

2.7 Rate Enhancement Due To The Tether Substituent

In this study, it was found that the *Z*-acid IMDA precursor **2.72** could not be fully characterised due to its highly reactive nature, undergoing an intramolecular cycloaddition at RT and even upon storage at 0°C. This reactivity was unexpected due to previous reports of the rate retarding effect of the ester tether (*vide supra*). In addition, compounds similar to **2.72** had been synthesised previously with the *Z*-acids **2.101**, **2.102** and **2.103** all being isolable at RT and stable at 0°C over extended periods of time (**Figure 2.17**).[17]

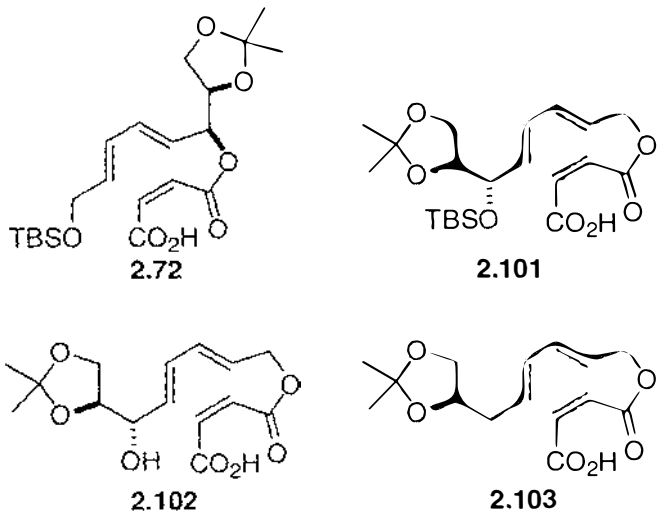


Figure 2.17

It is well known that alkyl substituents on an acyclic chain connecting two reacting centres result in an acceleration in the rate of the cyclisation. Recently this effect has been studied by Jung and Gervay.[18-20] The rates of the IMDA reactions of tether-substituted furfuryl methyl fumarates (**Figure 2.18**) were compared to those of the unsubstituted compounds.[19,20]

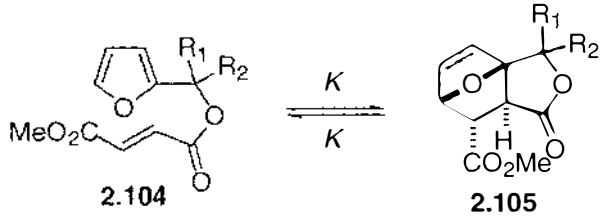


Figure 2.18

In the system studied by Jung and Gervay (**Figure 2.18**), substitution with a methyl group resulted in an eightfold increase in the relative rate of the IMDA reaction (**Table 2.2**).

Substrate (2.104)	**Relative Reaction Rate**
R_1 = H, R_2 = H	K_{rel} = 1
R_1 = H, R_2 = Me	K_{rel} = 8.35
R_1 = Me, R_2 = Me	K_{rel} = 2123

*Table of the relative rates of the IMDA reactions of varying furfuryl methyl fumarates (**2.104**) at 298K in CD_3CN.*[20]

Table 2.2

Substitution of the ester tether with two methyl groups correlated with a further dramatic increase in reaction rate, the rate of the dimethyl compound increased by a factor of 2000 when compared to that of the unsubstituted compound. Two theories have been developed to explain the rate increase which occurs upon alkyl substitution; angle compression and the reactive rotamer effect. Angle compression or the "Thorpe-Ingold effect" states that alkyl substitution on a central methylene causes compression of the internal angle due to methyl groups being larger than hydrogens (**Figure 2.19**). This angle compression then causes the reactive groups to be moved closer together.[18-20]

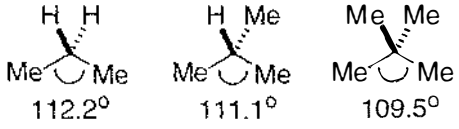


Figure 2.19

Jung and Gervay suggested that the contribution of angle compression to the rate enhancement was small and that the major factor in the rate increase was a conformational effect known as the reactive rotamer effect. In order for cyclisation to occur, the diene and dienophile must be close and this requires rotation about the central C-C bonds from the most stable *anti* conformer to the less favourable *gauche* conformation (the reactive rotamer). Substitution of one of the central C-C bonds with one or two alkyl groups decreases the energy difference between the *anti* and *gauche* conformers (**Figure 2.20**) and, hence, lowers the activation energy for cyclisation. However, it was conceeded by Jung and Gervay that the reason for the rate accelerations due to alkyl substitution was not entirely clear.[20]

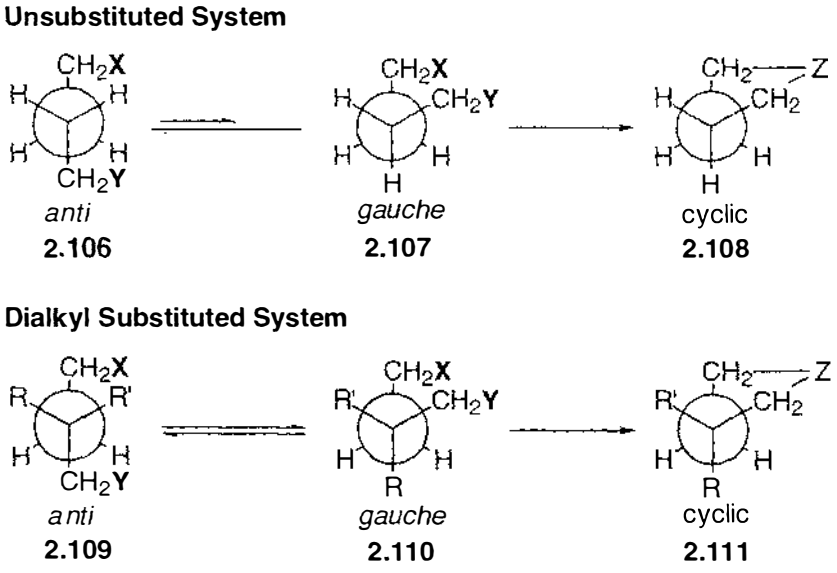


Figure 2.20

In the case of the ester-tethered IMDA precursor **2.72**, the tether is substituted with a bulky dioxolane ring, initially intended as a device to ensure stereocontrol. The presence of this sterically demanding substituent on the ester linkage appears to have the added effect of acting as a *rate enhancing element*. This effect appears most pronounced in the case of the *Z*-acid IMDA precursor **2.72**, although the *Z*-methyl ester **2.56** and propynoate **2.58** also show evidence of rate enhancement relative to unsubstituted derivatives.[17] As the stereochemistry at the substituted position has an effect on the conformations favoured in the transition state (*vide supra*), it is reasonable to expect that the stereochemistry at this centre would also impact upon the rate of cyclisation. A more detailed investigation of the effect of the dioxolane tether-substituent upon the rate of the IMDA reactions described in this study is required.

2.8 Summary

The goal of the work described in this chapter was to investigate the tether substituent-directed stereocontrol of IMDA reactions by using a bulky stereocontrolling tether substituent and a range of reactive dienophiles. Inspection of **Table 2.3** reveals that the dioxolane group provides some of the highest levels of π-diastereofacial selectivity in IMDA reactions of this type seen thus far.

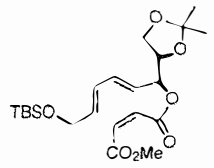
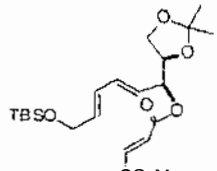
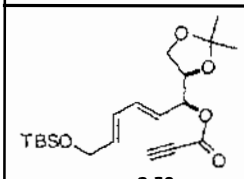
	π-Diastereofacial Selectivity	***Exo/Endo* Selectivity**
 **2.56**	92:8	—
 **2.57**	89:11	72:28
 **2.58**	92:8	—

Table 2.3

Notably, the use of a large, bulky substituent on the ester tether, whilst providing stereocontrol to the reaction, also appears to lead to increased reactivity of the IMDA precursors when compared to similar unsubstituted compounds.

The model study described in this chapter demonstrates that, despite being described as problematic, the use of an ester functional group as a tether is a very useful and efficient way of constructing precursors for IMDA reactions. Correct positioning of the ester tether (in conjugation with the dienophile) actually results in activation of the dienophile towards an IMDA reaction. In the maleate and fumarate examples, the electron withdrawing group at the terminal position of the dienophile (either in a *Z*- or *E*-orientation) also leads to a further increase in cycloaddition rate.

Moreover, "doubly activated" *E and Z*-dienophiles retain their strong preference for *exo* versus *endo* cycloaddition modes in these more complex substrates, thereby providing enantiomerically pure, highly functionalised cycloadducts with excellent synthetic potential.

2.9 References

(1) Lilly, M. J.; Sherburn, M. S. *Chem. Comm.* **1997**, 967-968.

(2) Fraser-Reid, B.; Benko, Z.; Guiliano, R.; Sun, K. M.; Taylor, N. *J. Chem. Soc., Chem. Commun.* **1984**, 1029-1030.

(3) Wu, Y.-L.; He, J.-F. *Tetrahedron* **1988**, *44*, 1933-1940.

(4) Birtwhistle, D. H.; Brown, J. M.; Foxton, M. W. *Tetrahedron* **1988**, *44*, 7309-7318.

(5) Uguen, D.; Dizière, R.; Tahri, A. *Tetrahedron Lett.* **1994**, *35*, 3937-3940.

(6) Eberle, M. K.; Weber, H.-P. *J. Org. Chem.* **1988**, *53*, 231-235.

(7) Kotsuki, H.; Kawamura, A.; Ochi, M.; Tokoroyama, T. *Chem. Lett.* **1981**, 917-920.

(8) Arseniyadis, S.; Brondi-Alves, R.; Wang, Q.; Yashunsky, D. V.; Potier, P. *Tetrahedron Lett.* **1994**, *35*, 7949-7952.

(9) Arseniyadis, S.; Brondi-Alves, R.; Yashunsky, D. V.; Potier, P.; Toupet, L. *Tetrahedron* **1997**, *53*, 1003-1014.

(10) White, J. D.; Nolen, E. G., Jr.; Miller, C. H. *J. Org. Chem.* **1986**, *51*, 1150-1152.

(11) Becher, J.; Nielsen, H. C.; Jacobsen, J. P.; Simonsen, O.; Clausen, H. *J. Org. Chem.* **1988**, *53*, 1862-1871.

(12) Hanessian, S. *Total Synthesis of Natural Products: the 'Chiron' Approach*; Pergamon Press: Oxford, 1983.

(13) Perlin, A. S.; Gonzales, F.; Lesage, S. *Carbohydrate Research* **1975**, *42*, 267-274.

(14) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.

(15) CS Chem3D Pro™ ; version 3.5.1; Cambridge Soft Corporation: Cambridge, Massachusetts, 1997.

(16) White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273-2280.

(17) Lilly, M. J. PhD. thesis, Massey University, 1998.

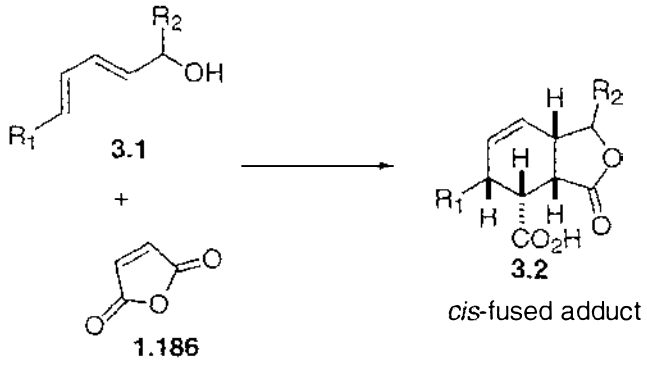
(18) Jung, M. E.; Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429-2432.

(19) Jung, M. E. *Synlett* **1989**, 186-190.

(20) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224-232.

3. THE STEREOCHEMICAL OUTCOMES OF INTERMOLECULAR AND INTRAMOLECULAR DIELS-ALDER REACTIONS ON DIENOLS

3.1 Introduction

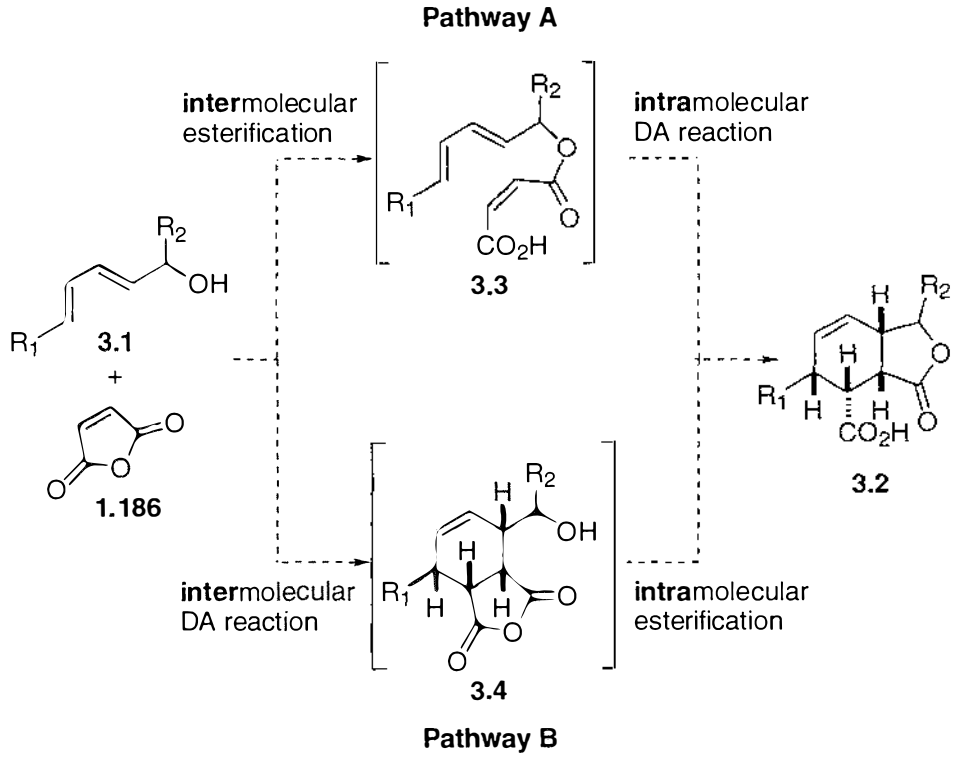


Scheme 3.1*

The reaction of 2,4-dien-1-ols **3.1** with maleic anhydride (MA) **1.186** to form *cis*-fused lactone acids such as **3.2** (**Scheme 3.1**) was first reported over fifty years ago[1,2] and has been widely used in target synthesis.[3-7] Although this reaction is well documented, the mechanistic details of this simple cascade reaction remain unclear. As pictured below, there are two possible pathways for the reaction to follow (**Scheme 3.2**). These pathways are proposed to consist of either an **inter**molecular esterification followed by an **intra**molecular DA reaction (*Pathway A*) or an **inter**molecular DA reaction followed by an **intra**molecular esterification (*Pathway B*). There is disagreement in the literature as to which is the most likely pathway of the reaction and this has caused confusion in explaining the stereochemical outcome of the reaction. A survey of all relevant literature examples is included in this section, followed by the aims of the current work and a description of reactions which have allowed us to uncover the mechanism of this transformation.

---

* The relative stereochemistry between an existing allylic stereocentre and newly created stereocentres will depend upon the nature of the R_2 substituent.

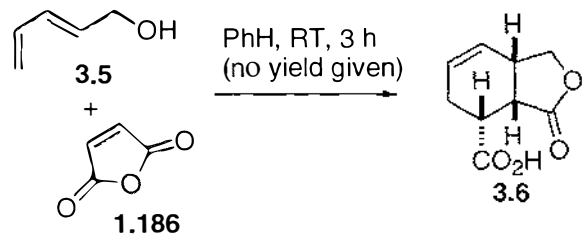


Scheme 3.2

3.1.1 Previous Examples Of Reactions Between MA And Dienols

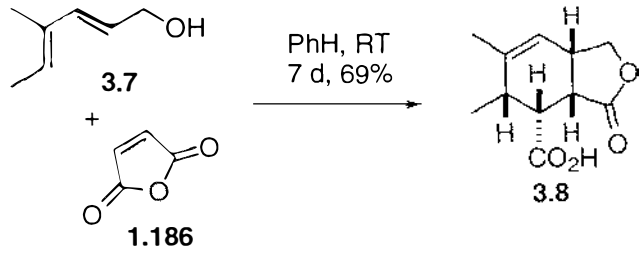
3.1.1.1 Examples With No Discussion Of Reaction Pathway

Heilbron *et al.* performed the first reported reactions between 2,4-dien-1-ols and MA, an example of which is the reaction between dienol **3.5** and MA in benzene at RT to produce the lactonic acid **3.6** (**Scheme 3.3**).[1] The stereochemistry of **3.6** was confirmed by an X-ray structure analysis performed by Sawyer *et al.*[8] No pathway was proposed for the reaction and it was uncertain whether esterification had taken place before or after cycloaddition.



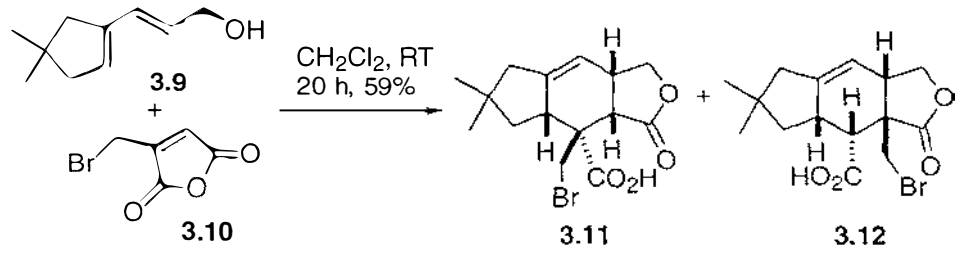
Scheme 3.3

Raphael and Owens[7] made use of the cycloaddition between (*E*,*E*)-4 methyl-hexa-2,4-dienol **3.7** and MA in their synthetic approach to the cytochalasans. The result of dissolving dienol **3.7** and MA in warm benzene and then standing for 7 days at RT was the *cis*-fused lactonic acid **3.8** (**Scheme 3.4**). The structure of this bicyclic lactone was confirmed by the X-ray structure analysis of a derivative performed by Jones and Kennard.[9]



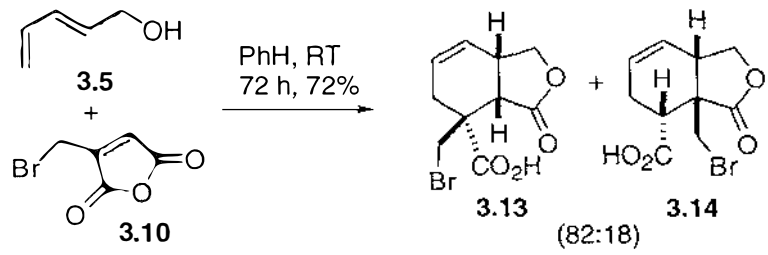
Scheme 3.4

Marasmic acid, a fungal metabolite, was the target of synthetic efforts by Greenlee and Woodward.[6] Dienol **3.9** was reacted with anhydride **3.10** in dichloromethane at RT for 20 hours producing a mixture of the *cis*-fused regioisomers **3.11** and **3.12** with the ratio of products being unstated (**Scheme 3.5**).



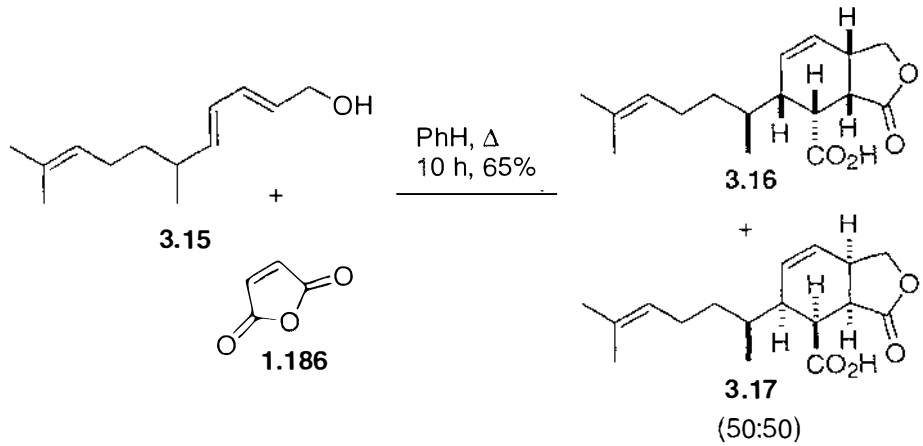
Scheme 3.5

In a similar reaction sequence to that performed by Greenlee and Woodward,[6] Arai *et al.* reacted dienol **3.5** with anhydride **3.10** in benzene at RT for 72 hours to produce a mixture of regioisomeric *cis*-fused cycloadducts **3.13** and **3.14**, important intermediates in the stereocontrolled synthesis of (±)-nor-sterepolide (**Scheme 3.6**).[5]



Scheme 3.6

In the final example in this section, Grieco and Nargund made use of a Diels-Alder strategy in a total synthesis of (±)-biflora-4,10(19),15-triene, a diterpene isolated from the glands of termite soldiers.[4] Diels-Alder addition and esterification of trienol **3.15**[†] and MA in benzene gave a 50:50 mixture of the two *endo* adducts **3.16** and **3.17** (**Scheme 3.7**).



Scheme 3.7

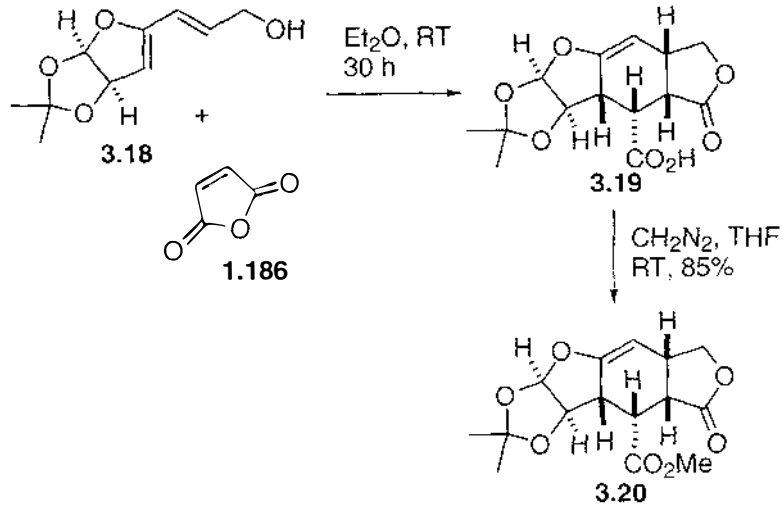
The examples described above make no comment on the nature of the pathway of the reaction between the dienols and the anhydride.

3.1.1.2 Examples Supporting Pathway B: Intermolecular DA Followed By Intramolecular Esterification

There is support in the literature for the reaction between 2,4-dien-1-ols and MA occurring *via* an **inter**molecular DA and then a subsequent **intra**molecular esterification (*Pathway B*, **Scheme 3.2**).[3,10-14]

Fraser-Reid *et al.* reacted diacetone glucose-derived dienol **3.18** with MA in diethyl ether at RT for 30 hours, resulting in a single *cis*-fused lactonic acid **3.19** (**Scheme 3.8**). Treatment of the crude acid with diazomethane produced methyl ester **3.20** in 85% yield.[14] The DA reaction exhibited an exclusive π-facial selectivity due to the sterically demanding dioxolane ring of the sugar-derived dienol, with addition occurring only from the convex surface of **3.18**.

[†] Trienol **3.15** was racemic, producing a 50:50 diastereomeric mixture of products, each of which is racemic. For clarity, only one enantiomer of each diastereomeric cycloadduct is shown.



Scheme 3.8

Whilst admitting the possibility of reaction between **3.18** and MA occurring *via Pathway A* (**Scheme 3.2**), Fraser-Reid *et al.* believed that the similar rate[‡] and yield of the intermolecular DA reaction of the corresponding protected alcohol **3.21** with MA to form the anhydride **3.22** (**Scheme 3.9**) provided evidence for the reaction mechanism of the unprotected alcohol **3.18** and MA to consist of an intermolecular DA and then intramolecular esterification.

Scheme 3.9

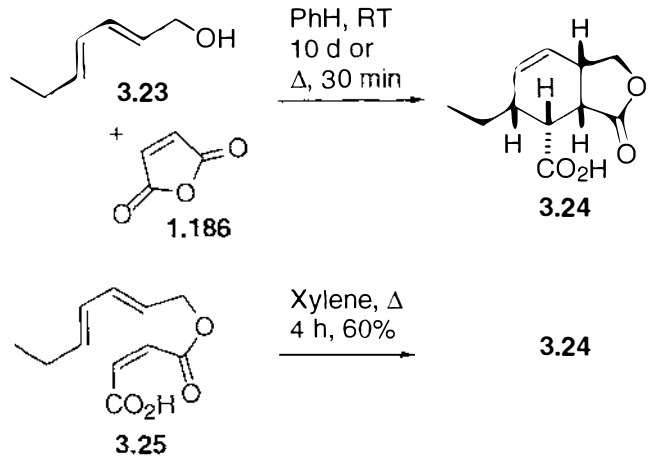
The simple dienol **3.23** was reacted with MA in benzene both at RT for 10 days and at reflux for 30 minutes (**Scheme 3.10**).[13] Under both sets of reaction conditions, a single *cis*-fused cycloadduct **3.24** resulted. To clarify the reaction pathway, Kim and Kim prepared acid **3.25** and heated it to reflux in both benzene and xylene, resulting in *cis*-fused lactone **3.24**.[§] Reaction was very sluggish in benzene with the higher boiling

---

[‡] Although it is difficult to compare the rate of a reaction performed in refluxing toluene with one performed in diethyl ether at RT.

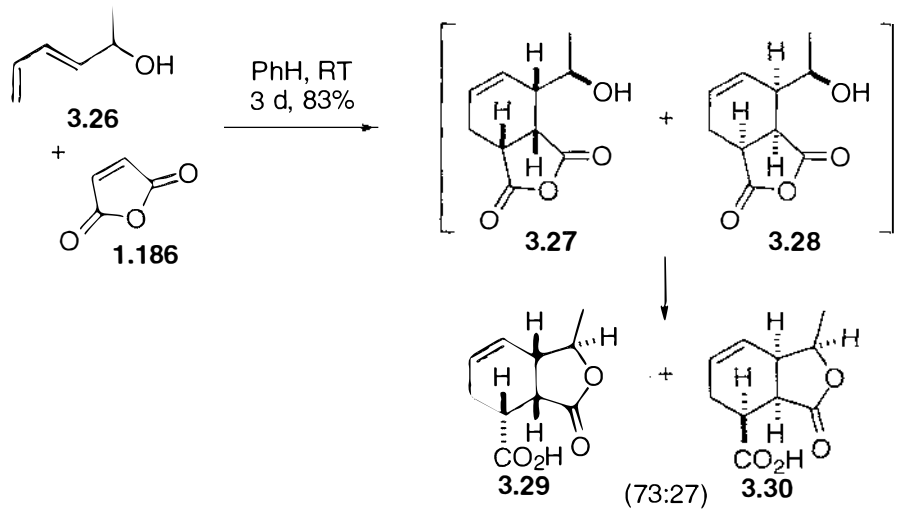
[§] The formation of *cis*-fused adduct **3.24** in this reaction is interesting as the IMDA reaction of ester-linked 1,3,8-nonatriene type systems usually results in *trans*-fused adducts (**Chapter 2**).

solvent xylene ultimately being used to effect reaction leading the authors to conclude that an intermolecular DA reaction must occur before esterification.



Scheme 3.10

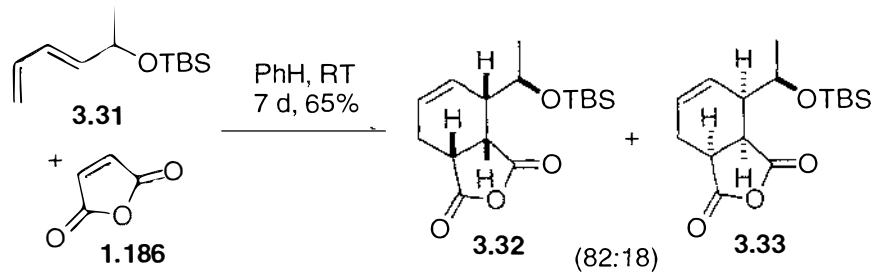
Similarly, Franck *et al.* believed the reaction between the racemic dienol **3.26** and MA consisted of an intermolecular DA reaction to form intermediates **3.27** and **3.28** and a subsequent intramolecular esterification to form products **3.29** and **3.30** in 83% yield and a 73:27 ratio (**Scheme 3.11**).[12] The presence of the methyl group proved sufficiently sterically demanding to hinder approach to one side of the diene and result in a moderate π-diastereofacial selectivity.



Scheme 3.11

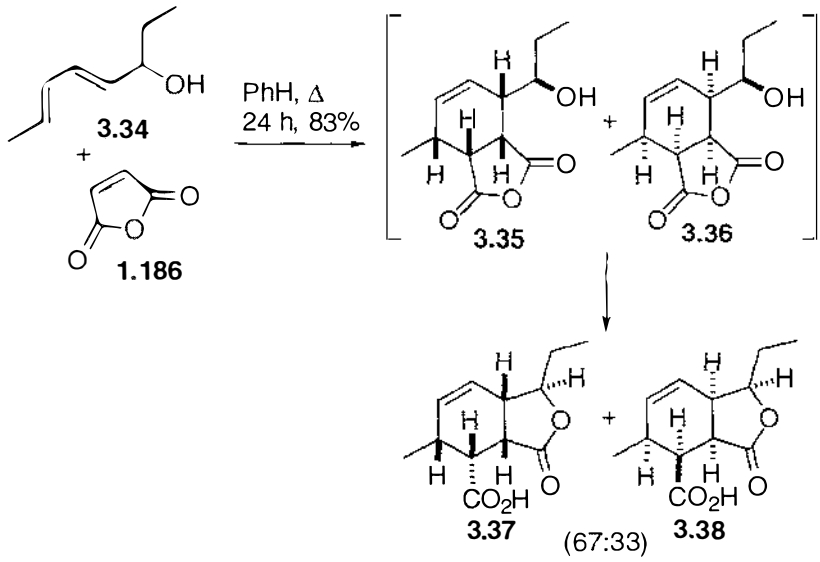
Corroborating evidence for the reaction following *Pathway B* (**Scheme 3.2**) came from the **inter**molecular DA reaction of the silylated derivative **3.31** with MA to form anhydrides **3.32** and **3.33** (**Scheme 3.12**). Protection of the alcohol as a silyl ether

prevented any possibility of esterification prior to the cycloaddition reaction. The similar rates and diastereomeric ratios, and identical product stereochemistries of the reactions of alcohols **3.31** and **3.26** with MA indicated to the authors that the unprotected alcohol **3.26** underwent an intermolecular DA reaction before esterification.



Scheme 3.12

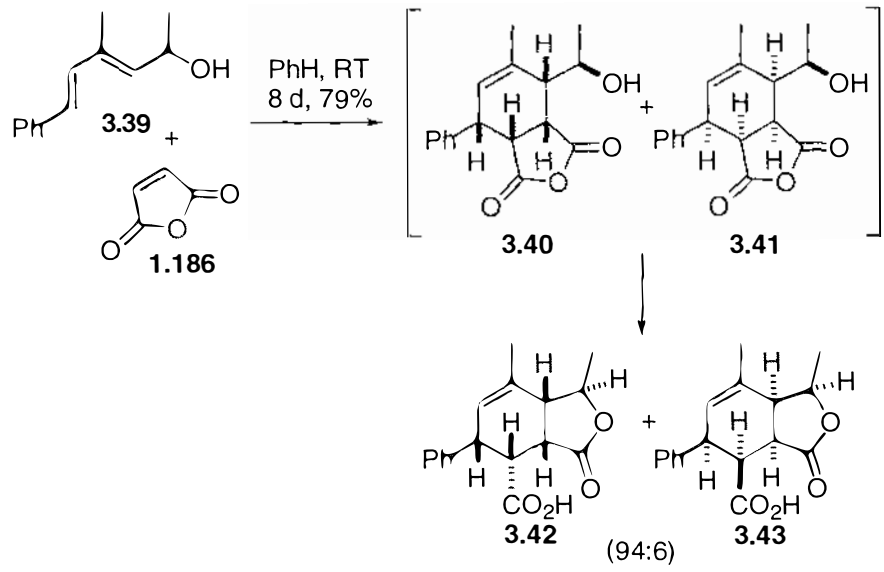
Arseniyadis *et al.* proposed that the reaction between chiral dienol **3.34** (present as a racemic mixture) and MA would proceed *via Pathway B*.[3,10] The reaction pathway was postulated to consist of an ***endo***-selective intermolecular DA reaction to form the diastereomeric intermediates **3.35** and **3.36** followed by a rapid **intra**molecular esterification to lactonic acids **3.37** and **3.38** (**Scheme 3.13**). However, the proposed intermediates were not isolated. The ethyl substituent of the dienol lent only a moderate degree of π-facial selectivity to the DA reaction (67:33).



Scheme 3.13

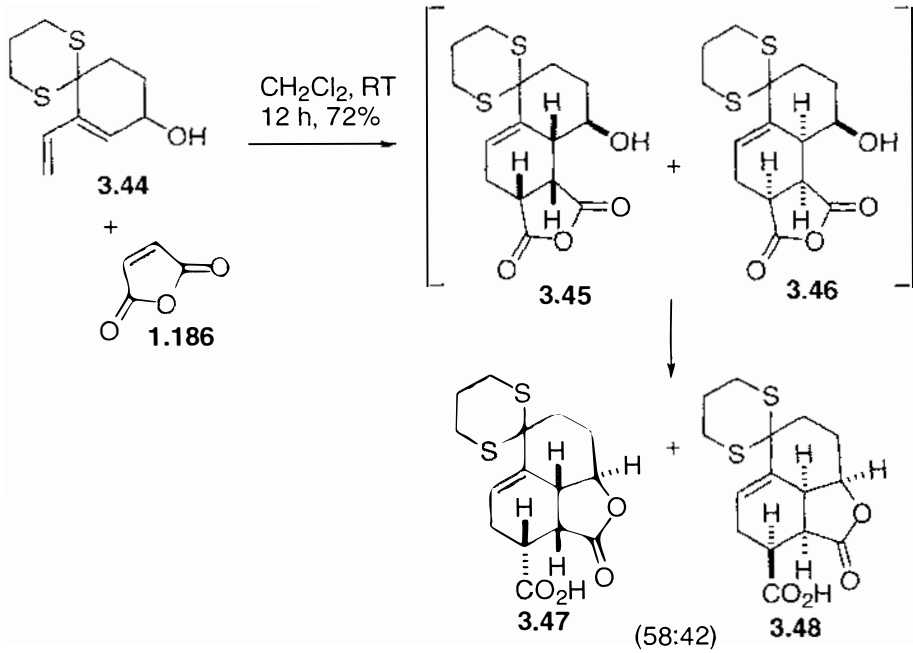
High π-facial selectivity was observed by Prein and co-workers in the cycloaddition reaction of the racemic chiral dienol **3.39** and MA (**Scheme 3.14**).[15] The combination of a *cis*-substituent on the diene leading to 1,3-allylic strain in the transition state and a

stereocentre at the hydroxyl group resulted in a 94:6 preference for the major cycloadduct **3.42**. Despite the mild reaction conditions the proposed intermediates were not isolated. Prein *et al.* believed the reaction to proceed *via* a DA reaction and then an esterification.



Scheme 3.14

Kanematsu *et al.* investigated the facial selectivity of the DA reaction of semi-cyclic dienes (**Scheme 3.15**).[11] Dienol **3.44** was reacted with MA in dichloromethane producing a mixture of the tricyclic lactones **3.47** and **3.48** in 72% yield and 58:42 ratio.



Scheme 3.15

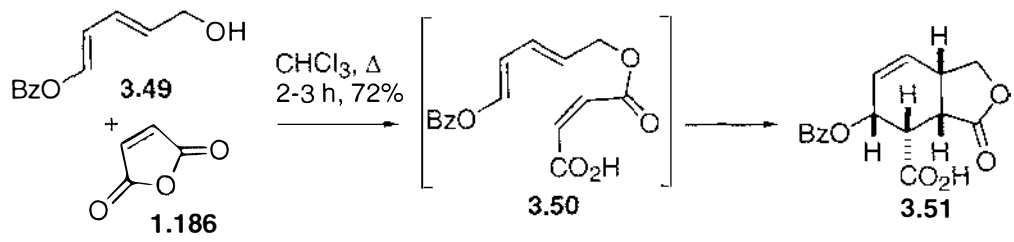
Kanematsu *et al.* proposed that the reaction pathway consisted of an *endo*-selective intermolecular DA reaction to give the unisolated intermediates **3.45** and **3.46** with a subsequent lactonisation to form the final products. Facial selectivity in this DA reaction was only slight (58:42) and was due to the dienophile approaching the diene with a slight preference from the *anti* face to the hydroxyl.

The examples described above were presumed to follow *Pathway B*, an intermolecular DA reaction followed by an intramolecular esterification. Although the proposed intermediates were not isolated, there is some evidence to support this version of events. When comparing the reaction of protected dienols with MA to produce anhydrides with that of the unprotected dienols to form lactones, similar product distributions, rates and yields were reported indicating a similar reaction pathway *i.e.* an initial DA reaction.[12,16] The use of silyl protecting groups, however, must alter both the steric and electronic attributes of the diene relative to the parent dienol. As such, the use of silyl ethers in elucidating the reaction pathway between dienols and MA must be treated with caution. In one example the half-ester of the dienol under investigation (the proposed intermediate if the reaction followed *Pathway A*) was prepared independently and found to be resistant to cyclisation under the same reaction conditions used for the successful "mix and heat" DA reaction.[13] This appears to eliminate the half-ester as a likely reaction intermediate and indicates that the reaction occurs *via Pathway B*.

3.1.1.3 Examples Supporting Pathway A: Intermolecular Esterification Followed By IMDA Reaction

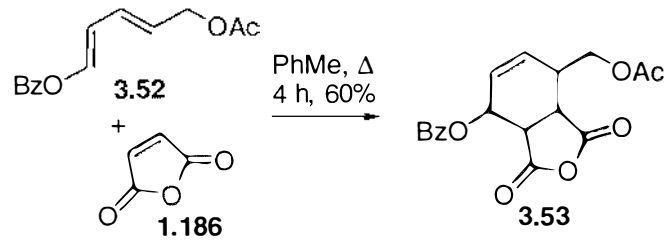
In contrast to the above examples, other groups have contended that *cis*-fused lactonic acids are formed *via* a pathway in which the formation of a maleate half-ester **3.3** occurs first, followed by an IMDA reaction (**Scheme 3.2**, - *Pathway A*).[17-24]

Becher *et al.* studied the reaction between oxygenated dienols and MA. The benzoyl substituted dienol **3.49** and MA were heated to reflux in chloroform to yield only the *cis*-fused cycloadduct **3.51** as a white crystalline adduct in 72% yield (**Scheme 3.16**).[17,18] The postulated intermediate, maleate half-ester **3.50**, was not isolated in these studies yet Becher *et al.* believed the reaction to proceed *via Pathway A* (**Scheme 3.2**).



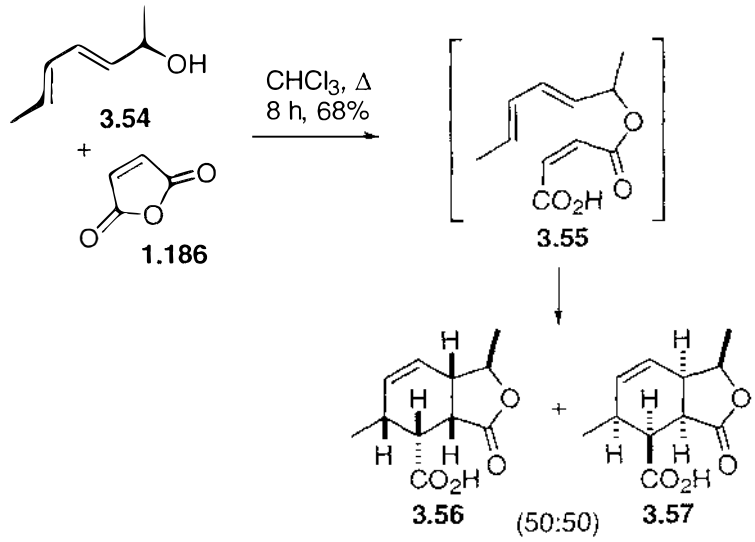
Scheme 3.16

Corroborative evidence for this pathway was that the acetate derivative of the pentadienol, **3.52**, underwent an **inter**molecular cycloaddition at elevated temperatures (reaction in refluxing toluene *versus* reaction in refluxing chloroform) (**Scheme 3.17**). Based upon the lack of reactivity of the acetate towards an intermolecular DA reaction, it was assumed that dienol **3.49** would undergo esterification before an intermolecular DA reaction could take place and thus, an IMDA reaction would occur. It must be noted, as with the silyl ethers (*vide supra*) that the acetate group would, in all likelihood, alter the steric and electronic characteristics of the system and hence the reactivity of the diene.



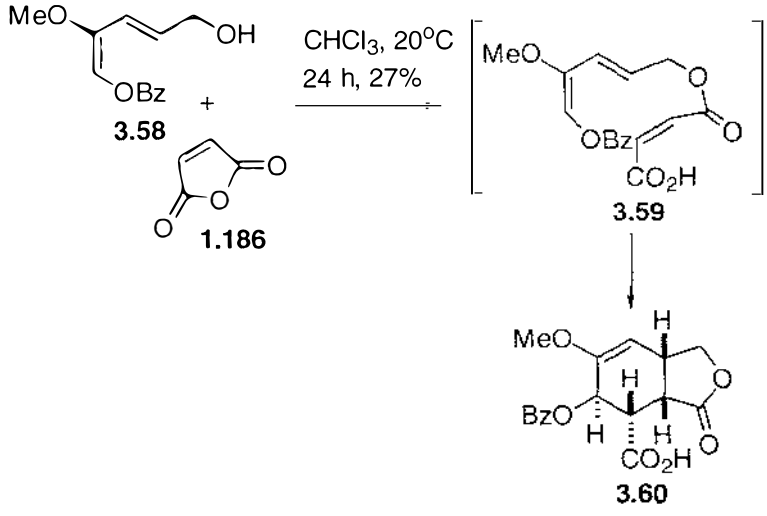
Scheme 3.17

Gree and Martelli reacted the racemic dienol **3.54** with MA in refluxing chloroform for 8 hours, resulting in a 50:50 mixture of the diastereoisomeric *cis*-fused cycloadducts **3.56** and **3.57** (**Scheme 3.18**).[20] It was assumed that the MA and dienol esterified to form a half-ester intermediate **3.55** before undergoing an IMDA reaction, however there was no evidence for this chain of events and, once again, the intermediate was not isolated. The lack of π–facial selectivity (both of the diastereoisomers are formed in equal amounts) is surprising when compared to the moderate selectivities shown by DA reactions on similarly substituted dienols performed by Franck *et al.* and Arseniyadis *et al.* (**Scheme 3.11** and **Scheme 3.13**).[3,10,12] The terminal methyl group of **3.54** appears to decrease the facial selectivity of the reaction (*c.f.* **Scheme 3.11**). The differing reaction conditions used in these reactions could also result in differing selectivities.[3,10,12,20]



Scheme 3.18

The reaction of the methoxy substituted *E,Z*-diene **3.58** with MA was investigated by Becher and co-workers (**Scheme 3.19**).[19] Reaction of dienol **3.58** and MA occurred at RT in chloroform (*c.f.* the reaction of unsubstituted all-*trans* dienol **3.49** with MA in $CHCl_3$ after prolonged reflux[18]) showing that both the electron donating group and *E,Z* geometry of the diene resulted in a more activated system for cycloaddition. Despite proposing the half-ester **3.59** as the reaction intermediate, Becher and co-workers did not isolate this adduct and assumed that the reaction followed *Pathway A* to produce *cis*-fused adduct **3.60**.



Scheme 3.19

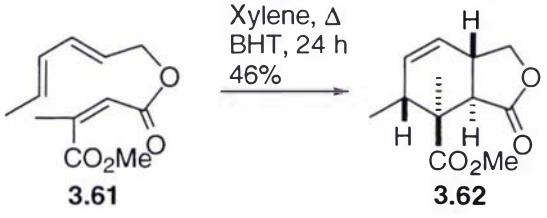
The evidence for the reaction between dienols and anhydrides to form lactonic acids following *Pathway A* is scant. The slow rate of acetate protected dienol **3.52** (which can

only react *via* an intermolecular DA) compared to that of its corresponding alcohol **3.49** has been cited as confirming the mechanism as intermolecular esterification with a subsequent IMDA reaction.

3.1.2 The Varying Stereochemical Outcomes Of The IMDA Reactions Of Esters And Acids

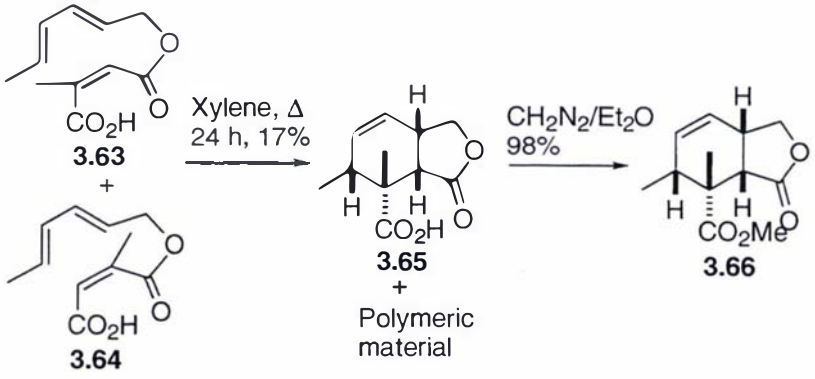
Possibly the most compelling evidence for the intramolecularity of the cycloaddition step in the formation of lactone acids is the ample literature precedent of *endo*-IMDA reactions of substituted maleate half-ester derivatives of dienols.

White and co-workers compared the IMDA reactions of citraconic anhydride-derived half-esters with those of the corresponding methyl esters.[21,22] When the citraconate-derived, methyl ester **3.61** was heated in refluxing xylene, a single adduct **3.62** was formed, the result of an *exo* transition state (**Scheme 3.20**).



Scheme 3.20

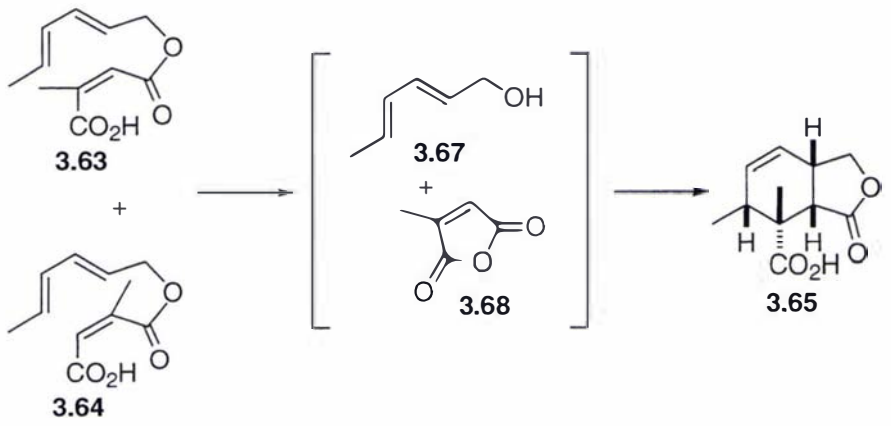
The citraconate half-esters **3.63** and **3.64** proved inseparable, therefore, White *et al.* heated the mixture of regioisomers in refluxing xylene (**Scheme 3.21**).



Scheme 3.21

Only the single cycloadduct **3.65** was produced, which was methylated for characterisation purposes. Lactone **3.65** was deduced to be the result of the IMDA reaction of **3.63** with the other half-ester isomer **3.64** producing only polymeric material.

From these results, White and co-workers deduced that esters and acids gave differing stereochemistries in the IMDA reaction. Recent work by Lilly, however, has demonstrated that the most likely sequence of events is breakdown of the citraconate esters to the dienol **3.67** and anhydride **3.68** followed by an **inter**molecular DA reaction producing (after lactonisation) the *cis*-fused adduct **3.65**.[25]

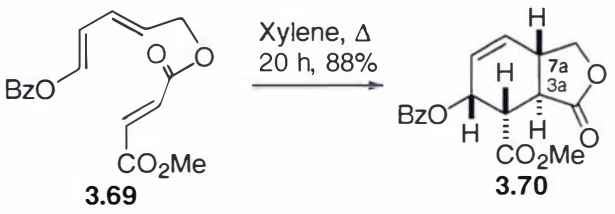


Scheme 3.22

A few years after White's initial studies, Becher *et al.* reported that the reaction of dienol **3.49** with MA gave only the *cis*-fused lactone **3.51** (**Scheme 3.16**).[17] The reaction pathway was described by Becher *et al.* as an **inter**molecular esterification followed by an IMDA reaction with the maleate half-ester intermediate **3.50** reportedly unisolable. The coupling constant between H3a and H7a (J = 8.5 Hz) confirmed the *cis*-fused ring junction of the product. After investigating the mother liquor from the crystallisation and finding no *trans*-fused adduct, Becher *et al.* deduced that the IMDA reaction of the proposed maleate half-ester intermediate **3.50** occurred exclusively via the *endo* transition state.

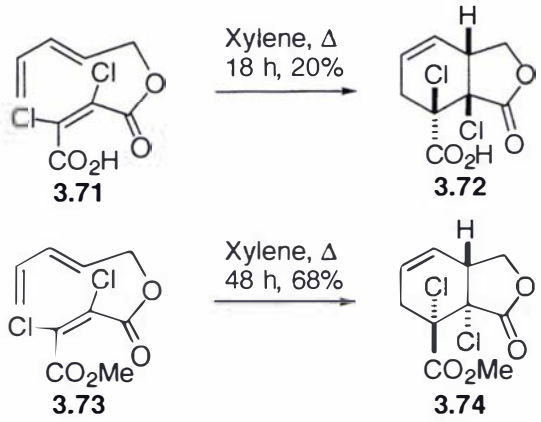
In contrast, when the fumarate ester **3.69** in which the dienophile is terminally substituted with a methyl ester group was heated to reflux in xylene only the *trans*-fused product **3.70** resulted (**Scheme 3.23**).[18] The coupling constant between the ring-junction protons ($J_{H3a\text{-}H7a}$ = 13.3 Hz) was indicative of a *trans*-fused lactone. From these and other results on related systems, Becher *et al.* concluded that IMDA reactions where the dienophile was terminally substituted with an ester group were selective for the *exo*

transition state whereas the IMDA reactions of triene acids were selective for the *endo* transition state.[17-19]



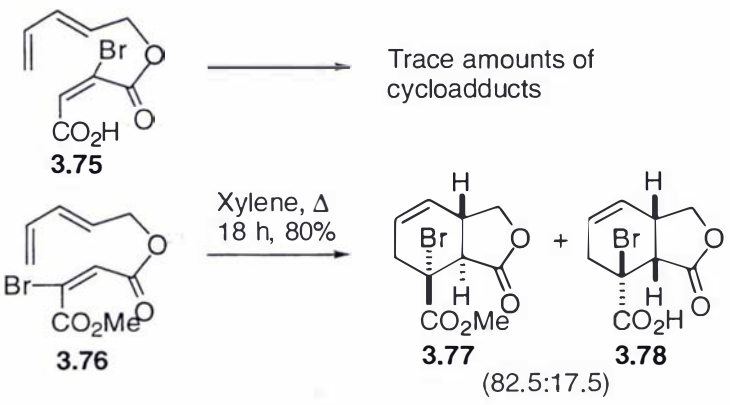
Scheme 3.23

Batchelor and Mellor studied the IMDA reactions of triene esters derived from dichloromaleic anhydride and bromomaleic anhydride.[23,24] The chlorinated half-ester **3.71** produced solely the *cis*-fused adduct **3.72** when heated to reflux in xylene (**Scheme 3.24**). The corresponding methyl ester **3.73** produced only a *trans*-fused adduct **3.74**.



Scheme 3.24

Bromo-substituted acid **3.75** gave only trace amounts of the expected cycloadducts. However the related bromine-substituted methyl ester **3.76** cyclised to form a 82.5:17.5 mixture of *trans* and *cis*-fused adducts (**Scheme 3.25**). The major product of the IMDA reaction was *trans*-fused **3.77**. These results confirmed the tenet that triene esters and triene acids cyclise *via* differing transition states.



Scheme 3.25

In addition to the results described above, Kim and Kim reacted the maleate half-ester **3.25** to produce only the *cis*-fused cycloadduct **3.24** as previously described (**Scheme 3.10**).[13]

The IMDA reactions of ester-linked trienes containing a dienophile terminally substituted with an ester group have been shown to be generally selective for *trans*-fused adducts and hence occur preferentially *via* an *exo* transition state (**Chapter 2**). Assuming that the pathway of reactions between dienols such as **3.1** and MA consists of an **inter**molecular esterification to form a maleate half-ester intermediate and then an **intra**molecular DA reaction leads to the conclusion that the IMDA reaction of ester-linked triene acids such as **3.3** produce *cis*-fused cycloadducts and proceed *via* an *endo* transition state. Therefore, it has been a previously accepted rule that the IMDA reactions of esters and acids proceed *via exo* and *endo* transition states respectively.[17-19,21,23,24] However, as the above overview of the literature concerning the reaction between dienols and MA shows, the reaction mechanism is not definitively known and the proposed intermediates for either pathway have not been observed nor isolated.

3.1.3 Scope And Aims Of This Investigation

It is clear from the foregoing review that only one example has appeared in the literature in which the preparation of a maleate half-ester was carried out prior to thermolysis.[13] The authors report the conversion of the precursor triene into the *endo* adduct, a stereochemical outcome in line with the other examples of carboxylic acid-terminated trienes (*vide supra*). Due to recent findings by Lilly[25,26] and since controversy still remains over the mechanism of this transformation (**Scheme 3.2**), it was decided that a more thorough investigation into the reaction pathway was warranted. This study involved:

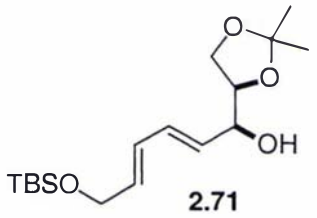
- A comparison of the outcomes of *three* related reactions of a chiral trienol and maleic anhydride; under "mix and heat" conditions, with pre-formation of the maleate half-ester and with prior formation of the corresponding triene methyl ester.

- A reinvestigation of Becher's "mix and heat" reaction (**Scheme 3.16**) using an NMR experiment and, once again, a comparison of the outcome of this reaction with those obtained from the thermolysis of the pre-formed maleate half-ester and the corresponding triene methyl ester.

3.2 The Stereochemical Outcomes Of An Intermolecular DA And An IMDA Reaction On A Chiral Dienol

3.2.1 Synthesis And IMDA Reaction Of The Maleate Half-Ester Of A Chiral Dienol

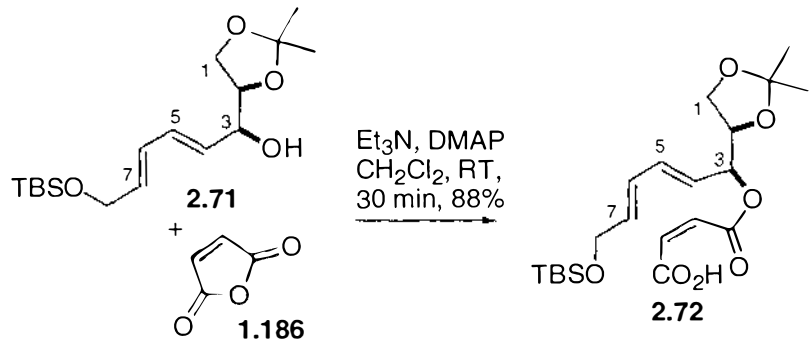
An enantiomerically pure, chiral dienol with steric bulk in close proximity to the hydroxy group **2.71** (**Figure 3.1**) was synthesised as described in **Chapter 2, Section 2.3.**



2.71

Figure 3.1

The maleate half-ester **2.72** was prepared by esterification of the dienol **2.71** with MA (**Scheme 3.26**). The maleate half-ester **2.72** proved to be unstable, undergoing an IMDA reaction when stored at 0°C, which made full characterisation of this triene difficult. The high reactivity of maleate half-ester **2.72** towards cycloaddition was unexpected and a possible explanation is the reactive rotamer effect caused by the dioxolane substituent on the ester tether.** Full characterisation of this reactive intermediate was not possible, however, the transformation of dienol **2.71** to maleate half-ester **2.72** was confirmed from the ^{1}H NMR spectrum. The disappearance of the hydroxyl peak (previously a broad singlet at 2.25 ppm) and the shift downfield of the C3 methine proton from 4.35 ppm (1H, tm, J = 6.1 Hz) to 5.51 ppm (1H, dd, J = 8.0, 4.1 Hz) indicated the formation of the new ester link. In addition, there was an increase in signals in the alkenic region due to additional vinylic protons corresponding to the presence of the maleate residue (6.51-6.14 ppm, 4H, m, H5, H7, maleate H's). Further confirmation of this structure (**2.72**) was obtained from its conversion to the more stable methyl ester (**Chapter 2**).

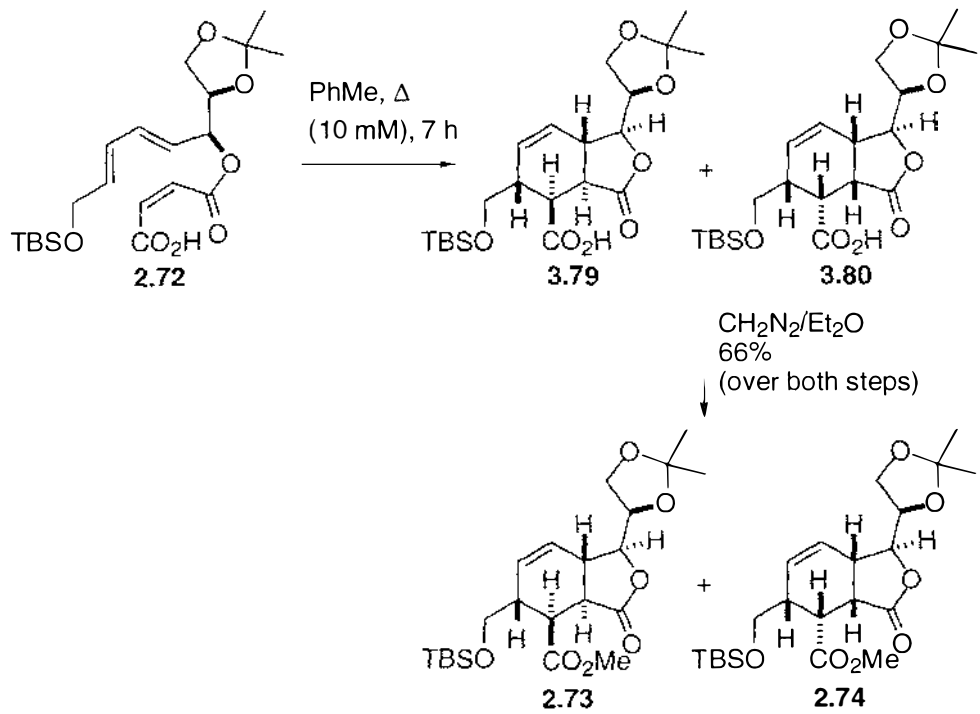


Scheme 3.26

Based on previous reports of the IMDA reactions of maleate half-esters, it was expected that the IMDA reaction of **2.72** would occur preferentially *via* the *endo* transition state to produce *cis*-fused adducts.[18,21-24] Surprisingly, the IMDA reaction (performed in refluxing toluene with a substrate concentration of 10 mM) produced a 86:14 mixture of *trans* and *cis*-fused bicyclic lactones **3.79** and **3.80** (**Scheme 3.27**) which were methylated and characterised. The reaction was both *exo* selective (86:14) and extremely π-facial selective (100:0). The preference for an *exo* adduct was consistent with the results of **Chapter 2** in which maleate and fumarate derived triene esters showed a preference for the *exo* transition state with ratios of 86:14 and 75:25 respectively. However, this *exo* preference was contrary to previous results reported in the literature

** Described more fully in **Chapter 2**.

for purported IMDA reactions of ester-tethered trienes with the dienophile terminally substituted with an acid group.[18,21-24]



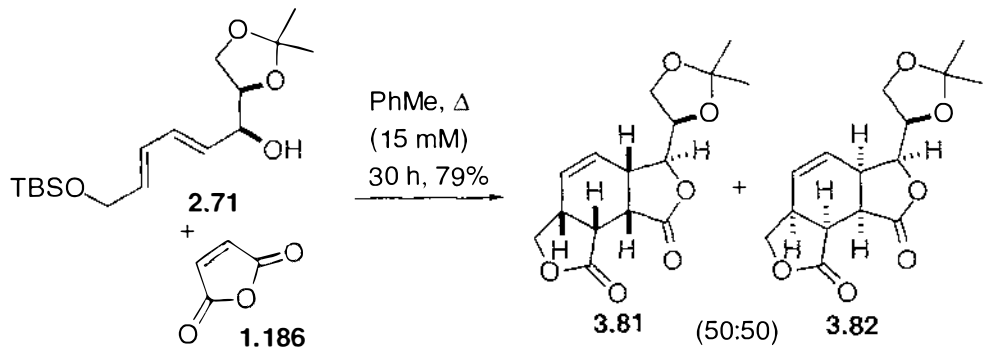
Scheme 3.27

The products of the IMDA reaction of acid **2.72** were characterised as the methyl esters and the structures assigned using NOESY and COSY NMR experiments. By converting the mixture of lactone acids (**3.79** and **3.80**) to the corresponding methyl esters *via* treatment with diazomethane a direct comparison of the product ratios and structures between the IMDA reaction of acid **2.72** with that of the methyl ester **2.56** was possible. It is important to note that there was no difference in either the products or the product ratios (86:14; *exo:endo* in both cases) between the IMDA reactions of the triene acid **2.72** and triene methyl ester **2.56**.

3.2.2 "Mix And Heat" DA Reaction Of The Chiral Dienol And MA

Previous studies of the IMDA reactions of maleate half-esters had used the "mix and heat" method where the dienol and MA were heated together and it was assumed that the half-ester was produced *in situ*.[17-20] These conditions were applied to the reaction of dienol **2.71** and MA. Dienol **2.71** and MA were dissolved in toluene and heated to reflux to

produce a 50:50 mixture of *cis*-fused *bis*-lactones **3.81** and **3.82**[††] in 79% yield, the result of an *endo*-selective DA reaction (**Scheme 3.28**). This result differs from that of that of the pre-formed half-ester reaction (86:14 *exo:endo* cycloadducts, **Scheme 3.26**) despite the fact that half-ester **2.72** would be the proposed intermediate in *Pathway A* (**Scheme 3.2**). The results reported above suggest that the reaction between the chiral dienol **2.71** and MA occurs *via Pathway B* (**Scheme 3.2**).



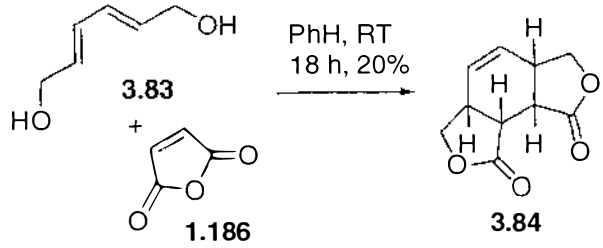
Scheme 3.28

An important facet of the "mix and heat" reaction of dienol **2.71** and MA is the lack of π-facial selectivity (a 50:50 mixture of diastereoisomers is produced) when compared to the IMDA reaction of the pre-formed maleate half ester **2.72** (an 86:14 mixture of diastereoisomers). This lack of facial selectivity is in agreement with a previous reaction of a 1-substituted-2,4-dien-1-ol,[20] however other groups have reported moderate to high facial preferences for such reactions.[3,10-12] Presumably the different stereochemical elements (*i.e.* allylic and homoallylic stereocentres) in dienol **2.71** are combining in a way that results in no overall π-facial discrimination.

Under the "mix and heat" reaction conditions, the TBS group was lost enabling the formation of the *bis*-lactone adducts. This did not occur during the IMDA reaction of maleate half-ester **2.72**, with neither of the two cycloadducts resulting from this reaction appearing as *bis*-lactones. In the *trans*-fused adduct **3.79**, the silyl ether and the carboxylic acid are not in the correct configuration for lactone formation. However, in the *cis*-fused adduct **3.80** these groups are in a favourable position yet lactonisation does not occur. A possible reason for this is in the differing reaction conditions used for the IMDA and "mix and heat" reactions. Both reaction methods used similar concentrations (15 mM for the "mix and heat" and 10 mM for the IMDA reaction) and were both performed in refluxing toluene, the difference being the presence of MA in the "mix and heat" reaction. It is conceivable that the acidic nature of the carboxylate salt allows the deprotection of the

[††] COSY and NOESY spectra for *bis*-lactone **3.82** are contained in the **Appendix**.

silyl group hence favouring the formation of the 5 membered lactone. A previous example in the literature of formation of a *bis*-lactone from a DA reaction involved the reaction of diene diol **3.83** with MA to give *bis*-lactone **3.84** (**Scheme 3.29**).[27] In this case both of the hydroxyl groups were unprotected but the reaction of diol **3.83** shows that if the silyl ether of dienol **2.71** is lost under the conditions of the intermolecular DA reaction, then ready formation of a *bis*-lactone will occur.



Scheme 3.29

3.2.3 A Comparison Of The IMDA And "Mix And Heat" Reactions

Previously, it has been reported that maleate half-esters of dienols undergo *endo*-selective IMDA reactions (**Scheme 3.2**) to form *cis*-fused adducts. The work in this thesis does indeed show the "mix and heat" reaction of the chiral dienol **2.71** and MA producing a *cis*-fused adduct. However, the IMDA reaction of the implied intermediate of *Pathway A* (**Scheme 3.2**), maleate half-ester **2.71**, gives a *trans*-fused cycloadduct. In addition, the IMDA reaction of **2.72** is highly facial selective (86:14) whereas the "mix and heat" reaction of dienol **2.71**, previously assumed to be an IMDA reaction, displayed a lack of facial selectivity (50:50).

These seemingly anomalous results prompted further investigation into the tenet that the IMDA reactions of maleate half-esters give preferentially *cis*-fused adducts, and indeed, into the mechanism of the "mix and heat" reaction.

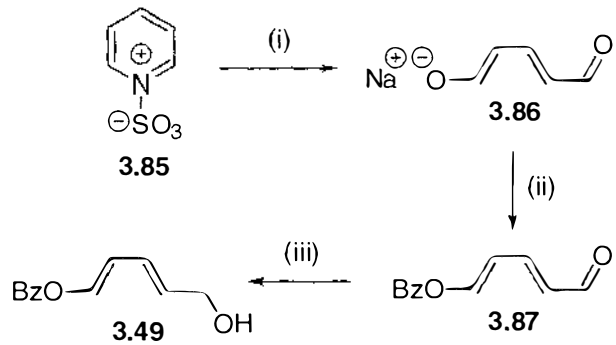
3.3 Investigation Into Previous Work

3.3.1 Description Of Previous Work By Becher *et al.*

As described in **Section 3.1.2** Becher *et al.* assumed that the "mix and heat" reaction of dienol **3.49** and MA followed a pathway in which the half-ester was formed *in situ* and then underwent an IMDA reaction. In order to investigate the results of Becher *et al.*, it was decided to attempt to synthesise the previously unisolated maleate half ester **3.50** and compare the results of the IMDA reaction with those obtained by the "mix and heat" method. Methylation of the maleate half-ester would then allow a direct comparison of the stereochemistries of the IMDA reactions of acids and esters.

3.3.2 Investigation Of Becher's Research

Dienol **3.49** was obtained using literature procedures.[28-31] Pyridinium-1-sulfonate **3.85** was treated with aqueous sodium hydroxide solution to provide sodium glutaconaldehyde dihydrate **3.86** (**Scheme 3.30**). Acylation of **3.86** with benzoyl chloride in pyridine yielded aldehyde **3.87**. Reduction of **3.87** with sodium borohydride gave dienol **3.49**.

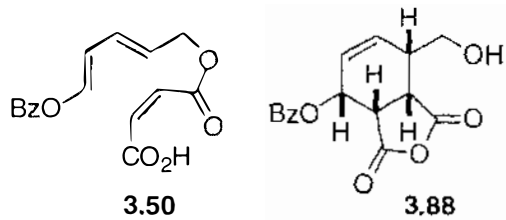


Scheme 3.30

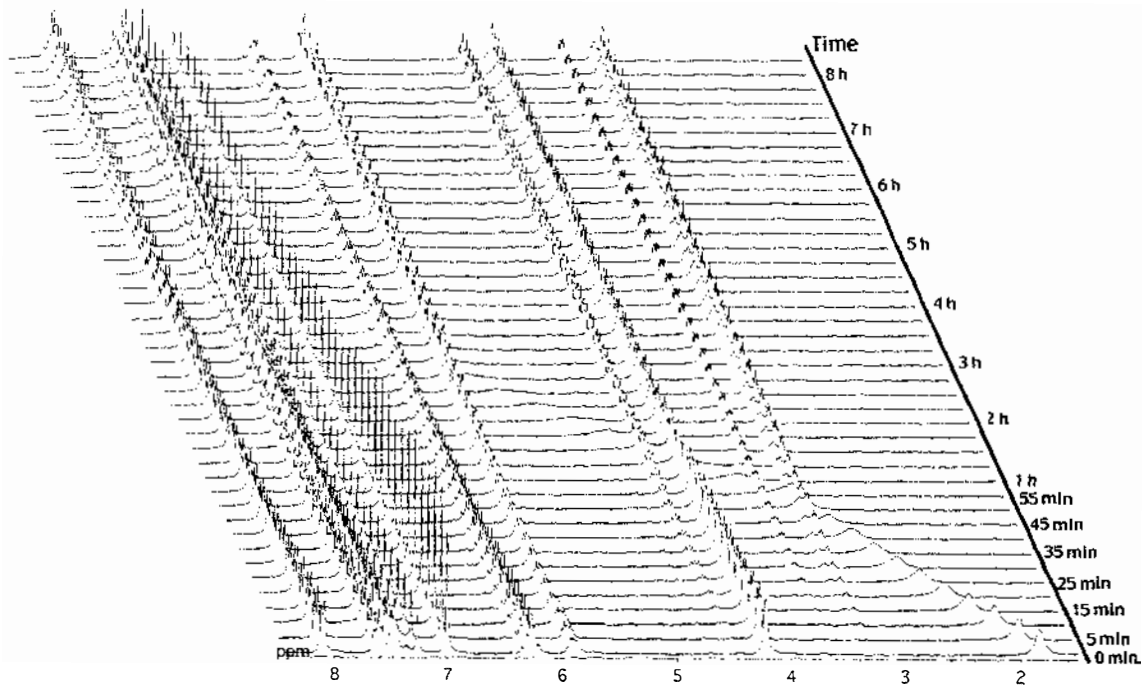
Reagents and Conditions: *(i) aq. NaOH, -5°C→60°C, 55%; (ii) BzCl, py, RT, 5 min, 60%; (iii) $NaBH_4$, 1,4-dioxane, RT, 16 h, 69%.*

3.3.2.1 Following The Progress Of The Reaction By ^1H NMR Spectroscopy

An NMR experiment was performed in order to provide evidence on the nature of the reaction between MA and dienol **3.49**. It was hoped that the formation of either the proposed *Pathway A* intermediate **3.50** or the proposed *Pathway B* intermediate **3.88** would be observed on the NMR timescale (**Scheme 3.31**). The dienol **3.49** and MA were dissolved in deuterated chloroform in an NMR tube and heated to 55°C for 8.5 hours, with ^{1}H NMR spectra recorded at 5 minute intervals.



Scheme 3.31



Stacked plot of ^1H NMR spectra against time, showing the course of the reaction between the dienol 3.49 and MA. Spectra are shown every 5 minutes for the first hour and then every 15 minutes subsequently.

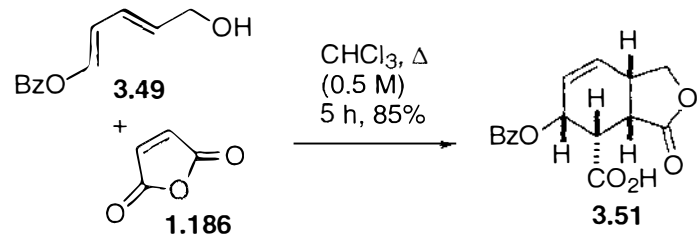
Figure 3.2

The stack plot (**Figure 3.2**) shows the clean conversion of the mixture of dienol **3.49** and MA (singlet at 7.1 ppm) to the lactonic acid **3.51**. Unfortunately, neither of the two proposed intermediates, **3.49** (*Pathway A*) or **3.88** (*Pathway B*), were observed.

During the conversion of the dienol **3.49** to the lactonic acid **3.51**, the second step (whether *Pathway A* or *B* - **Scheme 3.2**) must be much faster than the first as the intermediate can not be detected. Due to the ^{1}H NMR experiment providing no evidence for either *Pathway A* or *Pathway B*, a more thorough investigation was necessary.

3.3.2.2 A Comparison Of The "Mix And Heat" DA Reaction Of The Dienol And MA With The IMDA Reaction Of The Maleate Half-Ester

In order to confirm the stereochemistry of the product, the "mix and heat" reaction of dienol **3.49** and MA performed by Becher *et al.* was repeated in the laboratory. A mixture of dienol **3.49** and MA was refluxed in chloroform for 5 hours giving only the *cis*-fused cycloadduct **3.51** in high yield (85%) as a white solid (**Scheme 3.32**). The ^{1}H and ^{13}C NMR spectra of **3.51** were in agreement with those of the literature compound.[18] This confirmed the result obtained by Becher *et al.* in which the product of the reaction of dienol **3.49** and MA was the result of an *endo* transition state during the DA reaction.

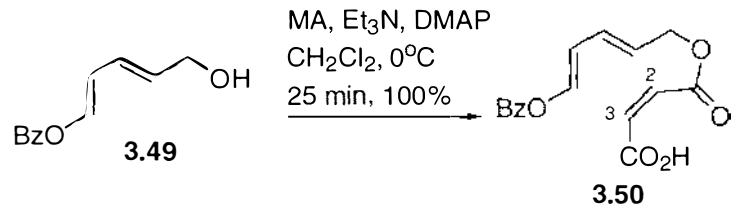


Scheme 3.32

By preparing the expected intermediate for *Pathway A*, the maleate half-ester **3.50**, and comparing its IMDA reaction to the "mix and heat" reaction between MA and dienol **3.49** described above, it was hoped to either confirm or disprove Becher's postulated mechanism.

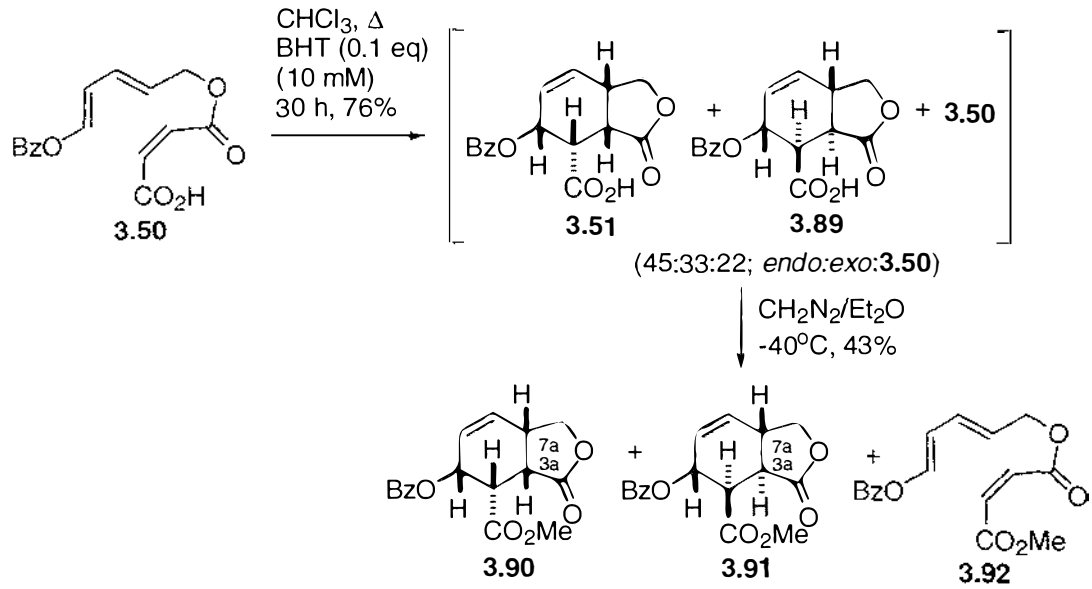
The previously prepared dienol **3.49** was esterified with MA in dichloromethane using triethylamine and DMAP to give **3.50** (**Scheme 3.33**). Unlike the maleate half-ester of the chiral dienol (**2.72**), the maleate half-ester **3.50** was easily isolated and fully characterised. A broad singlet at 10.42 ppm in the ^{1}H NMR spectrum indicated the

presence of the carboxylic acid proton. New peaks in the alkenic region confirmed the presence of the maleate alkenic protons (7.04-6.33 ppm, 2H, m, H2, H3). The ^{13}C NMR spectrum displayed three signals due to the carbonyl carbons: the benzoyl group, the ester tether functionality and the carboxylic acid group (166, 166 and 163 ppm). The IR spectrum displayed an H-bonded O-H stretch at 3089 cm^{-1}.



Scheme 3.33

The IMDA reaction of maleate half-ester **3.50** (**Scheme 3.34**) was performed using the conditions used by Becher and co-workers in their "mix and heat" DA reaction of dienol **3.49** and MA. Reaction was much slower than with the "mix and heat" method, with starting material remaining after 30 hours of heating in refluxing chloroform (the "mix and heat" reaction was found to be complete after 5 hours, **Scheme 3.32**). The IMDA reaction resulted in a 45:33:22 mixture of *endo* adduct **3.51**, *exo* adduct **3.89** and starting material **3.50** (**Scheme 3.34**).



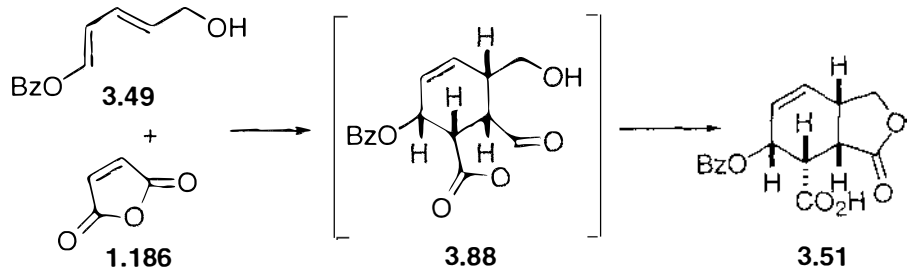
Scheme 3.34

To enable separation and easier handling, the mixture of acids **3.51**, **3.89** and **3.50** were methylated *in situ* with diazomethane to give *cis*-fused cycloadduct **3.90**, *trans*-fused cycloadduct **3.91** and the methylated starting material **3.92**. The *cis*-fused adduct **3.90** exhibited a characteristic *cis*-fused ring junction coupling constant ($J_{H3a\text{-}H7a}$ = 8.6 Hz). In contrast, the coupling constant between the H3a and H7a protons of **3.91** ($J_{H3a\text{-}H7a}$ = 13.6 Hz) indicated a *trans*-fused ring junction for this compound. Both cycloadducts were further identified using NOESY and COSY data (for COSY and NOESY spectra of **3.90** see **Appendix**).

It was decided to repeat the reaction in a higher boiling solvent in order for it to reach completion. The maleate half-ester **3.50** was refluxed in toluene with a substrate concentration of 10 mM for 2 hours to give an inseparable mixture of *cis*- and *trans*-fused adducts **3.51** and **3.89** in a 57:43 ratio and 71% yield. The ratio of *cis*- and *trans*-fused adducts remained the same as in the previous experiment (57:43) indicating that reaction temperature had no effect on the product ratio. The *cis*-fused adduct **3.51** and *trans*-fused adduct **3.89** were identified by comparison of the ^{1}H NMR spectrum of the mixture with ^{1}H NMR spectra of the literature compound **3.51**[18] and the previously identified methylated *trans*-fused adduct **3.91** (produced from the reaction carried out in chloroform described in **Scheme 3.34**).

The results of the IMDA reaction of the maleate half-ester **3.50** discussed above are inconsistent with the mechanism for the "mix and heat" reaction of dienol **3.49** and MA proposed by Becher and co-workers. In the study reported by Becher *et al.*, the result of reaction between dienol **3.49** and MA was a single *endo* cycloadduct.[18] However in the reaction described above, in which Becher's proposed intermediate for the "mix and heat" reaction undergoes an IMDA reaction, a mixture of both *endo* and *exo* results (57:43; *cis:trans*-fused).

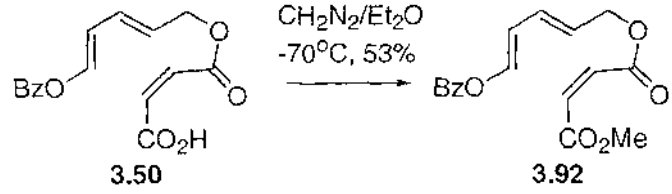
The differing stereochemical outcomes for the pre-formed half-ester and "mix and heat" procedures indicated that two different reaction pathways were operating. The reaction of the pre-formed maleate half-ester **3.50** was an **intra**molecular DA reaction. The "mix and heat" method as used previously in the literature had followed *Pathway B* (**Scheme 3.2**); i.e. an **inter**molecular DA reaction and a subsequent **intra**molecular esterification (**Scheme 3.35**).



Scheme 3.35

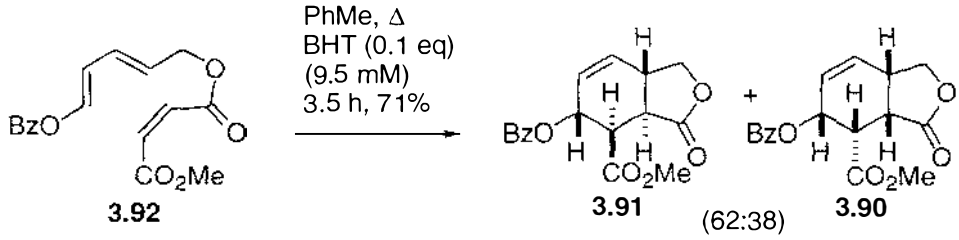
3.3.3 The IMDA Reaction Of The Maleate Methyl Ester

To further examine the stereoselectivity of the IMDA reaction in this series, methyl ester **3.92** was prepared. Treatment of acid **3.50** with an ethereal solution of diazomethane produced the methyl ester **3.92** in moderate yield (**Scheme 3.36**).



Scheme 3.36

The IMDA reaction of the maleate ester **3.92** was performed in refluxing toluene for 3.5 hours producing a 62:38 mixture of *exo:endo* cycloadducts **3.91** and **3.90** in 71% yield (**Scheme 3.37**). These products were identical by ^{1}H and ^{13}C NMR spectra to the methylated cycloadducts of the IMDA reaction of the maleate half-ester (**Scheme 3.34**).



Scheme 3.37

The preference of the IMDA reaction of ester **3.92** for the *exo* transition state and hence, the *trans*-fused adduct **3.91** was in agreement both with literature results for the IMDA reactions of esters and also the high *exo* preference shown by the IMDA reactions of the

esters described in **Chapter 2**. It was interesting to note that whilst the previously performed IMDA reaction of the fumarate ester **3.69** occurred exclusively *via* the *exo* transition state, the maleate ester **3.92** produced a significant amount of *cis*-fused product. This shows the importance of dienophile geometry in determining the stereochemistry of these ester-tethered IMDA reactions.

Finally, it should be noted that the IMDA reaction of the maleate methyl ester **3.92** shows a slightly greater preference for the *trans*-fused cycloadduct (62:38; *trans:cis*) when compared to the maleate half-ester **3.50** (57:43; *cis:trans*). More significantly, these results clearly show that the general rule put forward by previous investigators (acid substrates undergo exclusively *endo*-mode IMDA; ester substrates undergo exclusively *exo*-mode IMDA reactions) is incorrect.

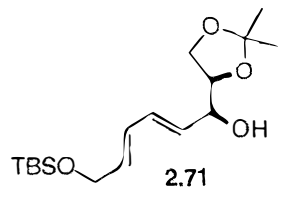
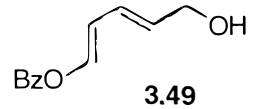
3.4 Summary

It is a well documented theory that the IMDA reactions of ester-linked trienes in which the dienophile has an ester as terminal substituent give rise to *exo* cycloadducts whereas those in which the dienophile has an acid as a terminal substituent give *endo* cycloadducts.[17-19,21-24] This general rule was based, in part, upon the assumption that the reaction of 2,4-dien-1-ols and MA proceeded *via* a pathway in which a maleate half-ester was formed *in situ* which then underwent an IMDA reaction (*Pathway A* - **Scheme 3.2**). However, a survey of the literature revealed that the pathway of the reaction between such dienols and MA is not definitively known.

The results of the IMDA reaction of a chiral maleate half-ester reported in this thesis (**Section 3.2**) differed from literature precedent in that there was a marked preference for the *trans*-fused cycloadduct (86:14; *trans:cis*). In contrast, the "mix and heat" reaction between chiral dienol **2.71** and MA produced only *cis*-fused products (**Table 3.1**). The IMDA reaction of half-ester **2.72** exhibited complete π-diastereofacial selectivity (100:0) yet the "mix and heat" reaction of dienol **2.71** showed no π-diastereofacial selectivity (50:50). These results prompted an investigation into the previously held assumption that a maleate half-ester was formed *in situ* during the "mix and heat" reaction of such dienols and MA.

Work performed by Becher *et al.*[17-19] was reinvestigated. It had been stated by Becher *et al.* that maleate half-ester **3.50** was unisolable, leading to use of the "mix and heat" method to study the supposed IMDA reaction. Contrary to the literature report, the intermediate proposed by Becher *et al.* was easily synthesised, isolated and fully

characterised. The IMDA reaction of this maleate half-ester **3.50** (and its corresponding methyl ester) was studied. Comparison of the stereochemistries of the resulting adducts to those of the "mix and heat" procedure (**Table 3.1**) indicated that the pre-formed maleate half-ester and "mix and heat" methods proceed *via* two different reaction pathways; one in which the DA reaction is intramolecular (*Pathway A* - **Scheme 3.2**) and one in which the DA reaction is intermolecular (*Pathway B* - **Scheme 3.2**).

Dienol	Mix And Heat *Endo:Exo*	Maleate Half-Ester *Endo:Exo*	Methyl Ester *Endo:Exo*
 **2.71**	100:0	14:86	14:86
 **3.49**	100:0	57:43	38:62

Product ratios (endo:exo) of the reactions between dienols and MA under differing conditions.

Table 3.1

The results of this work show that IMDA reactions of maleate half-esters of 2,4-dien-1-ols **3.1** produce mixtures of both *endo*- and *exo*-products but are generally *exo*-selective. Thermal reactions between 2,4-dien-1-ols **3.1** and MA, believed previously to be IMDA reactions following *Pathway A*, proceed by an initial *endo*-selective **inter**molecular DA reaction followed by **intra**molecular esterification (*Pathway B*). Therefore, previous reports describing these transformations as IMDA reactions actually involve **inter**molecular cycloadditions.

This work also has an important practical consideration. It can be seen that the stereochemistry of the reaction between dienols and MA can be controlled by effecting the cycloaddition either **inter**- or **intra**molecularly. This is a useful and significant result in view of the widespread use of the DA reaction in target synthesis.

3.5 References

(1) Heilbron, I. M.; Jones, E. R. H.; McCombie, J. T.; Weedon, B. C. L. *J. Chem. Soc.* **1945**, 84-87.

(2) Heilbron, I. M.; Jones, E. R. H.; McCombie, J. T.; Weedon, B. C. L. *J. Chem. Soc.* **1945**, 88-90.

(3) Arseniyadis, S.; Brondi-Alves, R.; Yashunsky, D. V.; Potier, P.; Toupet, L. *Tetrahedron* **1997**, *53*, 1003-1014.

(4) Grieco, P. A.; Nargund, R. P. *Tetrahedron Lett.* **1986**, *27*, 4813-4816.

(5) Arai, Y.; Takeda, K.; Masuda, K.; Koizumi, T. *Chem. Lett.* **1985**, 1531-1534.

(6) Greenlee, W. J.; Woodward, R. B. *Tetrahedron* **1980**, *36*, 3367-3375.

(7) Raphael, R. A.; Owens, C. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1504-1507.

(8) Griffiths, N.; Sawyer, L.; Taylor, P. *Acta Cryst.* **1992**, *C48*, 1320-1322.

(9) Jones, P. G.; Kennard, O. *Acta Cryst.* **1978**, *B34*, 2025-2027.

(10) Arseniyadis, S.; Brondi-Alves, R.; Wang, Q.; Yashunsky, D. V.; Potier, P. *Tetrahedron Lett.* **1994**, *35*, 7949-7952.

(11) Kanematsu, K.; Nagashima, S.; Takaoka, Y.; Kawakami, K.; Shiro, M. *Heterocycles* **1995**, *40*, 507-510.

(12) Franck, R. W.; Tripathy, R.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257-3262.

(13) Kim, D.; Kim, M. Y. *Arch. Pharm. Res.* **1986**, *9*, 19-20.

(14) Sun, K.-M.; Giuliano, R. M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4774-4780.

(15) Prein, M.; Adam, W.; Gläser, J.; Peters, K. *J. Am. Chem. Soc.* **1995**, *117*, 9190-9193.

(16) Fraser-Reid, B.; Benko, Z.; Guiliano, R.; Sun, K. M.; Taylor, N. *J. Chem. Soc., Chem. Commun.* **1984**, 1029-1030.

(17) Becher, J.; Ingendoh, A.; Clausen, H.; Nielsen, H. C. *Tetrahedron Lett.* **1985**, *26*, 1249-1252.

(18) Becher, J.; Nielsen, H. C.; Jacobsen, J. P.; Simonsen, O.; Clausen, H. *J. Org. Chem.* **1988**, *53*, 1862-1871.

(19) Becher, J.; Jorgensen, T.; Nielsen, H. C.; Malhotra, N. *J. Heterocyl. Chem.* **1992**, *29*, 1841-1845.

(20) Martelli, J.; Grée, D.; Kessabi, J.; Grée, R. *Tetrahedron* **1989**, *45*, 4213-4226.

(21) White, J. D.; Sheldon, B. G.; Solheim, B. A.; Clardy, J. *Tetrahedron Lett.* **1978**, *52*, 5189-5192.

(22) White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273-2280.

(23) Batchelor, M. J.; Mellor, J. M. *Tetrahedron Lett.* **1985**, *26*, 5109-5112.

(24) Batchelor, M. J.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 985-995.

(25) Lilly, M. J. PhD. thesis, Massey University, 1998.

(26) Lilly, M. J.; Sherburn, M. S. *Chem. Comm.* **1997**, 967-968.

(27) Bates, E. B.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 1854-1860.

(28) Becher, J. *Acta Chem. Scand.* **1972**, *26*, 3627-3635.

(29) Becher, J.; Haunso, N.; Pedersen, T. *Acta Chem. Scand.* **1975**, *B 29*, 124-132.

(30) Becher, J. *Synthesis* **1980**, 589-612.

(31) Becher, J. *Org. Synth.* **1980**, *59*, 79-84.

4. IMDA REACTIONS OF TETRAENES

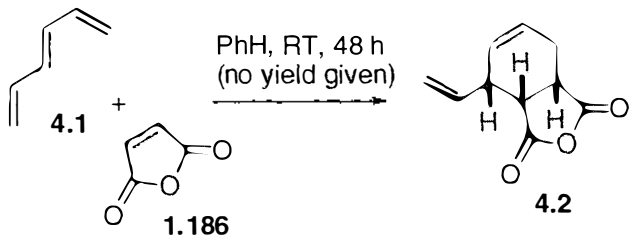
4.1 Introduction

4.1.1 Summary Of The Model Study Performed In Chapter 2

Studies of the IMDA reactions of chiral dienol derived esters (previously described in **Chapter 2**) have demonstrated both the ready reactivity and the very high stereoselectivity possible for the ester-tethered IMDA reaction. A logical extension to the IMDA reaction is to link it with a second DA reaction, either intermolecularly or intramolecularly, in order to construct more complex ring systems. This strategy would enable access to the tricyclic and tetracyclic systems of the natural products described in **Section 1.7** (**Chapter 1**). One method of ensuring that the functionality necessary for a second DA reaction (either intermolecular or intramolecular) is in place, is to use a conjugated tetraene as a *bis*-diene unit. In order to gather information on possible precursors to either a TIMDA reaction or a sequential IMDA/intermolecular DA reaction, the reactivity and selectivity of IMDA reactions of substrates consisting of a tetraene linked to a dienophile by an ester-tether needed to be investigated.

4.1.2 The Use Of Polyenes As Dienes In The DA Reaction

Alder and Schumacher first recognised the ability of conjugated polyenes to undergo the DA reaction, suggesting that trienes would be likely to react as substituted dienes albeit with a problem of regioselectivity due to the dienophile having a choice of dienes to react with.[1] It was also stated that tetraene, pentaenes and higher polyenes would be expected to react in a similar manner. This theory was reiterated in a review on the DA reaction by Sauer, in which conjugated polyenes were regarded as substituted butadienes.[2] An example of the propensity of polyenes to react as substituted dienes in the intermolecular DA reaction is the reaction of the conjugated triene, *E*-hexa-1,3,5-triene **4.1**, with maleic anhydride (MA) to produce the anhydride **4.2** (**Scheme 4.1**).[3,4] It is important to note the effect that the geometry of the conjugated polyene has on the rate of the DA reaction with all-*E* polyenes proving more reactive than their *Z* counterparts. For example, *E*-hexa-1,3,5-triene **4.1** underwent a DA reaction with MA at RT but *Z*-hexa-1,3,5-triene remained unreacted.[3]



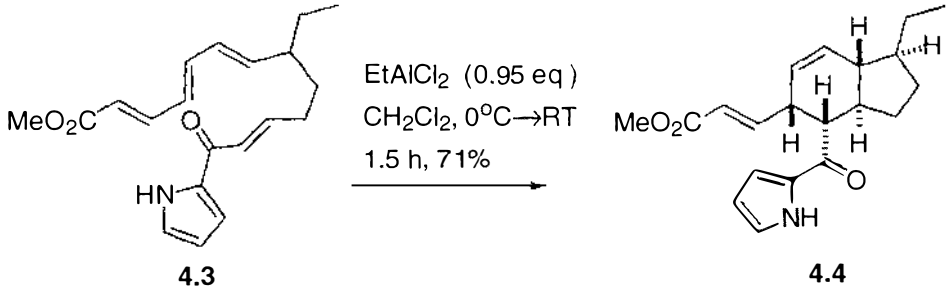
Scheme 4.1

4.1.2.1 The Use Of Conjugated Polyenes As Dienes In The IMDA Reaction

There are several previous examples of conjugated polyenes, such as trienes and tetraenes, being used as *dienes* in IMDA reactions. Of particular interest is that many of these examples feature the IMDA reaction of a conjugated polyene as the pivotal step in the synthesis of a natural product (such IMDA reactions have also been postulated as the key step in the biosynthesis of a wide range of natural products).

The antibiotic X-14547A has been the subject of several synthetic endeavours utilising the IMDA reaction of a conjugated triene or tetraene to construct the bicyclo[4.3.0]nonene ring system of the molecule.[5-8]

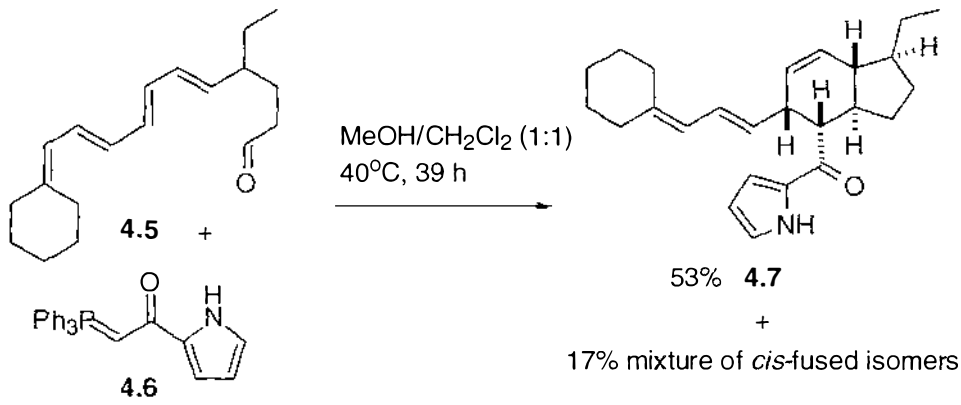
In the earliest synthesis using this approach, Roush and Myers treated racemic tetraene **4.3** with the Lewis acid, ethylaluminium dichloride.[5] This Lewis acid-mediated cyclisation was highly selective, producing the *trans*-fused adduct **4.4** in 71% yield with less than 5% yield of other stereoisomers (**Scheme 4.2**).



Scheme 4.2

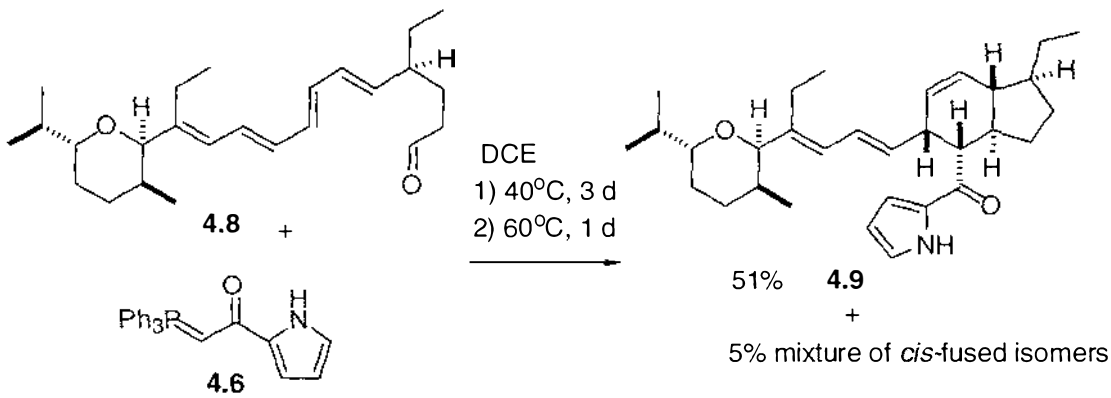
A variation of this reaction, in which the tetraene was formed *in situ* was less selective and led to a mixture of stereoisomers. The reduced selectivity was probably due to the more forcing reaction conditions used in this method (toluene at reflux, 25 hours).

Roush and Peseckis postulated that the biosynthesis of X-14547A involves the intramolecular cyclisation of a pentaene intermediate.[6] In a synthetic approach mimicking this, the racemic tetraene aldehyde **4.5** and phosphorane **4.6** were reacted in a tandem Wittig-IMDA reaction sequence. This produced a 53% yield of the desired *trans*-fused cycloadduct **4.7**, a model compound for X-14547A, and 17% of a mixture of two *cis*-fused isomers (**Scheme 4.3**).



Scheme 4.3

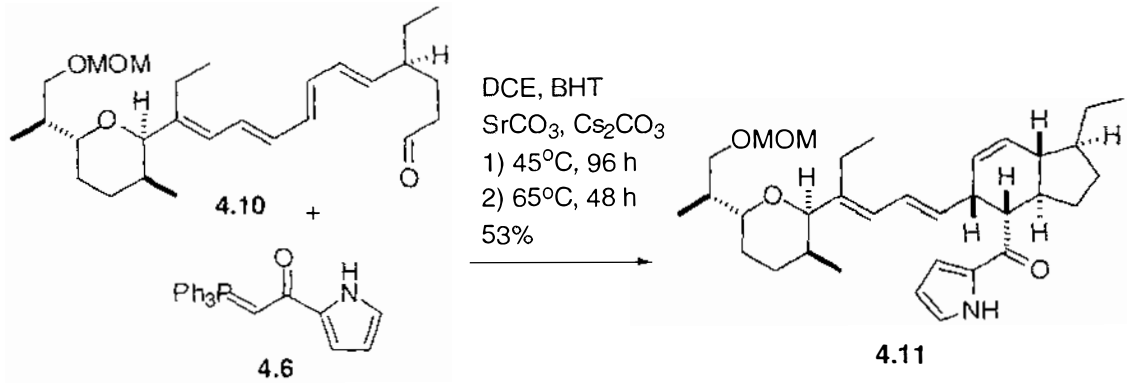
It must be noted that the previous reactions involved the use of racemic starting materials and hence were not enantioselective. In an extension of the work reported above,[6] enantiomerically pure tetraene aldehyde **4.8** was reacted with phosphorane **4.6**, producing 51% of *trans*-fused **4.9** and 5% of a mixture of *cis*-fused isomers (**Scheme 4.4**).[7]



Scheme 4.4

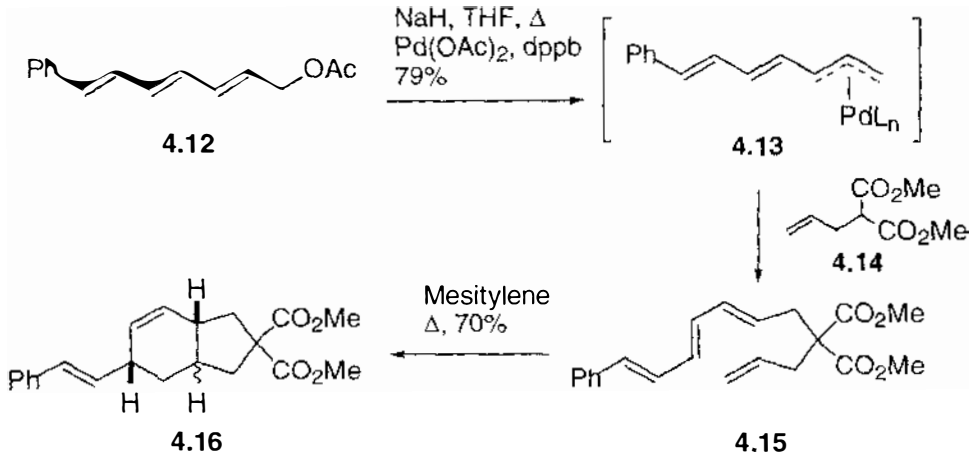
Boeckman and co-workers reported an efficient, enantioselective synthesis of X-14745A utilising the same tandem Wittig-IMDA approach as that used by Roush and Peseckis.[8] The Wittig reaction of optically pure aldehyde **4.10** and phosphorane **4.6** produced a

pentaene intermediate which immediately underwent an IMDA reaction to form the X-14745A intermediate **4.11** as a single enantiomer in 53% yield (**Scheme 4.5**). The tetraene of **4.10** proved to be unstable with a tendency towards polymerisation and a sensitivity to traces of acid in the reaction solution. The use of the inorganic bases $SrCO_3$ and Cs_2CO_3 alleviated problems caused by the acid sensitivity and the addition of BHT helped prevent polymerisation.



Scheme 4.5

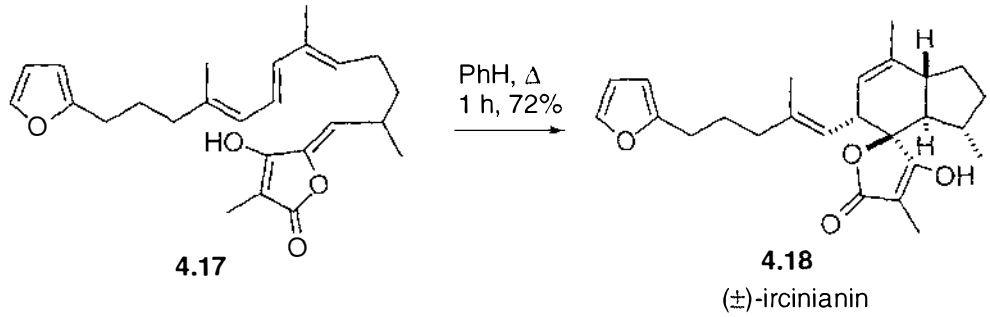
A way of overcoming the problem of the sensitivity of conjugated polyene substrates was proposed by Trost *et al.*[9] The unstable tetraene substrate **4.15** was generated by a palladium catalysed reaction immediately prior to intramolecular cyclisation (**Scheme 4.6**). The IMDA reaction of tetraene **4.15** gave the cycloadduct **4.16** in 70% yield (the stereochemistry at the ring-junction was not given).



Scheme 4.6

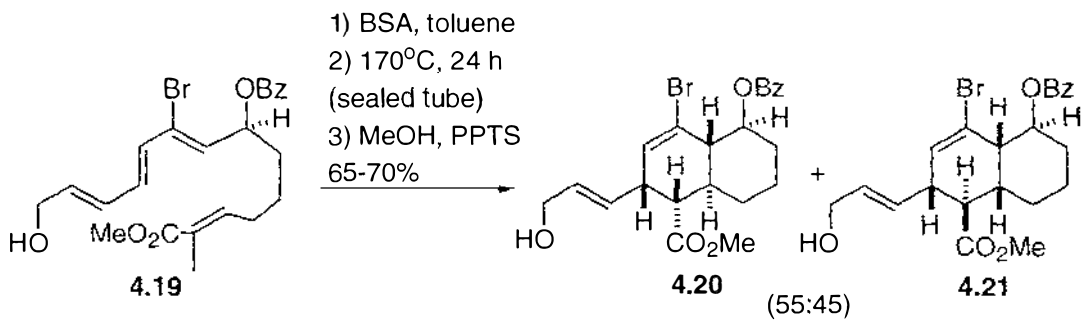
Ircinianin, a sesterterpene isolated from a marine sponge, is thought to be biosynthesised *via* an IMDA reaction. Yoshii and co-workers heated **4.17** in refluxing benzene to afford

racemic ircinianin **4.18** as the sole product in 72% yield (**Scheme 4.7**).[10] This IMDA reaction exhibited very high π-diastereofacial and *exo/endo* selectivity.



Scheme 4.7

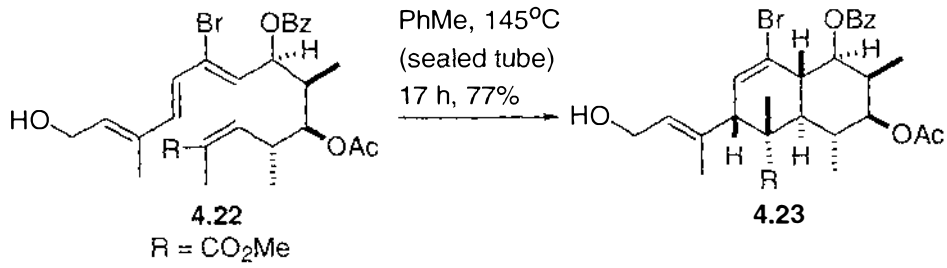
The first enantioselective synthesis of an intermediate towards the antibiotic chlorothricin featured the IMDA reaction of tetraene **4.19**.[11] The enantiomerically pure tetraene alcohol **4.19** was protected as the silyl ether with *bis*(trimethylsilyl)acetamide (BSA) and then heated in toluene in a sealed ampoule (**Scheme 4.8**). Deprotection of the silyl ether with catalytic pyridinium *p*-toluenesulfonate (PPTS) produced a mixture of diastereoisomers in 65-70% yield. The bromide group was intended to increase the selectivity of the reaction by providing increased $A^{1,3}$-strain and, indeed, a very high π-diastereofacial selectivity was evident. However, the *exo/endo* selectivity was minimal and only a slight preference for the *trans*-fused cycloadduct **4.20** was observed in the reaction.



Scheme 4.8

Kijanolide and tetronolide are two related natural products whose syntheses have involved, as a key step, the use of conjugated trienes in IMDA reactions.[12-15] Roush *et al.* synthesised a sub-unit of kijanolide and tetronolide *via* the intramolecular cyclisation of tetraene alcohol **4.22** (**Scheme 4.9**).[12] Analysis of the crude reaction mixture by 300 MHz ^{1}H NMR spectroscopy indicated a 97:3 ratio of cycloadducts and showed a very high selectivity towards the desired diastereomer **4.23**, isolated chromatographically in

77% yield. Again, it can be seen that substitution of the diene of the IMDA precursor with a bromide group results in high π-diastereofacial selectivity.

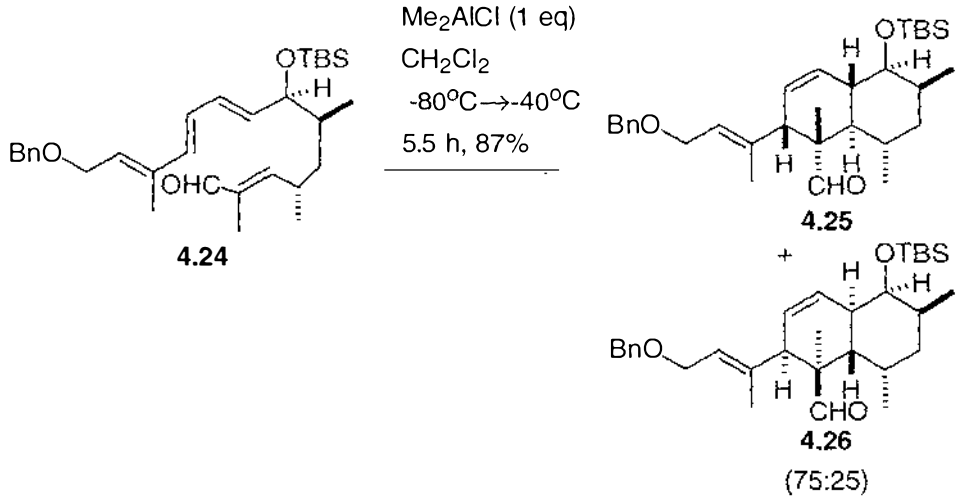


4.22
R = CO_2Me

4.23

Scheme 4.9

The same *trans*-octalin fragment of kijanolide and tetronolide was synthesised by Yoshii and co-workers.[13,14] It was found that Lewis acid-mediated cyclisation of silyl ether protected tetraene **4.24** produced a 75:25 mixture of diastereoisomers **4.25** and **4.26** in 87% yield (**Scheme 4.10**). Notably, although the *exo/endo* selectivity was high (100:0), the π-diastereofacial selectivity was not as great as for the bromine substituted examples described in **Scheme 4.8** and **Scheme 4.9**.



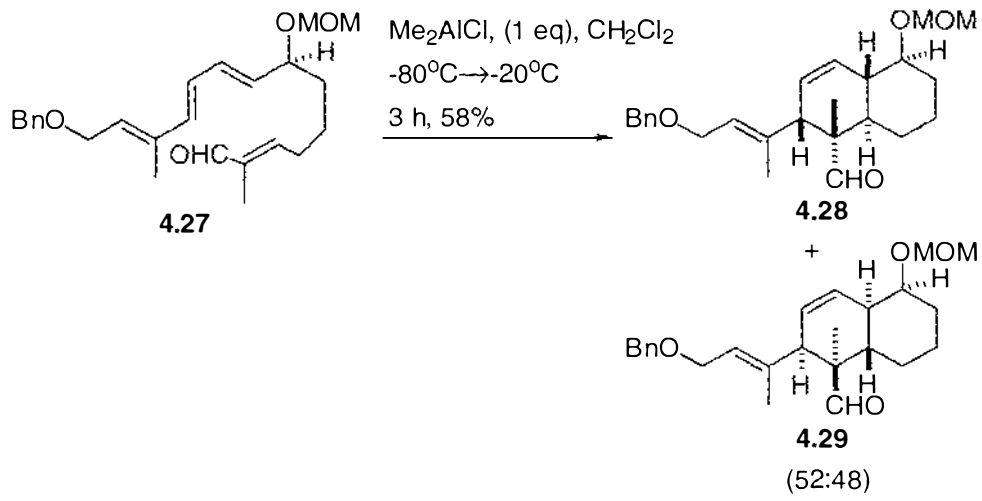
4.24

4.25

4.26
(75:25)

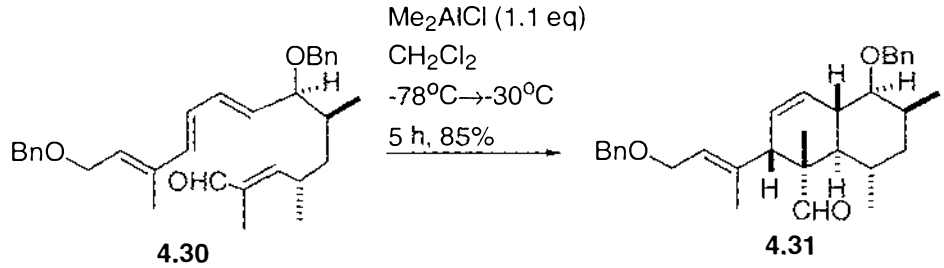
Scheme 4.10

The similar tetraene **4.27**, substituted with a MOM ether as opposed to a silyl ether, showed less π-diastereofacial selectivity with cyclisation affording a 52:48 mixture of cycloadducts **4.28** and **4.29** (**Scheme 4.11**).[14] Again, high levels of *exo:endo* selectivity were observed.



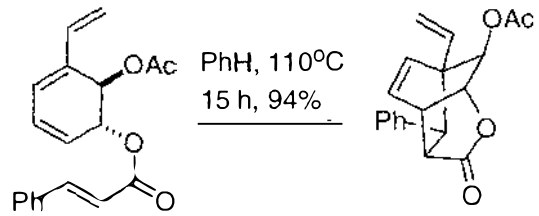
Scheme 4.11

In contrast to the slight π-diastereofacial selectivity of the unsubstituted diene precursors described above, Marshall *et al.* reported a high level of selectivity in the IMDA reaction of benzyl ether **4.30**.[15] The benzyl ether protected tetraene **4.30** cyclised in the presence of the Lewis acid dimethylaluminium chloride, to produce the single diastereoisomer **4.31** (**Scheme 4.12**). This example exhibited both high π-diastereofacial and high *exo/endo* selectivity.



Scheme 4.12

Zeylena, an interesting fused tricyclic compound, was the subject of study by Hudlicky and co-workers.[16] The styrene derived conjugated triene **4.32** was heated in benzene in a sealed ampoule for 15 hours to produce the tricyclic lactone **4.33** in high yield (**Scheme 4.13**). This could then be readily converted to zeylena acetate *via* a short three step reaction sequence. This example is of particular relevance to the work in this thesis as it consists of the IMDA reaction of a conjugated triene linked *via* an ester-tether to the dienophile.

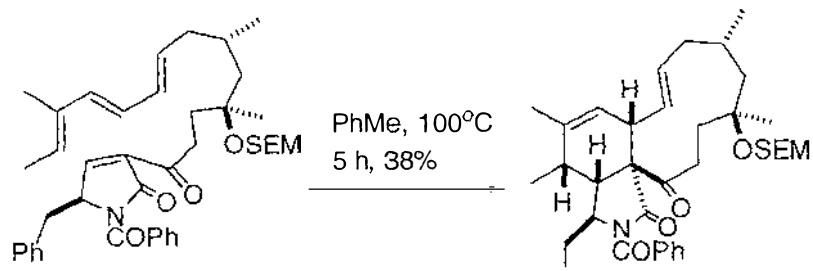


4.32 **4.33**

Scheme 4.13

An extensive review on cytochalasan syntheses was published by Thomas in 1991.[17] The cytochalasans are fungal metabolites with potent biological activities and have a general structure which lends itself well to a synthetic approach involving the IMDA reaction of a conjugated triene. Proxiphomin, the cytochalasins D, H and G and aspochalasin C have all been approached using this synthetic method.[17] Two selected examples from the 1991 review are described here.

In a total synthesis of cytochalasan H, the precursor **4.34** was heated in toluene for 5 hours with the only isolated product of this highly stereoselective cyclisation being cycloadduct **4.35**.[18]

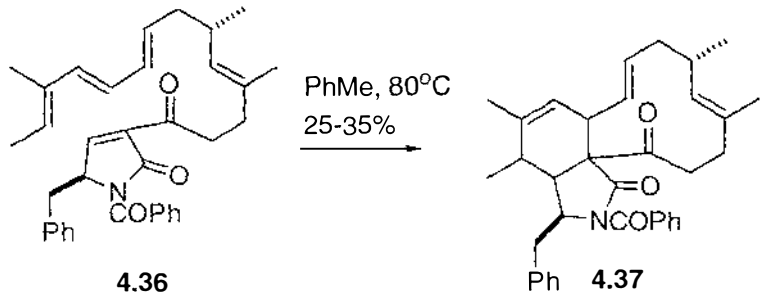


4.34 **4.35**

SEM = $CH_2OCH_2CH_2SiMe_3$

Scheme 4.14

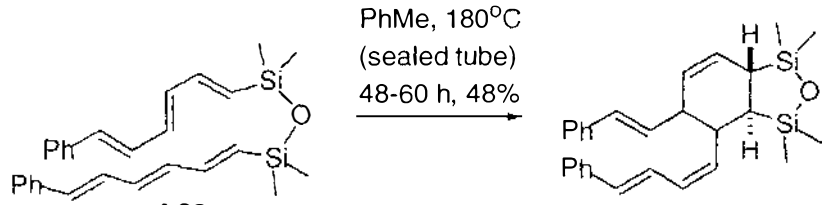
High stereoselectivity was also seen in the IMDA reaction of triene **4.36** (**Scheme 4.15**) to form the tricyclic adduct **4.37**, an intermediate in the total synthesis of cytochalasan D, in a very similar synthetic strategy to that used to obtain cytochalasan H.[19]



4.36 **4.37**

Scheme 4.15

A recent example of a conjugated triene used as the starting material in an IMDA reaction is notable because the dienophile also contains a triene moiety.[20] Hexaene **4.38** was heated in toluene in a sealed tube to selectively afford only the *trans*-fused cycloadduct **4.39** (**Scheme 4.16**).



4.38 **4.39**

Scheme 4.16

The examples described above show the wide-spread use of conjugated trienes and, to a lesser extent, conjugated tetraenes as starting materials in the IMDA reaction. It is noteworthy that IMDA reactions of conjugated polyenes have found considerable favour in the synthesis of natural products, indeed such precursors are implicated in the biosynthesis of several target compounds.[6,10]

4.1.2.2 Conjugated Tetraenes As Bis-Dienes

Previous work involving conjugated tetraenes as *bis*-diene units was performed by Kraus and Taschner.[21] The *bis*-dienes **4.40** and **4.41** (**Figure 4.1**) were prepared and reacted with a range of *bis*-dienophiles to form a tricyclic fluorenone skeleton.

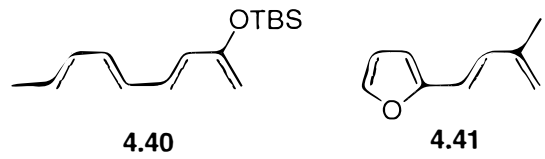
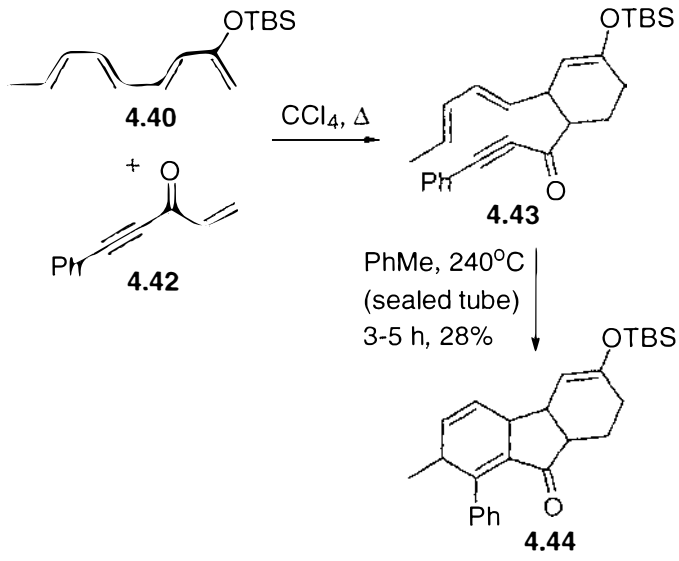


Figure 4.1

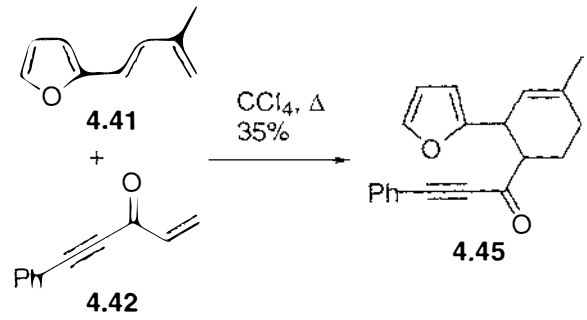
The silyl ether-substituted tetraene **4.40** underwent successful tandem inter-molecular/intramolecular DA reactions with a variety of *bis*-dienophiles. The reaction of tetraene **4.40** with *bis*-dienophile **4.42** produced the monocycloadduct **4.43**, which when heated in toluene in a sealed ampoule, further cyclised to the tricyclic adduct **4.44** (no stereochemistry provided) (**Scheme 4.17**).[21] This tandem reaction required harsh conditions and was low yielding (28%).



Scheme 4.17

The reaction of the furan-derived tetraene **4.41** proved less amenable to the tandem DA strategy, and reaction of **4.41** with the *bis*-dienophile **4.42** produced only the monocyclised adduct **4.45** (**Scheme 4.18**). No conditions were found for the further cyclisation of monoadduct **4.45**.[21] This result shows that the reactivity of *both* pairs of

dienes and dienophiles of the tetraene is crucial to a successful tandem DA reaction. For example, the reactivity of the furan diene and acetylenic dienophile of **4.45** is insufficient for cycloaddition, however, use of either a different diene or dienophile might have resulted in a successful second cyclisation.



Scheme 4.18

Kraus and Tashner commented that working with conjugated tetraenes is problematic.[21] Although both *bis*-dienes were able to be stored for a period of days at 0°C under an inert atmosphere, they were found to be unstable during prolonged storage.

4.1.2.3 Summary

Precedent for the use of conjugated polyenes has been established in both the intermolecular and intramolecular DA reactions. The work described in this thesis is concerned with stereocontrol of the IMDA reactions of tetraene alcohol-derived ester-tethered substrates such as **4.46** (**Figure 4.2**). Based on the results of the model study performed in **Chapter 2**, high π-diastereofacial selectivity can be achieved by including a sterically demanding substituent on the ester-tether between diene and dienophile.

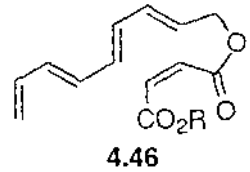
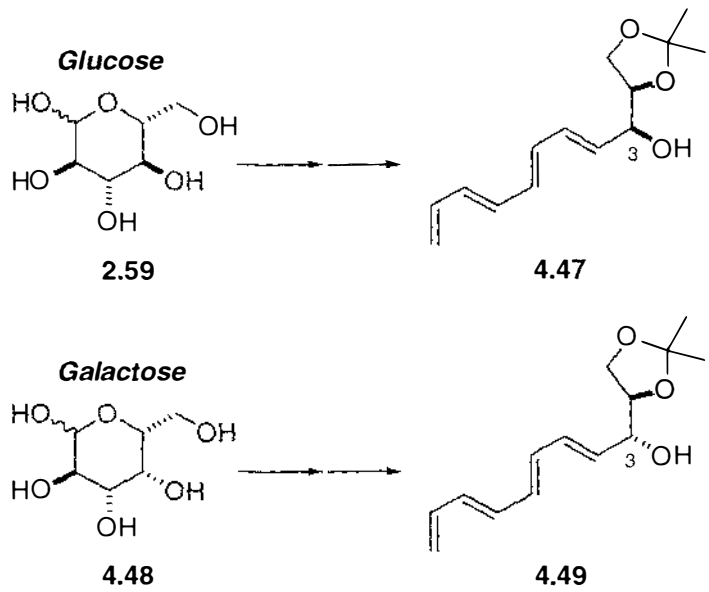


Figure 4.2

4.1.3 The Use Of Sugars As Enantiopure Building Blocks

The attraction of using a low molecular weight carbohydrate such as D-glucose **2.59** as a starting material was described in **Chapter 2**. D-Galactose **4.48** is another cheap and readily obtainable monosaccharide. Two conjugated tetraene alcohols **4.47** and **4.49** with differing stereogenic centres at C3 were synthesised from D-glucose and D-galactose respectively (**Scheme 4.19**). These enantiomerically pure tetraene alcohols were esterified to form *Z*- and *E*-methyl esters which were then cyclised in order to gain information about the ease and stereoselectivity of these IMDA reactions.



Scheme 4.19

From the results of the IMDA reactions performed on simple dienol esters (**Chapter 2**), it was expected that both the glucose and galactose-derived tetraene esters would exhibit a high degree of π-diastereofacial selectivity due to the bulky dioxolane substituent on the ester tether leading to increased $A^{1,3}$-strain in certain transition states. It seemed reasonable to assume that glucose-derived tetraene esters would have similar diastereoselectivities to the diene esters investigated in **Chapter 2**.

However, it was expected that a differing π-diastereofacial preference (to that previously observed for the glucose-derived substrates) would occur in the IMDA reactions of the galactose-derived esters, due to the differing stereochemistry at the C3 position. It was decided to investigate the effect of changing the stereochemistry at this allylic position upon the diastereoselectivity and rate of the IMDA reaction.

4.1.4 Aims Of This Investigation

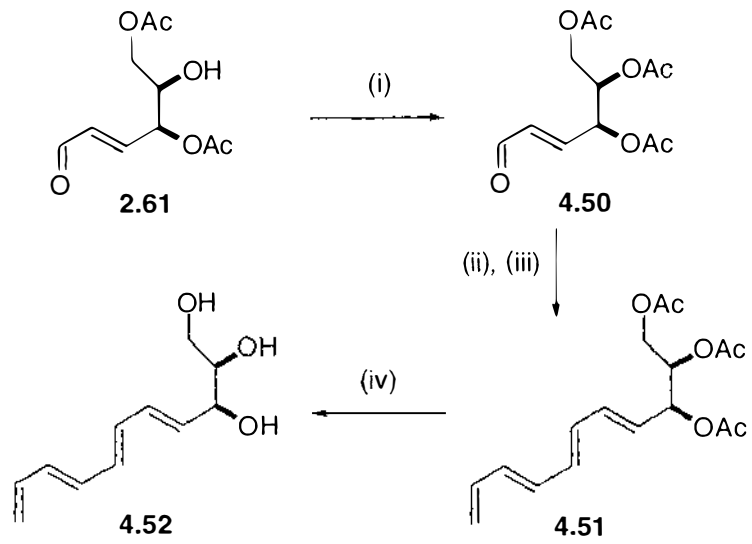
The aims of the work described in this chapter were twofold:

- Firstly, to further investigate the role of the substituent on the ester tether in determining the stereochemistry of the products of the ester-tethered IMDA reaction. In comparing the IMDA reactions of precursors derived from galactose to those derived from glucose (differing only in the stereochemistry at the C3 position), it was hoped to observe a reversal of the π-diastereofacial preference and a difference in the diastereoselectivity of the reaction.
- Secondly, the feasibility of the use of tetraenes in the ester-tethered IMDA reaction needed to be examined. This was of interest due to the potential use of a tetraene as a *bis*-diene moiety in either a TIMDA reaction or a sequential IMDA/intermolecular reaction.

4.2 Synthesis And Study Of A Glucose-Derived IMDA Precursor

4.2.1 Synthesis Of The Glucose-Derived Tetraene And IMDA Precursors

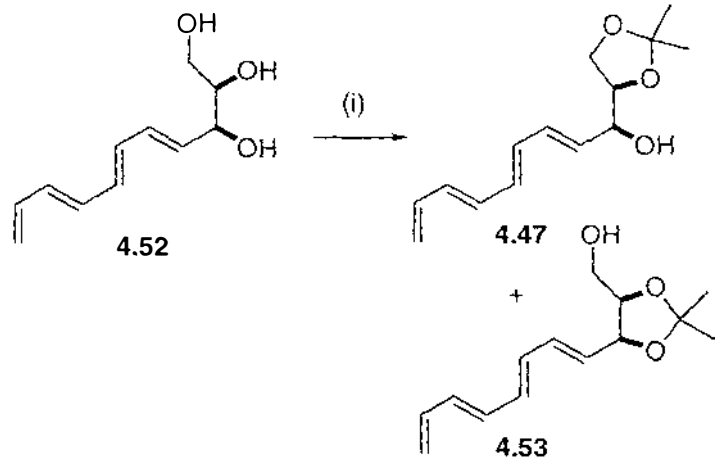
The starting material for the synthesis of the tetraene, (2*E*,4S,5R)-4,6-diacetoxy-5-hydroxy-2-hexenal **2.61**, had been previously prepared in the work discussed in **Chapter 2**. Protection of the free hydroxyl group of **2.61** using acetic anhydride and triethylamine, in the presence of DMAP, gave triacetoxy hexenal **4.50** in excellent yield (**Scheme 4.20**).[22] Wittig reaction of the α,β-unsaturated aldehyde **4.50** with the semi-stabilised ylide derived from *E*-2,4-pentadienylphosphonium bromide[23] resulted in a mixture of tetraenes shown by ^{1}H and ^{13}C NMR spectroscopy to be *E* and *Z* isomers at the newly formed carbon-carbon bond. The mixture of *E* and *Z* isomers was then subjected to radical isomerisation, using thiophenol and AIBN, resulting in the all-*E* tetraene **4.51**.



Reagents and Conditions: *(i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C, 5 min; (ii) E-2,4-pentadienylphosphonium bromide, n-BuLi, BHT, THF, -70°C→RT, 15 min, 70% (over 2 steps); (iii) PhSH, AIBN, BHT, hυ, 40 min (× 4), 56%; (iv) $KHCO_3$, H_2O/MeOH, RT, 4.5 h.*

Scheme 4.20

Removal of the acetate groups with aqueous $KHCO_3$ gave triol **4.52** which was unstable and prone to decomposition upon exposure to air and during chromatography. Construction of the bulky dioxolane group necessary for stereocontrol was achieved by reaction of triol **4.52** with 2,2-dimethoxypropane, which resulted in the formation of two tetraenes; the primary alcohol **4.53** and the desired secondary alcohol **4.47** (**Scheme 4.21**).

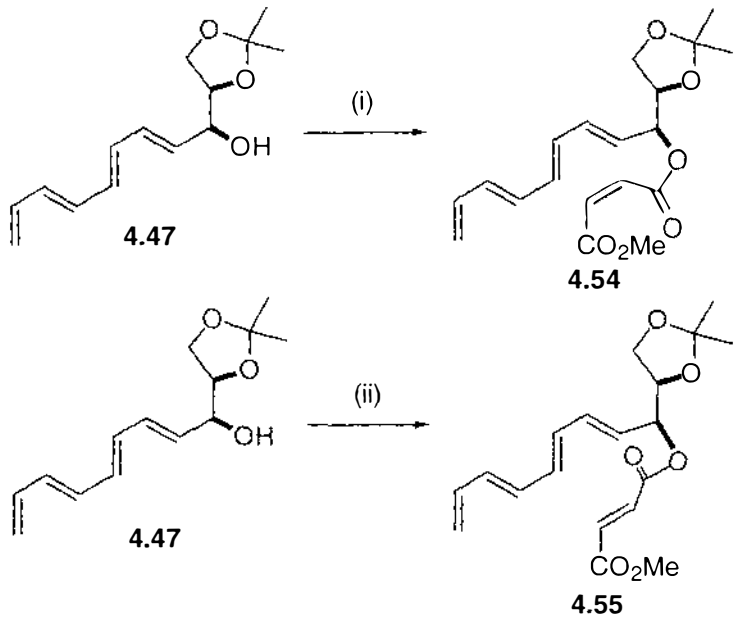


Reagents and Conditions: *(i) DMP, CSA , acetone, 0°C, overnight,* ***4.47****: 49% and* ***4.53****: 22% (over 2 steps from* ***4.51****).*

Scheme 4.21

In reactions analogous to those used to construct the IMDA precursors in **Chapter 2**, the tetraene alcohol **4.47** was used to synthesise both the *Z*-methyl and *E*-methyl esters.

Esterification of secondary alcohol **4.47** with MA followed by treatment with diazomethane gave the *Z*-methyl ester **4.54** (**Scheme 4.23**). Simple esterification of alcohol **4.47** with methyl hydrogen fumarate resulted in the *E*-methyl ester **4.55**.



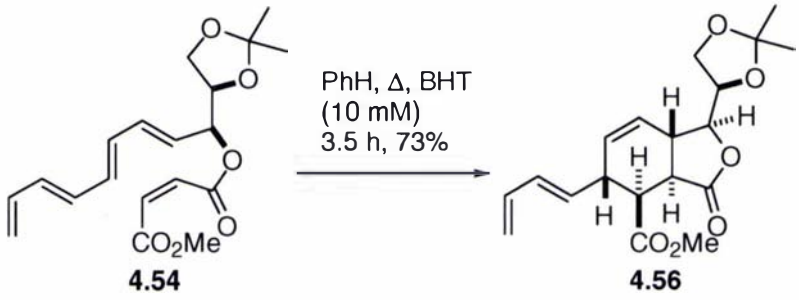
Reagents and Conditions: *(i) 1) MA, Et_3N, DMAP, BHT, CH_2Cl_2, 0°C, 1 h. 2) CH_2N_2/Et_2O, Et_2O, 5 min, 94%; (ii) methyl hydrogen fumarate, DCC, DMAP, BHT, CH_2Cl_2, RT, 20 min, 98%*

Scheme 4.22

The tendency to polymerise and the general instability of conjugated tetraenes has been previously noted.[21] Due to the known instability of these compounds, all of the IMDA reactions of these very sensitive tetraene esters were carried out in the presence of BHT (acting as an anti-oxidant), at 10 mM concentration and under an atmosphere of argon.

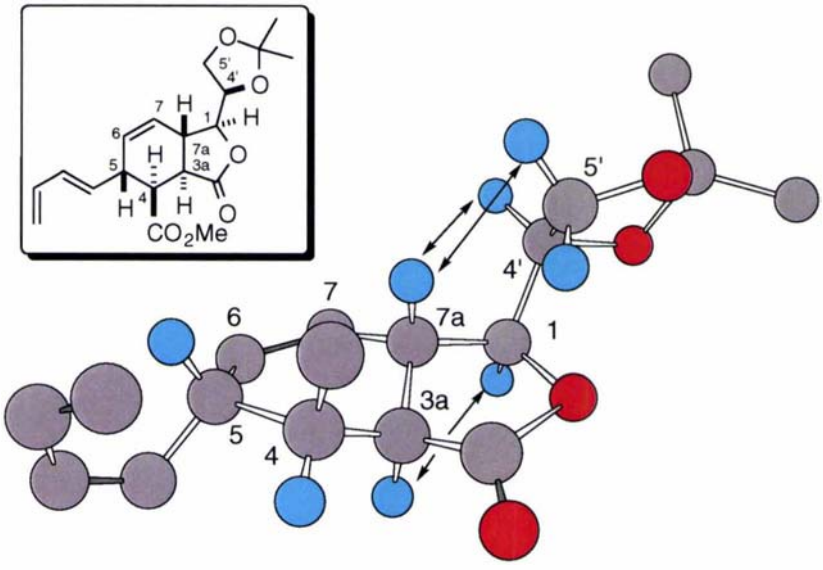
4.2.2 IMDA Reaction Of The *Z*-Methyl Ester

Thermolysis of the *Z*-methyl ester **4.54** in benzene resulted in an extremely clean conversion to a single diastereoisomer **4.56** in 73% yield (**Scheme 4.23**). The IMDA reaction was relatively fast, taking only 3.5 hours to reach completion. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy confirmed that no other cycloadduct had been formed in the reaction.



Scheme 4.23

The stereochemistry of cycloadduct **4.56** was determined by NMR spectroscopy, using COSY and NOESY experiments (see **Appendix**). The *trans*-ring fusion of lactone **4.56** was distinctly evident from the large coupling constant between the ring junction protons H3a and H7a ($J_{H3a\text{-}H7a}$ = 13.6 Hz) and, in turn, indicated that the product of this IMDA reaction resulted from an *exo* transition state.



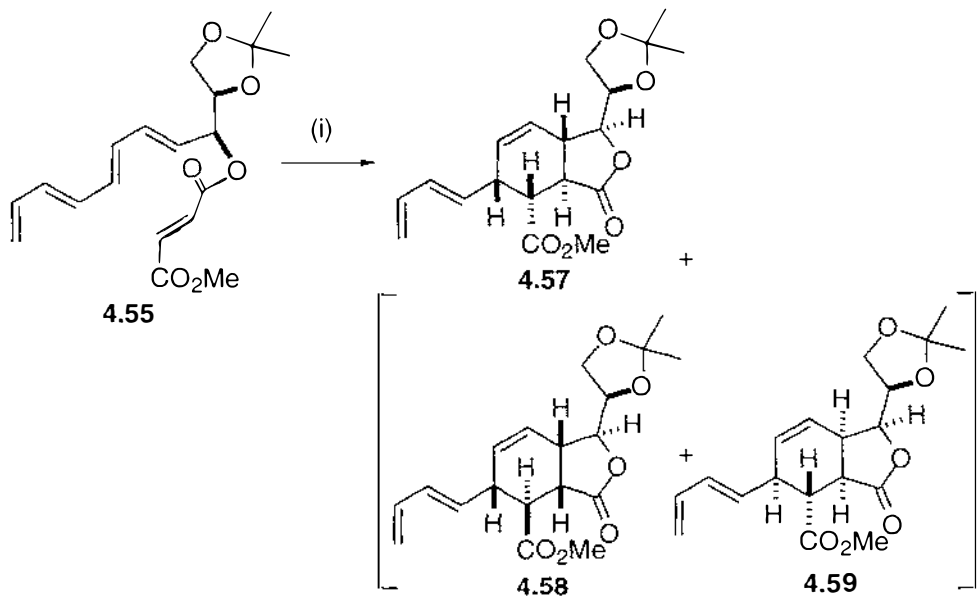
Chem 3D*[24] *structure of 4.56 with pertinent nOe enhancements (some atoms removed for clarity).

Figure 4.3

An nOe enhancement between H3a and H1 indicated that H3a was on the α-face of the molecule (**Figure 4.3**) whilst the nOe enhancement between H7a and *either* H4' *or* H5' (coincident signals) indicated that H7a was on the β-face of the molecule. This further supported the previous assignment of *trans*-ring junction geometry. The coupling constant between H3a and H4 ($J_{H3a\text{-}H4}$ = 3.1 Hz) showed the *cis* relationship between these protons and was consistent with retention of the dienophile stereochemistry. In addition, the lack of coupling between the protons on C4 and C5 suggested a dihedral angle of 90° between these protons which supported the proposed structure.

4.2.3 IMDA Reaction Of The *E*-Methyl Ester

The *E*-methyl ester **4.55** was heated in toluene for 6 hours (**Scheme 4.24**), with analysis of the crude reaction mixture by ^{1}H NMR spectroscopy indicating the presence of three diastereomeric cycloadducts in a 75:15:10 ratio (a very similar result to that of the analogous diene ester **2.57** (**Chapter 2**)).[†] It is interesting to note the slower rate of the IMDA reaction of **4.55** compared to that of the corresponding *Z*-ester **4.54** (toluene at reflux for 6 hours versus benzene at reflux for 3.5 hours).

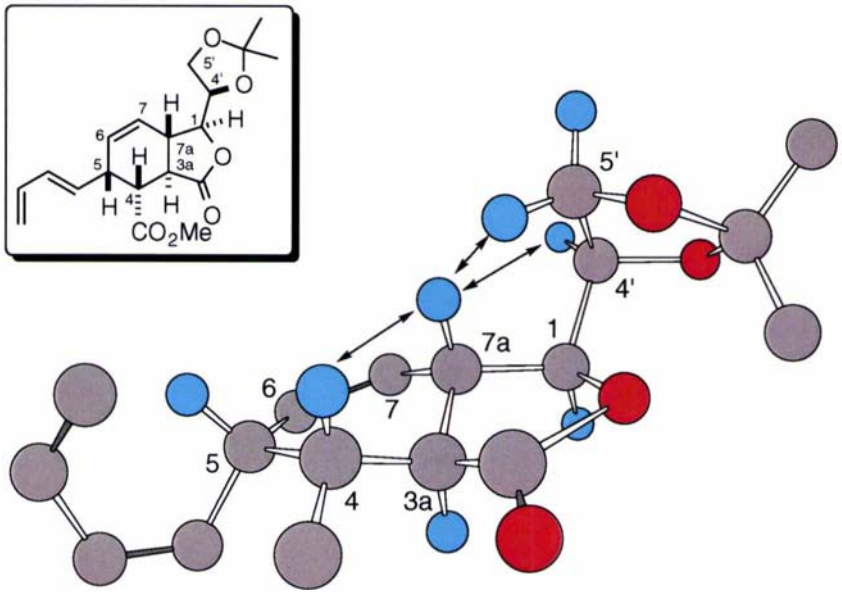


Reagents and conditions: *PhMe, (10 mM), 6 h, 85%.*

Scheme 4.24

The structure of the major diastereoisomer **4.57** was determined by COSY and NOESY experiments. The large coupling constant between H3a and H7a ($J_{H3a\text{-}H7a}$ = 13.6 Hz) indicated a *trans*-ring junction and hence an *exo* transition state (**Figure 4.4**). The nOe enhancement between protons H4 and H7a also supported a *trans* ring junction (this enhancement is only possible if H4 and H7a are on the same side of the molecule). Finally, the nOe enhancement between H7a and *either* H4' *or* H5' (coincident signals) indicated that H7a was on the β-face of the molecule.

[†] The *E*-methyl diene ester **2.57** produced a 72:17:11 mixture of three diastereoisomeric cycloadducts in 90% yield.



Chem 3D structure of 4.57 with pertinent nOe enhancements (some atoms removed for clarity).

Figure 4.4

The Structures Of The Two Minor Diastereoisomers

In addition to the major diastereoisomer **4.57**, two minor diastereoisomers were produced from the IMDA reaction of the *E*-methyl ester. As with the IMDA adducts of the analogous diene ester **2.57**, the minor diastereoisomers **4.58** and **4.59** shared similar retention factors (R_f = 0.26 and 0.27; 20:1 $CHCl_3/Et_2O$) which, on this occasion, prevented successful separation. This, combined with the small quantities of the minor isomers available for separation, resulted in samples of insufficient purity for characterisation and full structure analysis.

It seems reasonable to assume that the reaction of the tetraene *Z*-methyl ester **4.55** will mirror that of the diene *Z*-methyl ester **2.57** with the two minor diastereoisomers being the two *cis*-fused adducts **4.58** and **4.59**. Analysis of the signals in the 3.6-2.4 ppm region of the ^{1}H NMR spectrum of a mixture of these two minor isomers did indeed show the lack of a large coupling constant which would otherwise indicate the formation of a *trans*-fused adduct. In addition, comparison of the ^{1}H NMR spectrum of the mixture with the spectra of the previously identified minor adducts of the diene ester IMDA reaction allowed the structures to be tentatively assigned as **4.58** and **4.59**.

4.2.4 Stereoselectivity Of The IMDA Reactions Of The Glucose-Derived Esters

Stereoselectivity Of The IMDA Reaction Of The *Z*-Methyl Ester

The postulated transition state leading to the sole product of this IMDA reaction (cycloadduct **4.56**) has an *exo* mode of addition and minimises steric interactions between the dioxolane group and the allylic hydrogen (**Figure 4.5**).

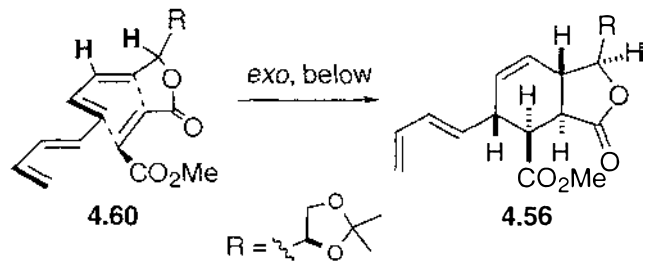


Figure 4.5

The other transition state in which the dienophile approaches from below (**4.61**) also minimises $A^{1,3}$-strain, however, this transition state involves the less favourable *endo* addition mode and cycloadduct **4.62** is therefore not observed.

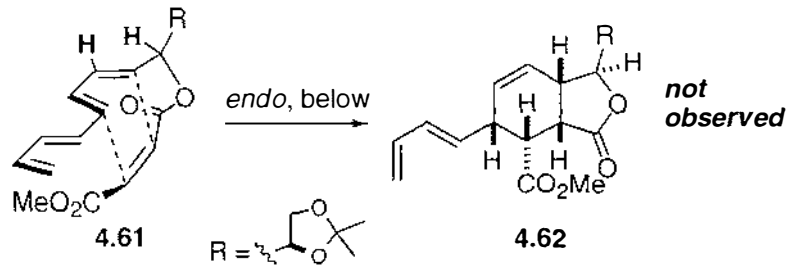


Figure 4.6

Approach of the dienophile from above the plane of the diene, as in transition states **4.63** and **4.65**, would result in increased $A^{1,3}$-strain in the transition state (**Figure 4.7**). Accordingly, neither of the diastereoisomers **4.64** and **4.66** were produced in the IMDA reaction of *Z*-methyl ester **4.54**.

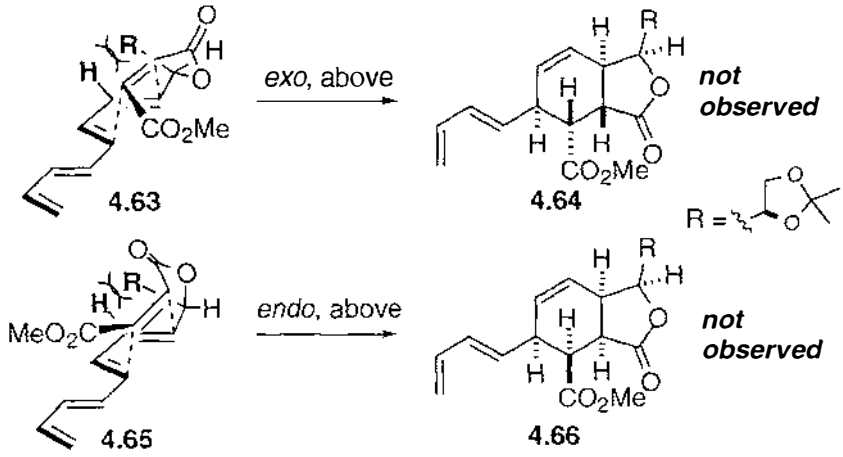


Figure 4.7

It is interesting that despite allylic strain being minimised in both of the transition states in which the dienophile approaches the diene from below (**Figure 4.5** and **Figure 4.6**), only a single diastereoisomer was produced in the reaction, the result of the *exo* addition mode. The strong preference for the *exo* (**4.60**) as opposed to the *endo* (**4.61**) mode of addition of this reaction when compared to the analogous diene ester (**Chapter 2**) is probably the result of greater steric hindrance in the transition state due to the pendant diene group.

Stereoselectivity Of The IMDA Reaction Of The *E*-Methyl Ester

The major diastereoisomer of the IMDA reaction of the *E*-methyl tetraene ester would have arisen from the transition state below (**4.67** in **Figure 4.8**) in which $A^{1,3}$-strain is minimised.

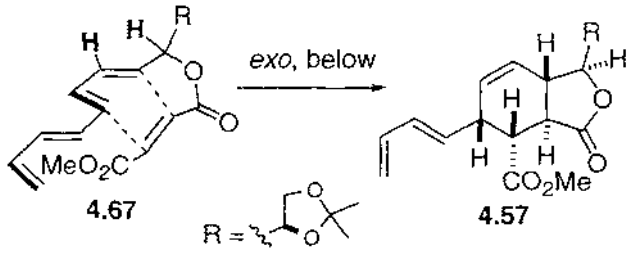


Figure 4.8

As in the *Z*-methyl ester case, a strong preference is shown for the *exo* mode of addition. However, the reaction is less selective than that of the *Z*-methyl ester IMDA reaction with three diastereomeric adducts being produced. One reason for this reduced selectivity could be that, although combining an *exo* mode of addition with a minimisation of

$A^{1,3}$-strain, the steric crowding of the pendant diene and the methyl ester groups in transition state **4.67** results in a lessened preference for this transition state and, consequently, the observation of the two minor *endo* adducts **4.58** and **4.59** (**Figure 4.9**).

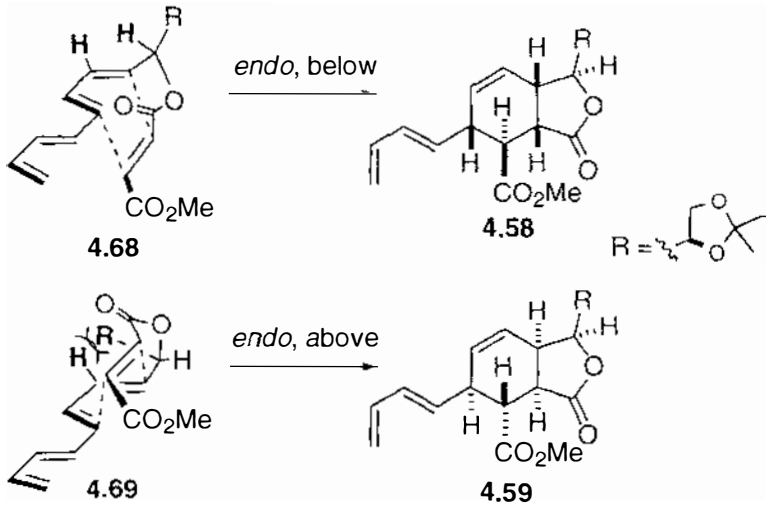


Figure 4.9

It must be noted that the two minor cycloadducts **4.58** and **4.59** could not be separated and, hence, the structures of these adducts are not known for certain. However, the ratio of products (obtained from the ^1H NMR spectrum of the crude reaction mixture) is consistent with that observed in the IMDA reaction of the analogous diene ester **2.57** (**Chapter 2**).

4.2.5 Summary Of The Stereoselectivities Of IMDA Reactions On The Glucose-Derived Esters

The *exo/endo* and π-diastereofacial selectivities of the IMDA reactions of the glucose-derived esters are shown below (**Table 4.1**).

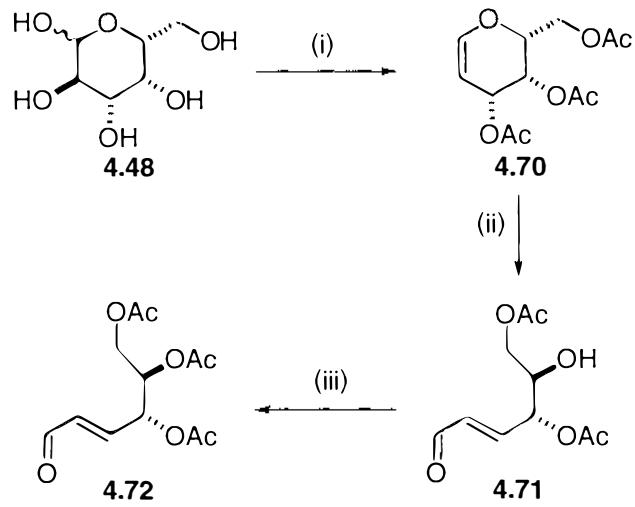
Substrate	*Exo/Endo* Selectivity	π-Diastereofacial Selectivity
Z-methyl ester	100:0	100:0
E-methyl ester	75:25	90:10

Table 4.1

4.3 Synthesis And Study Of The Galactose-Derived IMDA Precursor

4.3.1 Synthesis Of A Galactose-Derived Tetraene And IMDA Precursors

The galactose-derived alcohol **4.49** was synthesised in a very similar manner to the glucose-derived alcohol **4.47**. In an analogous preparation to that of tri-*O*-acetyl-D-glucal (**Chapter 2**),[22] D-galactose **4.48** was transformed into tri-*O*-acetyl-D-galactal **4.70**. The acid-catalysed, mercuric sulfate-assisted, ring-opening of tri-*O*-acetyl-D-galactal **4.70**, gave diacetoxy hexenal **4.71** in quantitative yield (**Scheme 4.25**).[22] Acetylation of the free hydroxyl group using acetic anhydride and triethylamine, under DMAP-mediated conditions, gave the triacetate **4.72** (**Scheme 4.25**).

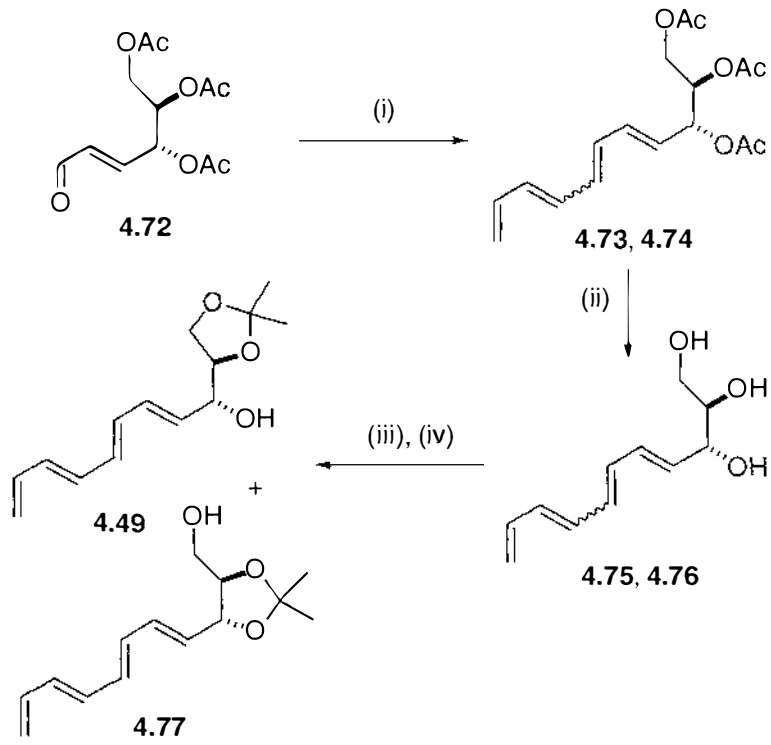


Reagents and Conditions: *(i) Ac_2O, Br_2/P, Zn/AcOH, 70%; (ii) $HgSO_4$, H_2SO_4, 1,4-dioxane, RT, 16 h, 99%; (iii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C, 5 min, 100%.*

Scheme 4.25

Wittig reaction of the triacetate **4.72** with the semi-stabilised ylide formed from *E*-2,4-pentadienylphosphonium bromide[23] resulted in an isomeric mixture of *E/Z* tetraenes (**Scheme 4.26**). The acetate groups of the isomeric tetraenes **4.73** and **4.74** were removed by mild hydrolysis with aqueous $KHCO_3$ in methanol to give a mixture of the triol compounds **4.75** and **4.76** which, similarly to the glucose series, were unstable and prone to decomposition upon exposure to air. Treatment of this mixture of triols with 2,2-dimethoxypropane in acetone, in the presence of a mild acid catalyst, resulted in the formation of a complex mixture of regio- and geometrical isomers. Radical isomerisation using thiophenol and AIBN gave a mixture of two all-*E* tetraene regioisomeric alcohols

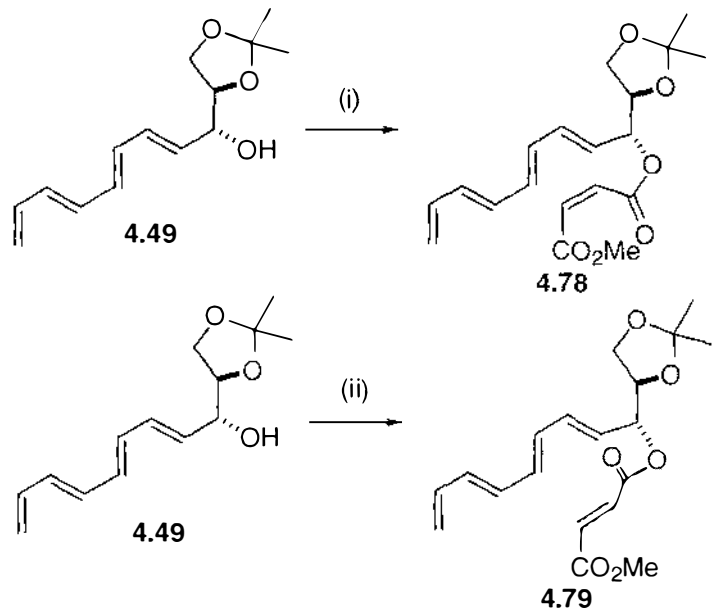
which, after column chromatography, yielded the primary alcohol **4.77** and the desired secondary alcohol **4.49**.



Reagents and Conditions: *(i) E-2,4-pentadienylphosphonium bromide, n-BuLi, BHT, THF, -70°C→RT, 15 min, 75%; (ii) $KHCO_3$, MeOH/H_2O, BHT, RT, 2.5 h; (iii) DMP, CSA, BHT, acetone, RT, 16 h; (iv) PhSH, AIBN, BHT, PhH, hυ, 25 min (× 4).* ***4.49****: 24%,* ***4.77****: 11% (yield over 3 steps from* ***4.73*** *and* ***4.74****).*

Scheme 4.26

Esterification of secondary alcohol **4.49** with MA followed by treatment with an ethereal diazomethane solution gave the *Z*-methyl ester **4.78** (**Scheme 4.27**) whereas the *E*-methyl tetraene ester **4.79** was prepared by simple esterification of the alcohol **4.49** with methyl hydrogen fumarate.

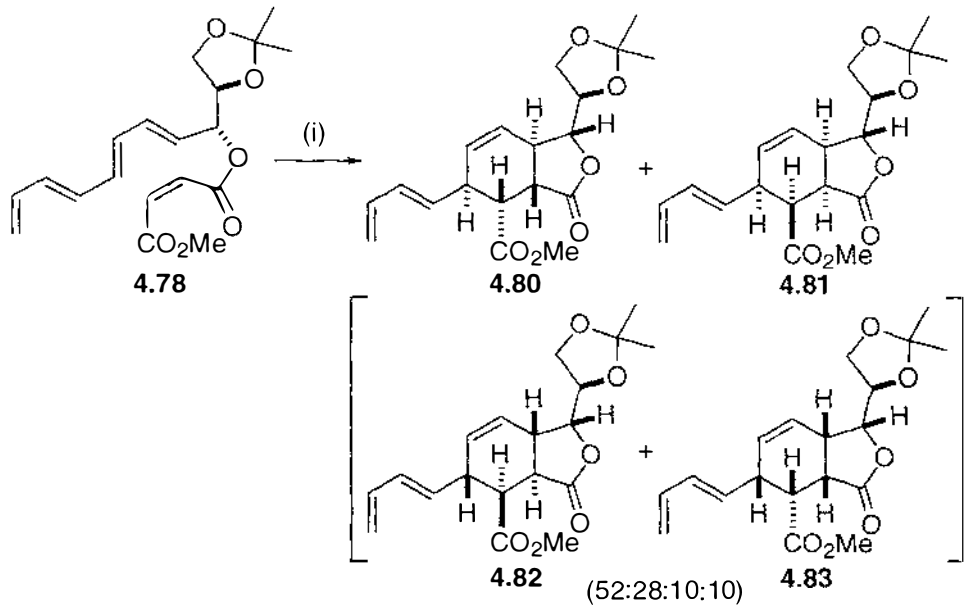


Reagents and Conditions: *(i) 1) MA, Et_3N, DMAP, BHT, CH_2Cl_2, 0°C, 5 h, 2) CH_2N_2/Et_2O, Et_2O, 5 min, 60%; (ii) methyl hydrogen fumarate, DCC, DMAP, BHT, CH_2Cl_2, RT, 15 min, 72%.*

Scheme 4.27

4.3.2 IMDA Reaction Of The *Z*-Methyl Ester

The IMDA reaction of the galactose-derived tetraene Z-methyl ester **4.78** was very rapid with the reaction complete after 30 minutes in refluxing benzene.

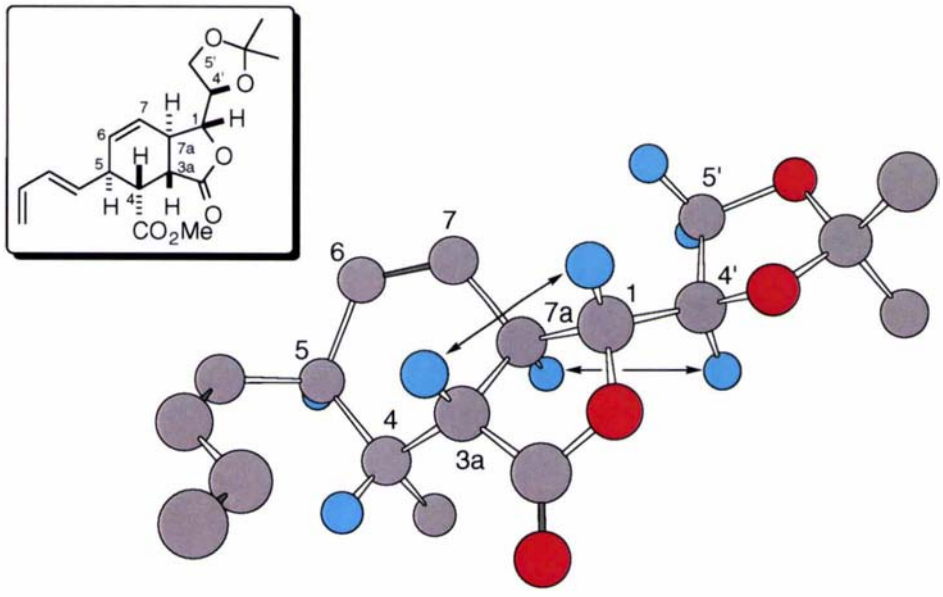


Reagents and Conditions: *(i) PhH, BHT, 10 mM, Δ, 30 min, 91%.*

Scheme 4.28

Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed that all four possible diastereoisomers had been produced in a 52:28:10:10 ratio. Both the major isomer and the second most abundant isomer could be isolated and their structures elucidated using NMR spectroscopic techniques. However, the two minor diastereoisomers were unable to be separated and characterised further.

The stereochemistry of the major diastereoisomer, lactone **4.80**, was elucidated by NMR spectroscopy, using COSY and NOESY experiments (see **Appendix**). The large coupling constant between the ring junction protons H3a and H7a ($J_{H3a\text{-}H7a}$ = 13.6 Hz) showed that lactone **4.80** possessed a *trans*-fused ring junction, resulting from an *exo*-transition state. An nOe enhancement between H7a and H4' indicated that H7a was on the α-face of the molecule (**Figure 4.10**). The nOe enhancement between H3a and H1 indicated that H3a was on the β-face of the molecule, further supporting the previous assignment of *trans*-ring junction geometry.

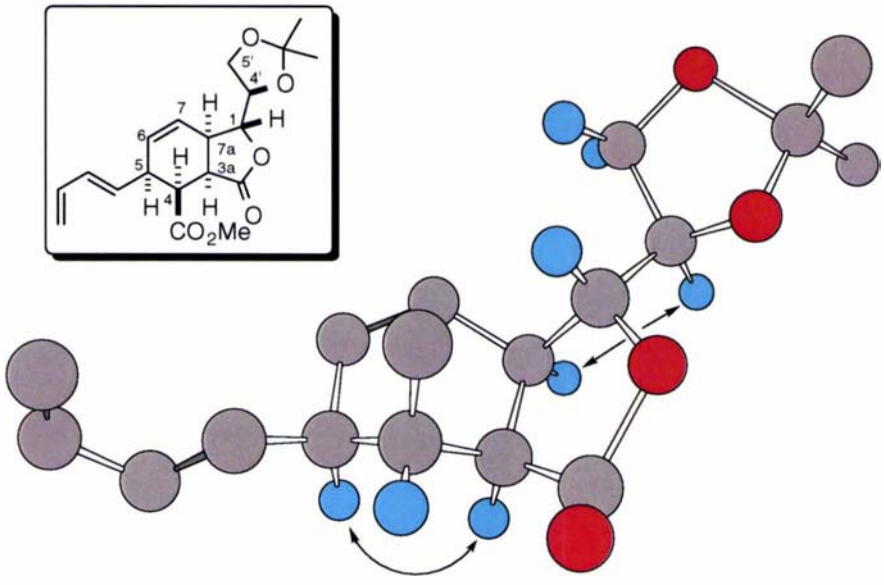


Chem 3D structure of 4.80 with pertinent nOe enhancements (some atoms removed for clarity).

Figure 4.10

The structure of the second most abundant diastereoisomer, lactone **4.81**, was determined in the following way. The nOe enhancement between H3a and H5 could only have arisen if these protons are on the same side of the molecule. Furthermore, these two protons are only on the same side of the molecule if the lactone possesses a *cis*-ring junction. Therefore, lactone **4.81** must have been one of the two possible *cis*-fused isomers. In addition, the nOe enhancement between H7a/H4 (coincident peaks) and H4' could only be

due to an interaction between H7a and H4'. Therefore, H7a was assigned as being on the α-face of the molecule (**Figure 4.11**).



Chem 3D structure of 4.81 with pertinent nOe enhancements (some atoms removed for clarity).

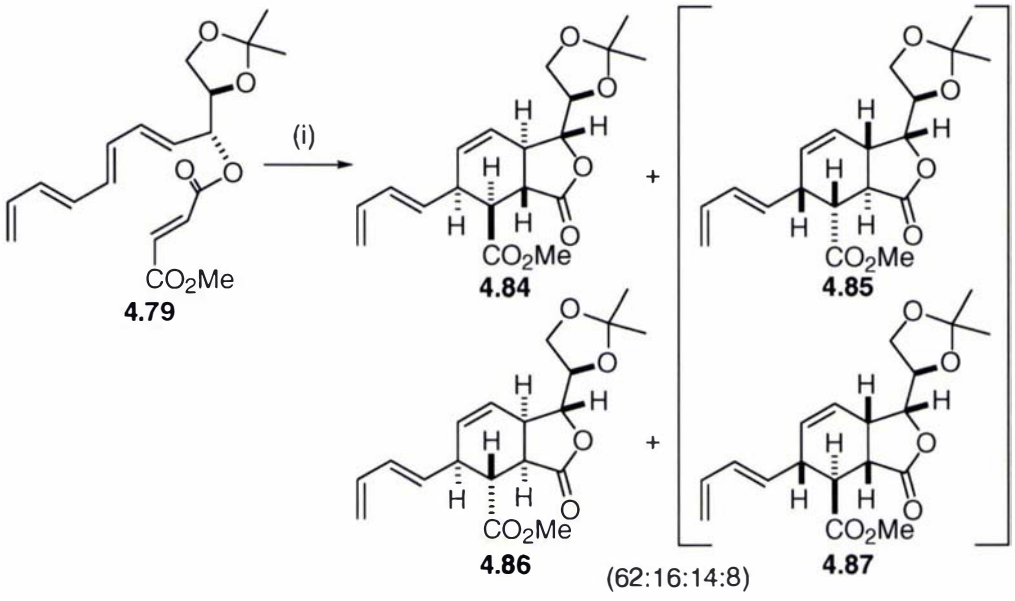
Figure 4.11

The Structures Of The Minor Diastereoisomers

The two minor diastereoisomers could not be separated. However, as there were four possible diastereoisomers, and two of those were assigned as described above, these two minor diastereoisomers were presumed to be lactones **4.82** and **4.83**. Fortunately, these two minor isomers were present in equal amounts in the crude reaction mixture which allowed the *exo:endo* and π-diastereofacial selectivities to be calculated as (62:38) and (80:20) respectively.

4.3.3 IMDA Reaction Of The *E*-Methyl Ester

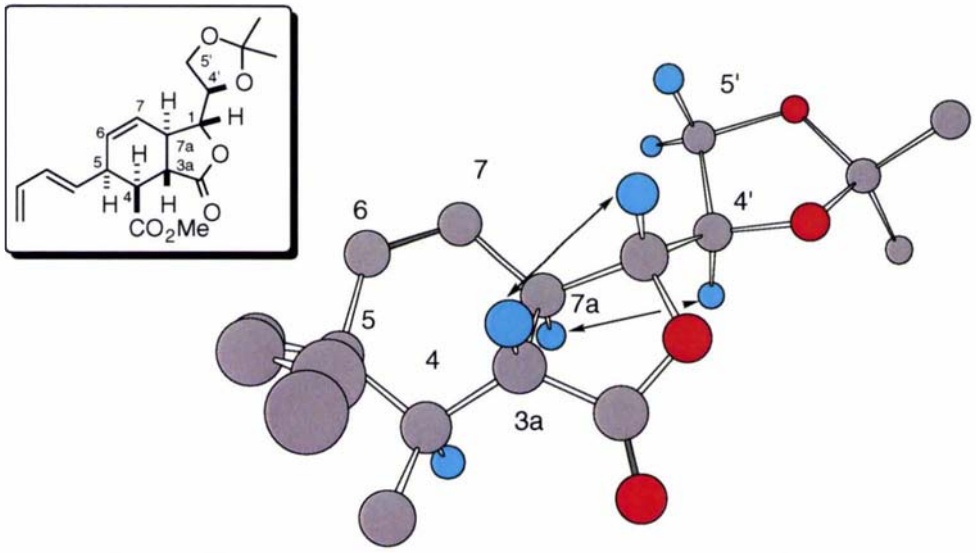
As in the glucose-derived series, *E*-methyl ester **4.79** required slightly more forcing conditions to cyclise than the corresponding *Z*-methyl ester (5 hours in toluene at reflux versus 30 minutes in benzene at reflux). Again, the galactose-derived *E*-methyl ester showed a decreased selectivity compared to the glucose variant with the ^{1}H NMR spectrum of the crude reaction mixture showing that all four diastereoisomers, **4.84**, **4.85**, **4.86** and **4.87**, had been produced in a 62:16:14:8 ratio (**Scheme 4.29**).



Reagents and Conditions: *(i) PhMe, BHT, 10 mMol conc., Δ, 5 h, 74%.*

Scheme 4.29

The structure of the major cycloadduct **4.84** was elucidated using COSY and NOESY NMR spectroscopy. Although the resonances of the ring junction protons (H3a and H7a) were nearly coincident, a shift reagent NMR experiment and subsequent expansion of the NOESY and COSY spectra allowed the nOe enhancements due to H3a and H7a to be differentiated.



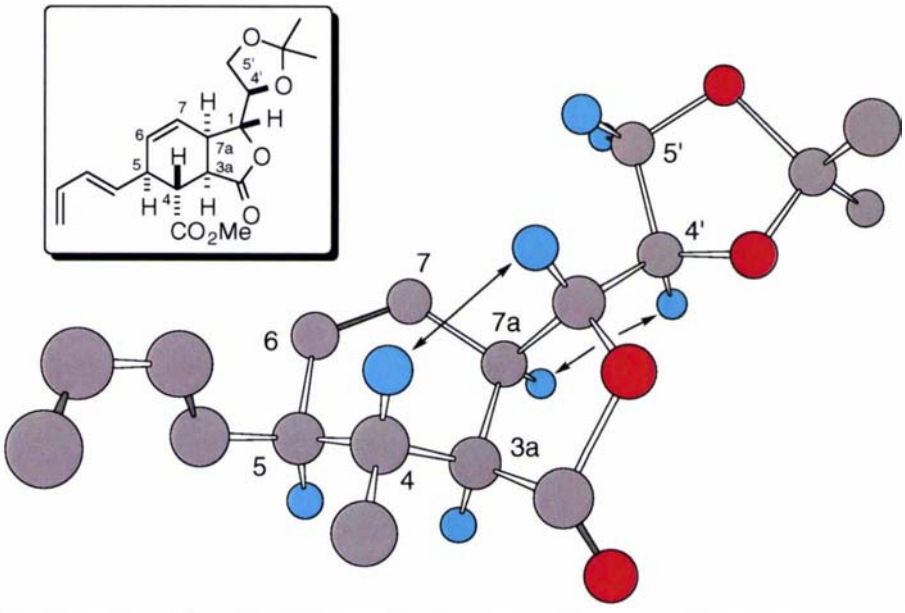
Chem 3D structure of 4.84 with pertinent nOe enhancements (some atoms removed for clarity).

Figure 4.12

An nOe enhancement between H3a and H1 was due to H3a being on the β-face of the molecule whilst the nOe enhancement between H7a and H5' allowed H7a to be assigned as on the α-face (**Figure 4.12**). This also identified the molecule as possessing a *trans*

ring junction, which was supported by a large coupling constant between the ring junction protons ($J_{H3a\text{-}H7a}$ = 13.6 Hz).

The structure of one of the minor diastereoisomers, lactone **4.86**, was established as follows. The nOe enhancement between H7a and H4' indicated that H7a was on the α-face of the molecule, whilst the small coupling between the ring junction protons ($J_{H3a\text{-}H7a}$ = 9.0 Hz) was characteristic of a *cis*-fused lactone (**Figure 4.13**). This assignment was further supported by an nOe enhancement between H4 and H1, indicating that these protons were on the same side of the molecule.



Chem 3D structure of 4.86 with pertinent nOe enhancements (some atoms removed for clarity).

Figure 4.13

The Structures Of The Other Minor Diastereoisomers

As with the products of the IMDA reaction of the *Z*-methyl ester **4.78**, two of the minor cycloadducts proved to be inseparable and, therefore, these lactones were unable to characterised. However, by a process of elimination, it was possible to state that these lactones must be the other *exo* and other *endo* isomers, **4.85** and **4.87**, respectively. From an analysis of the ^{1}H NMR spectrum of this mixture of diastereoisomers it was possible to identify peaks due to the *exo* component (3.47 ppm, *J* = 14.1, 11.9 Hz, H3a; 2.81 ppm, *J* = 11.9, 6.8 Hz, H4) and hence assign the methyl ester peaks due to the *exo* and *endo* isomer as 3.70 ppm and 3.73 ppm respectively. This enabled the ratio of all four diastereoisomers in the ^{1}H NMR of the crude reaction mixture to be determined as 62:16:14:8 (**4.84**:**4.85**:**4.86**:**4.87**) and the *exo*/*endo* and π-diastereofacial selectivities to be calculated as (78:22) and (76:24) respectively.

4.3.4 Stereoselectivity Of The IMDA Reactions Of The Galactose-Derived Tetraene Esters

Stereoselectivity Of The IMDA Reaction Of The *Z*-Methyl Ester

The postulated transition state **4.88** of the major diastereoisomer **4.80** has both a minimised $A^{1,3}$-strain and a favourable *exo* mode of addition (**Figure 4.14**). The transition state leading to the second most abundant diastereoisomer, **4.81**, whilst occurring *via* the less favourable *endo* mode, also has a minimised $A^{1,3}$-strain.

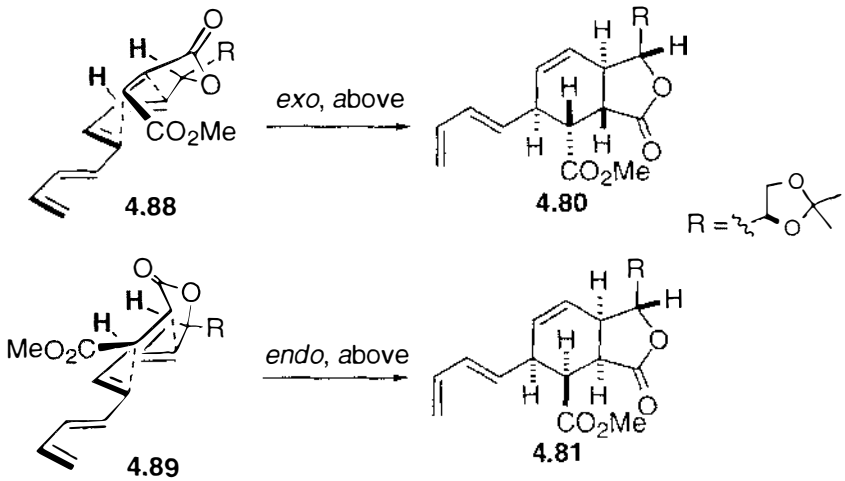


Figure 4.14

Both of the minor diastereoisomers of this reaction, **4.82** and **4.83**, (present as an inseparable mixture) derive from transition states (**4.90** and **4.91**) with a degree of $A^{1,3}$-strain due to steric interaction between the bulky dioxolane ring and the allylic hydrogen (**Figure 4.15**).

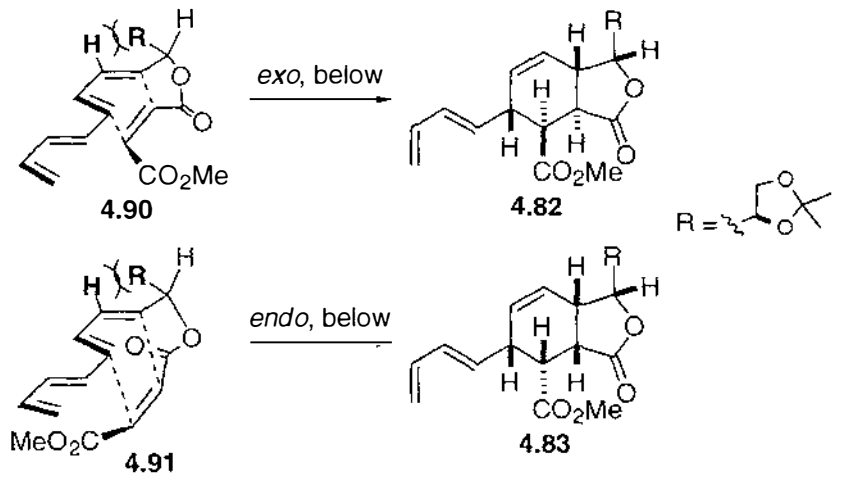


Figure 4.15

Stereoselectivity Of The IMDA Reaction Of The *E*-Methyl Ester

Once again, the major diastereoisomer of this IMDA reaction arose from an *exo* mode of addition in which $A^{1,3}$-strain was minimised, as depicted in the postulated transition state **4.92** (**Figure 4.16**).

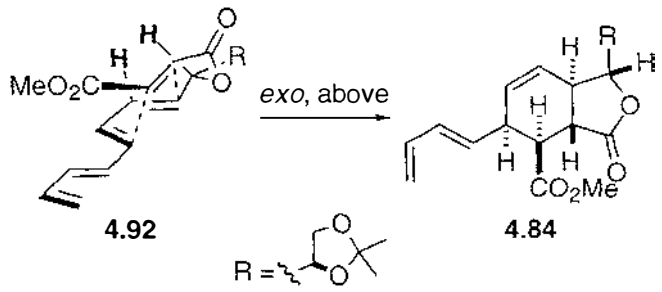


Figure 4.16

The major diastereoisomer **4.84** was produced in substantially greater quantities than any of the three minor diastereoisomers (64:16:14:8). The two diastereoisomers produced in intermediate amounts showed an interesting pattern of selectivity. Cycloadduct **4.85** was produced in slightly greater quantity than **4.86** despite having a transition state (**4.93**) with an unfavourable steric interaction between the dioxolane ring and the allylic H group. However, diastereoisomer **4.85** was the result of an *exo* mode of addition. The more minor diastereoisomer **4.86** did have a minimised $A^{1,3}$-strain yet was also the result of the less favourable *endo* addition mode.

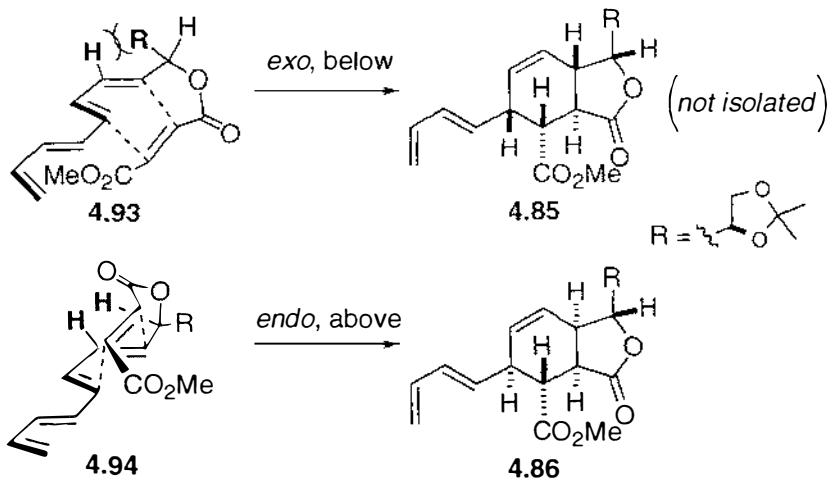


Figure 4.17

Diastereoisomer **4.87** was produced in least quantity and its postulated transition state has both $A^{1,3}$-strain and an *endo* mode of addition.

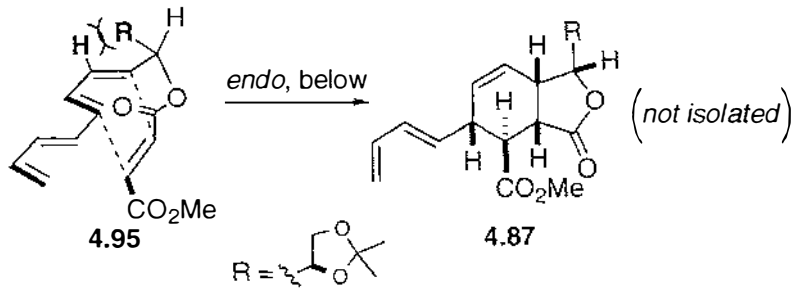


Figure 4.18

4.3.5 Summary Of The Stereoselectivities Of IMDA Reactions On The Galactose-Derived Esters

The *exo/endo* and π-diastereofacial selectivities of the IMDA reactions of the galactose-derived esters are shown below (**Table 4.2**).

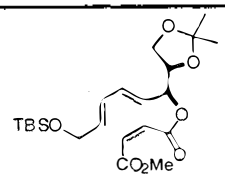
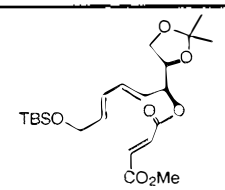
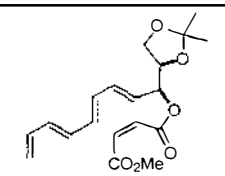
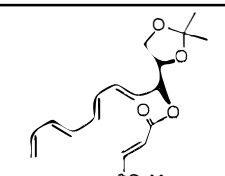
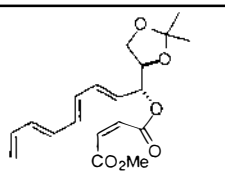
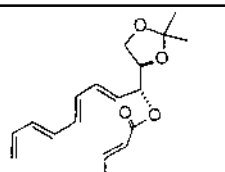
Substrate	*Exo/Endo* Selectivity	π-Diastereofacial Selectivity
Z-methyl ester	61:39	80:20
E-methyl ester	78:22	76:24

Table 4.2

It was thought that, with a reversal of the stereogenic centre at C3, there would be a reversal in the π-diastereofacial selectivity of the IMDA reaction. Although the major cycloadduct in the galactose-derived examples is as expected, the production of *all* four possible diastereoisomers indicates a loss of stereoselectivity when compared to the IMDA reactions of the glucose-derived examples. The galactose- and glucose-derived substrates share a diastereomeric relationship, differing at only one of the two stereogenic centres. Due to possessing a stereogenic centre, the role of the dioxolane tether substituent upon the stereochemical outcome of these IMDA reactions is not straightforward. There is a clear contribution from both stereogenic centres to the high levels of stereocontrol observed in the glucose-derived substrates when compared to the galactose-derived examples.

4.4 Summary

A summary of the results of IMDA reactions performed on glucose and galactose-derived *Z*-methyl and *E*-methyl esters is given below. (**Table 4.3**).

Substrate	Reaction Solvent‡	Time	*Exo/Endo* Selectivity	π-Diastereo-Facial Selectivity	Yield (%)
 **2.56**	Toluene	19 h	86:14	100:0	100
 **2.57**	Toluene	39 h	72:28	89:11	90
 **4.54**	Benzene	3.5 h	100:0	100:0	73
 **4.55**	Toluene	6 h	75:25	90:10	85
 **4.78**	Benzene	0.5 h	61:39	80:20	91
 **4.79**	Toluene	5 h	78:22	76:24	74

‡ *All of the IMDA reactions were performed at reflux in the given solvent*

Table 4.3

Several important conclusions can be drawn from the results of these model studies:

- Firstly, *Z*-methyl esters tend to have a shorter reaction time than the corresponding *E*-methyl esters and require less forcing conditions for a successful IMDA reaction.

- Secondly, in general, the glucose-derived substrates show a greater degree of stereocontrol than the galactose-derived substrates. This suggests that both the C3 stereogenic centre **and** the stereogenic centre of the dioxolane group contribute to the favouring of a preferred transition state in the cyclisation.

- Finally, extremely high levels of both *exo/endo* and π-diastereofacial selectivity are observed in the case of both the diene and tetraene glucose-derived *Z*-methyl esters.

This investigation into IMDA reactions of glucose- and galactose-derived tetraene esters has shown the synthetic utility of conjugated tetraenes. The high yields of the reactions described in this chapter, when combined with the high levels of stereoselectivity observed, bode well for the incorporation of conjugated tetraenes into a TIMDA precursor.

4.5 References

(1) Alder, K.; Schumacher, M. *Fortsch. Chem. Org. Naturst.* **1953**, *10*, 66-118.

(2) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 211-230.

(3) Hwa, J. C. H.; de Benneville, P. L.; Sims, H. J. *J. Am. Chem. Soc.* **1960**, *82*, 2537-2540.

(4) Farmer, E. H.; Warren, F. L. *J. Chem. Soc.* **1929**, 897-909.

(5) Roush, W. R.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509-1511.

(6) Roush, W. R.; Peseckis, S. M. *Tetrahedron Lett.* **1982**, *23*, 4879-4882.

(7) Roush, W. R.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem.* **1984**, *49*, 3429-3432.

(8) Boeckman Jr., R. K.; Enholm, E. J.; Demko, D. M.; Charette, A. B. *J. Org. Chem.* **1986**, *51*, 4743-4745.

(9) Trost, B. M.; Lautens, M.; Hung, M.-H.; Carmichael, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 7641-7643.

(10) Yoshii, E.; Takeda, K.; Sato, M. *Tetrahedron Lett.* **1986**, *27*, 3903-3906.

(11) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327-4330.

(12) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541-3544.

(13) Yoshii, E.; Takeda, K.; Kobayashi, T.; Saito, K. *J. Org. Chem.* **1988**, *53*, 1092-1095.

(14) Yoshii, E.; Takeda, K.; Yano, S. *Tetrahedron Lett.* **1988**, *29*, 6951-6954.

(15) Marshall, J. A.; Salovich, J. M.; Shearer, B. G. *J. Org. Chem.* **1990**, *55*, 2398-2403.

(16) Hudlicky, T.; Seone, G.; Pettus, T. *J. Org. Chem.* **1989**, *54*, 4239-4243.

(17) Thomas, E. J. *Acc. Chem. Res.* **1991**, *24*, 229-235.

(18) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 507-518.

(19) Thomas, E. J.; Merifield, E. *J. Chem. Soc., Chem. Commun.* **1990**, 464-466.

(20) Luh, T.-Y.; Chen, R.-M.; Weng, W.-W. *J. Org. Chem.* **1995**, *60*, 3272-3273.

(21) Kraus, G. A.; Taschner, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 1974-1977.

(22) Perlin, A. S.; Gonzales, F.; Lesage, S. *Carbohydrate Research* **1975**, *42*, 267-274.

(23) Näf, F.; Decorzant, R.; Thommen, W.; Willhalm, B.; Ohloff, G. *Helv. Chim. Acta* **1975**, *58*, 1016-1037.

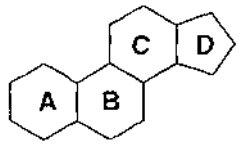
(24) CS Chem3D Pro™ ; version 3.5.1; Cambridge Soft Corporation: Cambridge, Massachusetts, 1997.

5. Preliminary Investigations Towards TIMDA Reactions

5.1 Introduction

5.1.1 A New Synthetic Strategy Towards Tetracyclic Systems

Steroids and related compounds are amongst the most potent biologically active compounds known and even small amounts can have dramatic physiological effects. The female and male sex hormones, adrenocortical hormones and cholesterol are all examples of steroids. Steroids are derivatives of the cyclopentano perhydrophenanthrene ring system **5.1** (**Figure 5.1**).



5.1

Figure 5.1

Steroids and steroid-like compounds, are constantly being isolated from various natural sources. Many of these naturally occurring steroids have important biological activity and hence, great potential for medicinal applications. Examples of such potentially useful natural products are spongiadiol **5.2**, isospongiadiol **5.3** and epispongiadiol **5.4** which were all isolated from the Caribbean sea sponge, *Spongia linnaeus* (**Figure 5.2**).[1] All three of these furanoditerpenes have shown activity against the Herpes simplex type 1 virus and P 388 murine leukaemia cells. Efficient and flexible syntheses are required if these complex natural products are to be commercially useful.

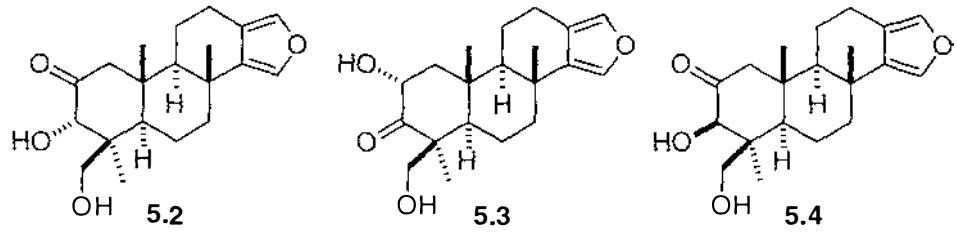
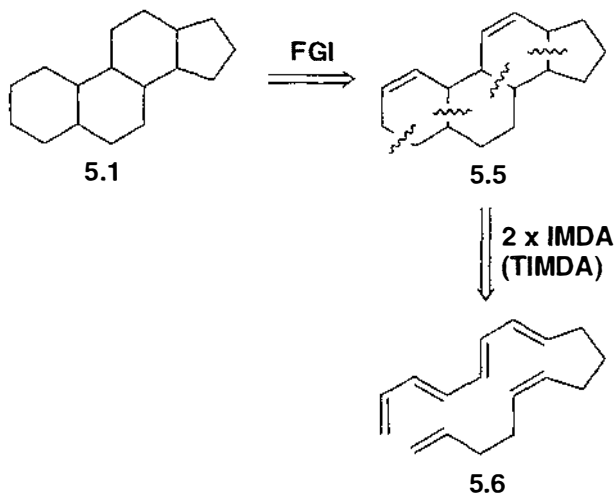


Figure 5.2

There are two main ways of accessing these pharmaceutically useful compounds: modification of readily available analogues or precursors or by total synthesis. Total synthesis has the advantage of allowing for the preparation of enantiomers and derivatives not readily available by degradation or functional group interconversions.

As described in **Chapter 1** (**Section 1.8**), one possible method of increasing the efficiency of synthetic transformations is by using a tandem reaction sequence. A tandem intramolecular DA (TIMDA) reaction is one in which the components necessary for two DA reactions are linked *via* a tether in the starting material. The initial DA reaction allows the subsequent DA reaction to occur, either instantaneously (*tandem cascade* reaction) or with additional energy, reagent or catalyst (*tandem consecutive* reaction). Owing to the difficulty of preparing suitable precursors, there are very few examples of TIMDA reactions in the literature.[2,3]

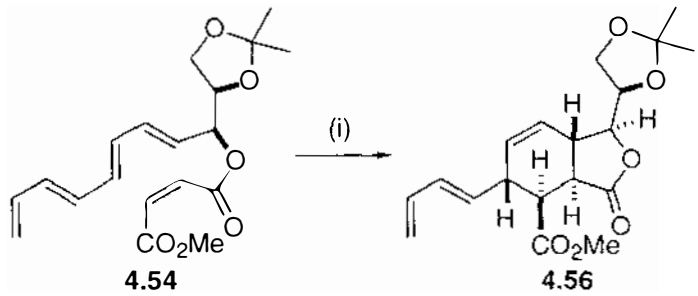
A disconnection analysis of the cyclopentano perhydrophenanthrene nucleus **5.1** of the steroids indicates that a TIMDA reaction between a *bis*-dienophile tethered to a *bis*-diene would be an elegant and efficient method of synthesis (**Scheme 5.1**). This powerful transformation would create four carbon-carbon bonds and eight new stereocentres in a single reaction. Ideally the *bis*-diene and *bis*-dienophile units would both be accessible using short synthetic routes from inexpensive (*i.e.* sugar-derived) starting materials. The *bis*-diene unit would consist of a conjugated tetraene. Previous work with a tetraene as a *bis*-diene unit was performed by Kraus and Taschner in the synthesis of the tricyclic fluorenone skeleton (**Section 4.1.2.2**, **Chapter 4**).[4]



Scheme 5.1

5.1.2 Description And Aims Of This Investigation

Model studies on a diene and two diastereomeric tetraene systems have demonstrated the ease of construction of IMDA precursors consisting of a diene and dienophile unit tethered *via* an ester-linkage (**Chapter 2**, **Chapter 4**). The feasibility of the IMDA reactions of such ester-linked precursors was shown with particularly high stereoselectivity being exhibited by the glucose-derived substrates. For example, the IMDA reaction of the tetraene ester **4.54** exhibited complete diastereoselectivity, producing only the single cycloadduct **4.56** (**Scheme 5.2**). Both the ease of cyclisation (3.5 hours, benzene at reflux) and the high stereoselectivity of the IMDA reaction boded well for the use of a conjugated tetraene as a *bis*-diene unit in a TIMDA reaction.



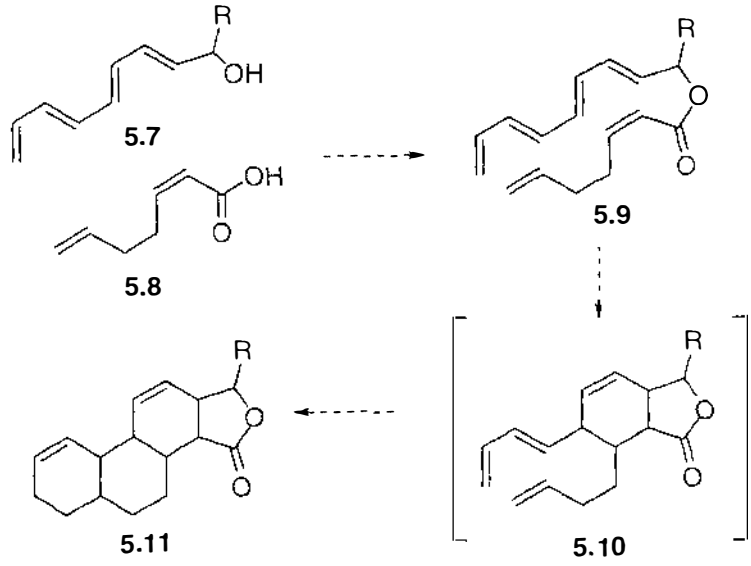
4.54 **4.56**

Reagents and Conditions: *(i) PhH, Δ, 10 mM, BHT, Ar, 3.5 h, 73%.*

Scheme 5.2

As demonstrated by the model studies (**Chapter 2**, **Chapter 4**), a synthetically facile way of connecting the *bis*-dienophile and *bis*-diene components of a TIMDA precursor is with an ester tether. The ester tether has been associated with decreased reaction rates (**Section 1.6.1**, **Chapter 1**), however, it was expected that this problem could be overcome by appropriate activation of the *bis*-dienophile. Ideally both the *bis*-dienophile and *bis*-diene portions of the DA precursor will be synthesised from monosaccharides.

During the TIMDA reaction, four new carbon-carbon bonds and eight new stereocentres are formed. This means that control of stereoselectivity in the TIMDA reaction is very important. Including a bulky substituent on the ester tether had resulted in high diastereoselectivities in the IMDA reactions previously described in this thesis. In a similar manner, the incorporation of a stereocontrolling element (R) on the ester tether of precursor **5.9** could be expected to lend a degree of stereoselectivity to the TIMDA reaction (**Scheme 5.3**).



Scheme 5.3

If required, the lactone of **5.11** could be converted to the cyclopentane ring of the steroid skeleton later in the synthesis.[5] It is hoped that this TIMDA methodology will be applicable to a wide range of tetracyclic natural products and enable access to many novel and useful steroids.

5.2 Retinol-Derived Substrate

The ideal starting point for an investigation of the TIMDA reaction is to connect readily available *bis*-diene and *bis*-dienophile units and subsequently attempt cyclisation. Retinol **5.12** is a commercially available source of a *bis*-diene unit for a TIMDA precursor (**Figure 5.3**) and has been used previously in IMDA reactions.

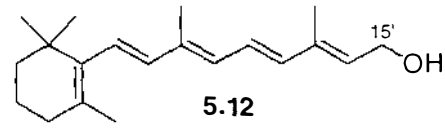
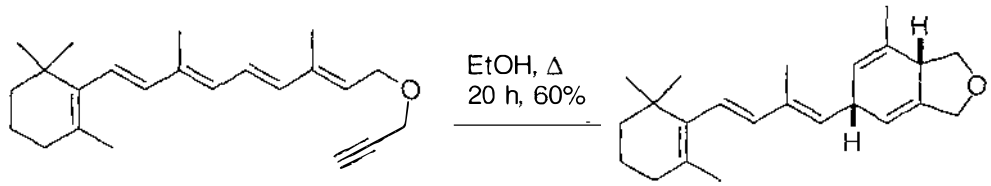


Figure 5.3

For example, Shealy and co-workers heated the retinyl propynyl ether **5.13** in refluxing ethanol for 20 hours producing cycloadduct **5.14** in good yield (**Scheme 5.4**).[6] The conjugated tetraene of retinol is substituted with methyl groups which may serve to

increase the activation of the *bis*-diene unit towards cycloaddition. Hence, due both to literature precedent and ready availability, retinol was the first choice for a *bis*-diene unit.



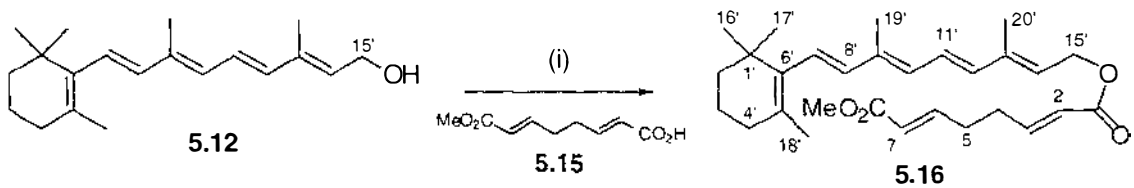
5.13 5.14

Scheme 5.4

The choice of a *bis*-dienophile unit was also dictated by ease of access with the succinaldehyde-derived monoacid **5.15** (next section) already having been synthesised by another member of the research group.[7] Hence, with both the *bis*-diene and *bis*-dienophile components at hand, a retinyl ester derivative was considered an easily accessible and viable TIMDA precursor and a prime candidate for investigation.

5.2.1 Synthesis and Attempted TIMDA Reaction

The retinyl ester **5.16** was synthesised in good yield by esterification of all-*trans* retinol **5.12** with *bis*-dienophile monoacid **5.15** (**Scheme 5.5**). Characteristic signals due to the retinyl and monoacid components of the precursor were easily identifiable in the ^{1}H NMR spectrum of the product. A shift downfield in the position of the methylene protons at position C15' from 4.30 ppm in retinol to 4.81 ppm indicated the formation of the adjacent ester tether. This was also supported by the presence of carbonyl stretches at 1725 and 1659 cm^{-1} in the IR spectrum which were due to the newly-formed ester tether and the methyl ester of the *bis*-dienophile.

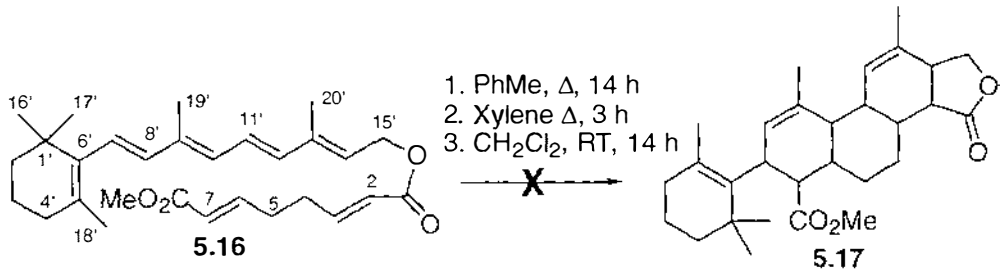


5.12 5.15 5.16

Reagents and conditions: *(i) DCC, DMAP, CH_2Cl_2, RT, 16 h, 73%.*

Scheme 5.5

All attempts to induce a TIMDA reaction of the ester **5.16** and thus form pentacyclic adduct **5.17** were unsuccessful (**Scheme 5.6**).



Scheme 5.6

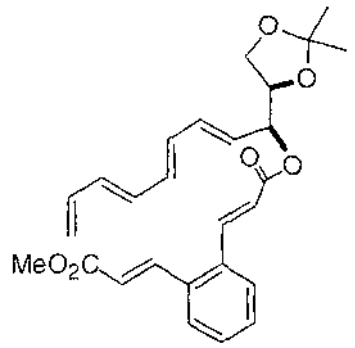
After heating a solution of the retinyl ester **5.16** in toluene at reflux for 14 hours, there was no change by TLC. Further analysis by ^{1}H NMR spectroscopy revealed a decrease in intensity in the signals for the C9' and C13' methyl groups at 1.92 ppm and 1.73 ppm and the emergence of new signals at 4.83 ppm, 5.52 ppm, 6.17-6.09 ppm, 6.25 ppm and 6.72-6.60 ppm. The new signals corresponded to new peaks for the H15', H14', H10', H11', H12', H7' and H8' protons and were due to a difference in the structure of the retinyl ester **5.16** caused by an isomerisation about one or more of the alkenic bonds of the conjugated pentaene unit. Heating the ester **5.16** in refluxing xylene for 3 hours produced the same result. Stirring the retinyl ester **5.16** in dichoromethane at RT for 14 hours resulted in no reaction with no change in the starting material detected by ^{1}H NMR spectroscopy. All of these reactions described were performed in the presence of BHT, under an atmosphere of argon, with a substrate concentration of 5 mM and in the absence of light. It was concluded that the isomerisation observed must have been a thermolytic process.

It is of interest to note that Shealy *et al.* observed a marked decrease in the propensity of the 13-*cis*-retinyl 2-propynyl ether to undergo IMDA reaction compared to the all-*trans*-retinyl propynyl ether **5.13**.[6] The possibility of isomerisation of the retinyl moiety of ester **5.16** under the reaction conditions described above is therefore undesirable and a potential hindrance to a successful TIMDA reaction. Due to the unfavourable results of the retinyl ester **5.16**, it was decided to try other tetraene esters with more activated dienophiles.

5.3 Phthalate-Derived Substrate

5.3.1 Synthesis And Attempted TIMDA Reaction

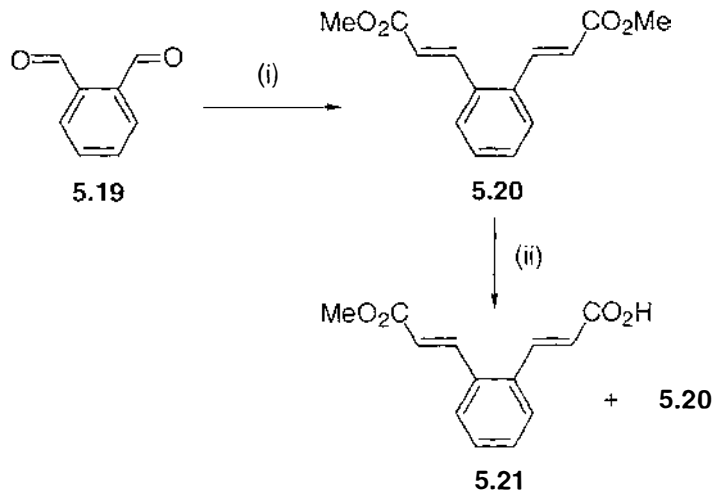
The next TIMDA precursor investigated was ester **5.18** created from the previously synthesised tetraene alcohol **4.47** and a phthalate-derived monoacid (**Figure 5.4**). It was hoped that the extended conjugation in the *bis*-dienophile unit of **5.18** would increase the activation of the individual dienophile units and hence the rate of the TIMDA reaction whilst the bulky dioxolane ring ester tether substituent would lend stereocontrol to the cyclisation.



5.18

Figure 5.4

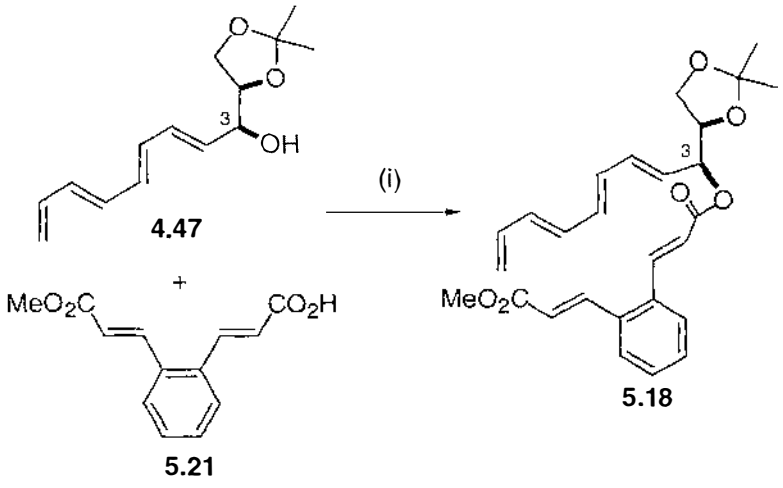
The *bis*-dienophile portion of the ester **5.18** was synthesised from phthalate dicarboxaldehyde. Wittig reaction of the dialdehyde **5.19** with carbomethoxymethylene triphenylphosphorane produced the *E,E*-dimethyl diester **5.20**. Hydrolysis of the diester with lithium hydroxide gave a mixture of the monoacid **5.21**, some recovered starting material and unrecoverable diacid.



Reagents and Conditions: *(i) carbomethoxymethylene triphenylphosphorane, CH_2Cl_2, RT, 3 h, 95%; (ii) $LiOH.H_2O$, THF/H_2O (1:1), 30°C, 1 h, monoacid* ***5.21*** *22%, recovered SM* ***5.20*** *38%.*

Scheme 5.7

The phthalate-derived monoacid **5.21** was then reacted with tetraene alcohol **4.47**[†] using a DCC/DMAP coupling procedure to give the tetraene ester **5.18** in good yield (**Scheme 5.8**). The ^{1}H NMR spectrum of the product showed the expected signals due to the tetraene and phthalate moieties of the ester. A shift downfield of H3 from 4.40-4.35 ppm to 5.53 ppm indicated the formation of the ester linkage which was confirmed by the presence of a strong C=O stretch at 1718 cm^{-1}. High resolution mass spectrometry showed a parent ion consistent with ester **5.18**.

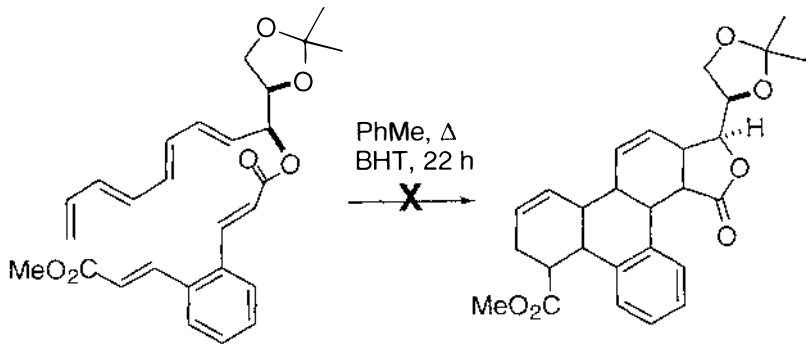


Reagents and Conditions: *(i) DCC, DMAP, BHT, CH_2Cl_2, RT, Ar, 2 h, 65%.*

Scheme 5.8

[†] The synthesis of the glucose-derived tetraene alcohol **4.47** is fully described in **Chapter 4**.

The tetraene ester **5.18** was heated at reflux in toluene in the presence of BHT for 22 hours (**Scheme 5.9**). There was no discernible change by TLC and further spectroscopic analysis by ^{1}H NMR revealed that no reaction had taken place.



5.18 **5.22**

Scheme 5.9

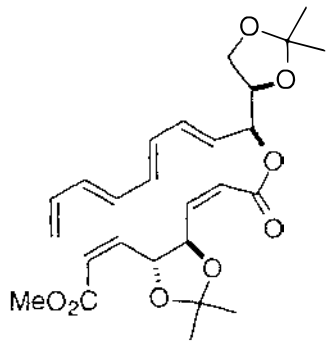
The failure of TIMDA precursor **5.18** to cyclise raised questions as to the influence of steric and electronic factors associated with the *bis*-dienophile upon the proposed TIMDA reaction. It was assumed that the inability of the substrate to react in either an IMDA or a TIMDA reaction was due to unfavourable steric factors and insufficient activation of the dienophile units. Although it possessed extended conjugation through to both activating groups, the phthalate-derived ester **5.18** was sterically congested by the presence of the aromatic ring which could have resulted in its lack of reactivity towards cyclisation.

5.4 *Bis*-*Z*-Dienophile Precursor

5.4.1 Synthesis Of The *Bis*-*Z*-Dienophile Precursor

Previous work on a tetraene system (**Chapter 4**) had shown that the single IMDA reaction of a tetraene ester containing a *bis*-diene and a *Z*-methyl ester as dienophile was both highly stereoselective (giving only a single diastereoisomer) and rapid (with a reaction time of only 3.5 hours). Thus, it was envisioned that a *bis*-dienophile unit composed of two *Z*-alkenes would be very favourable for a stereoselective TIMDA reaction. A *bis*-dienophile unit derived from 3,4-*O*-isopropylidene-D-mannitol and consisting of two *Z*-alkenes had been synthesised by another member of the research group.[8] It was decided to synthesise the TIMDA precursor **5.23** by connecting this *bis*-dienophile unit to the tetraene alcohol **4.47** and study its reactivity (**Figure 5.5**).

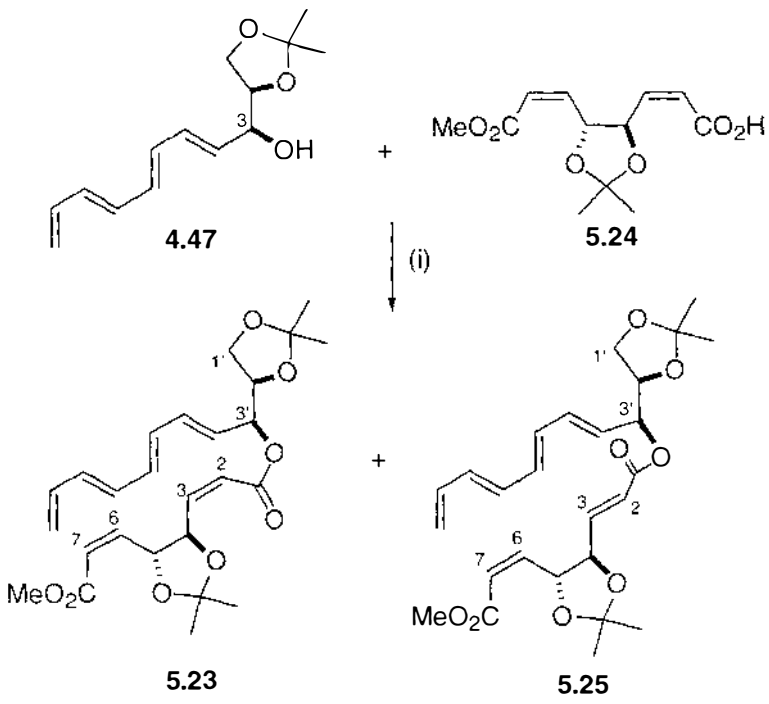
Although the dioxolane ring was recognised as having a sterically restrictive nature, it was hoped that the differing substitution pattern (1,2-dioxygenation of the *bis*-dienophile) compared to the phthalate derived substrate might be more favourable towards a TIMDA reaction.



5.23

Figure 5.5

Although it was assumed that it would be a simple procedure to form the ester **5.23** from alcohol **4.47** and monoacid **5.24**, reaction of these two substrates under DCC/DMAP-mediated coupling conditions resulted in an inseparable mixture of two isomeric products (**Scheme 5.10**). The ^{13}C NMR spectrum had twice as many peaks as expected for the ester product and appeared to indicate a major and a minor product. This was borne out by the complex ^{1}H NMR spectrum which contained signals that could be assigned to the desired *Z,Z* ester **5.23** as well as additional peaks due to the other isomer.



Reagents and Conditions: *(i) DCC, DMAP, BHT, CH_2Cl_2, RT, Ar, 15.5 h, 72%.*

Scheme 5.10

One of these additional signals was a doublet of doublets at 7.00 ppm[‡] with a large coupling constant of 15.6 Hz which allowed tentative assignment of the minor isomer as being the *Z,E*-substrate **5.25**. Close inspection of the 3.8-3.7 ppm region of the ^{1}H NMR spectrum revealed two double doublets at 3.82 and 3.76 ppm due to the H1 proton of the major and minor isomer respectively which allowed the ratio of the major (*Z,Z*) to minor (*Z,E*) isomer to be calculated as 60:40. The fact that the methyl ester peaks were coincident at 3.67 ppm was a strong indication that only an isomerisation of the C2-C3 alkene proximate to the ester tether had occurred as an *E*-methyl ester (which would have been due to an isomerisation at the C6-C7 alkene) would be expected to be further downfield (*c.f.* the *E,E* monoacid **5.32**, $-CO_2CH_3$ at 3.78 ppm).

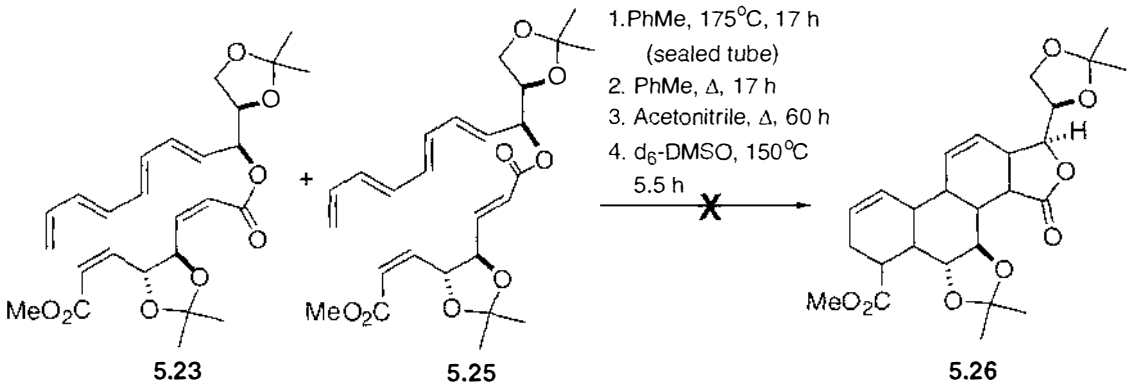
5.4.2 Attempted TIMDA Reactions

The mixture of isomeric tetraene esters **5.23** and **5.25** was heated in toluene in a sealed reaction vessel at 175°C for 17 hours resulted in destruction of the starting material with no cycloadduct being observed either by TLC or by ^{1}H NMR analysis. It was judged that

---

‡ These signals were consistent with values for a similar *E* alkenic monoacid (**5.32**) described later in this chapter.

these conditions were too harsh and the reaction was repeated using refluxing toluene for 17 hours. Again, no change from starting material was observed by TLC analysis or ^{1}H NMR spectroscopy.



Scheme 5.11

Jung and Gervay have investigated the effects of solvent polarity upon the rate of ester-tethered IMDA reactions and have discovered that the use of polar solvents can result in a large rate increase.[9-11] This rate increase has been attributed to polar solvents contributing more towards the stabilisation of the polar transition state of the IMDA reaction. Applying this theory to these tetraene ester systems, it was hoped that as substrates **5.23** and **5.25** had proven unreactive towards a TIMDA reaction in refluxing benzene or toluene, they would be amenable to the use of polar solvents such as acetonitrile or DMSO and thus result in a successful TIMDA reaction (**Scheme 5.11**).

The mixture of tetraene esters **5.23** and **5.25** was heated at reflux in acetonitrile and the progress of the reaction followed by ^{1}H NMR spectroscopy. After 36 hours no reaction had taken place and only starting material was observed by both TLC ananlysis and ^{1}H NMR spectroscopy. After additional heating (a further 24 hours at reflux), analysis by TLC showed the appearance of a baseline spot whilst the ^{1}H NMR spectrum contained three new methyl peaks. However, there was no evidence of a cycloaddition having occurred as the ^{1}H NMR spectrum did not contain any characteristic signals in the 2.2-3.6 ppm region. It was presumed that the additional methyl peaks were due to hydrolysis of the ester linkage of the starting material.

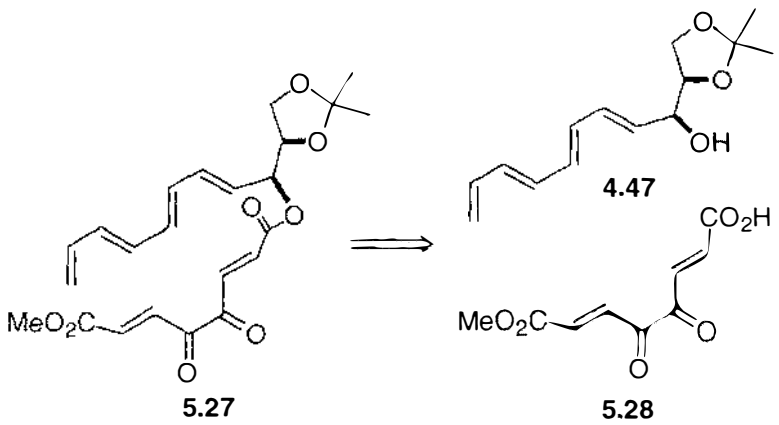
Repeating the reaction in the more polar solvent DMSO did not produce the desired TIMDA adducts either. An NMR tube containing a solution of the esters **5.23** and **5.25** in d_6-DMSO (9 mM) was heated in an oil bath at 150°C. After 1.5 hours, cyclisation had not occurred, although the ^{1}H NMR spectrum showed the emergence of another methyl ester peak. After further heating (4 hours), analysis by ^{1}H NMR spectroscopy showed

many different methyl ester groups present, yet, no signals due to cycloaddition. Destruction of the starting materials was presumed to have occurred.

The inability of *Z,Z*-dienophile ester **5.23** and *Z,E*-dienophile ester **5.25** to cyclise in either an IMDA or TIMDA sense demonstrates the difficulties involved in the selection of substrates for TIMDA reactions. It is possible that, as with the phthalate derivative, in the case of the *Z,E*-dienophile ester **5.25**, the dioxolane ring of the dienophile unit results in a sterically congested transition state and hence does not allow successful cyclisation. However, this does not apply to the *Z,Z*-dienophile ester **5.23** due to the differing geometry of the dienophile closest to the ester-tether. In addition, electronic effects need to be considered and it must be realised that neither of the alkenes of the *bis*-dienophile are doubly activated (*c.f.* the dienophiles of the successful IMDA reactions described in **Chapters 2** and **4**).

5.5 Diketone-Activated *Bis*-Dienophile

5.5.1 Introduction



Scheme 5.12

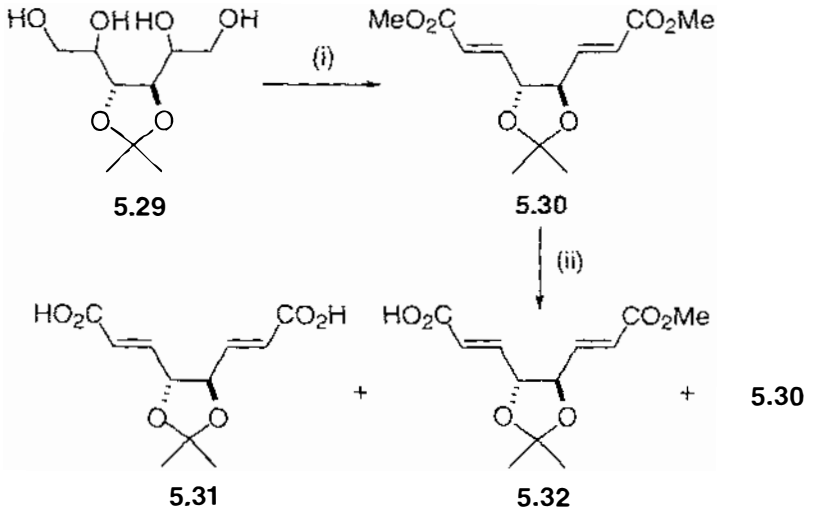
IMDA reactions on both a model diene system and two diastereomeric tetraenes (**Chapters 2** and **4**) have shown the ease of cyclisation when the dienophile is activated both internally and terminally with electron-withdrawing groups. These results are also supported by examples in the literature demonstrating the increased reactivity of such doubly activated dienophiles compared to their singly activated analogues.[12] With the results of **Chapter 2** and **Chapter 4** in mind, it was decided that in order for a TIMDA

reaction to be successful, the *bis*-dienophile would need the dienophile in conjugation with the ester-linkage to be further activated by an additional electron-withdrawing group.

The TMDA precursor **5.27** (**Scheme 5.12**) was selected due to the apparent ease of synthesis of the *bis*-dienophilic unit **5.28** from 3,4-*O*-isopropylidene-D-mannitol. 3,4-*O*-Isopropylidene-D-mannitol was regarded as a desirable starting material because it is readily obtainable from mannitol,[13] an inexpensive sugar available in bulk quantities.

5.5.2 Synthesis of *Bis*-Dienophile Moiety

A "one-pot" procedure was used in which oxidative cleavage of the 1,2-diols of 3,4-*O*-isopropylidene-D-mannitol **5.29** with sodium periodate was followed by Horner-Emmons reaction with trimethyl phosphonoacetate to give the dimethyl ester **5.30** (**Scheme 5.13**) in excellent yield.

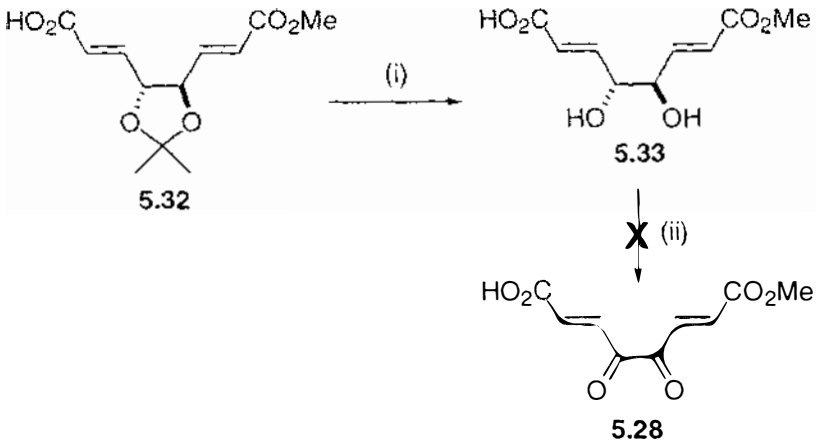


Reagents and Conditions: *(i) 1) aq. $NaHCO_3$, aq. $NaIO_4$, RT, 1 h, 2) aq. K_2CO_3, $(MeO)_2P(O)CO_2Me$, RT, overnight, 82%; (ii) LiOH, THF/H_2O/MeOH (4:1:1), RT, 5.5 h, (recovered SM* ***3.50*** *28%, monoacid* ***5.32*** *48%, diacid* ***5.31*** *24%).*

Scheme 5.13

The presence of the methyl ester groups was confirmed by the presence of a carbonyl stretch at 1728 cm^{-1} in the IR spectrum and a singlet at 3.75 ppm in the ^1H NMR. The stereochemistry of the newly formed alkene bonds was confirmed by signals in the alkenic region at 6.87 ppm (ddd) and 6.13 ppm (d) sharing a large coupling constant of J = 15.6 Hz. Hydrolysis of the diester **5.30** with lithium hydroxide resulted in a statistical mixture of diacid **5.31**, the desired monoacid **5.32** and recovered starting material **5.30** which was easily separated into its components by using a combination of aqueous

extraction and chromatography. The 1,2-diol of the monoacid **5.32** was unmasked by treatment with Amberlite resin to give the diol **5.33**, an assignment which was supported by the appearance of a broad singlet at 3.16 ppm in the ^{1}H NMR spectrum and the disappearance of signals at 1.47 and 1.48 ppm previously due to the methyl hydrogens of the isopropylidene group. Unfortunately, attempts to oxidise the diol **5.33** to the desired 1,2-diketone **5.28** proved unsuccessful despite two different oxidants being tried; Dess-Martin periodinane and MnO_2. Neither reagent resulted in oxidation and there was no change from starting material either by TLC or ^{1}H NMR spectroscopy (**Scheme 5.14**).

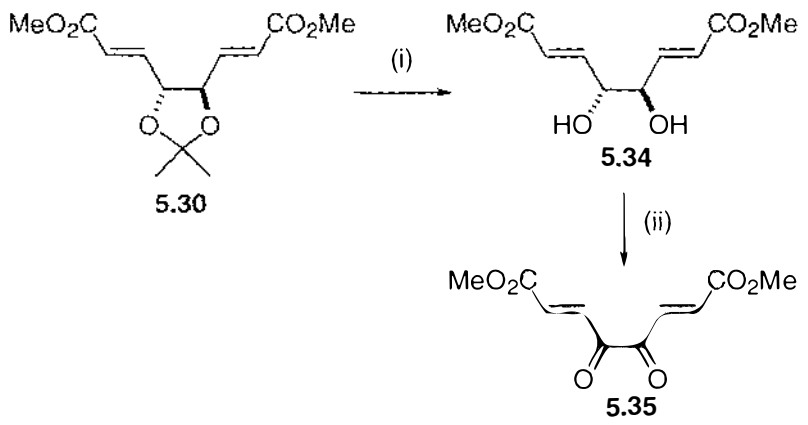


Reagents and Conditions: *(i) H^+ (Amberlite-118 resin), CH_3CN/H_2O (95:5), reflux, 1 h, 53%; (ii) attempted oxidations - (a) Dess-Martin periodinane, EtOAc, RT, 3 h; (b) MnO_2, EtOAc, RT, overnight.*

Scheme 5.14

Due to the failure to oxidise diol **5.33** to the desired diketone **5.28**, a new synthetic route was devised. It was decided to create the required diketone functionality early on in the synthesis and then hydrolyse the ester moiety later to give the appropriate monoacid.

Dimethyl diester **5.30** was treated with Amberlite resin resulting in 1,2-diol **5.34**, a white solid, in excellent yield (**Scheme 5.15**). A signal at 2.76 ppm in the ^{1}H NMR spectrum and O-H stretches at 3396, 3288 cm^{-1} in the IR spectrum confirmed the presence of the hydroxyl groups.

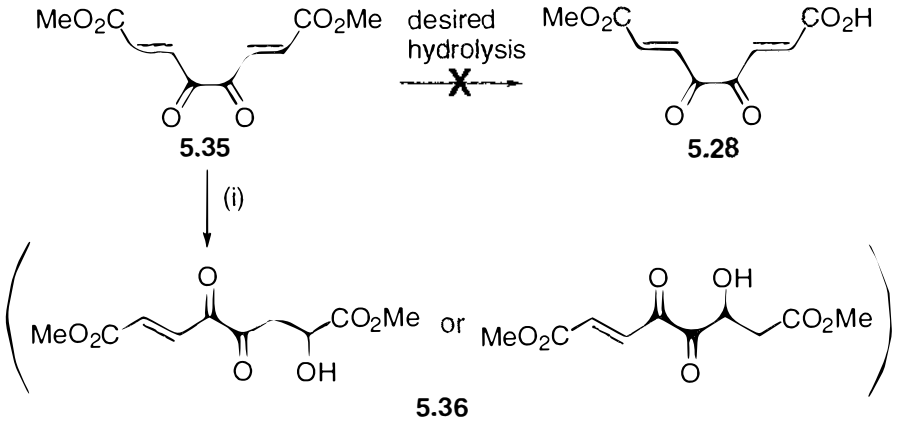


Reagents and Conditions: *(i) H^+ (Amberlite-118 resin), MeOH/H_2O (5:1), Δ, 4.5 h, 80%; (ii) Dess-Martin periodinane, CH_2Cl_2, RT, 2 h, 60%.*

Scheme 5.15

Successful oxidation of diol **5.34** with Dess-Martin periodinane gave the diketone **5.35** as an orange powder. The creation of the diketone functionality was evident by the loss of signals at 4.33-4.26 ppm (the H4 and H5 protons of the starting material), a signal at 186.0 ppm in the ^{13}C NMR spectrum and a strong C=O stretch at 1687 cm^{-1} in the IR spectrum. A C=O stretch at 1719 cm^{-1} was consistent with the presence of the α,β-unsaturated methyl esters.

Hydrolysis of dimethyl diester **5.35** was then attempted, using the same conditions as previously (LiOH, THF/MeOH/H_2O) (**Scheme 5.16**). Unfortunately, hydrolysis to the desired monoacid **5.28** did not occur. Rather, it was believed that a conjugate addition of hydroxide ion to one of the alkenic bonds of diketone **5.35** took place producing one of the regioisomeric secondary alcohols **5.36**.



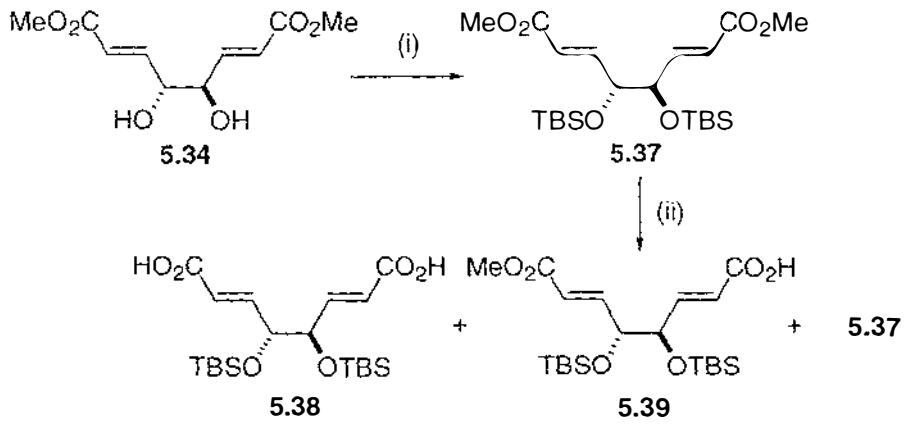
Reagents and Conditions: *(i) LiOH, THF/MeOH/H_2O (4:1:1), RT, 6.5 h, (53% based on recovered **5.35**).*

Scheme 5.16

Spectral analysis of **5.36** showed four carbonyl peaks at 175.2, 169.8, 166.7 and 162.3 ppm due to the two ketones, the saturated methyl ester group and the α,β-unsaturated methyl ester respectively. A signal at 74.5 ppm indicated the presence of a carbon bearing a hydroxyl group. A very broad peak at 8.15 ppm in the ^{1}H NMR also gave evidence for an H-bonded hydroxyl group. Alternative conditions for hydrolysis of the dimethyl diester **5.35** (LiOH, pyridine at reflux, 5 hours)[14] were also tried but this resulted in decomposition of the starting material **5.35** with none of the desired product **5.28** being formed.

The synthetic effort toward *bis*-dienophile **5.28** described above failed when attempting to hydrolyse the dimethyl diester **5.35** to the desired monoacid **5.30**. However, this synthetic attempt resulted in valuable information being gained. It was demonstrated that oxidising a 1,2-diol to a 1,2-diketone using Dess-Martin perodinane was possible providing the oxidation was performed on a diester rather than a monoacid. The initial synthetic strategy (**Scheme 5.13**) had shown that hydrolysis to the monoacid required for coupling to the tetraene (*bis*-dienophile) was successful on a protected 1,2-diol. With these two results in mind, the following synthesis was undertaken.

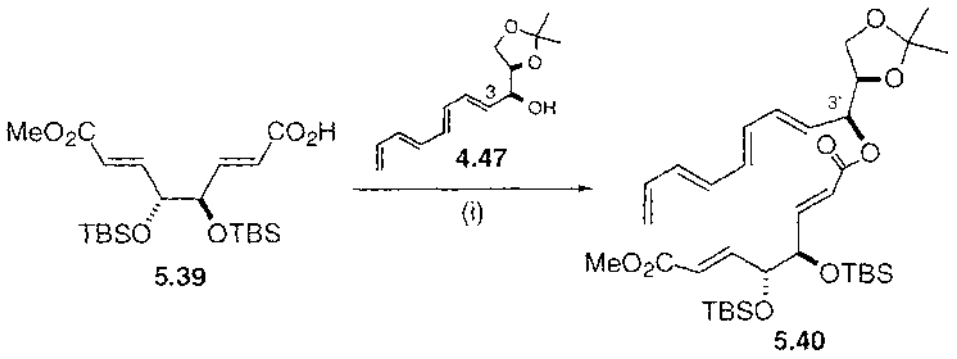
The 1,2-diol of dimethyl ester **5.34** was protected as a *bis* silyl ether using *tert*-butyldimethylsilyl chloride to give **5.37** in excellent yield (**Scheme 5.17**). Hydrolysis of **5.37** with lithium hydroxide resulted in a easily separable mixture of recovered starting material **5.37**, diacid **5.38** and the desired monoacid **5.39**. The IR spectrum of the monoacid **5.39** had a very strong, broad absorption centring at 2957 cm^{-1} which, along with the loss of symmetry in both the ^{1}H and ^{13}C NMR spectra (when compared to the starting material), confirmed the presence of the carboxylic acid group.



Reagents and Conditions: *(i) imidazole, TBSCl, DMF, RT, 11 h, 95%; (ii) LiOH, THF/MeOH/H_2O (4:1:1), RT, 2.5 h, (SM **5.37** 24%, monoacid **5.39**, 32%, diacid **5.38** 44%).*

Scheme 5.17

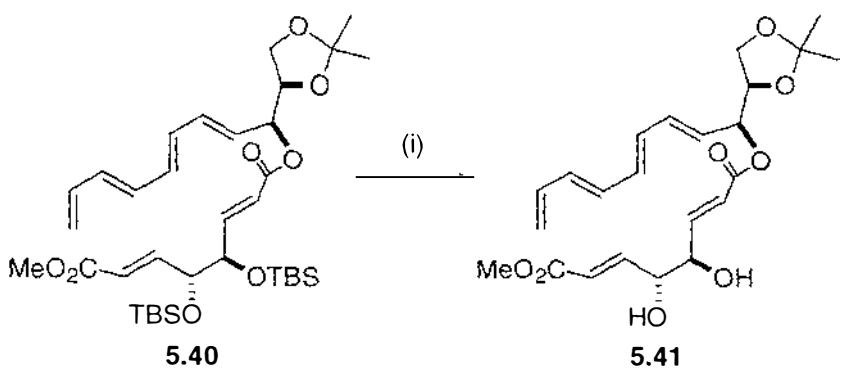
Esterification of the monoacid **5.39** with the previously described (**Chapter 4**) alcohol **4.47** produced ester **5.40** in moderate yield (**Scheme 5.18**). Confirmation of the desired product was provided by the requisite molecular ion being observed by high resolution mass spectroscopy, whilst the ^{1}H and ^{13}C NMR spectra were consistent with the product structure. In particular, a shift downfield of H3' from 4.40-4.35 ppm in the tetraene alcohol to 5.45 ppm in the product indicated the formation of an ester link at this position.



Reagents and Conditions: *(i) DCC, DMAP, BHT, CH_2Cl_2, 5 h, 46%.*

Scheme 5.18

Treatment of the disilylated ester **5.40** with TBAF resulted in the removal of the silyl ethers to give diol **5.41** (**Scheme 5.19**). Evidence for this was provided by the loss of signals in the ^{1}H NMR spectrum previously due to the silyl ether peaks (0.94, 0.11 and 0.08 ppm in the spectrum of the starting material) and the appearance of a broad singlet at 3.02 ppm due to the hydroxyl groups. The IR spectrum contained a broad, strong peak at 3443 cm^{-1}.



Reagents and Conditions: *(i) TBAF, BHT, THF, 0°C, 15 min, 53%.*

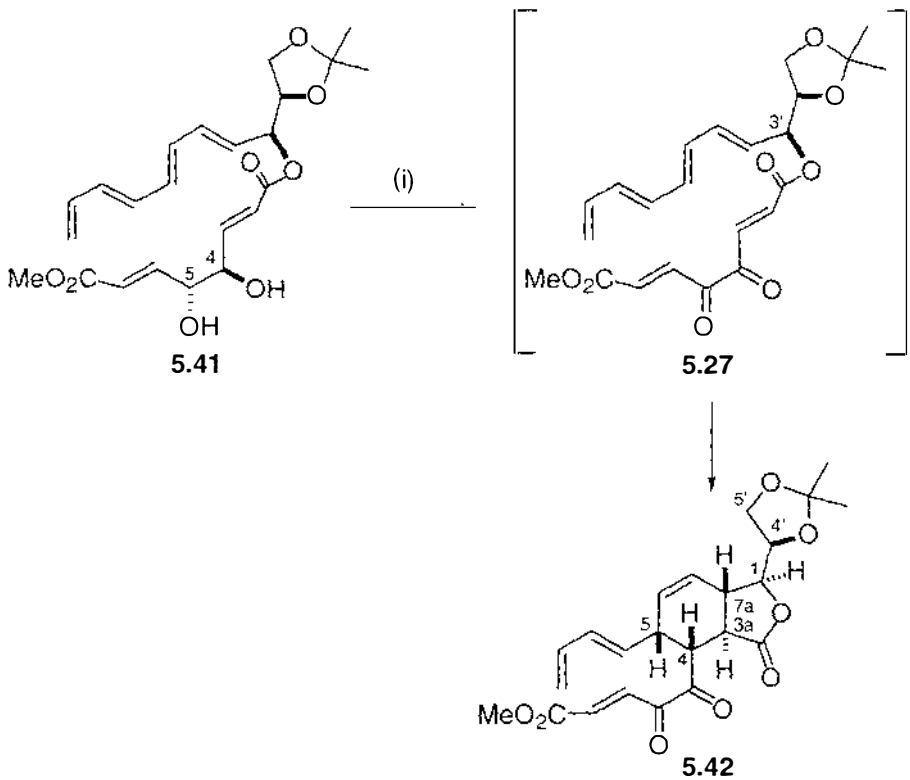
Scheme 5.19

The diol **5.41** showed a tendency towards decomposition upon handling despite the usual precautions (BHT, argon) being taken.

5.5.3 Preliminary Results

Despite difficulties in the synthesis and the inherent instability of the diol **5.41** leading to a scarcity of this useful intermediate, a preliminary study could be performed into the possibilities of this precursor with respect to the TIMDA reaction.

The oxidation reaction was performed on small scale, and although the product was not fully characterised, the initial ^{1}H NMR spectroscopic results are very promising. Whilst treatment of the diol **5.41** with Dess-Martin periodinane would have resulted in the formation of the diketone **5.27**, it was formed as an intermediate with analysis of the ^{1}H NMR spectrum of the product revealing new signals which strongly indicated that an IMDA reaction had occurred.

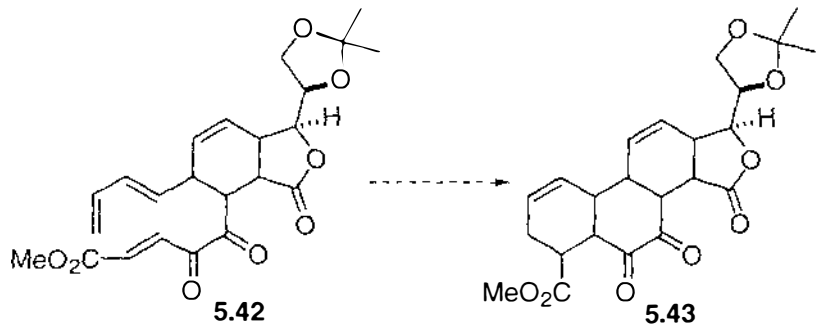


Reagents and Conditions: *(i) Dess-Martin periodinane, BHT, CH_2Cl_2, RT, 1 h.*

Scheme 5.20

The appearance of a doublet of doublets at 3.90 ppm and a multiplet at 2.79-2.63 ppm were believed to be due to the H3a and H7a protons of the newly formed cyclohexene ring. These assignments were made by comparison with the ^{1}H NMR spectrum of the previously characterised *E*-methyl ester IMDA adduct **4.57**. Of particular interest was the large coupling constant ($J_{H3a\text{-}H7a}$ = 13.8 Hz) of the doublet of doublets at 2.95 ppm, which was consistent with a *trans*-ring junction geometry between protons H3a and H7a. New signals at 3.90 ppm (dd, J = 11.6, 7.5 Hz) and 3.79-3.77 ppm (m) were assigned to H4 and H5 respectively. The disappearance of the signal due to the methine proton at the ester-tether of the starting material (5.44, dd, J = 7.3, 4.8 Hz, H3') and an increase in signals in the 4.07-4.03 ppm region indicated the formation of a lactone.

As stated previously, cyclisation was an unexpected result. The conditions of the Dess-Martin oxidation are very mild (the oxidation reaction proceeded at RT in dichloromethane and was complete after 1 hour) and the fact that an IMDA reaction appeared to occur under these mild conditions indicates the highly reactive nature of this diketone *bis*-dienophile unit. From the ^{1}H NMR spectrum, it appears that the doubly activated dienophile proximate to the ester-linkage reacted with the diene of the tetraene closest to the ester tether. It is hoped that the other dienophile (furthest from the ester-tether) will also be highly activated towards a second IMDA reaction. An attempt was made to thermolyse the initial cycloadduct **5.42** in toluene at reflux. In the event, there was insufficient material to follow the progress of reaction by using either TLC or NMR techniques. Therefore, it remains to be seen whether the pendant diene and dienophile groups of **5.42** will react in a second IMDA reaction to produce a precursor to the steroid skeleton **5.43** (**Scheme 5.21**).



5.42 **5.43**

Scheme 5.21

In order to complete investigation of this area, more of intermediate **5.41** needs to be synthesised and the oxidation of this diol needs to be repeated on larger scale so as to produce enough of the monocyclised adduct for both full characterisation and for subsequent cyclisation reactions.

5.6 Future Directions

These preliminary studies indicate that the construction of a suitable precursor for a successful TIMDA reaction is clearly not a simple task. It is not known for certain why the retinyl-derived (**5.16**), phthalate-derived (**5.18**) or *Z*,*Z*-dienophile (**5.23**) TIMDA precursors were reluctant to cyclise. However, much information has been gained from these attempted TIMDA reactions.

The retinyl ester **5.16** underwent an isomerisation under the reaction conditions and failed to produce a TIMDA adduct. Previous literature studies have shown the lack of reactivity towards cyclisation of tetraenes containing *Z* alkenes and the results reported in this thesis appear to reinforce this. In addition, the *bis*-dienophile portion of the ester was believed to be insufficiently activated towards the TIMDA reaction.

The phthalate, *Z*,*Z*-dienophile and *Z*,*E*-dienophile esters, **5.18**, **5.23** and **5.25**, all contained steric elements that increased the rigidity of these compounds. This rigidity may have prevented the precursors from obtaining the necessary transition states for cyclisation. Alternatively, it is likely that the *bis*-dienophile moieties of these substrates were also insufficiently activated for IMDA reaction.

The most promising area encountered during these investigations is that involving the diketone functionalised *bis*-dienophile (precursor **5.27**) which could be seen by ^{1}H NMR analysis to form an IMDA adduct, the expected intermediate in a TIMDA reaction. Hence, the studies reported in this chapter seem to indicate that double activation of the dienophile proximate to the ester-tether is necessary for the first IMDA reaction of the TIMDA sequence. This necessity for a doubly-activated dienophile is in keeping with the results in **Chapter 2** and **Chapter 4**, where the double activation of the dienophiles both by conjugation with the ester tether and by a terminal electron-withdrawing group resulted in facile, highly stereoselective IMDA reactions.

However, it is not known whether the second IMDA reaction in the tandem sequence requires additional activation in order to occur. It may be, that after the first IMDA reaction, the pendant diene and dienophile are in close proximity and, hence, more likely to cyclise. In fact, it is possible that unfavourable dipole-dipole interactions caused by the 1,2-diketone functionality may hold the monocycloadduct **5.42** in a conformation where the diene and dienophile are not in a suitable position to react.

Another important point to consider is the stereochemistry arising from the first IMDA reaction. From the model studies performed in **Chapters 2** and **4**, we can state that a *Z*-dienophile results in a faster rate and more highly stereoselective IMDA reaction than an *E*-dienophile. However, an *E*-dienophile proximate to the ester tether results in a product stereochemistry in which the pendant diene and dienophile are on the same side of the molecule, favourable for a second IMDA reaction.

With these facts in mind, TIMDA precursors for investigation may prove to be esters such as **5.27** and **5.44** containing *bis*-dienophiles activated by a diketone functionality (**Figure 5.6**).The use of a metal to form a bidentate complex with the diketone of the *bis*-dienophile would ensure that the precursor is in a favourable conformation for cyclisation.

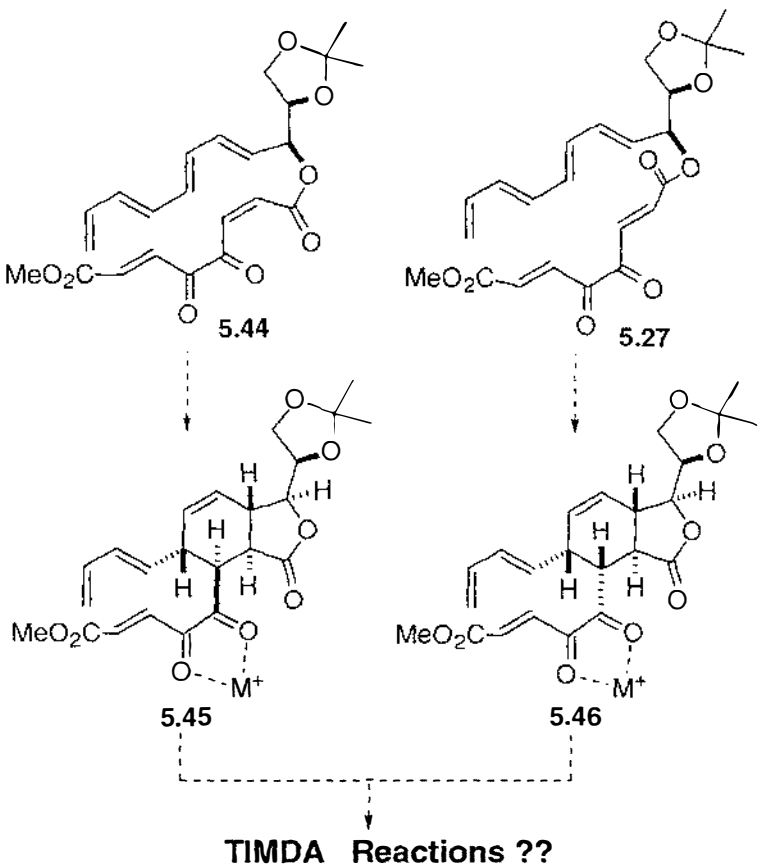


Figure 5.6

In conclusion, the initial results of the diketone substrate **5.27** are very promising and have provided valuable information for directing efforts towards a successful TIMDA reaction in the future.

5.7 References

(1) Zoretic, P. A.; Wang, M.; Zhang, Y.; Shen, Z. *J. Org. Chem.* **1996**, *61*, 1806-1813.

(2) Giguerre, R. J.; Hansen, J. A.; Goldberg, D. R. *Tetrahedron Lett.* **1993**, *34*, 8003-8006.

(3) Giguerre, R. J.; Brodney, M. A.; O'Leary, J. P.; Hansen, J. A. *Synth. Comm.* **1995**, *25*, 521-531.

(4) Kraus, G. A.; Taschner, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 1974-1977.

(5) Clive, D. L. J.; Manning, H., W.; Boivin, T., L. B.; Postema, M., H. D. *J. Org. Chem.* **1993**, *58*, 6857-6873.

(6) Shealy, Y. F.; Riordan, J. M.; Frye, J. L.; Campbell, S. R. *Tetrahedron* **1996**, *52*, 405-424.

(7) Lilly, M. J. PhD. thesis, Massey University, 1998.

(8) Jones, B. thesis, Massey University, 1997.

(9) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469-5470.

(10) Jung, M. E. *Synlett* **1989**, 186-190.

(11) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224-232.

(12) Toyota, M.; Wada, Y.; Fukumoto, K. *Heterocycles* **1993**, *35*, 111-114.

(13) Takano, S.; Kurotaki, A.; Ogasawara, K. *Synthesis* **1987**, 1075-1078.

(14) Elsinger, F. *Org. Synth.* **1965**, *45*, 7-11.

6. EXPERIMENTAL

6.1 General Experimental Details

Solvents and reagents, where necessary, were dried or purified according to the methods of Perrin and Amarego.[1] Benzene, toluene, xylene, THF and diethyl ether were purified and dried by distillation from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. All moisture sensitive reactions were performed under an argon (Ar) atmosphere using oven dried (150°C) glassware.

Reactions were generally monitored by thin layer chromatography (TLC) performed using pre-coated Merck Kieselgel 60 F_{254} silica plates. Visualisation was by use of a UV lamp (254 nm) and by staining with aqueous $KMnO_4$ solution or anisaldehyde in ethanolic sulphuric acid followed by strong heating. Where indicated, reactions were followed by ^1H NMR.

Column chromatography was performed using Merck Kieselgel 60 [230-400 mesh] silica gel with the eluent mixture indicated. Radial chromatography was performed on a 7924T chromatotron (Harrison Research) using 230 mm diameter glass plates pre-coated with a slurry of silica gel 60 HF_{254} (63-200 μm, Merck)/calcium sulfate hemihydrate (BDH) (13%) and oven dried overnight (150°C).

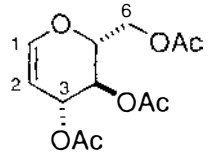
Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ solution at ambient temperature using a JEOL JNM-GX270 spectrometer. 400 MHz and 600 MHz NMR spectra were obtained using Bruker spectrometers at Sydney University. ^1H NMR spectra were generally obtained at 270 MHz and chemical shifts (δ) are expressed in parts per million (ppm) downfield shift relative to $CDCl_3$ (7.27 ppm). The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet and br, broad. Coupling constants (*J*) were given in Hertz (Hz). ^{13}C NMR spectra were obtained at 68 MHz and data is expressed in parts per million downfield shift relative to $CDCl_3$ (77.0 ppm). Spectral assignments were made and product stereochemistries were elucidated using the double resonance techniques COSY, HETCOR and NOESY. Both high and low resolution mass spectra were obtained using a Varian VG70-250S double focusing magnetic sector mass spectrometer. Electron impact (EI) was carried out at 40 or 70 eV as stated in the experimental. Data was reported as *m/z* (relative intensity). IR absorbance spectra were collected using a Perkin Elmer PARAGON 1000 FT-IR spectrometer. Solid samples were prepared as KBr discs and liquid samples as thin films

between NaCl plates. The data was reported in wavenumbers (cm^{-1}). Optical rotation ($[\alpha]_D$) measurements were measured on an Optical Activity Limited AA-100 polarimeter with the concentration expressed in g/100 mL. The path length for the sample solutions was 1.0 dm. UV spectra were recorded on a Shimadzu UV-3101PC scanning spectrophotometer. Melting points of crystalline materials were measured on a Reichert hot stage apparatus and are uncorrected.

6.2 Chapter Two Experiments

6.2.1 Synthesis Of The Dienol

Tri-*O*-acetyl-D-glucal 2.60[2,3]



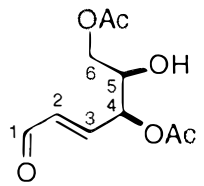
2.60

Tri-*O*-acetyl-D-glucal **2.60** was prepared according to the method described by Roth[2] and Lichtenthaler[3] with the modifications described below. D-Glucose monohydrate **2.62** (55g, 0.31 mol) was added to a mixture of Ac_2O (200 mL) and 70% perchloric acid (1.2 mL) over the course of 0.5 h. Care was taken to keep the temperature between 30°C and 40°C. After cooling in an ice/salt bath, PBr_3 (35 mL, 0.37 mol) was added with continuous stirring. The reaction temperature was kept below 20°C. Once addition was complete, H_2O (15 mL) was added over 0.5 h, keeping the reaction temperature below 20°C, and the reaction was then stirred for 3 h at RT. The reaction mixture was filtered to remove solid impurities. The filtrate contained crude *tetra-O*-acetyl-α-D-glucopyranosyl-bromide.

$NaOAc.3H_2O$ (200 g, 1.47 mol) was dissolved in H_2O (290 mL) and glacial AcOH (200 mL) and the solution cooled in an ice/salt bath. Zn dust (110 g, 1.68 mol) and $CuSO_4.5H_2O$ (11 g , 44 mmol) were added to the solution. When the blue colour had disappeared, the crude *tetra-O*-acetyl-α-D-glucopyranosylbromide solution was added gradually over 1 h, keeping the temperature below 0°C. The reaction mixture was stirred at 0°C. After 2.5 h, the reaction mixture was filtered and the filter paper washed with 50% AcOH. H_2O (500 mL, 0°C) was added to the combined filtrates and the solution was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic fractions were washed

with ice-cold H_2O, sat. aq. $NaCO_3$ and ice-cold H_2O. The organic solution was dried ($CaCl_2$), filtered and the solvent removed *in vacuo*. The crude oil was dissolved in benzene (50 mL) and the solvent removed *in vacuo*. The residual syrup was dissolved in Et_2O (60 mL) with warming and hexane (40 mL) was added and the solution filtered to remove solid impurities. After cooling, fine cream coloured crystals appeared (42 g, 51%, MP 55-57°C). R_f = 0.30, 3:1 Hex/EtOAc. ^{1}H NMR δ/ppm 6.45 (1H, dd, *J* = 6.1, 1.3 Hz), 5.34-5.29 (1H, m), 5.20 (1H, dd, *J* = 7.4, 5.9 Hz), 4.82 (1H, dd, *J* = 6.2, 3.3 Hz), 4.38 (1H, dd, *J* = 11.7, 5.4 Hz), 4.26-4.14 (3H, m), 2.07 (3H, s), 2.06 (3H, s), 2.02 (3H, s). ^{13}C NMR δ/ppm 170.5, 170.3, 169.4, 145.5, 99.0, 73.4, 67.4, 67.2, 61.4, 21.0, 20.8, 20.6. ^{1}H and ^{13}C NMR spectra were in accordance with literature values.[4]

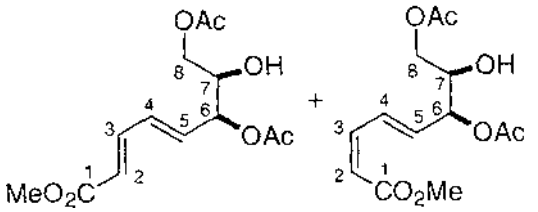
(2*E*,4S,5R)-4,6-Diacetoxy-5-hydroxy-2-hexenal 2.61[5]



2.61

This was prepared according to the method of Perlin.[5] Tri-*O*-acetyl-D-glucal **2.60** (1.23 g, 4.53 mmol) was dissolved in 1,4-dioxane (8 mL). 5 mmol H_2SO_4 (7 mL) and mercuric sulfate (46 mg, 0.15 mmol) were added and the reaction solution stirred at RT overnight. After quenching with $BaSO_4$ (147 mg, 0.75 mmol), the reaction solution was filtered through celite and then diluted with CH_2Cl_2 (50 mL). The aqueous and organic fractions were separated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 15 mL). The organic fractions were combined, washed with saturated brine and dried (Na_2SO_4). The solvent was removed *in vacuo*, resulting in the title compound as a straw coloured oil (1.04 g, 100%, R_f = 0.11 (2:1 Hex/EtOAc)). $[\alpha]_D^{18^\circ}$ = +5.3°, (c = 3.28, CH_2Cl_2). ^{1}H NMR δ/ppm 9.58 (1H, d, *J* = 7.8 Hz, H1), 6.89 (1H, dd, *J* = 16.0, 5.1 Hz, H3), 6.25 (1H, ddd, *J* = 16.0, 7.8, 1.6 Hz, H2), 5.56 (1H, ddd, *J* = 6.0, 5.1, 1.6 Hz, H4), 4.20 (2H, d, *J* = 5.1 Hz, H6), 4.10-4.03 (1H, m, H5), 2.82 (1H, br s, -OH), 2.16 (3H, s, -C(O)CH_3), 2.11 (3H, s, -C(O)CH_3). ^{13}C NMR δ/ppm 193 (C1), 171, 169 (-O*C*(O)CH_3, -O*C*(O)CH_3), 150, 133 (C3, C2), 72.4, 70.6, 64.5 (C6, C5, C4), 20.7 (3 × -CH_3). IR (thin film) υ_{max} 3457, 2960, 2856, 1744, 1692, 1373, 1231, 1121, 1089, 1045 and 872 cm^{-1}.

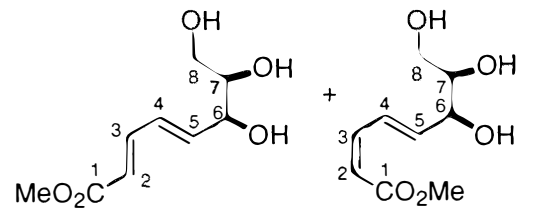
Methyl (2*E*,4*E*,6S,7R)-6,8-diacetoxy-7-hydroxy-2,4-octadienoate 2.62 and methyl (2*Z*,4*E*,6S,7R)-6,8-diacetoxy-7-hydroxy-2,4-octadienoate 2.63



2.62, 2.63

(Carbomethoxymethylene)triphenylphosphorane (1.42 g, 4.24 mmol) was added to a stirred solution of (2*E*,4S,5R)-4,6-diacetoxy-7-hydroxy-2-hexenal **2.61** (0.92 g, 4.04 mmol) in dry Et_2O (12 mL) under Ar at RT. After 4h the solvent was removed *in vacuo* to give a brown oil. Column chromatography, eluting with Hex/EtOAc (1:2) gave the product diene esters (R_f= 0.45) as a straw coloured oil (0.92 g, 80%) as a 3:1 mixture of *E* and *Z* isomers about the newly formed double bond. Found: M^+, 286.1059; $C_{13}H_{18}O_7$ requires 286.1053. ^{1}H NMR δ/ppm 7.37-7.21 (1H, m, H3), 6.56-6.38 (1H, m, H4), 6.14-6.05 (1H, m, H5), 5.98-5.71 (1H, m, H2), 5.09-4.89 (1H, m, H6), 4.45-4.30 (1H, m, H7), 4.18-4.02 (2H, m, H8), 3.76-3.74 (6H, 2 × s, 2 × $-CH_3$), 2.14-2.02 (6H, 4 × s, $-OC(O)CH_3$). IR (thin film) υ_{max} 3281, 3058, 2953, 1742, 1649,1619, 1437, 1227, 1041 and 722 cm^{-1}. *m/z* (EI, 70 eV) 286 (M^+, 1 %), 184 (17), 142 (31), 124 (7), 110 (13), 103 (9), 81 (9) and 43 (100).

Methyl (2*E*,4*E*,6S,7R,)-6,7,8-trihydroxy-2,4-octadienoate 2.64 and methyl (2*Z*,4*E*,6S,7R,)-6,7,8-trihydroxy-2,4-octadienoate 2.65

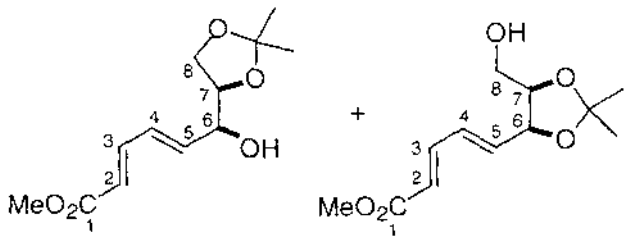


2.64, 2.65

A solution of $KHCO_3$ (2.16 g, 21.6 mmol) in H_2O (12 mL) was added dropwise to a stirred solution of the diacetates **2.62** and **2.63** (921 g, 3.20 mmol) in MeOH (70 mL) and the resulting solution was stirred at RT, under Ar, for 4.5h (all solvents were deoxygenated using an ultrasonicator). The MeOH was removed *in vacuo* at ambient temperature and the residue was diluted with H_2O (25 mL) and extracted with *sec*-butanol/EtOAc (10% v/v; 6 × 25 mL). After drying ($MgSO_4$/Na_2SO_4), the solvent was removed *in vacuo* to afford a yellow oil. Purification by column chromatography

(EtOAc) gave the product triols (R_f = 0.30) as a straw coloured oil (395 mg, 1.95 mmol, 61%). Found: MH^+ 203.0913, $C_9H_{15}O_5$ requires 203.0919. ^{1}H NMR δ/ppm 7.27 (1H, dd, *J* = 15.3, 10.9 Hz, H3), 6.65-6.40 (1H, m, H4), 6.21-6.08 (1H, m, H5), 5.93-5.68 (1H, m, H2), 4.36-4.38 (1H, m, H6), 3.74 (3H, s, $-CO_2CH_3$), 3.72-3.73 (3H, m, 2 × H8, H7), 3.48 (3H, br s, -OH). IR (thin film) υ_{max} 3389, 2925, 1715, 1644, 1620, 1438, 1039, 724 cm^{-1}; *m/z* (EI, 70 eV) 203 (MH^+, 1%), 142 (100), 124 (19), 109 (81), 81 (100), 61 (31), 53 (58) and 43 (39).

Methyl (2*E*,4*E*,6S,7R)-7,8-*O*-isopropylidene-6,7,8-trihydroxy-2,4-hexadienoate 2.67 and methyl (2*E*,4*E*,6S,7R)-6,7-*O*-isopropylidene-6,7,8-trihydroxy-2,4-octadienoate 2.66



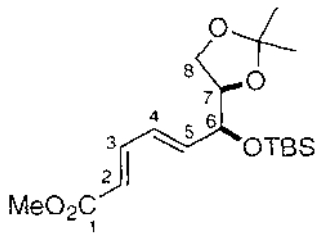
2.67, 2.66

To a solution of the triols **2.64** and **2.65** (0.39 g, 1.93 mmol) in acetone (15 mL) under Ar in an ice/salt bath (*ca.* O°C), 2,2-dimethoxy propane (1.90 mL, 15.4 mmol) and camphor sulfonic acid (45 mg, 0.19 mmol) were added. The resulting mixture was stirred at O°C for 3h, the acetone was removed *in vacuo* and the residue diluted with Et_2O (50 mL) and washed with sat. aq. $NaHCO_3$, H_2O and saturated brine. After drying ($MgSO_4$/Na_2SO_4), the solvent was removed *in vacuo* to afford a mixture of 2*E*/*Z* and dioxolane regioisomers as a colourless oil (480 mg). The crude oil was dissolved in benzene (30 mL) and thiophenol (19.5 μL, 0.19 mmol) and AIBN (16 mg, 0.097 mmol) were added under Ar. The stirred solution was heated to reflux whilst irradiating with visible light (250 W tungsten filament sun lamp) for 1 h before being recharged with thiophenol (19.5 μL, 0.19 mmol) and AIBN (16 mg, 0.10 mmol). The reaction was judged to be complete by ^{1}H NMR after a further 1 h. After removing the benzene *in vacuo*, the crude oil was purified by column chromatography eluting with Hex/EtOAc (3:1) to give the desired **secondary alcohol 2.67** (R_f = 0.21) as a colourless oil (219 mg, 48%). Found: M-CH_3^+, 227.0918; $C_{11}H_{15}O_5$ requires 227.0919. $[\alpha]_D^{17^\circ} = +1.3^\circ$, (c = 1.43, CH_2Cl_2). ^{1}H NMR δ/ppm 7.28 (1H, dd, *J* = 15.2, 10.9 Hz, H3), 6.52 (1H, dddd, *J* = 15.2, 10.9, 1.6, 0.8 Hz, H4), 6.07 (1H, dd, *J* = 15.2, 5.1 Hz, H5), 5.93 (1H, dm, *J* = 15.2 Hz, H2), 4.45 (1H, td, *J* = 4.5, 1.3 Hz, H6), 4.16 (1H, td, *J* = 6.6, 4.5 Hz, H7), 3.96 (1H, dd, *J* = 8.4, 6.6 Hz, $H8_\alpha$), 3.89 (1H, dd, *J* = 8.4, 6.6 Hz, $H8_\beta$),

3.76 (3H, s, $-CO_2CH_3$), 1.91 (1H, br s, -OH), 1.46, 1.37 (6H, 2 × s, $-C(CH_3)_2$). ^{13}C NMR δ/ppm 167 ($-CO_2CH_3$), 143, 139, 129, 121 (C3, C5, C4, C2), 110 ($-C(CH_3)_2$), 77.8, 71.1, 64.8 (C6, C7, C8), 51.6 ($-CO_2CH_3$), 26.5, 25.1 ($-C(CH_3)_2$). IR (thin film) υ_{max} 3458, 2989, 2953, 2892, 1714, 1651, 1621, 1270, 1146, 1068 and 851 cm^{-1}. *m/z* (EI, 70 eV) 227 ($M-CH_3^+$, 12%), 185 (9), 142 (34), 101 (100), 73 (17) and 43 (47).

Further elution gave the **primary alcohol 2.66** (R_f = 0.12) as a colourless oil (156 mg, 34%). Found: $M-CH_3^+$, 227.0918; $C_{11}H_{15}O_5$ requires 227.0919. ^1H NMR δ/ppm 7.28 (1H, dd, *J* = 15.3, 10.9 Hz, H3), 6.45 (1H, ddd, *J* = 15.3, 10.9, 0.6 Hz, H4), 6.10 (1H, dd, *J* = 15.3, 6.8 Hz, H5), 5.92 (1H, d, *J* = 15.3 Hz, H2), 4.76 (1H, t, *J* = 6.8 Hz, H6), 4.35-4.28 (1H, m, H7), 3.75 (3H, s, $-CO_2CH_3$), 3.57-3.55 (2H, m, H8), 2.0 (1H, br s, -OH), 1.53, 1.40 (6H, 2 × s, $-C(CH_3)_2$). IR (thin film) υ_{max} 3436, 2987, 2952, 1722, 1645, 1691, 1239, 1144, 1070 and 856 cm^{-1}. *m/z* (EI, 70 eV) 227 ($M-CH_3^+$, 4%), 142 (11), 111 (14), 101 (100), 59 (14) and 43 (50).

Methyl (2*E*,4*E*,6S,7R)-7,8-*O*-isopropylidene-6-*tert*-butyldimethylsilyl-oxy-7,8-dihydroxy-2,4-octadienoate 2.68

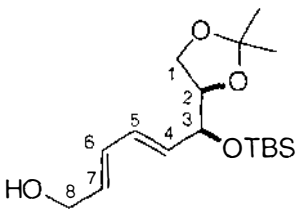


2.68

Imidazole (612 mg, 8.99 mmol) and *tert*-butyldimethylsilylchloride (653 mg, 4.31 mmol) were added to a stirred solution of the alcohol **2.67** (871 mg, 3.60 mmol) in dry DMF (2 mL) under Ar at RT. After stirring for 1.5 h, more imidazole (245 mg, 3.60 mmol) and *tert*-butyldimethylsilylchloride (271 mg, 1.80 mmol) were added. After a further 2h, the reaction mixture was diluted with Et_2O (30 mL) and washed with H_2O (50 mL). The aqueous fraction was extracted with Et_2O (4 × 60 mL). The organic fractions were combined and washed with saturated brine. The solution was dried ($MgSO_4$/Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by column chromatography eluting with Hex/EtOAc (2:1) to afford the silyl ether **2.68** (R_f = 0.81) as a pale yellow oil (1.26 g, 98%). Found: $M-CH_3^+$, 341.1788; $C_{17}H_{29}O_5Si$ requires 341.1784. $[\alpha]_D^{21^*}$ = -12.2°, (c = 4.37, CH_2Cl_2). ^1H NMR δ/ppm 7.29 (1H, dd, *J* = 15.4, 10.9 Hz, H3), 6.39 (1H, dddd, *J* = 15.2, 10.9, 1.2, 0.6 Hz, H4), 6.13 (1H, dd, *J* = 15.2, 5.7 Hz, H5), 5.90 (1H, d, *J* = 15.4 Hz, H2), 4.24-4.20 (1H, m, H6),

4.02-3.88 (3H, m, H7, 2 × H8), 3.75 (3H, s, $-CO_2CH_3$), 1.42, 1.34 (6H, 2 × s, $-C(CH_3)_2$), 0.91 (9H, s, $-SiC(CH_3)_3$), 0.09, 0.03 (6H, 2 × s, $-Si(CH_3)_2-$). ^{13}C NMR δ/ppm 167 (C1), 144, 142, 129, 121 (C4, C2, C3, C5), 110 ($-C(CH_3)_2$), 78.8, 73.1, 66.2(C6, C7, C8), 51.6 ($-CO_2CH_3$), 26.8, 25.9 ($-C(CH_3)_2$), 25.8, 25.4 ($-Si(CH_3)_2-$), 25.7 ($-SiC(CH_3)_3$), 18.2 ($-SiC(CH_3)_3$). IR (thin film) υ_{max} 2987, 2954, 2932, 2887, 2858, 1723, 1650, 1619, 1260, 1230, 1132, 1073, 1003 and 838 cm^{-1}. *m/z* (EI, 70 eV) 341 ($M-CH_3^+$, 5%), 256 (47), 241 (33), 101 (100), 73 (53) and 43 (34).

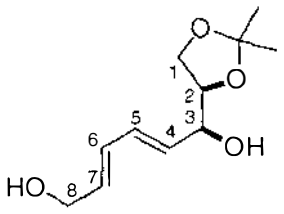
(2R,3S,4*E*,6*E*)-1,2-*O*-Isopropylidene-3-*tert*-butyldimethylsilyloxy-4,6-octadiene-1,2,8-triol 2.69



2.69

The protected diene ester **2.68** (610 mg, 1.71 mmol) was dissolved in Et_2O (30 mL) at -70°C. A solution of DIBAl-H in hexane (3.4 mL, 1.5 M, 5.0 mmol) was added dropwise, with stirring under Ar. After 0.25 h, the reaction mixture was quenched with 2% (w/w) aq. NaOH (30 mL) and extracted with Et_2O (100 mL). The organic fraction was washed with H_2O (100 mL) followed by sat. aq. Rochelle's salt (100 mL). The combined aqueous fractions were back-extracted with Et_2O (50 mL). The combined organic fractions were finally washed with saturated brine and dried ($MgSO_4/Na_2SO_4$). Removing the solvent *in vacuo* gave the primary alcohol **2.69** as a pale yellow oil (562 mg, 100%), sufficiently pure for the next step (R_f = 0.47, Hex/EtOAc (2:1)). Found: M^+, 328.2064; $C_{17}H_{32}O_4Si$ requires 328.2070. $[\alpha]_D^{21°}$ = -7.9° (c = 1.06, CH_2Cl_2). ^1H NMR δ/ppm 6.30-6.20 (2H, m, H5, H6), 5.88-5.79 (1H, m, H7), 5.71-5.63 (1H, m, H4), 4.20-4.14 (3H, m, H2, 2 × H8), 4.00-3.92 (2H, m, 2 × H1), 3.93 (1H, dd, *J* = 4.8, 3.8 Hz, H3), 1.58 (1H, br s, -OH), 1.41, 1.34 (6H, 2 × s, $-C(CH_3)_2$, 0.89 (9H, s, $-SiC(CH_3)_3$), 0.08, 0.03 (6H, 2 × s, $-Si(CH_3)_2$). ^{13}C NMR δ/ppm 134, 132, 131, 131 (C1, C5, C6, C7), 109 ($-C(CH_3)_2$), 79.0, 73.4, 66.2, 63.3 (C1, C2, C3, C8), 26.8, 25.5 ($-C(CH_3)_2$), 25.9 ($-SiC(CH_3)_3$), 18.3 ($-SiC(CH_3)_3$), -4.03 ($-Si(CH_3)_2-$). IR (thin film) υ_{max} 3418, 2986, 2955, 2930, 2866, 2858, 1688, 1643, 1072 and 837 cm^{-1}. *m/z* (EI, 70 eV) 328 (M^+, 3%), 227 (51), 210 (37), 101 (100), 73 (66) and 43 (26).

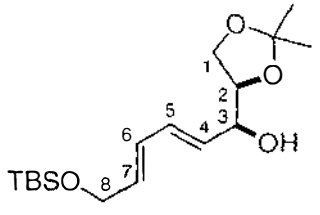
(2R,3S,4*E*,6*E*)-1,2-*O*-Isopropylidene-4,6-octadiene-1,2,3,8-tetraol 2.70



2.70

Tetrabutylammonium fluoride (3.34 mL of 1.0 M soln. in THF, 3.30 mmol) was added to a stirred solution of the silyl ether **2.69** (550 mg, 1.67 mmol) in dry THF (30 mL) at RT under Ar. After 0.5 h, the reaction was quenched by the addition of sat. aq. NH_4Cl (6 mL) and H_2O (6 mL). After dilution with Et_2O (100 mL) the aqueous fraction was removed and back-extracted with Et_2O (50 mL). The combined organic fractions were washed with saturated brine and dried ($MgSO_4/Na_2SO_4$). The solvent was removed *in vacuo* to give the crude product which was purified by column chromatography (Hex/EtOAc (1:2) to yield the desired diol **2.70** (R_f = 0.11) as a pale yellow oil (326 mg, 87%). Found: M-CH_3^+, 199.0967; $C_{10}H_{15}O_4$ requires 199.0970. $[\alpha]_D^{17^\circ}$ = -2.7° (c = 3.33, CH_2Cl_2). ^{1}H NMR δ/ppm 6.25 (1H, dd, *J* = 14.8, 10.5 Hz, H5), 6.15 (1H, dd, *J* = 14.5, 10.5 Hz, H6), 5.76 (1H, dt, *J* = 14.5, 5.6 Hz, H7) 5.57 (1H, dd, *J* = 14.8, 5.9 Hz, H4), 4.19 (1H, t, *J* = 5.9 Hz, H3), 4.07 (2H, d, *J* = 5.6 Hz, 2 × H8), 3.99 (1H dd, *J* = 6.4, 4.8 Hz, H2), 3.91-3.28 (2H, m, 2 × H1), 2.80 (2H, br s, 2 × -OH), 1.35, 1.27 (6H, 2 × s, -$C(CH_3)_2$). ^{13}C NMR δ/ppm 133, 131, 131, 130 (C4, C5, C6, C7), 109 (-$C(CH_3)_2$), 78.2, 71.4, 64.8, 63.13 (C1, C2, C3, C8), 26.5, 25.2 (-$C(CH_3)_2$). IR (thin film) υ_{max} 3417, 2987, 2934, 1679, 1155, 1066 and 849 cm^{-1}. *m/z* (EI, 70 eV) 199 (M-CH_3^+, 4%), 101 (100), 96 (20), 73 (19), 59 (16) and 43 (54).

(2R,3S,4*E*,6*E*)-1,2-*O*-Isopropylidene-8-*tert*-butyldimethylsilyloxy-4,6-octadiene-1,2,3-triol 2.71

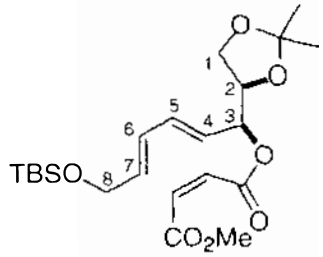


2.71

The diene-diol **2.70** (307 mg, 1.43 mmol) was dissolved in dry DMF (1 mL) and, with stirring under Ar, imidazole (244 mg, 3.58 mmol) and *tert*-butyldimethylsilylchloride

(259 mg, 1.72 mmol) were added in two portions. After 1 h, the reaction mixture was diluted with Et_2O (15 mL) and H_2O (20 mL), then the aqueous fraction was extracted with Et_2O (3 × 40 mL). The combined organic fractions were washed with saturated brine and dried ($MgSO_4/Na_2SO_4$). Removing the solvent *in vacuo* gave the crude product as a pale yellow oil. Purification by column chromatography, eluting with Hex/EtOAc (4:1), gave the desired monosilyl ether **2.71** (R_f = 0.31) as a straw coloured oil (466 mg, 99%). Found: M-CH_3^+, 313.1832; $C_{16}H_{29}O_4Si$ requires 313.1835. $[\alpha]_D^{16^\circ}$ = +1.7°, (c = 3.25, CH_2Cl_2). ^{1}H NMR δ/ppm 6.36 (1H, ddd, *J* = 14.8, 10.5, 1.2 Hz, H5), 6.29-6.19 (1H, m, H6), 5.80 (1H, dt, *J* = 14.6, 5.1 Hz, H7), 5.61 (1H, dd, *J* = 14.8, 6.1 Hz, H4), 4.35 (1H, tm, *J* = 6.1 Hz, H3), 4.22 (2H, d, *J* = 5.1 Hz, 2 × H8), 4.13 (1H, td, *J* = 6.6, 4.3 Hz, H2), 3.97 (1H, dd, *J* = 8.2, 6.5 Hz, $H1_\alpha$), 3.91 (1H, dd, *J* = 8.2, 6.8 Hz, $H1_\beta$), 2.25 (1H, br s, -OH), 1.45, 1.37 (6H, 2 × s, -$C(CH_3)_2$), 0.92 (9H, s, -$SiC(CH_3)_3$), 0.10, 0.07 (6H, 2 × s, -$Si(CH_3)_2$-). ^{13}C NMR δ/ppm 133, 131, 131, 130 (C4, C5, C6, C7), 109 (-$C(CH_3)_2$), 78.3, 71.4, 64.9, 63.0 (C1, C2, C3, C8), 26.5, 25.2 (-$C(CH_3)_2$), 24.1 (-$SiC(CH_3)_3$), 13.7 (-$SiC(CH_3)_3$), -5.09 (-$Si(CH_3)_2$-). IR (thin film) υ_{max} 3374, 2962, 2934, 2878, 1156, 1067, 993, 853 cm^{-1}. *m/z* (EI, 70 eV) 313 (M-CH_3^+, 3%), 121 (9), 101 (100), 75 (34) and 43 (20).

(2R,3S,4*E*,6*E*)-1,2-*O*-Isopropylidene-8-*tert*-butyldimethylsilyloxy-1,2-dihydroxy-4,6-octadien-3-yl methyl (2*Z*)-2-butenedioate 2.56

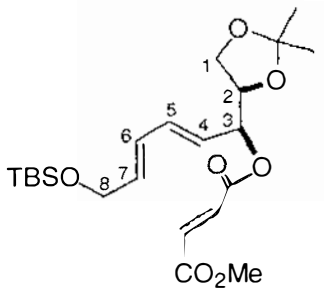


2.56

Triethylamine (181 μL, 1.30 mmol), MA (179 mg, 1.82 mmol) and DMAP (10 mg, 0.08 mmol) were added to a solution of the secondary alcohol **2.71** (266 mg, 0.81 mmol) in CH_2Cl_2 (20 mL). The reaction solution was stirred at RT under Ar for 2h. After dilution with CH_2Cl_2 (80 mL), the reaction solution was washed with 10% aq. HCl then H_2O and the aqueous fractions were back-extracted with CH_2Cl_2. The combined organic fractions were washed with saturated brine and dried ($MgSO_4/Na_2SO_4$). Removal of the solvent *in vacuo* afforded the crude acid **2.72** as a yellow oil (428 mg) which was immediately dissolved in Et_2O (15 mL) and treated with a solution of diazomethane (*ca.* 0.5 M) in Et_2O until a yellow colour persisted. The solvent was removed *in vacuo* to give an oil which was purified by column chromatography, eluting with Hex/EtOAc (2:1) to afford the

maleate ester **2.56** (R_f = 0.45) as a pale yellow oil (257 mg, 72%). Found: M-CH_3^+, 425.1992; $C_{21}H_{33}O_7$ requires: 425.1996. ^{1}H NMR δ/ppm 6.37 (1H, dd, *J* = 14.9, 10.5 Hz, H5), 6.29-6.19 (3H, m, H6, $RO_2CHCHCO_2R'$), 5.83 (1H, dt, *J* = 14.6, 4.7 Hz, H7), 5.63 (1H, dd, *J* = 14.9, 7.4 Hz, H4), 5.42 (1H, dd, *J* = 7.4, 5.1 Hz, H3), 4.29-4.18 (3H, m, 2 × H8, H2), 4.06 (1H, dd, *J* = 8.5, 6.5 Hz, H1$_\alpha$), 3.81 (1H, dd, *J* = 8.5, 6.3 Hz, H1$_\beta$), 3.76 (3H, s, -CO_2CH_3), 1.40, 1.35 (6H, 2 × s, -$C(CH_3)_2$), 0.90 (9H, s, -$SiC(CH_3)_3$), 0.06 (6H, s, -$Si(CH_3)_2$-). ^{13}C NMR δ/ppm 165, 164 (-O_2CCHCHCO_2CH_3), 135, 135, 130, 129, 128, 125 (C4, C5, C6, C7, $RO_2CHCHCO_2R'$), 110 (-$C(CH_3)_2$), 76.5, 75.0, 66.0, 63.1 (C1, C2, C3, C8), 52.2 (-CO_2CH_3), 26.4, 25.3 (-$C(CH_3)_2$), 26.0 (-$SiC(CH_3)_3$), 18.5 (-$SiC(CH_3)_3$), -5.17 (-$Si(CH_3)_2$-). IR (thin film) υ_{max} 2988, 2955, 2931, 2887, 2857, 1738, 1732, 1644, 1255, 1212, 1108, 1070 and 838 cm^{-1}. *m/z* (EI, 70 eV) 425 (M-CH_3^+, 8%), 187 (34), 113 (29), 101 (100), 89 (29), 73 (35) and 43 (24).

(2R,3S,4*E*,6*E*)-1,2-*O*-Isopropylidene-8-*tert*-butyldimethylsilyloxy-1,2-dihydroxy-4,6-octadien-3-yl methyl (2*E*)-2-butenedioate 2.57

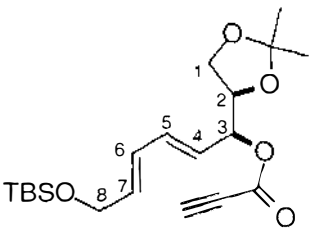


2.57

Methyl hydrogen fumarate (95 mg, 0.73 mmol), DCC (162 mg, 0.79 mmol) and DMAP (7.4 mg, 0.06 mmol) were added to a stirred solution of the secondary alcohol **2.71** (199 mg, 0.61 mmol) in CH_2Cl_2 (15 mL) under Ar at RT. After 1h, the reaction solution was diluted with Et_2O (50 mL) and filtered. The filtrate was washed with 10% aq. HCl, then sat. aq. $NaHCO_3$, H_2O and finally saturated brine. After drying ($MgSO_4$/Na_2SO_4), the solvent was removed *in vacuo* to give an oil which was purified by column chromatography, eluting with Hex/EtOAc (5:1) to give the fumarate ester **2.57** (R_f = 0.33) as an oil (234 mg, 88%). Found: M-CH_3^+, 425.2012; $C_{21}H_{33}O_7Si$ requires 425.1996. $[\alpha]_D^{17^\circ}$ = -16.5° (c = 2.65, CH_2Cl_2). ^{1}H NMR δ/ppm 6.90 (2H, s, RO_2CC*H*C*H*CO_2CH_3), 6.35 (1H, dd, *J* = 14.5, 10.6 Hz, H5), 6.23 (1H, ddt, *J* = 14.5, 10.6, 1.5 Hz, H6), 5.84 (1H, dt, *J* = 14.5, 4.6 Hz, H7), 5.62 (1H, dd, *J* = 14.5, 7.3 Hz, H4), 5.49 (1H, dd, *J* = 7.3, 4.6 Hz, H3), 4.29-4.21 (3H, m, 2 × H8, H2), 4.07 (1H, dd, *J* = 8.4, 6.6 Hz, H1$_\alpha$), 3.84 (1H, dd, *J* = 8.4, 6.2 Hz, H1$_\beta$), 3.82 (3H, s,

-CO_2CH_3), 1.40, 1.36 (6H, 2 × s, -$C(CH_3)_2$), 0.92 (9H, s, -$SiC(CH_3)_3$), 0.07 (6H, s, -$Si(CH_3)_2$-). ^{13}C NMR δ/ppm 165, 164 ($RO_2CCHCHCO_2CH_3$) 135, 135, 134, 133, 128, 125 ($RO_2CCHCHCO_2CH_3$, C4, C5, C6, C7), 110 (-$C(CH_3)_2$), 76.5, 74.7, 65.5, 63.0 (C1, C2, C3, C8), 52.3 (-CO_2CH_3), 26.3, 25.2 (-$C(CH_3)_2$), 25.9 (-$SiC(CH_3)_3$), 18.4 (-$SiC(CH_3)_3$), -5.22 (-$Si(CH_3)_2$-). IR (thin film) υ_{max} 2989, 2955, 2887, 2858, 1732, 1645, 1259, 1156, 1104, 1071, 840 cm^{-1}. *m/z* (EI, 70 eV) 383 (M-$C_4H_9^+$, 12%), 187 (44), 113 (33), 101 (100), 73 (32) and 43 (26).

(2S,3R,4*E*,6*E*)-1,2-*O*-Isopropylidene-8-*tert*-butyldimethylsilyloxy-1,2-dihydroxy-4,6-octadien-3-yl propynoate 2.58



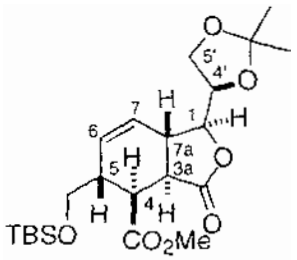
2.58

Propiolic acid (178 mL, 2.89 mmol), DCC (642 mg, 3.11 mmol) and DMAP (24 mg, 0.20 mmol) were added sequentially to a solution of the secondary alcohol **2.71** (225 mg, 0.68 mmol) in CH_2Cl_2 (10 mL) under Ar at RT. The reaction mixture was stirred overnight before being diluted with Et_2O and filtered through celite. The filtrate was washed successively with 10% aq. HCl, sat. aq. $NaHCO_3$, H_2O and saturated brine, dried ($MgSO_4$/Na_2SO_4) and then the solvent removed *in vacuo.* Radial chromatography was carried out using Hex/EtOAc (4:1) to give the desired propynoate ester (R_f = 0.59) as a yellow oil (0.15 g, 0.39 mmol, 57%). Found: M-CH_3^+, 365.1783; $C_{19}H_{29}O_5Si$ requires: 365.1784. $[\alpha]_D^{20°}$ = -22°, (c = 1.19, CH_2Cl_2). ^{1}H NMR δ/ppm 6.36 (1H, dd, *J* = 14.9, 10.6 Hz, H5), 6.28-6.17 (1H, m, H6), 5.85 (1H, dt, *J* = 14.7, 4.8 Hz, H7), 5.58 (1H, dd, *J* = 14.9, 7.5 Hz, H4), 5.44 (1H, dd, *J* = 7.5, 4.9 Hz, H3), 4.27-4.21 (3H, m, H2, 2 × H8), 4.05 (1H, dd, *J* = 8.6, 6.6 Hz, $H1_\alpha$), 3.83 (1H, dd, *J* = 8.6, 6.1 Hz, $H1_\beta$), 2.94 (1H, s, -CCH), 1.41, 1.35 (6H, 2 × s, -$C(CH_3)_2$), 0.90 (9H, s, -$SiC(CH_3)_3$), 0.06 (6H, s, -$Si(CH_3)_2$-). ^{13}C NMR δ/ppm 151 (-CO_2R), 136, 135, 128, 124 (C4, C5, C6, C7), 110 (-$C(CH_3)_2$), 76.4, 75.8, 75.4, 74.4, 65.6, 63.0 (-*C*CH, C1, C2, C3, C8), 26.3, 25.4 (-$C(CH_3)_2$), 26.0 (-$SiC(CH_3)_3$), 18.5 (-$SiC(CH_3)_3$), -5.17 (-$Si(CH_3)_2$-). IR (thin film) υ_{max} 2931, 2857, 2117, 1715, 1223, 837 cm^{-1}. *m/z* (EI, 70 eV) 365 (M-CH_3^+, 5%), 195 (14), 127 (40), 101 (100), 73 (42) and 43 (27).

6.2.2 IMDA Reaction Of (2R,3S,4*E*,6*E*)-1,2-*O*-Isopropylidene-8-*tert*-butyldimethylsilyloxy-1,2-dihydroxy-4,6-octadien-3-yl methyl (2*Z*)-2-butenedioate 2.56

A solution of the maleate ester **2.56** (106 mg, 0.24 mmol) in toluene (48 mL) was heated to reflux in the presence of BHT (5 mg, 0.02 mmol) under Ar for 19 h. The solvent was removed *in vacuo*. ^{1}H NMR analysis of the reaction mixture indicated the presence of two compounds in an 86:14 ratio. Purification by column chromatography, eluting with Hex/Et_2O (1:1) gave a mixture of the two diastereoisomeric cycloadducts (106 mg, 100%). Repeated column chromatography using the same solvent system separated the two diastereoisomers **2.73** and **2.74** (R_f = 0.35 and 0.24).

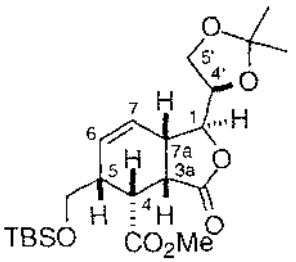
Methyl (1S,3aR,4S,5R,7aS)-5-*tert*-butyldimethylsilyloxymethyl-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 2.73



2.73

Colourless oil, (R_f = 0.35). Found: M^+, 440.2235; $C_{22}H_{36}O_7Si$ requires 440.2230. $[\alpha]_D^{18^\circ}$ = -19.4°, (c = 4.80, CH_2Cl_2). ^{1}H NMR δ/ppm 6.14 (1H, dt, *J* = 10.1, 2.0 Hz, H7), 5.62 (1H, dt, *J* = 10.1, 3.2, H6), 4.25-4.19 (1H, m, H4'), 4.16 (1H, dd, *J* = 8.6, 6.2 Hz, H5'$_\alpha$) 4.07-4.01 (1H, m, H5'$_\beta$), 3.91 (1H, dd, *J* = 10.0, 7.7 Hz, H1), 3.77-3.73 (1H, m, -CH_αOSi-), 3.71 (3H, s, -CO_2CH_3), 3.55 (1H, dd, *J* = 10.3, 6.6 Hz, -CH_βOSi-), 3.33 (1H, d, *J* = 3.7, H4), 3.10-2.98 (1H, m, H7a), 2.91-2.85 (1H, m, H5), 2.64 (1H, dd, *J* = 13.6, 3.7 Hz, H3a), 1.46, 1.37 (6H, 2 × s, -$C(CH_3)_2$), 0.89 (-$SiC(CH_3)_3$), 0.07, 0.06 (6H, 2 × s, -$Si(CH_3)_2$-). ^{13}C NMR δ/ppm 173, 172 (-CO_2CH_3, C3), 129, 127 (C6, C7), 110 (-$C(CH_3)_2$), 81.5, 77.5, 67.2, 65.8 (C1, C4', C5', -CH_2OSi-), 52.1 (-CO_2CH_3), 42.6, 42.0, 40. 8, 38.3 (C3a, C4, C5, C7a), 26.8, 25.1 (-$C(CH_3)_2$), 25.8 (-$SiC(CH_3)_3$), 18.3 (-$SiC(CH_3)_3$), -5.34 (-$Si(CH_3)_2$-). IR (thin film) υ_{max} 2988, 2954, 2930, 2887, 2857, 1794, 1735, 1254, 1215, 1108, 993 and 838 cm^{-1}. *m/z* (EI, 70 eV) 425 (M-CH_3^+, 19%), 383 (100), 119 (5), 101 (14), 89 (34) and 73 (21).

Methyl (1S,3aS,4R,5R,7aS)-5-*tert*-butyldimethylsilyloxymethyl-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 2.74



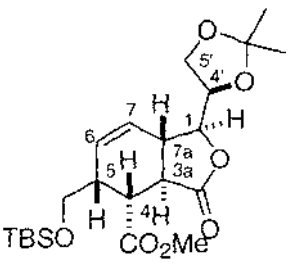
2.74

Colourless oil, (R_f = 0.24). Found: M^+, 440.2241; $C_{22}H_{36}O_7Si$ requires 440.2230. $[\alpha]_D^{18^\circ}$ = -3.9°, (c = 0.85, CH_2Cl_2). ^1H NMR δ/ppm 5.87-5.76 (2H, m, H6, H7), 4.29-4.24 (1H, m, H1), 4.19-4.12 (2H, m, H5'$_\alpha$, H4'), 4.01-3.97 (1H, m, H5'$_\beta$), 3.84 (1H, dd, *J* = 9.7, 7.0 Hz, -CH_αOSi-), 3.69 (3H, s, -CO_2CH_3), 3.57 (1H, dd, *J* = 9.7, 8.2 Hz, -CH_βOSi-), 3.34 (1H, t, *J* = 5.4 Hz, H4), 3.22 (1H, dd, *J* = 10.8, 5.5 Hz, H3a), 3.14-3.03 (1H, m, H7a), 2.70-2.60 (1H, m, H5), 1.46, 1.38 (6H, s, -$C(CH_3)_2$), 0.90 (9H, s, -$SiC(CH_3)_3$), 0.07 (6H, s, -$Si(CH_3)_2$-). ^{13}C NMR δ/ppm 176, 172 (-CO_2CH_3, C3), 128, 127 (C6, C7), 110 (-$C(CH_3)_2$), 83.3, 77.2, 67.3, 64.3 (C1, C4', C5', -CH_2OSi-), 51.9 (-CO_2CH_3), 40.4, 40.0, 39.7, 38.4 (C3a, C4, C5, C7a), 26.8, 25.2 (-$C(CH_3)_2$), 25.9 (-$SiC(CH_3)_3$), 18.36 (-$SiC(CH_3)_3$), -5.29 (-$Si(CH_3)_2$-). IR (thin film) υ_{max} 2986, 2953, 2930, 2886, 2856, 1779, 1738, 1256, 1208, 1087, 1019 and 837 cm^{-1}. *m/z* (EI, 70 eV) 425 (M-CH_3^+, 12%), 383 (100), 325 (10), 101 (12), 89 (35) and 73 (24).

6.2.3 IMDA Reaction Of (2R,3S,4*E*,6*E*)-1,2-*O*-Isopropylidene-8-*tert*-butyldimethylsilyloxy-1,2-dihydroxy-4,6-octadien-3-yl methyl (2*E*)-2-butenedioate 2.57

A solution of the fumarate ester **2.57** (67 mg, 0.15 mmol) in toluene (15 mL) was heated to reflux in the presence of BHT (3.3 mg, 0.02 mmol) under Ar for 39 h. The solvent was removed *in vacuo*. ^1H NMR analysis of the reaction mixture indicated the presence of three products in a 72:17:11 ratio. Purification by column chromatography, eluting with Hex/Et_2O (4:1) gave a mixture of the three diastereoisomeric cycloadducts (60.3 mg, 90%). Repeated column chromatography and HPLC provided pure samples of the major (R_f = 0.20) and both minor (R_f = 0.21), (R_f = 0.27) diastereoisomers.

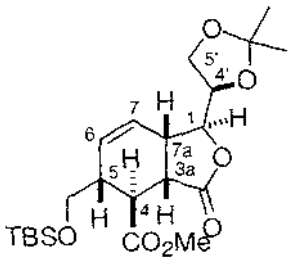
Methyl (1S,3aR,4R,5R,7aS)-5-*tert*-butyldimethylsilyloxymethyl-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 2.75



2.75

The major diastereoisomer **2.75** was a colourless oil, (R_f = 0.20). Found: M-CH_3^+, 425.2000; $C_{21}H_{33}O_7Si$ requires 425.1996. $[\alpha]_D^{19^\circ}$ = -126°, (c = 0.028, $CHCl_3$). ^1H NMR 600 MHz (CD_3CN) δ/ppm 6.20 (1H, dt, *J* = 10.0, 2.0 Hz, H7), 5.86 (1H, dt, *J* = 10.0, 3.3 Hz, H6), 4.33 (1H, td, *J* = 6.6, 4.6 Hz, H4'), 4.23 (1H, dd, *J* = 8.9, 6.5 Hz, H5'$_\alpha$), 4.18 (1H, dd, *J* = 10.4, 6.7 Hz, H1), 4.03 (1H, dd, *J* = 8.9, 4.5 Hz, H5'$_\beta$), 3.80 (3H, s, -CO_2CH_3), 3.74 (1H, dd, *J* = 10.6, 6.1 Hz, -CH_αOSi-), 3.65 (1H, dd, *J* = 10.6, 4.8 Hz, -CH_βOSi-), 3.10 (1H, dd, *J* = 11.8, 7.2 Hz, H4), 3.06 (1H, dd, *J* = 13.0, 11.8 Hz, H3a), 2.89-2.86 (1H, m, H5), 2.82-2.77 (1H, m, H7a), 1.52, 1.44 (6H, 2 × s, -$C(CH_3)_2$), 0.99 (9H, s, -$SiC(CH_3)_3$), 0.16, 0.15 (6H, 2 × s, -$Si(CH_3)_2$). ^{13}C NMR 100 MHz ($CDCl_3$) δ/ppm 173.8, 171.8 (-CO_2CH_3, C3), 131.8, 126.2 (C6, C7), 110.8 (-$C(CH_3)_2$), 81.9, 77.9 (C1, C4'), 68.0, 64.3 (C5', -CH_2OSi-), 52.5 (-CO_2CH_3), 46.1, 42.9, 42.8, 41.4 (C3a, C4, C5, C7a), 27.5, 25.7 (-$C(CH_3)_2$), 26.5 (-$SiC(CH_3)_3$), 18.9 (-$SiC(CH_3)_3$), -4.9 (-$Si(CH_3)_2$-). IR (thin film) υ_{max} 2927, 2855, 1793, 1741, 1257, 1211, 1153, 1097, 985 and 840 cm^{-1}. *m/z* (EI, 70 eV) 425 (M-CH_3^+, 30%), 410 (13), 383 (100), 163 (12), 115 (17), 101 (33), 89 (69) and 73 (60).

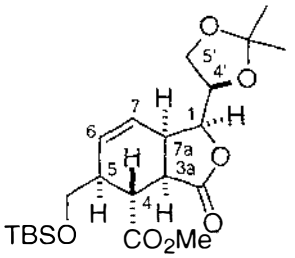
Methyl (1S,3aS,4S,5R,7aS)-5-*tert*-butyldimethylsilyloxymethyl-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 2.76



2.76

The diastereoisomer formed in intermediate amount was **2.76**, colourless oil, (R_f = 0.21). Found: M-CH_3^+, 425.2001; $C_{21}H_{33}O_7Si$ requires 425.1996. $[\alpha]_D^{19^\circ}$ = -37°, (c = 0.017, $CHCl_3$). ^{1}H NMR 600 MHz, ($CDCl_3$) δ/ppm 5.84 (1H, ddd, *J* = 10.2, 3.3, 2.1 Hz, H6), 5.76 (1H, ddd, *J* = 10.2, 3.5, 2.2 Hz, H7), 4.19 (1H, td, *J* = 6.6, 4.4 Hz, H4'), 4.14 (1H, dd, *J* = 8.9, 6.5 Hz, H5'$_\alpha$), 4.02 (1H, dd, *J* = 6.9, 5.6 Hz, H1), 3.92 (1H, dd, *J* = 8.9, 4.4 Hz, H5'$_\beta$), 3.73 (3H, s, -CO_2CH_3), 3.54 (1H, dd, *J* = 9.9, 6.4 Hz, -CH_αOSi-), 3.51 (1H, dd, *J* = 10.0, 6.4 Hz, -CH_βOSi-), 3.24 (1H, dd, *J* = 8.5, 7.7 Hz, H3a), 3.13-3.10 (1H, m, H7a), 2.94 (1H, dd, *J* = 7.6, 6.2 Hz, H4), 2.73-2.69 (1H, m, H5), 1.45, 1.36 (6H, 2 × s, -$C(CH_3)_2$), 0.89 (9H, s, -$SiC(CH_3)_3$), 0.47, 0.38 (6H, 2 × s, -$Si(CH_3)_2$). ^{13}C NMR 100 MHz ($CDCl_3$) δ/ppm 176.2, 173.9 (-CO_2CH_3, C3), 129.4, 125.5 (C6, C7), 110.3 (-$C(CH_3)_2$), 83.6, 76.7 (C1, C4'), 66.8, 64.9 (C5', -CH_2OSi-), 52.2 (-CO_2CH_3), 39.9, 39.7, 39.5, 37.2 (C3a, C4, C5, C7a), 26.6, 24.9 (-$C(CH_3)_2$), 25.8 (-$SiC(CH_3)_3$), 18.3 (-$SiC(CH_3)_3$), -5.5, -5.6 (-$Si(CH_3)_2$-). IR (thin film) υ_{max} 2926, 1780, 1736, 1461, 1372, 1257, 1107 and 838 cm^{-1}. *m/z* (EI, 70 eV) 425 (M-CH_3^+, 28%), 383 (100), 325 (12), 235 (15), 115 (20), 101 (61), 89 (86) and 73 (71).

Methyl (1S,3aR,4R,5S,7aR)-5-*tert*-butyldimethylsilyloxymethyl-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 2.77



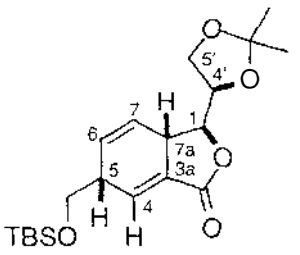
2.77

The minor stereoisomer **2.77** was a colourless oil, (R_f = 0.27). Found: M-CH_3^+, 425.1998; $C_{21}H_{33}O_7Si$ requires 425.1996. $[\alpha]_D^{19^\circ}$ = +82°, (c = 0.035, $CHCl_3$). ^1H NMR 600 MHz, (CD_3CN) δ/ppm 6.02 (1H, ddd, *J* = 10.5, 4.3, 2.1 Hz, H6), 5.94 (1H, dt, *J* = 10.6, 2.3 Hz, H7), 4.57 (1H, dd, *J* = 8.5, 6.1 Hz, H1), 4.28 (H, ddd, *J* = 8.5, 6.1, 4.7 Hz, H4'), 4.21 (1H, dd, *J* = 8.7, 6.2 Hz, H5'$_\alpha$), 3.99 (1H, dd, *J* = 8.7, 4.6 Hz, H5'$_\beta$), 3.78 (3H, s, -CO_2CH_3), 3.66 (1H, dd, *J* = 9.9, 6.3 Hz, -CH_αOSi-), 3.49 (1H, dd, *J* = 9.9, 8.5 Hz, -CH_βOSi-), 3.45 (1H, dd, *J* =8.2, 3.4 Hz, H3a), 3.43-3.39 (1H, m, H7a), 3.35 (1H, t, *J* = 2.8 Hz, H4), 2.85-2.75 (1H, m, H5), 1.51, 1.44 (6H, 2 × s, -$C(CH_3)_2$), 1.02 (9H, s, -$SiC(CH_3)_3$), 0.18, 0.17 (6H, 2 × s, -$Si(CH_3)_2$-). ^{13}C NMR 100 MHz ($CDCl_3$) δ/ppm 177.2, 174.9 (-CO_2CH_3, C3), 131.1, 123.6 (C6, C7), 110.5 (-$C(CH_3)_2$), 81.3, 74.4 (C1, C4'), 68.5, 66.1 (C5', -CH_2OSi-), 53.1 (-CO_2CH_3), 40.5, 39.5, 38.7, 36.2 (C3a, C4, C5, C7a), 27.6, 25.8 (-$C(CH_3)_2$), 26.5 (-$SiC(CH_3)_3$), 18.9 (-$SiC(CH_3)_3$), -4.7, -4.8 (-$Si(CH_3)_2$-). IR (thin film) υ_{max} 2953, 2927, 2855, 1783, 1735, 1254, 1198, 1145, 1105, 1061 and 838 cm^{-1}. *m/z* (EI, 70 eV) 425 (M-CH_3^+, 17%), 410 (29), 383 (81), 235 (16), 115 (25), 101 (97), 89 (100) and 73 (82).

6.2.4 IMDA Reaction Of (2S,3R,4*E*,6*E*)-1,2-*O*-Isopropylidene-8-*tert*-butyldimethylsilyloxy-1,2-dihydroxy-4,6-octadien-3-yl propynoate 2.58

A solution of the propynoate ester **2.58** (42 mg, 0.11 mmol) in toluene (11 mL) was heated to reflux in the presence of BHT (2.4 mg, 0.01 mmol) under Ar for 17 h. The solvent was removed *in vacuo*. ^1H NMR analysis of the reaction mixture indicated the presence of two compounds in a 92:8 ratio. Purification by column chromatography, eluting with Hex/Et_2O (4:1) gave an inseparable mixture of the two possible diastereoisomeric cycloadducts **2.78** and **2.79** (R_f = 0.20) (32 mg, 77%). Data is reported for the major diastereoisomer **2.78**.

(1S,7aS,5R)-5-*tert*-Butyldimethylsilyloxymethyl-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-1,3,5,7a-tetrahydro-3-isobenzofuranone 2.78



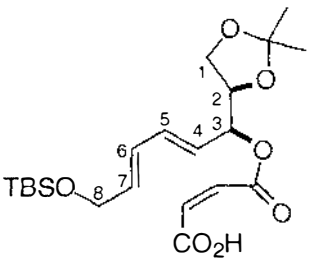
2.78

Found: M-CH_3^+, 365.1794; $C_{19}H_{29}O_5Si$ requires 365.1784. $[\alpha]_D^{16^\circ}$ = +9.9°, (c = 1.40, CH_2Cl_2). ^{1}H NMR δ/ppm 6.86 (1H, p, *J* = 1.5 Hz, H4), 6.02 (1H, ddd, *J* = 9.7, 2.9, 2.0 Hz, H6), 5.79 (1H, dp, *J* = 9.7, 1.6 Hz, H7), 4.25 (1H, dq, *J* = 6.2, 4.0 Hz, H4'), 4.19 (1H, dd, *J* = 8.6, 6.2 Hz, H5'$_\alpha$), 4.04 (1H, dd, *J* = 8.6, 4.0 Hz, H5'$_\beta$), 3.92 (1H, dd, *J* = 9.0, 8.1 Hz, H1), 3.74 (1H, dd, *J* = 9.6, 6.6 Hz, -CH_αOSi-), 3.63 (1H, dd, *J* = 9.6, 7.5 Hz, -CH_βOSi-), 3.40-3.29 (1H, m, H7a), 3.12-3.01 (1H, m, H5), 1.46, 1.39 (6H, 2 × s, -C(CH_3)$_2$), 0.90 (9H, s, -SiC(CH_3)$_3$), 0.07 (6H, s, -Si(CH_3)$_2$-). ^{13}C NMR δ/ppm 168 (C3), 135 (C4), 129, 128, 125 (C3a, C6, C7), 110 (-C(CH_3)$_2$), 81.9, 77.8 (C1, C4'), 67.3, 65.1 (-CH_2OSi-, C5'), 42.5, 40.9 (C5, C7a), 26.9, 25.1 (-C(*C*H_3)$_2$), 25.9 (-SiC(*C*H_3)$_3$), 18.35 (-Si*C*(CH_3)$_3$), -5.28 (-Si(CH_3)$_2$-). IR (thin film) υ_{max} 2988, 2954, 2930, 2986, 2858, 1777, 1258, 1114 and 839 cm^{-1}. *m/z* (EI, 70 eV) 365 (M-CH_3^+, 26%), 323 (29), 248 (67), 101 (58), 89 (88) and 73 (100).

6.3 Chapter Three Experiments

6.3.1 Reactions Of The Chiral Dienol 2.71

(2S,3S,4*E*,6*E*)-1,2-*O*-isopropylidene-8-*tert*-butyldimethylsilyloxy-1,2-dihydroxyl-4,6-octadien-3-yl hydrogen (2*Z*)-2-butenedioate 2.72

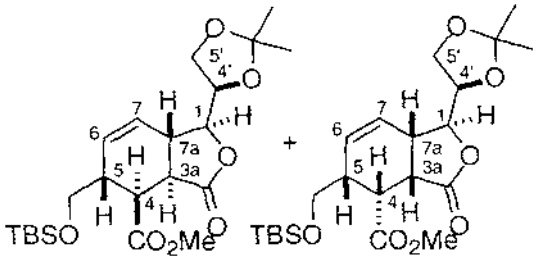


2.72

Triethylamine (443 μL, 3.18 mmol), MA (439 mg, 4.47 mmol) and DMAP (24 mg, 0.20 mmol) were added to a solution of (2R,3S,4*E*,6*E*)-1,2-*O*-isopropylidene-8-(tert-butyldimethylsilyloxy-6,6-octadiene-1,2,3-triol **2.71** (653 mg, 1.99 mmol) in CH_2Cl_2 (20 mL) and the reaction mixture stirred at RT under Ar. After 30 min, the reaction solution was diluted with CH_2Cl_2 (30 mL) and then washed with 10% aqueous HCl and H_2O. The aqueous fractions were back-extracted with CH_2Cl_2 and then the combined organic fractions washed with saturated brine and dried ($MgSO_4$/Na_2SO_4). Removing the solvent *in vacuo* afforded a yellow oil (896 mg crude) which was purified by column chromatography, eluting with AcOH in EtOAc, isolating the title compound **2.72** as an unstable pale yellow oil (746 mg, 88%, $R_f = 0.49$). ^{1}H NMR δ/ppm 6.51-6.14 (4H, m, H5, H6, -$RO_2CCHCHCO_2H$), 5.90 (1H, dt, *J* = 14.8, 4.6 Hz, H7), 5.67-5.58 (1H, m, H4), 5.51 (1H, dd, *J* = 8.0, 4.1 Hz, H3), 4.31 (1H, td, *J* = 6.3, 4.1 Hz, H2), 4.24 (2H, dm, *J* = 4.6 Hz, 2 × H8), 4.09 (1H, dd, *J* = 8.5, 6.6 Hz, $H1_\alpha$), 3.85 (1H, dd, *J* = 8.5, 6.1 Hz, $H1_\beta$), 1.41, 1.37 (6H, 2 × s, -$C(CH_3)_2$), 0.92 (9H, s, -$SiC(CH_3)_3$), 0.08 (6H, s, -$Si(CH_3)_2$-).

6.3.1.1 IMDA Reaction Of (2S,3S,4E,6E)-1,2-O-Isopropylidene-8-tert-butyldimethylsilyloxy-1,2-dihydroxyl-4,6-octadien-3-yl hydrogen (2Z)-2-butenedioate 2.72

Methyl (1S,3aR,4S,5R,7aS)-5-*tert*-butyldimethylsilyloxymethyl-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 2.73 and methyl (1S,3aS,4R,5R,7aS)-5-*tert*-butyldimethylsilyloxymethyl)-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 2.74



2.73, 2.74

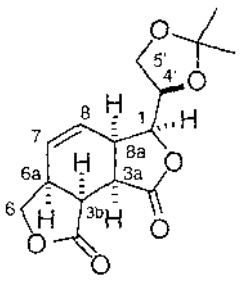
(2S,3S,4*E*,6*E*)-1,2-*O*-isopropylidene-8-*tert*-butyldimethylsilyloxy-1,2-dihydroxyl-4,6-octadien-3-yl hydrogen (2*Z*)-2-butenedioate **2.72** (49 mg, 0.15 mmol) was heated in toluene at reflux, in the presence of BHT (2.5 mg, 0.02 mmol), under Ar, overnight. The toluene was removed *in vacuo* and the residue was diluted with Et_2O. The crude cycloadducts were treated with an ethereal solution of diazomethane (*ca.* 0.5 M) until a yellow colour persisted. The solvent was removed *in vacuo* to give the title compounds **2.73** and **2.74**. Purification by column chromatography, using Hex/Et_2O (1:1), gave two diastereoisomers (86:14, 66%) identical by ^1H and ^{13}C NMR to the cycloadducts of (2S,3S,4*E*,6*E*)-1,2-*O*-isopropylidene-8-*tert*-butyldimethylsilyloxy-1,2-dihydroxyl-4,6-octadien-3-yl methyl (2*Z*)-2-butenedioate **2.56**.

6.3.1.2 Intermolecular DA Reaction Of (2R,3S,4E,6E)-1,2-O-Isopropylidene-8-tert-butyldimethylsilyloxy-6,6-octadiene-1,2,3-triol 2.71 And MA

(2R,3S,4*E*,6*E*)-1,2-*O*-isopropylidene-8-*tert*-butyldimethylsilyloxy-6,6-octadiene-1,2,3-triol **2.71** (150 mg, 0.46 mmol) was dissolved in toluene (30 mL). MA (45 mg, 0.46 mmol) and BHT (10 mg, 0.05 mmol) were added and the reaction solution heated to reflux for 30 h. The solvent was removed *in vacuo* and the crude oil purified by column

chromatography (1:1 Hex/EtOAc) to give two diastereoisomeric *bis*-lactones **3.82** and **3.81**, both *endo* adducts, in a 1:1 ratio (104 mg, 79%, R_f = 0.53, R_f = 0.43).

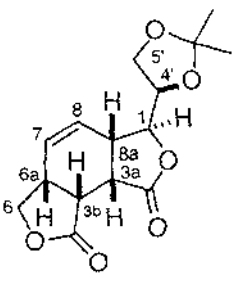
(1S,3aR,3bS,6aS,8aR)-1-(4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,4-dioxo-1,3,3a,3b,4,6,6a,8a-octahydro-3,4-dioxo-benzo[1,2-c:3,4-c']-difuran 3.82



3.82

R_f = 0.53. Found: M^+, 294.1102; $C_{15}H_{18}O_6$ requires 294.1103. $[\alpha]_D^{20°}$ = -13.4°, (c = 0.65, acetone). ^{1}H NMR δ/ppm 6.09 (1H, dt, *J* = 10.6, 1.8 Hz, H8), 5.97 (1H, ddd, *J* = 10.4, 3.8, 2.2 Hz, H7), 4.53 (1H, t, *J* = 8.6 Hz, $H6_\alpha$), 4.36 (1H, dd, *J* = 9.0, 5.3 Hz, H1), 4.16-4.11 (2H, m, H4', $H5'_\alpha$), 4.02-3.95 (1H, m, $H5'_\beta$), 3.84 (1H, dd, *J* = 10.3, 8.7 Hz, $H6_\beta$), 3.39 (1H, t, *J* = 6.8 Hz, H3a), 3.32-3.26 (1H, m, H8a), 3.23-3.17 (1H, m, H6a), 2.99 (1H, dd, *J* = 9.5, 6.7 Hz, H3b), 1.44, 1.36 (6H, 2 × s, $-C(CH_3)_2$). ^{13}C NMR δ/ppm 176, 174 (C3, C4), 127, 124 (C7, C8), 110 ($-C(CH_3)_2$), 80.5, 73.2, 71.6, 67.9 (C1, C4', C5', C6), 38.8, 37.5, 35.7, 34.4 (C8a, C3a, C3b, C6a), 27.0, 25.11 ($-C(CH_3)_2$). IR (thin film) υ_{max} 2988, 2916, 1770, 1382, 1266, 1208, 1189, 1166, 1146, 1054, 1018 and 736 cm^{-1}. *m/z* (EI, 70 eV) 294 (M^+, 1%), 279 ($M-CH_3^+$, 69), 219 (19), 101 (100), 91 (42), 73 (20), 55 (16) and 43 (47).

(1S,3aS,4R,5R,7aS)-1-(4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,4-dioxo-1,3,3a,3b,4,6,6a,8a-octahydro-3,4-dioxo-benzo[1,2-c:3,4-c']-difuran 3.81



3.81

R_f = 0.43. Found: M^+, 294.1109; $C_{15}H_{18}O_6$ requires 294.1103. $[\alpha]_D^{19°}$ = +17.6°, (c =

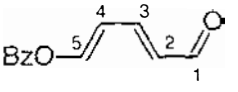
0.94, CH_2Cl_2). ^{1}H NMR δ/ppm 6.03 (1H, ddd, *J* = 10.2, 3.3, 2.2 Hz, H8), 5.89 (1H, dt, *J* = 10.2, 2.2 Hz, H7), 4.49 (1H, dd, *J* = 8.8, 5.7 Hz, $H6_\alpha$), 4.30 (1H, td, *J* = 6.7, 4.8 Hz, H4'), 4.16 (1H, dd, *J* = 9.0, 6.6 Hz, $H5'_\alpha$), 4.13-4.09 (1H, m, $H6_\beta$), 3.95 (1H, t, *J* = 7.5 Hz, H1), 3.90 (1H, dd, *J* = 8.9, 4.7 Hz, $H5'_\beta$), 3.37-3.23 (3H, m, H3a, H3b, H6a), 3.16-3.07 (1H, m, H8a), 1.39, 1.32 (6H, 2 × s, $-C(CH_3)_2$). ^{13}C NMR δ/ppm 175, 175 (C3, C4), 128, 127 (C7, C8), 110 ($-C(CH_3)_2$), 83.2, 77.2, 71.4, 67.4 (C1, C4', C5', C6), 38.0, 37.5, 36.7, 35.9 (C3a, C3b, C6a, C8a), 26.8, 25.1 ($-C(CH_3)_2$). IR (thin film) υ_{max} 2987, 2932, 1770, 1374, 1248, 1208, 1180, 1142, 1061, 1037, 1016 and 844 cm^{-1}. *m/z* (EI, 70 eV) 279 ($M-CH_3^+$, 100%), 219 (24), 101 (82), 91 (35)m 73 (19), 55 (24) and 43 (52).

6.3.2 Investigation Into Previous Work

6.3.2.1 Synthesis Of The Dienol, Maleate Half-Ester And Methyl Ester

The syntheses of pyridinium-1-sulfonate and sodium glutaconaldehyde were carried out according to literature procedures.[6].

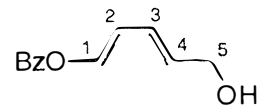
(2*E*,4*E*)-5-Benzoyloxy-2,4-pentadienal 3.87[7]



3.87

Benzoyl chloride (1.69 mL, 14.5 mmol) was added to a suspension of sodium glutaconaldehyde dihydrate **3.87** (1.50 g, 9.61 mmol) in pyridine (12 mL, 0.15 mol) at 0°C. After stirring for 5 min, the reaction mixture was cooled to 0°C, H_2O (25 mL) was added and the solid product collected by filtration. Purification by recrystallisation ($EtOH/H_2O$) gave the aldehyde as a cream coloured solid (1.17 g, 60%). ^{1}H NMR δ/ppm 9.59 (1H, d, *J* = 7.9 Hz, H1), 8.13-8.04 (3H, m, aryl CH), 7.66 (1H, tt, *J* = 7.5, 1.3 Hz, H5), 7.54-7.48 (2H, m, aryl CH), 7.20 (1H, dd, *J* = 15.2, 11.5 Hz, H3), 6.46 (1H, t, *J* = 11.5 Hz, H4), 6.25 (1H, dd, *J* = 15.2, 7.9 Hz, H2). ^{13}C NMR δ/ppm 192.8 (C1), 162.5 ($-CO_2R$), 147.9, 145.5, 134.2, 131.7, 130.1, 128.6, 127.7 (C2, C3, C5, 4 × aryl C), 113.7 (C4). Both ^{1}H and ^{13}C NMR spectra were in accordance with literature data.[7]

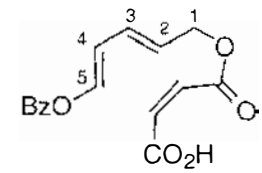
(1*E*,3*E*)-1-Benzoyloxy-5-hydroxy-1,3-pentadiene 3.49[7]



3.49

Sodium borohydride (0.04 g, 1.04 mmol) was added to a solution of (2*E*,4*E*)-5-benzoyloxy-2,4-pentadienal **3.49** (1.06 g, 5.22 mmol) in 1,4-dioxane (20 mL) at 10°C. After 4 h, more $NaBH_4$ (0.04 g, 1.04 mmol) was added and the reaction solution stirred for a further 3 h. The reaction solution was poured into H_2O (110 mL) at 0°C and extracted with Et_2O (3 × 80 mL). The organic fractions were dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude solid was purified by recrystallisation (Et_2O/pentane) yielding cream coloured crystals (733 mg, 69%, MP 81-83°C). ^{1}H NMR δ/ppm 8.11-8.08 (2H, m, aryl CH), 7.67-7.58 (2H, aryl CH), 7.51-7.45 (2H, m, aryl CH, H1), 6.34-6.20 (2H, m, H2, H3), 5.95-5.85 (1H, m, H4), 4.22 (2H, d, *J* = 5.7 Hz, 2 × H5), 1.74 (1H, s, -OH). ^{13}C NMR δ/ppm 162.5 (-CO_2R), 138.6, 133.5, 132.1, 129.8, 128.4, 128.6, 125.9 (C1, C3, C4, 4 × aryl C), 115.2 (C2), 63.3 (C5).

(2*E*,4*E*)-5-Benzoyloxy-2,4-pentadien-1-yl hydrogen (2*Z*)-2-butenedioate 3.50

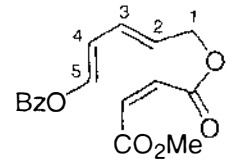


3.50

An ice cooled solution of 1-(benzoyloxy)-5-hydroxy-1*E*,3*E*-pentadiene **3.49** (0.20 g, 0.99 mmol) in dry CH_2Cl_2 (6.0 mL) was treated with Et_3N (220 mL, 1.58 mmol), MA (218 mg, 2.22 mmol) and DMAP (12.0 mg, 0.10 mmol). After 0.5 h, the reaction mixture was diluted with CH_2Cl_2 and washed with 10% (v/v) HCl and then H_2O. The aqueous fractions were back-extracted with CH_2Cl_2. The combined organic fractions were then washed with saturated brine and dried (Na_2SO_4/$MgSO_4$). Removal of the solvent *in vacuo* gave a crude oil. Purification by column chromatography (5% acetic acid in EtOAc) gave the title compound as a clear oil (298 mg, 100%, R_f = 0.30) Found: M^+, 302.0780; $C_{16}H_{14}O_6$ requires 302.0790. ^{1}H NMR δ/ppm 10.42 (1H, br s, -CO_2H), 8.10-8.07 (2H, m, aryl CH), 7.69 (1H, d, *J* = 12.1 Hz, H5), 7.61 (1H, tt, *J* = 7.3, 2.0 Hz, aryl CH), 7.50-7.45 (2H, m, aryl CH), 7.04-6.33 (3H, m, H3,

$RO_2CCHCHCO_2H$), 6.22 (1H, t, J = 11.5 Hz, H4), 5.81 (1H, dt, J = 14.8, 6.8 Hz, H2), 4.79 (2H, d, J = 6.8 Hz, H1) . ^{13}C NMR δ/ppm 166.4, 166.2, 163.0 ($-CO_2H$, 2 × $-CO_2R$), 140.0, 136.3, 134.7, 130.8, 129.8, 129.7, 128.4, 128.3, 124.5 (C2, C3, C5, $RO_2CCHCHCO_2H$, 4 × aryl CH), 114.4 (C4) and 66.7 (C1). IR (thin film) υ_{max} 3089, 3035, 1780, 1733, 1665, 1633, 1479, 1263, 1130, 979, 710 and 679 cm^{-1}. *m/z* (EI, 70 eV) 302 (M^+, 2%), 122 (19), 105 (100), 91 (12), 77 (45) and 54 (17).

(2*E*,4E)-5-Benzoyloxy-2,4-pentadien-1-yl methyl (2*Z*)-2-butenedioate 3.92

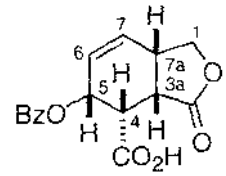


3.92

An ethereal solution of CH_2N_2 was added, drop wise, to a solution of (1*E*,3*E*)-1-benzoyloxy-1,3-pentadien-5-yl hydrogen (2*Z*)-2-butenedioate **3.50** (65.3 mg, 0.22 mmol) in Et_2O (5 mL) at -70°C. After methylation was complete, the solvent was removed *in vacuo* and the crude oil purified by column chromatography (2:1 Hex/Et_2O) giving the title compound as an oil (36.2 mg, 53%, R_f = 0.23). Found: M^+, 316.0946; $C_{17}H_{16}O_6$ requires 316.0947. ^1H NMR δ/ppm 8.13-8.09 (2H, m, aryl CH), 7.69 (1H, d, J = 11.9 Hz, H5), 7.62 (1H, tt, J = 7.5, 1.3 Hz, aryl CH), 7.51-7.45 (2H, m, J = 7.5 Hz, aryl CH), 6.37 (1H, ddt, J = 14.8, 11.1, 1.1 Hz, H3), 6.28-6.19 (3H, m, H4, $RO_2CCHCHCO_2CH_3$), 5.90-5.79 (1H, m, H2), 4.76 (2H, d, J = 6.8 Hz, 2 × H1), 3.80 (3H, s, $-CO_2CH_3$). ^{13}C NMR δ/ppm 165.5, 164.7, 163.1 (3 × $-CO_2CH_3$) 139.7, 133.7, 129.9, 129.8, 129.8, 129.6, 129.6, 128.5, 125.7, (C2, C3, C5, $RO_2CCHCHCO_2CH_3$, 4 × aryl C), 115 (C4), 65 (C1), 52 ($-CO_2CH_3$). IR (thin film) υ_{max} 3079, 3027, 2952, 1732, 1664, 1645, 1632, 1452, 1437, 1397, 1263, 1162, 1130, 978, 756 and 709 cm^{-1}. *m/z* (EI, 70 eV) 316 (M^+, 14%), 211 (60), 203 (77), 187 (22), 179 (29), 162 (24), 135 (64) and 119 (33).

6.3.2.2 Intermolecular DA Reaction Between (1E,3E)-1-Benzoyloxy-5-hydroxy-1,3-pentadiene 3.49 And MA

(3aS,4R,5R,7aS)-5-Benzoyloxy-3-oxo-1,1,3,3a,4,5,7a-septahydro-4-isobenzofurancarboxylic acid 3.51[8]



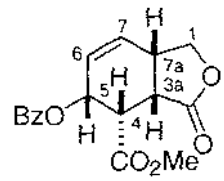
3.51

(1*E*,3*E*)-1-Benzoyloxy-5-hydroxy-1,3-pentadiene **3.49** (100 mg, 0.49 mmol) was dissolved in chloroform (1 mL). MA (48.0 mg, 0.49 mmol) was added and the reaction solution heated to reflux. After 5 h, the solvent was removed *in vacuo* and the resulting solid purified by column chromatography, eluting with Hex/EtOAc (1:1), to give a white solid (125 mg, 85%, R_f = 0.38). ^{1}H NMR δ/ppm 7.98-7.94 (2H, m, aryl CH), 7.44 (1H, tt, *J* = 7.3, 1.9 Hz, aryl CH), 7.36-7.30 (2H, m, aryl CH), 6.16 (1H, ddd, *J* = 9.9, 5.5, 2.0 Hz, H6), 5.86 (1H, d, *J* = 3.1 Hz, H7), 5.83-5.78 (1H, m, H5), 4.39 (1H, dd, *J* = 9.0, 7.0 Hz, H1$_\alpha$), 4.11 (1H, dd, *J* = 9.0, 1.3 Hz, H1$_\beta$), 3.61 (1H, dd, *J* = 8.6, 4.8 Hz, H3a), 3.31-3.24 (1H, m, H7a), 3.08 (1H, t, *J* = 4.3 Hz, H4). ^{13}C NMR 175.8, 171.5, 166.2 (-CO_2H, -CO_2R, C3), 132.8 (C7), 131.3, 129.8, 129.5, 128.0 (4 × aryl C), 126.6 (C6), 70.3 (C1), 63.8 (C5), 41.1 (C4), 36.3, 36.3 (C3a, C7a).

6.3.2.3 IMDA Reactions Of (2E,4E)-5-Benzoyloxy-2,4-pentadien-1-yl hydrogen (2Z)-2-butenedioate 3.50

(2*E*,4*E*)-5-Benzoyloxy-2,4-pentadien-1-yl hydrogen (2*Z*)-2-butenedioate **3.50** (84.2 mg, 0.28 mmol) in chloroform (28 mL) was heated to reflux in the presence of BHT (6.10 mg, 0.03 mmol) for 30 h. The reaction solution was cooled to -40°C and treated with an ethereal solution of CH_2N_2 (*ca.* 0.5 M) until methylation was complete by TLC. The solvent was removed *in vacuo* and the resulting oil was purified by passage through a plug of silica to give a mixture of *endo* isomer:*exo* isomer:starting material in a 55:33:22 ratio (67 mg, 76%). Repeated column chromatography, eluting with Hex/Et_2O (1:1), gave pure samples of the methylated starting material **3.92** (7.4 mg, 9%, R_f = 0.32), *exo* adduct **3.91** (10.4 mg, 12%, R_f = 0.14) and the *endo* adduct **3.90** (19.6 mg, 22%, R_f = 0.06).

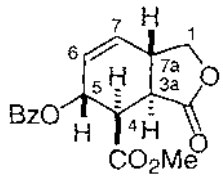
Methyl (3aS,4R,5R,7aS)-5-benzoyloxy-3-oxo-1,1,3,3a,4,5,7a-septahydro-4-isobenzofurancarboxylate 3.90



3.90

(R_f = 0.06). Found: M^+, 316.0961; $C_{17}H_{16}O_6$ requires 316.0947. ^{1}H NMR δ/ppm 8.07-8.09 (2H, m, aryl CH), 7.53 (1H, tt, *J* = 7.3, 1.5 Hz, aryl CH), 7.46-7.40 (2H, m, aryl CH), 6.27 (1H, ddd, *J* = 10.1, 5.3, 1.8 Hz, H6), 5.94-5.90 (2H, m, H7, H5), 4.46 (1H, dd, *J* = 9.2, 7.3 Hz, H1$_\alpha$), 4.19 (1H, dd, *J* = 9.2, 1.3 Hz, H1$_\beta$), 3.74 (3H, s, -CO_2CH_3), 3.68 (1H, dd, *J* = 8.6, 5.1 Hz, H3a), 3.37-3.32 (1H, m, H7a), 3.19 (1H, t, *J* = 4.2 Hz, H4). ^{13}C NMR δ/ppm 174.7, 169.2, 166.0 (-CO_2CH_3, -CO_2R, C3), 132.9 (C7), 131.1, 130.0, 129.6, 128.3 (4 × aryl C), 127.0 (C6), 70.2 (C1), 63.5 (C5), 52.3 (-CO_2CH_3), 41.4 (C4), 36.4, 36.2 (C3a, C7a). IR (thin film) υ_{max} 3060, 2987, 2954, 2916, 1781, 1739, 1714, 1601, 1584, 1452, 1437, 1267, 1212, 1178, 1110, 1027 and 735 cm^{-1}. *m/z* (EI, 70 eV) 316 (M^+, 3%), 211 (47), 179 (18), 105 (100) and 77 (20).

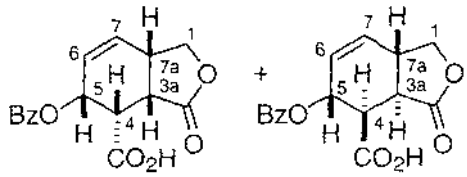
Methyl (3aR,4S,5R,7aS)-5-benzoyloxy-3-oxo-1,1,3,3a,4,5,7a-septahydro-4-isobenzofurancarboxylate 3.91



3.91

(R_f = 0.14). ^{1}H NMR δ/ppm 8.05-8.02 (2H, m, aryl CH), 7.63-7.60 (1H, m, aryl CH), 7.49-7.43 (2H, m, aryl CH), 6.21 (1H, dt, *J* = 9.0, 1.8 Hz, H7), 6.07-6.00 (2H, m, H6, H5), 4.61 (1H, t, *J* = 7.6 Hz, H1$_\alpha$), 4.00 (1H, dd, *J* = 11.4, 8.1 Hz, H1$_\beta$), 3.79 (3H, s, -CO_2CH_3), 3.59 (1H, d, *J* = 3.5 Hz, H4), 3.32-3.20 (1H, m, H7a), 2.77 (1H, dd, *J* = 13.6, 3.5 Hz, H3a). ^{13}C NMR δ/ppm 173.4, 169.1, 165.1 (-CO_2CH_3, -CO_2R, C3), 133.4 (C7), 129.7, 129.6, 129.3, 128.4 (4 × aryl C), 127.4 (C6), 70.0, 69.0 (C1, C5), 52.7 (-CO_2CH_3), 43.3 (C4), 41.3 (C3a), 36.6 (C7a). IR (thin film) υ_{max} 3029, 2955, 1790, 1732, 1714, 1602, 1268, 1178, 1096 and 757 cm^{-1}.

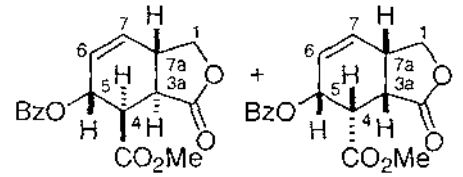
(3aS,4R,5R,7aS)-5-Benzoyloxy-3-oxo-1,1,3,3a,4,5,7a-septahydro-4-isobenzofurancarboxylic acid 3.51 and (3aR,4S,5R,7aS)-5-benzoyloxy-3-oxo-1,1,3,3a,4,5,7a-septahydro-4-isobenzofurancarboxylic acid 3.89



3.51, 3.89

A solution of (2*E*,4*E*)-5-benzoyloxy-2,4-pentadien-1-yl hydrogen (2*Z*)-2-butenedioate **3.50** (96.8 mg, 0.32 mmol) in toluene (32.0 mL) was heated under reflux, in the presence of BHT (7 mg, 0.03 mmol), for 2h. The solvent was removed *in vacuo.* Analysis of the crude reaction mixture by ^{1}H NMR indicated the presence of two stereoisomeric cycloadducts in a 57:43 *endo:exo* ratio. Purification by column chromatography, eluting with EtOAc/AcOH gave an inseparable mixture (R_f = 0.30) of the *endo* and *exo* isomers (71.3 mg, 71%), identified by comparison of the ^{1}H NMR spectrum with those of the methylated adducts prepared in the previous experiment.

6.3.2.4 IMDA Reaction Of Methyl (2E,4E)-5-benzoyloxy-2,4-pentadien-1-yl (2Z)-2-butenedioate 3.92



3.91, 3.90

(2*E*,4*E*)-5-Benzoyloxy-2,4-pentadien-1-yl methyl (2*Z*)-2-butenedioate **3.92** (30 mg, 0.09 mmol) was dissolved in toluene (9.50 mL) with BHT (2.2 mg, 0.01 mmol) present. The reaction solution was heated to reflux for 3.5 h. The solvent was removed *in vacuo* and the crude material was purified using column chromatography (4:1 Hex/Et_2O) to give an *exo* adduct **3.91** and an *endo* adduct **3.90** in a 62:38 ratio (21.4 mg, 71%, R_f = 0.43, 0.10). These were identical by ^{1}H NMR to the methylated adducts of the IMDA reaction of (2*E*,4*E*)-5-benzoyloxy-2,4-pentadien-1-yl hydrogen (2*Z*)-2-butenedioate described previously.

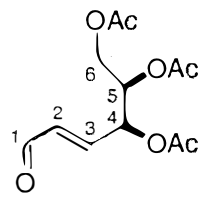
6.3.2.5 Timed NMR Experiment

(1*E*,3*E*)-1-Benzoyloxy-5-hydroxy-1,3-pentadiene **3.49** (10 mg, 0.05 mmol) was dissolved in $CDCl_3$ in an NMR tube. MA (4.8 mg, 0.05 mmol) was added and the NMR tube inserted in a JEOL 270 MHz NMR spectrometer. The sample was heated to 55°C and an ^1H NMR spectrum recorded at 5 min intervals for an 8.5 h period.

6.4 Chapter Four Experiments

6.4.1 Glucose Series Experimental

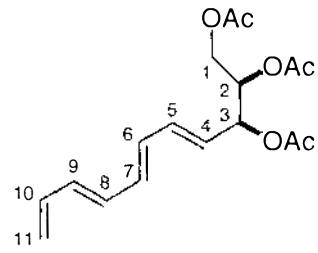
(2*E*,4S,5R)-4,5,6-Triacetoxy-2-hexenal 4.50[5]



4.50

A solution of (4S,5R,2*E*)-4,6-diacetoxy-5-hydroxy-2-hexenal **2.61** (8.46g, 36.7 mmol) in CH_2Cl_2 (50 mL) was cooled to 0°C. After the addition of Et_3N (7.68 mL, 55.1 mmol), Ac_2O (4.33 mL, 45.9 mmol) and DMAP (449 mg, 3.70 mmol), the reaction solution was stirred for 5 min. The reaction was quenched with sat. aq. $NaHCO_3$ (40 mL) and the mixture stirred vigorously for 10 min. After dilution with CH_2Cl_2 (100 mL), the organic layer was separated and washed with sat. aq. $NaHCO_3$ (10 mL), 10% aq. HCl (2 × 10 mL) and H_2O (10 mL). The washings were combined and back-extracted with CH_2Cl_2 (3 × 40 mL). The combined organic fractions were washed with saturated brine (10 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound **4.50** (R_f = 0.50, 1:1 Hex/EtOAc) as a pale yellow oil (9.91 g, 99%). $[\alpha]_D^{20^\circ}$ = +11.7°, (c = 4.05, CH_2Cl_2). ^1H NMR δ/ppm 9.53 (1H, dd, *J* = 7.7, 0.9 Hz, H1), 6.70 (1H, dd, *J* = 15.8, 5.1 Hz, H3), 6.22 (1H, ddm, *J* = 15.8, 7.7 Hz, H2), 5.71 (1H, tm, *J* = 5.0 Hz, H4), 5.26-5.20 (1H, m, H5), 4.21-4.16 (2H, m, 2 × H6), 2.09, 2.04, 2.00 (9H, 3 × s, 3 × -OC(O)CH_3). ^{13}C NMR δ/ppm 192.1 (C1), 170.1, 169.6, 169.0 (3 × -O*C*(O)CH_3), 147.8, 133.4 (C2, C3), 70.8, 70.3, 61.2 (C4, C5, C6), 20.6, 20.6 (coincident peaks, -OC(O)*C*H_3). IR (thin film) υ_{max} 2967, 2839, 1747, 1694, 1654, 1436, 1373, 1222, 1127, 1048, 978 and 736 cm^{-1}. ^1H and ^{13}C NMR data was in accordance with literature values.[5]

(2R,3S,4*E*,6*E*,8*E*,10*E*)-1,2,3-Triacetoxy-4,6,8,10-undecatetraene 4.51



4.51

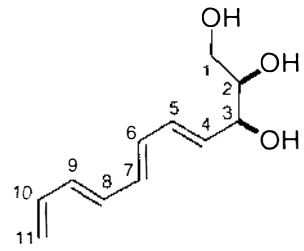
A solution of *n*-BuLi in THF (21.7 mL, 32.7 mmol) was added rapidly, dropwise, to a cooled (-70°C) suspension of pentadienylphosphonium bromide[9] (13.4 g, 32.7 mmol) in dry THF (86 mL) under an atmosphere of Ar. The reaction solution was allowed to warm to RT over 10 min with the ylide solution developing an intense dark blood-red colour.

A solution of (2*E*,4S,5R)-4,5,6-triacetoxy-2-hexenal **4.50** (8.90 g, 32.7 mmol) in dry THF was cooled to -70°C (under an atmosphere of Ar) and the ylide solution (97.1 mL, 29.4 mmol) was added over 15 min with the temperature kept at -70°C. After 15 min, the reaction was quenched with sat. aq. NH_4Cl (30 mL) and allowed to warm to RT. After dilution with Et_2O (200 mL) and addition of BHT (10 mg, 0.05 mmol), the organic layer was separated and washed with H_2O (50 mL). The combined aqueous fractions were back-extracted with Et_2O (100 mL). The combined organic portions were then washed with saturated brine (10 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude oil was purified by column chromatography (3:1 Hex/EtOAc) to yield a mixture of *E/Z* isomeric tetraenes (R_f = 0.37) as a colourless oil (8.31 g, 70%).

Thiophenol (104 μL, 1.02 mmol), AIBN (83.0 mg, 0.51 mmol) were added to a solution of *E/Z* isomeric triacetate tetraenes (2.73 g, 8.46 mmol) in dry benzene, in the presence of BHT (50 mg, 0.23 mmol), under Ar, and the reaction solution irradiated with UV/visible light for 40 min. This process was repeated four times with the reaction being recharged with thiophenol (104 μL, 1.02 mmol) and AIBN (83.0 mg, 0.51 mmol) each time until the reaction was judged complete by ^{1}H NMR spectroscopy. The solvent was removed *in vacuo* and the crude oil purified by column chromatography (Hex/EtOAc (3:1)) to afford the title compound **4.51** (R_f = 0.29) as a pale yellow oil (1.53 g, 56%). Found: M^+, 322.1420; $C_{17}H_{22}O_6$ requires 322.1416. $[\alpha]_D^{21°}$ = +39.9°, (c = 2.18, CH_2Cl_2). ^{1}H NMR δ/ppm 6.43-6.19 (6H, m, H5, H6, H7, H8, H9, H10), 5.60 (1H, dd, *J* = 14.8, 7.8 Hz, H4), 5.50 (1H, dd, *J* = 7.8, 4.8 Hz, H3), 5.28-5.21 (1H, m, $H11_\alpha$), 5.13 (1H,

dd, J = 9.6, 1.8 Hz, H11$_\beta$), 4.23 (1H, dd, J = 12.1, 3.7 Hz, H1$_\alpha$), 4.21 (1H, m, H2), 4.16 (1H, dd, J = 12.1, 6.8 Hz, H1$_\beta$), 2.07, 2.06, 2.04 (9H, 3 × s, 3 × -OC(O)CH$_3$). ^{13}C NMR δ/ppm 170.3, 169.8, 169.4 (3 × -O*C*(O)CH$_3$), 136.6, 135.2, 134.7, 132.4, 131.2, 125.4 (C4, C5, C6, C7, C8, C9, C10), 118.1 (C11), 72.4, 71.6, 61.9 (C1, C2, C3), 21.0, 20.9, 20.8 (3 × -OC(O)*C*H$_3$). IR (thin film) υ_{max} 3089, 3024, 2966, 1738, 1616, 1643, 1573, 1437, 1221, 1049, 1014, 905 and 604 cm^{-1}. UV λ_{max} (Et$_2$O) 309 nm (ε 39 758), 295.5 (46 788), 284 (34 050) and 199 (6 716). *m/z* (EI, 70 eV) 322 (M$^+$, 2%), 262 (10), 160 (66), 145 (14), 135 (41), 117 (16), 91 (11) and 43 (100).

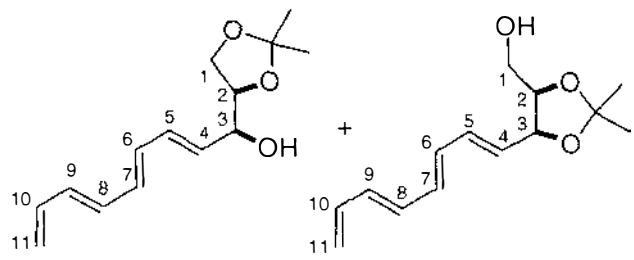
(2R,3S,4*E*,6*E*,8*E*,10*E*)-1,2,3-Trihydroxy-4,6,8,10-undecatetraene 4.52



4.52

(2R,3S,4*E*,6*E*,8*E*,10*E*)-1,2,3-Triacetoxy-4,6,8,10-undecatetraene **4.51** (1.39 g, 4.32 mmol) was dissolved in dry, degassed MeOH (90 mL) under Ar in the presence of the anti-oxidant BHT (95.6 mg, 0.43 mmol). A solution of KHCO$_3$ (2.93 g, 29.0 mmol) in H$_2$0 (20 mL) was added dropwise and the reaction mixture stirred at RT for 2 h. The MeOH was removed *in vacuo* and the resulting solution diluted with H$_2$O (30 mL) and extracted with 10% (v/v) *sec*-butanol/EtOAc (7 × 40 mL). Removal of the solvent *in vacuo* afforded the title compound as a cloudy pale yellow oil which, due to a tendency to decompose upon handling, was used in the next reaction step without further purification. A small sample was purified by column chromatography (100% EtOAc, R$_f$ = 0.27) for characterisation purposes. Found: M$^+$, 196.1096; C$_{11}$H$_{16}$O$_3$ requires 196.1099. $[\alpha]_D^{20°}$ = -32.3°, (c = 0.71, MeOH). ^{1}H NMR (DMSO) δ/ppm 6.45-6.20 (6H, m, H5-H10), 5.90 (1H, dd, J = 15.2, 6.2 Hz, H4), 5.29-5.10 (2H, m, H11$_\alpha$, H11$_\beta$), 4.89 (1H, d, J = 5.3 Hz, H3), 4.70-4.56 (1H, m, H2), 5.53-4.40 (1H, m, H1$_\alpha$), 4.00-3.94 (1H, m, H1$_\beta$), 3.38 (3H, br s, 3 × -OH). ^{13}C NMR (DMSO) δ/ppm 137.2, 136.5, 133.8, 133.6, 132.9, 131.4, 129.8 (C4-C10), 117.4 (C11), 75.4, 72.1 (C2, C3), 63.3 (C1). IR (KBr disc) υ_{max} 3332, 2931, 2892, 1439, 1098, 1042, 1016 and 997 cm^{-1}. *m/z* (40 eV) 196 (M$^+$, 41%), 135 (100), 117 (42), 105 (36), 91 (65), 79 (53), 67 (40) and 41 (34).

(2R,3S,2*E*,4*E*,6*E*,8*E*)-1,2-*O*-Isopropylidene-1,2,3-trihydroxy-4,6,8,10-undecatetraene 4.47 and (2R,3S,2*E*,4*E*,6*E*,8*E*)-2,3-*O*-isopropylidene-1,2,3-trihydroxy-4,6,8,10-undecatetraene 4.53



4.47, 4.53

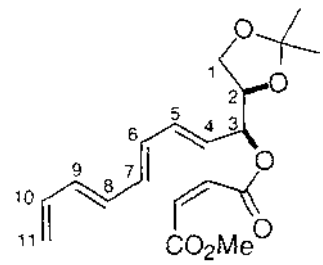
2,2-Dimethoxypropane (1.10 mL, 8.65 mmol), CSA (40.2 mg, 0.17 mmol) and BHT (50 mg, 0.23 mmol) were added to a solution of triol **4.52** (849 mg, 4.33 mmol) in acetone (140 mL) at 0°C under Ar. After stirring overnight at RT, additional 2,2-dimethoxypropane (1.10 mL, 8.65 mmol) and CSA (40.2 mg, 0.17 mmol) were added. This was repeated after 1 h. After 1 h, the acetone was removed *in vacuo*, the cloudy residue diluted with Et_2O (90 mL) and washed with sat. aq. $NaHCO_3$ (2 x 5 mL) and H_2O (5 mL). The combined aqueous fractions were back-extracted with Et_2O (30 mL). The combined organic fractions were washed with saturated brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by column chromatography using Hex/Et_2O (2:1) afforded the desired secondary alcohol **4.47** (R_f = 0.31) as a colourless oil (498 mg, 49%) and the regioisomeric primary alcohol **4.53** (R_f = 0.22) (224 mg, 22%).

Secondary alcohol 4.47, (R_f = 0.31). Found: M^+, 236.1419; $C_{14}H_{20}O_3$ requires 236.1412. $[\alpha]_D^{20°}$ = -46.8°, (c = 0.86, CH_2Cl_2). ^1H NMR δ/ppm 6.46-6.23 (6H, m, H5-H10), 5.66 (1H, dd, *J* = 14.9, 5.9 Hz, H4), 5.25 (1H, dd, *J* = 16.3, 1.7 Hz, $H11_\alpha$), 5.12 (1H, *J* = 9.9, 1.7 Hz, $H11_\beta$), 4.40-4.35 (1H, m, H3), 4.12 (1H, dd, *J* = 6.6, 4.4 Hz, H2), 3.97 (1H, dd, *J* = 8.4, 6.4 Hz, $H1_\alpha$), 3.91 (1H, dd, *J* = 8.4, 6.7 Hz, $H1_\beta$), 2.18 (1H, d, *J* = 2.9 Hz, -OH), 1.46, 1.37 (6H, 2 × s, $-C(CH_3)_2$). ^{13}C NMR δ/ppm 136.8, 134.0, 133.4, 132.8, 132.2, 132.1, 130.4 (C4-C10), 117.7 (C11), 109.4 ($-\mathit{C}(CH_3)_2$), 78.2, 71.5, 64.8 (C1, C2, C3), 26.5, 25.2 ($-C(\mathit{C}H_3)_2$). IR (thin film) υ_{max} 3458, 2986, 2880, 1455, 1382, 1372, 1246, 1208, 1156, 1107, 1064, 1007, 857 and 679 cm^{-1}. *m/z* (EI, 70 eV) 236 (M^+, 17%), (161, 7), 135 (6), 117 (7), 101 (100), 91 (16), 79 (10), 73 (21), 59 (10) and 43 (46).

Primary alcohol 4.53, (R_f = 0.22). Found: M^+, 236.1412; $C_{14}H_{20}O_6$ requires 236.1412. $[\alpha]_D^{19°}$ = -31.7°, (c = 1.42, CH_2Cl_2). ^1H NMR δ/ppm 6.42-6.26 (6H, m, H5-H10), 5.69 (1H, dd, *J* = 15.1, 7.5 Hz, H4), 5.26 (1H, d, *J* = 16.3 Hz, $H11_\alpha$), 5.14 (1H, d, *J* = 9.6 Hz, $H11_\beta$), 4.12 (1H, dd, *J* = 9.2, 7.5 Hz, H3), 3.96 (1H, dd, *J* = 11.2,

5.3 Hz, H1$_\alpha$), 3.69 (1H, dd, *J* = 11.2, 6.7 Hz, H1$_\beta$), 3.57-3.50 (1H, m, H2), 1.53, 1.44 (6H, 2 × s, -C(CH$_3$)$_2$). ^{13}C NMR δ/ppm 136.7, 134.2, 134.0, 133.9, 132.7, 131.9, 129.9 (C4-C10), 117.8 (C11), 98.7 (-*C*(CH$_3$)$_2$), 75.6, 66.8, 64.1 (C1, C2, C3), 28.8, 19.4 (-C(*C*H$_3$)$_2$). IR (thin film) υ_{max} 3441, 2991, 2938, 2876, 1643, 1614, 1479, 1456, 1380, 1221, 1201, 1160, 1070, 1009, 897, 874 and 680 cm^{-1}. UV λ_{max} (Et$_2$O) 310 nm (ε 53, 776), 296 (69 587) and 284 (61 247). *m/z* (EI, 70 eV) 236 (M$^+$, 34%), 205 (15), 135 (51), 117 (24), 106 (37), 101 (37), 91 (56), 79 (28), 59 (100) and 43 (68).

(2R,3S,2*E*,4*E*,6*E*,8*E*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-4,6,8,10-undecatetraen-3-yl methyl (2*Z*)-2-butenedioate 4.54

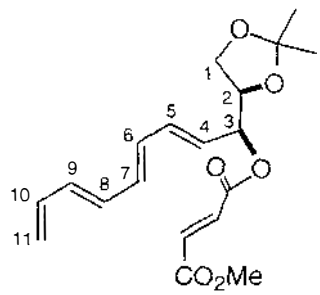


4.54

Triethylamine (57.4 μL, 0.41 mmol), MA (56.8 mg, 0.58 mmol), DMAP (3.1 mg, 0.03 mmol) and BHT (2.4 mg, 0.01 mmol) were added to a solution of tetraene alcohol **4.47** (60.8 mg, 0.26 mmol) in dry CH_2Cl_2 (5 mL), under Ar, at 0°C. After 1h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 10% aq. HCl (5 mL) and H_2O (5 mL). The aqueous fractions were back-extracted with CH_2Cl_2 (10 mL) and then the combined organics were washed with saturated brine (5 mL), dried ($MgSO_4$/Na_2SO_4) and the solvent removed *in vacuo*. The crude acid was dissolved in Et_2O (5 mL) and an ethereal CH_2N_2 solution (*ca.* 0.5 M) was added until methylation was complete by TLC. The solvent was removed *in vacuo* and the crude oil was purified by column chromatography (1:1 Hex/Et_2O) to afford the methyl ester **4.54** (R_f = 0.32) as a colourless oil (84.4 mg, 94%). Found: M$^+$, 348.1584; $C_{19}H_{24}O_6$ requires 348.1573. $[\alpha]_D^{19°}$ = -17.8°, (c = 0.97, CH_2Cl_2). ^{1}H NMR δ/ppm 6.46-6.25 (8H, m, H5-H10, RO$_2$CC*H*C*H*CO$_2$CH$_3$), 5.69 (1H, dd, *J* = 15.2, 0.7 Hz, H4), 5.44 (1H, ddd, *J* = 7.5, 5.3, 0.7 Hz, H3), 5.26 (1H, dd, *J* = 16.5, 1.8 Hz, H11$_\alpha$), 5.13 (1H, dd, *J* = 9.7, 1.8 Hz, H11$_\beta$), 4.27 (1H, dd, *J* = 11.6, 0.3 Hz, H2), 4.07 (1H, dd, *J* = 8.6, 6.6 Hz, H1$_\alpha$), 3.83 (1H, dd, *J* = 8.6, 6.2 Hz, H1$_\beta$), 3.78 (3H, s, -CO$_2$CH$_3$), 1.42, 1.36 (6H, 2 × s, -C(CH$_3$)$_2$). ^{13}C NMR δ/ppm 165.3, 163.9 (RO$_2$*C*CHCH*C*O$_2$CH$_3$), 136.7, 135.3, 134.5, 132.6, 131.7, 129.9, 129.4, 126.0 (C4-C10, RO$_2$C*C*H*C*HCO$_2$CH$_3$), 118.0 (C11), 110.0 (-C(CH$_3$)$_2$), 76.5, 75.1 (C2, C3), 66.1 (C1), 52.2 (-CO*C*H$_3$), 26.4, 25.3

(-C(CH_3)$_2$). IR (thin film) υ_{max} 2988, 2953, 1790, 1732, 1651, 1644, 1455, 1436, 1392, 1372, 1214, 1162, 1070, 1010 and 845 cm^{-1}. UV λ_{max} (CH_2Cl_2) 315 nm (ε 89 906), 300 (103 261) and 288 (73 063). *m/z* (EI, 70 eV) 348 (M^+, 8%), 333 (M-CH_3^+, 22), 143 (28), 129 (28), 113 (59), 101 (100), 91 (31), 73 (29 and 43 (51).

(2R,3S,2*E*,4*E*,6*E*,8*E*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-4,6,8,10-undecatetraen-3-yl methyl (2*E*)-2-butenedioate 4.55

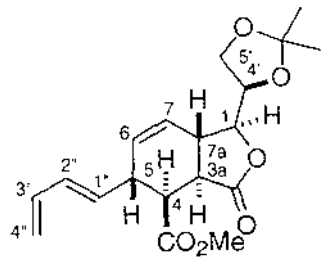


4.55

Methyl hydrogen fumarate (55.1 mg, 0.42 mmol), DCC (87.4 mg, 0.42 mmol), DMAP (7.0 mg, 0.06 mmol) and BHT (5.45 mg, 0.03 mmol) were added to a solution of tetraene alcohol **4.47** (66.7 mg, 0.28 mmol) in dry CH_2Cl_2 (7 mL) under Ar and the reaction mixture stirred for 20 min. After dilution with Et_2O (50 mL), the organic layer was separated and washed with 10% aq. HCl (5 mL), sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL). The combined aqueous fractions were back-extracted with Et_2O (15 mL). The combined organics were then washed with saturated brine (5 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by column chromatography using Hex/Et_2O (2:1) gave the fumarate ester **4.55** (R_f = 0.29) as a colourless oil (97.6 mg, 98%). Found: M^+, 348.1588; $C_{19}H_{24}O_6$ requires 348.1573. $[\alpha]_D^{16°}$ = -89.3°, (c = 2.20, CH_2Cl_2). ^{1}H NMR δ/ppm 6.90 (2H, s, $RO_2CCHCHCO_2CH_3$), 6.45-6.21 (6H, m, H5-H10), 5.66 (1H, dd, *J* = 15.0, 7.5 Hz, H4), 5.48 (1H, dd, *J* = 7.5, 4.8 Hz, H3), 5.25 (1H, dd, *J* = 16.3, 1.8 Hz, H11$_\alpha$), 5.13 (1H, dd, *J* = 10.1, 1.8 Hz, H11$_\beta$), 4.27 (1H, td, *J* = 6.2, 4.8 Hz, H2), 4.07 (1H, dd, *J* = 8.5, 6.6 Hz, H1$_\alpha$), 3.83 (1H, dd, *J* = 8.5, 6.2 Hz, H1$_\beta$), 3.81 (3H, s, -CO_2CH_3), 1.40, 1.36 (6H, 2 × s, -C(CH_3)$_2$). ^{13}C NMR δ/ppm 165, 164 ($RO_2CCHCHCO_2CH_3$), 137, 135, 135, 135, 134, 133, 133, 131, 126 (C4-C10, $RO_2CCHCHCO_2CH_3$), 118 (C11), 110 (-*C*(CH_3)$_2$), 76.5, 74.9 (C2, C3), 65.7 (C1), 52.3 (-CO_2CH_3), 26.4, 25.2 (-C(CH_3)$_2$). IR (thin film) υ_{max} 2988, 2953, 2888, 1726, 1644, 1305, 1259, 1156, 1071, 1010 and 851 cm^{-1}. UV λ_{max} (Et_2O) 204 nm (ε 27 435), 285 (43 026), 297 (57 919), 310 (48 556). *m/z* (EI, 70 eV) 348 (M^+, 10%), 143 (13), 113 (33), 101 (100), 91 (9), 73 (11) and 43 (20).

6.4.1.1 IMDA Reaction Of (2R,3S,2E,4E,6E,8E)-1,2-O-Isopropylidene-1,2-dihydroxy-4,6,8,10-undecatetraen-3-yl methyl (2Z)-2-butenedioate 4.54

Methyl (1S,3aR,4S,5R,7aS)-5-((1*E*,3*E*)-1,3-butadien-1-yl)-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 4.56



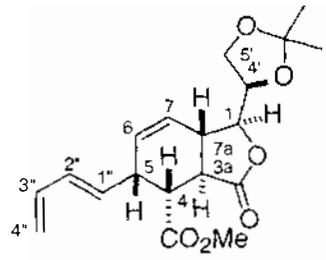
4.56

The maleate ester **4.54** (59.9 mg, 0.17 mmol) was dissolved in dry benzene (17 mL), under Ar, in the presence of BHT (3.8 mg, 0.02 mmol). The reaction solution was heated to reflux for 3.5 h. The solvent was removed *in vacuo* and the crude material purified by column chromatography (Hex/Et_2O (1:1)) to afford a single cycloadduct **4.56** (R_f = 0.33) as an oil (44.0 mg, 73%). Found, M^+, 348.1559; $C_{19}H_{24}O_6$ requires 348.1573. $[\alpha]_D^{20°}$ = -98.5°, (c = 2.71, CH_2Cl_2). ^1H NMR δ/ppm 6.32 (1H, dt, *J* = 16.7, 10.1 Hz, H3"), 6.16-6.03 (2H, m, H2", H7), 5.76 (1H, dd, *J* = 15.4, 6.6 Hz, H1"), 5.67 (1H, dt, *J* = 10.1, 3.5 Hz, H6), 5.20 (1H, d, *J* = 16.7 Hz, H4"$_\alpha$), 5.10 (1H, *J* = 10.1 Hz, H4"$_\beta$), 4.23-4.14 (2H, m, H4', H5'$_\alpha$), 4.05-3.91 (2H, m, H1, H5'$_\beta$), 3.72 (3H, s, -CO_2CH_3), 3.59 (1H, broad s, H5), 3.11 (1H, d, *J* = 3.1 Hz, H4), 2.99 (1H, tq, *J* = 13.6, 2.2 Hz, H7a), 2.48 (1H, dd, *J* = 13.6, 3.1 Hz, H3a), 1.46, 1.36 (6H, 2 × s, -$C(CH_3)_2$). ^{13}C NMR δ/ppm 173.3, 171.3 (C3, -CO_2CH_3), 136.0 (C3"), 134.4 (C1"), 132.5 (C2"), 129.9 (C6), 126.0 (C7), 117.5 (C4"), 110.0 (-$C(CH_3)_2$), 81.6, 77.4 (C1, C4'), 67.4 (C5'), 52.3 (-CO_2CH_3), 41.7 (C4), 41.3 (C3a), 41.1 (C5), 41.0 (C7a), 26.82, 25.0 (-$C(CH_3)_2$). IR (thin film υ_{max} 2988, 2954, 1790, 1732, 1455, 1436, 1372, 1216, 1155, 1104, 1069, 1007, 979 and 840 cm^{-1}. *m/z* (EI, 70 eV) 348 (M^+, 6%), 333 ($M-CH_3^+$, 78), 185 (32), 143 (38), 129 (73), 101 (100), 91 (50), 73 (32) and 43 (69).

6.4.1.2 IMDA Reaction Of (2R,3S,2E,4E,6E,8E)-1,2-O-Isopropylidene-1,2-dihydroxy-4,6,8,10-undecatetraen-3-yl methyl (2E)-2-butenedioate 4.55

The fumarate ester **4.55** (70.0 mg, 0.20 mmol) was dissolved in dry toluene (20 mL), in the presence of BHT (3.90 mg, 0.02 mmol), under an atmosphere of Ar. The reaction solution was heated to reflux for 6 h. Analysis by ^{1}H NMR spectroscopy indicated the presence of three products in a 75:15:10 ratio. The solvent was removed *in vacuo* with purification by column chromatography, using Hex/$CHCl_3$/Et_2O (3:2:1), affording a mixture of the three diastereoisomeric cycloadducts (R_f = 0.24, 0.20, 0.18) as an oil (59.2 mg, 85%). Repeated column chromatography provided a pure sample of the major diastereoisomer (R_f = 0.18) but the minor diastereoisomers (R_f = 0.24, 0.20) were formed in limited quantities and were not able to be isolated in sufficient purity for characterisation and full structure elucidation.

Methyl (1S,3aR,4R,5R,7aS)-5-((1*E*,3*E*)-1,3-butadien-1-yl)-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 4.57



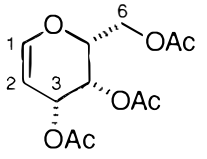
4.57

R_f = 0.18. Found: M^+, 348.1588; $C_{19}H_{24}O_6$ requires 348.1573. $[\alpha]_D^{20^\circ}$ = -159.1°, (c = 1.99, CH_2Cl_2). ^{1}H NMR δ/ppm 6.28 (1H, dt, *J* = 16.7, 10.1 Hz, H3"), 6.11 (1H, dt, *J* = 10.1, 1.8 Hz, H7), 6.06 (1H, dd, *J* = 14.9, 10.5 Hz, H2"), 5.62 (1H, ddd, *J* = 10.1, 2.5, 1.8 Hz, H6), 5.49 (1H, dd, *J* = 14.9, 8.8 Hz, H1"), 5.19 (1H, dd, *J* = 16.7, 1.3 Hz, H4"$_\alpha$), 5.08 (1H, dd, *J* = 10.1, 1.3 Hz, H4"$_\beta$), 4.21-4.09 (2H, m, H4', H5'$_\alpha$), 4.06-3.97 (2H, m, H1, H5'$_\beta$), 3.69 (3H, s, -CO_2CH_3), 3.41-3.33 (1H, m, H5), 3.03 (1H, dd, *J* = 11.4, 7.5 Hz, H4), 2.76 (1H, dd, *J* = 13.6, 11.4 Hz, H3a), 2.62 (1H, tq, *J* = 9.7, 2.0 Hz, H7a), 1.47, 1.37 (6H, 2 × s, -$C(CH_3)_2$). ^{13}C NMR δ/ppm 172.7, 170.3 (-CO_2CH_3, C3), 136.0, 133.6, 131.3, 130.9, 124.6 (C3", C1", C6, C7, C2"), 117.7 (C4"), 110.1 (-$C(CH_3)_2$), 81.2, 77.5 (C1, C4'), 67.4 (C5'), 51.8 (-CO_2CH_3), 45.2, 44.2, 41.7, 41.1 (C4, C3a, C7a, C5), 26.9, 25.1 (-$C(CH_3)_2$). IR (thin film) υ_{max} 2987,

2951, 1789, 1734, 1383, 1373, 1267, 1203, 1152, 1063, 1003, 852 and 737 cm^{-1}. *m/z* (EI, 40 eV) 348 (M^+, 13%), 333 ($M-CH_3^+$, 41), 188 (24), 129 (32), 101 (100), 91 (23), 73 (20) and 43 (33).

6.4.2 Galactose Series Experimental

Tri-*O*-acetyl-D-galactal 4.70[3]



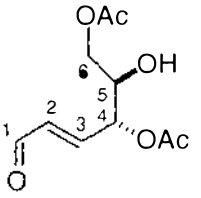
4.70

Tri-*O*-acetyl-D-galactal was prepared according to the method described by Roth[2] and Lichtenhaler[3] with the modifications described below. D-galactose **4.48** (55g, 0.31 mol) was added to a mixture of Ac_2O (200 mL) and 70% perchloric acid (1.2 mL) over the course of 1 h. Care was taken to keep the temperature between 30°C and 40°C. After cooling in an ice/salt bath, PBr_3 (25 mL, 0.26 mol) was added dropwise with continuous stirring. The reaction temperature was kept below 20°C. Once addition was complete, H_2O (15 mL) was added over 0.5 h, keeping the reaction temperature below 20°C, and the reaction was then stirred for 3 h at RT. The reaction mixture was filtered to remove solid impurities. The filter paper was washed with glacial AcOH (10 mL). The filtrate contained crude tetra-*O*-acetyl-α-D-galacto-pyranosylbromide.

$NaOAc.3H_2O$ (200 g, 1.47 mol) was dissolved in H_2O (290 mL) and glacial AcOH (200 mL) and the solution cooled in an ice/salt bath. Zn dust (110 g, 1.68 mol) and $CuSO_4.5H_2O$ (11 g , 44 mmol) were added to the solution. When the blue colour had disappeared, the crude tetra-*O*-acetyl-α-D-galactopyranosylbromide solution was added gradually over 1 h, keeping the temperature below 0°C. The reaction mixture was stirred at 0°C. After 3 h, the reaction mixture was filtered and the filter paper washed with 50% AcOH. H_2O (500 mL, 0°C) was added to the combined filtrates and the solution was extracted with CH_2Cl_2 (6 × 100 mL). The combined organic fractions were washed with ice-cold H_2O, sat. aq. $NaCO_3$ and ice-cold H_2O. The organic solution was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude oil was dissolved in benzene (50 mL) and the solvent removed *in vacuo*. Distillation of the residual syrup (126-130°C, 0.05 mm Hg) afforded the title compound **4.70** as a clear, straw-coloured oil (33.7 g, 41%, R_f = 0.42 (1:1 Hex/EtOAc)). $[\alpha]_D^{20°}$ = +16.5°, (c = 11.31, CH_2Cl_2).

^{1}H NMR δ/ppm 6.43 (1H, dd, *J* = 6.4, 1.6 Hz), 5.54-5.51 (1H, m), 5.40 (1H, dt, *J* = 4.5, 1.5 Hz), 4.70 (1H, ddd, *J* = 6.4, 2.6, 1.5 Hz), 4.32-4.19 (3H, m), 2.10 (3H, s), 2.06 (3H, s), 2.00 (3H, s). ^{13}C NMR δ/ppm 170.3, 170.0, 169.9, 145.2, 98.7, 72.6, 63.8, 63.7, 61.9, 20.8, 20.7, 20.6. IR (thin film) υ_{max} 3472, 3023, 2968, 1750, 1652, 1433, 1372, 1226, 1149, 1066, 1046, 930 and 753 cm^{-1}.

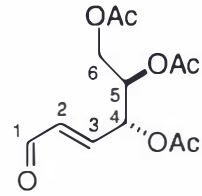
(2*E*,4R,5R)-4,6-Diacetoxy-5-hydroxy-2-hexenal 4.71[5]



4.71

This was prepared according to the method of Perlin.[5] Tri-*O*-acetyl-D-galactal **4.70** (9.94 g, 36.5 mmol) was dissolved in 1,4-dioxane (59 mL). A solution of 5 mM H_2SO_4 (63 mL) and $HgSO_4$ (368 mg, 1.24 mmol) were added and the reaction solution stirred at RT overnight. After quenching with $BaSO_4$ (1.19 g, 6.03 mmol), the reaction solution was filtered through celite and then diluted with CH_2Cl_2 (100 mL). The aqueous and organic fractions were separated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic fractions were washed with saturated brine and dried over Na_2SO_4. Removing the solvent *in vacuo* gave the title compound **4.71** (R_f = 0.14, 1:1 Hex/EtOAc) as a straw coloured oil (8.40 g, 99%). $[\alpha]_D^{18°}$ = +29.2°, (c = 12.8, CH_2Cl_2). ^{1}H NMR δ/ppm 9.59 (1H, d, *J* = 7.7 Hz, H1), 6.85 (1H, dd, *J* = 15.8, 4.5 Hz, H3), 6.28 (1H, ddd, *J* = 15.8, 7.7, 1.5 Hz, H2), 5.63 (1H, td, *J* = 4.5, 1.5 Hz, H4), 4.28-4.18 (1H, m, H5), 4.14-4.06 (2H, m, 2 × H6), 2.8 (1H, broad s, -OH), 2.18, 2.10 (6H, 2 × s, -OC(O)CH_3). ^{13}C NMR δ/ppm 193 (C1), 171, 169 (-O*C*(O)CH_3), 150, 132 (C2, C3), 77.2, 72.1, 64.7 (C4, C5, C6), 20.4 (2 × -OC(O)*C*H_3). IR (thin film) υ_{max} 3093, 3037, 2969, 1746, 1695, 1652, 1480, 1435, 1373, 1223, 1148, 1075 and 685 cm^{-1}. All data was in accordance with literature values.[5]

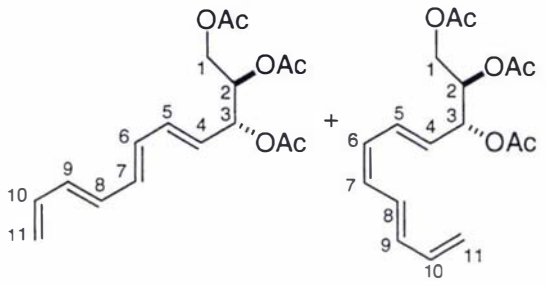
(2*E*,4R,5R)-4,5,6-Triacetoxy-2-hexenal 4.72



4.72

(2*E*,4R,5R)-4,6-Diacetoxy-2-hydroxy-4-hexenal **4.71** (4.20 g, 18.2 mmol) was dissolved in CH_2Cl_2 (25 mL) and the solution cooled in an ice/salt bath. Triethylamine (3.80 mL, 27.4 mmol), Ac_2O (2.15 mL, 22.8 mmol) and DMAP (223 mg, 1.80 mmol) were added and the reaction solution stirred for 5 min. Saturated aqueous $NaHCO_3$ (40 mL) was added and the reaction solution stirred vigorously for 5 min. After dilution of the reaction solution with CH_2Cl_2 (50 mL), the organic fraction was separated and washed with saturated aqueous $NaHCO_3$ (5 mL), 10% aqueous HCl (2 × 10 mL) and H_2O (5 mL). The combined washings were back-extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with saturated brine, dried over Na_2SO_4 and the solvent removed *in vacuo* to yield the title compound **4.72** (Rf = 0.44, 1:1 Hex/EtOAc) as a yellow oil (4.97 g, 100%). $[\alpha]_D^{17^\circ}$ = +18.3°, (c = 2.74, CH_2Cl_2). ^{1}H NMR δ/ppm 9.53 (1H, d, *J* = 7.7 Hz, H1), 6.70 (1H, dd, *J* = 15.8, 4.6 Hz, H3), 6.20 (1H, ddd, *J* = 15.8, 7.7, 1.5 Hz, H2), 5.72 (1H, td, *J* = 4.6, 1.5 Hz, H4), 5.34-5.29 (1H, m, H5), 4.30 (1H, dd, *J* = 11.8, 4.6 Hz, $H6_\alpha$), 4.04 (1H, dd, *J* = 11.8, 6.6 Hz, $H6_\beta$), 2.14, 2.05, 2.03 (9H, 3 × s, -OC(O)CH_3). ^{13}C NMR δ/ppm 191.9 (C1), 170.0, 169.5, 169.0 (3 × (-O*C*(O)CH_3)), 148.4, 133 (C2, C3), 70.2, 70.0, 61.5 (C4, C5, C6), 20.6, 20.6, 20.5 (3 × -OC(O)*C*H_3).

(2R,3R,4*E*,6*E*,8*E*,10*E*)-1,2,3-Triacetoxy-4,6,8,10-undecatetraene 4.73 and (2R,3R,4*E*,6*Z*,8*E*,10*E*)-1,2,3-triacetoxy-4,6,8,10-undecatetraene 4.74

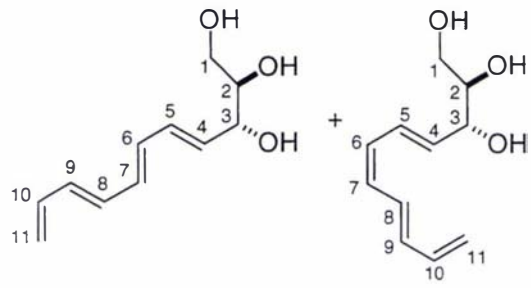


4.73, 4.74

The phosphonium salt (6.19 g, 15.1 mmol) was suspended in dry THF (40 mL) under Ar. The reaction solution was cooled to -70°C and *n*-BuLi (10.04 mL, 1.50 M, 15.1 mmol) was added dropwise. The reaction solution was then allowed to warm to RT over 5 min.

(2*E*,4R,5R)-4,5,6-Triacetoxy-2-hexenal **4.72** (4.10 g, 15.1 mmol) was dissolved in dry THF (40 mL) under Ar and cooled to -70°C. The ylide solution (45 mL, 0.30 M, 13.6 mmol) was added dropwise to the reaction solution. After 15 min, the reaction was quenched with saturated aqueous ammonium chloride (15 mL) and allowed to warm to RT. After dilution with Et_2O (100 mL), the organic and aqueous fractions were separated and the organic fraction washed with H_2O. The combined aqueous fractions were back-extracted with Et_2O (50 mL). The combined organic fraction was then washed with saturated brine and dried over Na_2SO_4. Removing the solvent *in vacuo* gave a brown oil (8.17 g). Purification by column chromatography (3:1 Hex/EtOAc) gave the mixture of tetraenes **4.73** and **4.74** (R_f = 0.30) as a clear oil (3.27 g, 75%). Found: M^+, 322.1410; $C_{17}H_{22}O_6$ requires 322.1416. ^1H NMR δ/ppm 6.85-5.91 (6H, m, H5-H10), 5.63-5.47 (2H, m, H3, H4), 5.31-5.12 (2H, m, 2 × H11), 4.37-4.30 (1H, m, $H1_\alpha$), 4.05-3.99 (1H, m, $H1_\beta$), 2.09-2.06 (9H, m, 3 × -OC(O)CH_3). IR (thin film) υ_{max} 3090, 3033, 2961, 1746, 1642, 1460, 1434, 1372, 1221, 1047, 1013 and 683 cm^{-1}. *m/z* (EI, 70 eV) 322 (M^+, 5%), 262 (6), 160 (70), 145 (12), 135 (46), 117 (14), 91 (9), 79 (7) and 43 (100).

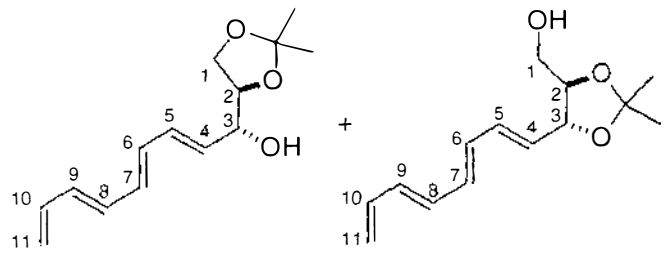
(2R,3R,4*E*,6*E*,8*E*,10*E*)-1,2,3-Trihydroxy-4,6,8,10-undecatetraene 4.75 and (2R,3R,4*E*,6*Z*,8*E*,10*E*)-1,2,3-trihydroxy-4,6,8,10-undecatetraene 4.76



4.75, 4.76

The mixture of (2R,3R,4*E*,6*E*,8*E*,10*E*)-1,2,3-triacetoxy-4,6,8,10-undecatetraene **4.73** and (2R,3R,4*E*,6*Z*,8*E*,10*E*)-1,2,3-triacetoxy-4,6,8,10-undecatetraene **4.74** (1.56 g, 4.9 mmol) was dissolved in MeOH (106 mL), under Ar, and BHT (102 mg, 0.5 mmol) was added. A solution of $KHCO_3$ (3.28 g, 32.8 mmol) in H_2O (20 mL) was added dropwise to the reaction solution. The reaction solution was stirred at RT for 2.5 h. The MeOH was removed *in vacuo* and the residue diluted with H_2O (20 mL) and extracted with *sec*-butanol/EtOAc (10% v/v; 5 × 30 mL). The solvent was then removed from the combined fractions *in vacuo* and any residual H_2O was removed by azeotroping with benzene to afford the title compounds, a mixture of *E/Z* isomers about the C6-C7 bond, (R_f = 0.38, 100% EtOAc) as a cloudy, pale yellow oil (1.99 g). The crude material was not subjected to column chromatography due to concerns about the stability of the trihydroxy tetraene. Found: M^+, 196.1091; $C_{11}H_{16}O_3$ requires 196.1099. ^{1}H NMR δ/ppm 6.88-6.65, 6.51-6.23, 6.08-6.02 (6H, m, H5-H10), 5.80-5.72 (1H, m, H4), 5.31-5.15 (2H, m, 2 × H11), 4.32-4.23 (1H, m, H2), 3.81-3.63 (3H, m, 2 × H1, H3), 2.30-2.05 (3H, m, -OH). ^{13}C NMR δ/ppm 136.7, 134.4, 133.8, 133.1, 132.8, 132.7, 132.3, 132.2, 131.8, 129.7, 128.8, 127.9, 127.3, 125.3, (C4-C10, both isomers), 117.9, 117.4 (C11, both isomers), 74.4, 72.7, 63.3 (C1, C2, C3, both isomers). IR (thin film) υ_{max} 3645, 3374, 2956, 2916, 2871, 1431, 1391, 1360, 1314, 1231, 1157, 1120 and 860 cm^{-1}. *m/z* (EI, 70 eV) 196 (M^+, 38%), 135 (100), 117 (42), 105 (39), 91 (78), 79 (54), 67 (38) and 41 (40).

(2R,3R,2*E*,4*E*,6*E*,8*E*)-1,2-*O*-Isopropylidene-1,2,3-trihydroxy-4,6,8,10-undecatetraene 4.49 and (2R,3R,2*E*,4*E*,6*E*,8*E*)-2,3-*O*-isopropylidene-1,2,3-trihydroxy-4,6,8,10-undecatetraene 4.77



4.49, 4.77

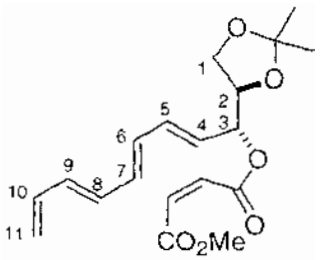
The mixture of *E* and *Z* isomers, (2R,3R4*E*,6*E*,8*E*,10*E*)-1,2,3-trihydroxy-4,6,8,10-undecatetraene and (2R,3R,4*E*,6*Z*,8*E*,10*E*)-1,2,3-trihydroxy-4,6,8,10-undecatetraene **4.75** and **4.76**, (0.959 g, 4.9 mmol), was dissolved in acetone (150 mL) and BHT (100 mg, 0.45 mmol) was added. 2,2-Dimethoxypropane (0.60 mL, 4.9 mmol) and CSA (23 mg, 0.10 mmol) were added to the reaction solution. After 2 h, more 2,2-dimethoxypropane (2.4 mL, 19.6 mmol) and CSA (46 mg, 0.20 mmol) were added and the reaction solution stirred overnight. The acetone was removed *in vacuo* and the residue diluted with Et_2O and washed with $NaHCO_3$ and H_2O. The combined aqueous was then back-extracted with Et_2O. The combined organic fractions were washed with saturated brine and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford a complex mixture of 6*E*/*Z* and dioxolane regioisomers as a yellow oil (1.26 g). This was dissolved in benzene (80 mL) and thiophenol (48 μL, 0.47 mmol) and AIBN (37 mg, 0.23 mmol) were added under Ar. The stirred solution was irradiated with visible light for 25 min. This process was repeated four times until the isomerisation was complete by ^{1}H NMR. After removing the benzene *in vacuo*, the crude oil was purified by column chromatography using Hex/EtOAc (1:1) to give the desired secondary alcohol, **4.49**, (273 mg, 1.15 mmol, 24% over 3 steps, R_f = 0.25) and the primary alcohol, **4.77** (126 mg, 0.53 mmol, 11% over 3 steps, R_f. = 0.20).

Secondary alcohol 4.49, (R_f = 0.25). Found: M^+, 236.1419; $C_{14}H_{20}O_3$ requires 236.1412. $[\alpha]_D^{19°}$ = +28.5°, (c = 0.31, CH_2Cl_2). ^{1}H NMR δ/ppm 6.47-6.25 (6H, m, H5-H10), 5.65 (1H, dd, *J* = 14.9, 6.6 Hz, H4), 5.27 (1H, dd, *J* = 16.2, 1.7 Hz, $H11_\alpha$), 5.15 (1H, dd, *J* = 9.6, 1.7 Hz, $H11_\beta$), 4.16-3.98 (3H, m, 2 × H1, H3), 3.83-3.76 (1H, m, H2), 2.59 (1H, d, *J* = 3.5 Hz, -OH), 1.49, 1.40 (6H, 2 × s, $-C(CH_3)_2$). ^{13}C NMR δ/ppm 137, 134, 134, 133, 132, 131 (C4-C10), 118 (C11), 110 ($-C(CH_3)_2$), 78.8, 73.7, 65.8 (C1, C2, C3), 26.8, 25.3 ($-C(CH_3)_2$). IR (thin film) υ_{max} 3439, 2987, 1694, 1372, 1214, 1157, 1066, 1010 and 857 cm^{-1}. UV λ_{max} (Et_2O) 309 nm (ε 39 974), 295 (48 737), 285 (38 104) and 202 (13 292). *m/z* (EI, 70 eV) 236 (M^+, 20%), 205 (9), 161(7),

101 (100), 73 (12), 91 (11) and 43 (19).

Primary alcohol 4.77, (R_f = 0.20). Found: M^+, 236.1414; $C_{14}H_{20}O_3$ requires 236.1412. $[\alpha]_D^{20}$ = +23.4°, (c = 1.29, CH_2Cl_2). ^1H NMR δ/ppm 6.43-6.24 (6H, m, H5-H10), 5.66 (1H, dd, *J* = 14.9, 7.7 Hz, H4), 5.25 (1H, dd, *J* = 16.3, 1.5 Hz, $H11_\alpha$), 5.13 (1H, dd, *J* = 9.6, 1.5 Hz, $H11_\beta$), 4.39 (1H, t, *J* = 7.8 Hz, H3), 4.08-3.75 (2H, m, 2 × H1), 3.63-3.56 (1H, m, H2), 2.07 (1H, br s, -OH), 1.45 (6H, s, $-C(CH_3)_2$). ^{13}C NMR δ/ppm 136.7, 134.4, 134.4, 134.0, 132.9, 131.7, 129.1 (C4-C10), 117.9 (C11), 109.1 ($-C(CH_3)_2$), 81.2, 77.8, 60.7 (C1, C2, C3), 27.2, 27.0 ($-C(CH_3)_2$). IR (thin film) υ_{max} 3640, 3452, 2956, 2872, 1644, 1432, 1371, 1232, 1161, 1113, 1049, 1008, 900, 861, 169 and 739 cm^{-1}. UV λ_{max} (Et_2O) 310 nm (ε 25 993), 296 (32 261), 284 (26 977) and 202 (17 296). *m/z* (EI, 70 eV) 236 (M^+, 45%), 161 (37), 147 (27), 117 (56), 106 (100), 91 (94), 78 (37), 59 (43) and 43 (70).

(2R,3R,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-4,6,8,10-undecatetraen-3-yl methyl (2*Z*)-2-butenedioate 4.78

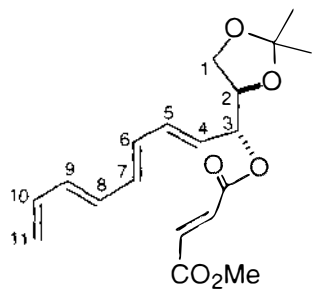


4.78

Tetraenol **4.49** (24.1 mg, 0.10 mmol) was dissolved in dry CH_2Cl_2 (2 mL) under Ar with BHT (2.0 mg, 0.01 mmol) present and cooled using an ice/salt bath. Triethylamine (22.7 μL, 0.16 mmol), MA (22.5 mg, 0.23 mmol) and DMAP (1.3 mg, 0.01 mmol) were added to the reaction solution. After 3 h, more MA (12 mg, 0.12 mmol) and DMAP (1.3 mg, 0.01 mmol) were added. After an additional 2 h, the reaction solution was diluted with CH_2Cl_2 (20 mL) and washed with 10% aqueous HCl (2 mL) and H_2O (2 mL). The combined aqueous fractions were back-extracted with CH_2Cl_2 (10 mL). The organics were then washed with saturated brine (2 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude acid was then dissolved in Et_2O (5 mL) and an ethereal solution of CH_2N_2 (*ca.* 0.5 M) was added until methylation was complete by TLC. Purification by column chromatography using Hex/Et_2O (1:1) gave the title compound **4.78** (R_f = 0.31) as an oil (14.0 mg, 40%). Found: M^+, 348.1594 ;$C_{18}H_{24}O_6$ requires 348.1573. $[\alpha]_D^{20}$ = +78.9°, (c = 0.70, CH_2Cl_2). ^1H NMR δ/ppm 6.49-6.21 (8H, m, H5-H10, $RO_2CCHCHCO_2CH_3$), 5.61 (1H, dd, *J* = 15.3, 7.8 Hz, H4), 5.44 (1H, dd, *J* = 7.8, 6.6 Hz, H3), 5.27 (1H, dd, *J* = 16.4, 1.7 Hz, $H11_\alpha$), 5.15 (1H, dd,

J = 9.9, 1.8 Hz, H11$_\beta$), 4.28 (1H, dd, J = 12.3, 6.4 Hz, H2), 4.02 (1H, dd, J = 8.8, 6.6 Hz, H1$_\alpha$), 3.83-3.79 (1H, m, H1$_\beta$), 3.78 (3H, s, -CO_2CH_3), 1.43, 1.36 (6H, 2 × s, -$C(CH_3)_2$). ^{13}C NMR δ/ppm 165.4, 164.0 ($RO_2CCHCHCO_2CH_3$), 136.7, 136.0, 134.8, 132.5, 131.5, 129.8, 129.5, 125.6, 124.9 (C4-C10, $RO_2CCHCHCO_2CH_3$), 118.1 (C11), 110.1 (-$C(CH_3)_2$), 76.1, 75.9, 65.6 (C1, C2, C3), 52.3 (-CO_2CH_3), 26.5, 25.5 (-$C(CH_3)_2$). IR (thin film) υ_{max} 2988.4, 2953.1, 1733.6, 1643.5, 1436.0, 1392.3, 1214.0, 1161.6, 1010.5 and 847.4 cm^{-1}. *m/z* (EI, 70 eV) 348 (M^+, 7%), 218 (32), 117 (34), 113 (37), 101 (100), 99 (45), 91 (36), 85 (23) and 43 (44).

(2R,3R,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-4,6,8,10-undecatetraen-3-yl methyl (2*E*)-2-butenedioate 4.79



4.79

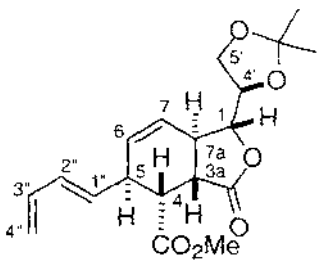
Tetraenol **4.49** (100.2 mg, 0.42 mmol) was dissolved in dry CH_2Cl_2 (12 mL), under Ar, with BHT (6.4 mg, 0.03 mmol) present. After addition of DCC (131 mg, 0.64 mmol), monomethyl fumarate (83 mg, 0.64 mmol) and DMAP (10.4 mg, 0.08 mmol), the reaction solution was stirred for 15 min. The reaction solution was diluted with Et_2O (100 mL) and the organic phase separated. The organic layer was washed with dilute HCl, sat. aq. $NaHCO_3$ and H_2O. The aqueous fraction was back-extracted with Et_2O and the combined organic fractions washed with saturated brine. After drying over Na_2SO_4, the solvent was removed *in vacuo* affording a crude oil which was then purified by column chromatography (using Hex/Et_2O (3:1)) to give the title compound **4.79** as a clear colourless oil (106 mg, 72%, R_f = 0.22, 3:1 Hex/Et_2O) Found: M^+, 348.1571; $C_{19}H_{24}O_6$ requires 348.1573. $[\alpha]_D^{21°}$ = +97.3°, (c = 0.55, CH_2Cl_2). ^{1}H NMR δ/ppm 6.86 (2H, s, $RO_2CCHCHCO_2CH_3$), 6.45-6.17 (6H, m, H5-H10), 5.56 (1H, dd, J = 15.0, 8.1 Hz, H4), 5.40 (1H, dd, J = 7.8, 7.3 Hz, H3), 5.23 (1H, d, J = 16.1 Hz, H11$_\alpha$), 5.11 (1H, d, J = 9.8 Hz, H11$_\beta$), 4.23 (1H, dd, J = 12.6, 6.3 Hz, H2), 4.09 (1H, dd, J = 14.4, 7.3 Hz, H1$_\alpha$), 3.99 (1H, dd, J = 8.5, 6.6 Hz, H1$_\beta$), 3.78 (3H, s, -CO_2CH_3), 1.40, 1.33 (6H, 2 × s, -$C(CH_3)_2$). ^{13}C NMR δ/ppm 165, 164 ($RO_2CCHCHCO_2CH_3$), 137, 136, 135, 135, 133, 133, 132, 131, 125 (C4-C10, $RO_2CCHCHCO_2CH_3$), 118 (C11), 110 ($C(CH_3)_2$), 76.1, 65.6, 60.3 (C1, C2, C3), 52.2

(-CO_2CH_3), 26.4, 25.3 (-$C(CH_3)_2$). IR (thin film) υ_{max} 2988, 2954, 1790, 1725, 1644, 1435, 1372, 1298, 1258, 1224, 1155, 1070, 1009 and 846 cm^{-1}. UV λ_{max} (Et_2O) 209 nm (ε 14 331), 286 (27 633), 297 (38 836) and 311 (33 254). *m/z* (EI, 70 eV) 348 (M^+, 9%), 143 (12), 113 (32), 101 (100), 91 (8), 73 (9) and 43 (18).

6.4.2.1 IMDA Reaction Of (2R,3R,4E,6E,8E,10E)-1,2-O-Isopropylidene-1,2-dihydroxy-4,6,8,10-undecatetraen-3-yl methyl (2Z)-2-butenedioate 4.78

(2R,3R,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-4,6,8,10-undecatetraen-3-yl methyl (2*Z*)-2-butenedioate **4.78** (44 mg, 0.13 mmol) was dissolved in dry toluene (15 mL) and BHT (2.9 mg, 0.01 mmol) was added. The solution was heated to reflux, under Ar, for 30 min. The solvent was removed *in vacuo* with ^1H NMR analysis of the crude reaction mixture indicating the presence of four diastereomeric cycloadducts as a 52:28:10:10 (R_f = 0.29, 0.15, 0.22, 0.22, (2:3 Hex/Et_2O)). Purification *via* repeated column chromatography yielded the major and one of the minor diastereoisomers cycloadducts, **4.80** and **4.81** respectively. The other two minor diastereoisomers, **4.82** and **4.83**, (R_f = 0.22, 0.22) proved to be inseparable.

Methyl (1R,3aS,4R,5S,7aR)-5-((1*E*,3*E*)-1,3-butadien-1-yl)-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 4.80

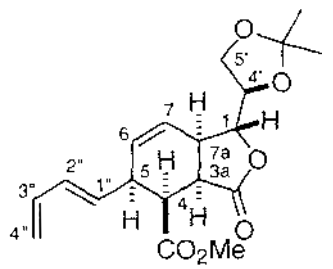


4.80

R_f = 0.29, (2:3 Hex/Et_2O). Found: M^+, 348.1578; $C_{19}H_{24}O_6$ requires 348.1573. $[\alpha]_D^{20°}$ = +163.8°, (c = 0.95, CH_2Cl_2). ^1H NMR δ/ppm 6.33 (1H, dt, *J* = 16.9, 10.3 Hz, H3"), 6.07 (1H, dd, *J* = 15.2, 10.3 Hz, H2"), 5.95 (1H, dt, *J* = 9.9, 1.8 Hz, H1"), 5.80 (1H, d, *J* = 6.6 Hz, H6), 5.75-5.68 (1H, m, H7), 5.20 (1H, dd, *J* = 16.9, 1.3 Hz, $H4"_\alpha$), 5.11 (1H, dd, *J* = 9.9, 1.3 Hz, $H4"_\beta$), 4.42 (1H, td, *J* = 6.6, 4.2 Hz, H4'), 4.20-4.12 (2H, m, H1, $H5'_\alpha$), 4.00 (1H, dd, *J* = 8.6, 6.6 Hz, $H5'_\beta$), 3.75 (3H, s, -CO_2CH_3), 3.62-3.59 (1H, m, H5), 3.14 (1H, d, *J* = 2.9 Hz, H4), 3.11-3.05 (1H, m, H7a), 2.50

(1H, dd, J = 13.6, 3.3 Hz, H3a), 1.46, 1.40 (6H, 2 × s, -C(CH_3)$_2$). ^{13}C NMR δ/ppm 173.1, 171.3 (-CO$_2$CH$_3$, C3), 136.0 (C3"), 134.4 (C6), 132.6 (C2"), 130.7 (C7), 124.9 (C1"), 117.6 (C4"), 110.1 (-C(CH$_3$)$_2$), 80.9 (C1), 74.5 (C4'), 65.1 (C5'), 52.4 (-CO$_2$$CH_3$), 41.9 (C4), 41.6 (C3a), 41.1 (C5), 37.3 (C7a), 26.1, 25.3 (-C(CH$_3$)$_2$). IR (thin film) υ_{max} 2988, 2953, 1790, 1732, 1434, 1372, 1221, 1158, 1106, 1070, 981 and 754 cm^{-1}. *m/z* (EI, 70 eV) 348 (M$^+$, 9%), 333 (M-CH$_3^+$, 66), 234 (26), 185 (28), 157 (24), 143 (31), 129 (65), 101 (100), 91 (38) and 43 (67).

Methyl (1R,3aR,4S,5S,7aR)-5-((1*E*,3*E*)-1,3-butadien-1-yl)-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 4.81



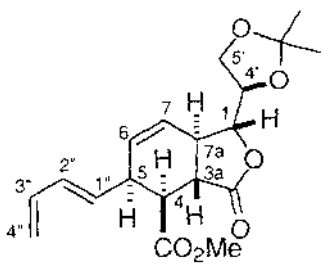
4.81

R_f = 0.16 (2:3 Hex/Et$_2$O). Found: M$^+$, 348.1574; $C_{19}H_{24}O_6$ requires 348.1573. $[\alpha]_D^{23°}$ = -151°, (c = 0.26, CH_2Cl_2). ^{1}H NMR δ/ppm 6.36 (1H, dt, J = 16.9, 10.1 Hz, H3"), 6.16-6.04 (2H, m, H2", H1"), 5.82 (1H, dd, J = 15.2, 6.4 Hz, H7), 5.74-5.68 (1H, m, Hz, H6), 5.17 (1H, d, J = 16.9 Hz, H4"$_\alpha$), 5.09 (1H, dd, J = 10.1, 1.7 Hz, H4"$_\beta$), 4.54 (1H, d, J = 7.0 Hz, H1), 4.30-4.25 (1H, m, H5'$_\alpha$), 4.12 (1H, dd, J = 8.3, 6.8 Hz, H4'), 4.00 (1H, t, J = 8.2 Hz, H5'$_\beta$), 3.73 (3H, s, -CO$_2$CH$_3$), 3.67-3.60 (1H, m, H5), 3.38-3.32 (2H, m, H4, H7a), 3.14-3.07 (1H, m, H3a), 1.35, 1.31 (6H, 2 × s, -C(CH$_3$)$_2$). ^{13}C NMR δ/ppm 175.12, 171.72 (-CO$_2$CH$_3$, C3), 136.3 (C3"), 134.3 (C7), 133.3 (C2"), 130.3 (C6), 124.4 (C1"), 117.1 (C4"), 110.2 (-C(CH$_3$)$_2$), 77.5 (C1), 74.9 (C4'), 65.6 (C5'), 52.4 (-CO$_2$$CH_3$), 42.3 (C3a), 41.2 (C5), 38.2, 37.7 (C4, C7a), 25.9, 25.7 (-C(CH$_3$)$_2$). IR (thin film) υ_{max} 3035, 2988, 2935, 1791, 1736, 1372, 1221, 1159, 1071 and 981 cm^{-1}. *m/z* (EI, 70 eV) 348 (M$^+$, 9%), 333 (M-CH$_3^+$, 52), 234 (51), 185 (32), 157 (43), 143 (40), 129 (68), 101 (100), 91 (44) and 43 (71).

6.4.2.2 IMDA Reaction Of (2R,3R,4E,6E,8E,10E)-1,2-O-Isopropylidene-1,2-dihydroxy-4,6,8,10-undecatetraen-3-yl methyl (2E)-2-butenedioate 4.79

(2R,3R,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-4,6,8,10-undecatetraen-3-yl methyl (2*E*)-2-butenedioate **4.79** (80.7 mg, 0.23 mmol) was heated to reflux in toluene (23 mL) in the presence of BHT (5.10 mg, 0.02 mmol) under Ar for 5h. The solvent was removed *in vacuo*. Analysis of the reaction mixture by ^{1}H NMR spectroscopy indicated the presence of four compounds in a 60:16:14:10 ratio (R_f = 0.43, 0.31, 0.53, 0.31, (5:1, CH_3Cl/Et_2O)). Initial purification by column chromatography (1:1 Hex/Et_2O) gave a mixture of the four diastereoisomers (53.5 mg, 74%). Further purification by repeated column chromatography (5:1 CH_3Cl/Et_2O) isolated the major diastereoisomer **4.84** (R_f = 0.43) and one of the minor diastereoisomers **4.86** (R_f = 0.53). The remaining diastereoisomers, **4.85** and **4.87**, (R_f = 0.31, 0.31) proved to be inseparable.

Methyl (1R,3aS,4S,5S,7aR)-5-((1*E*,3*E*)-1,3-butadien-1-yl)-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 4.84

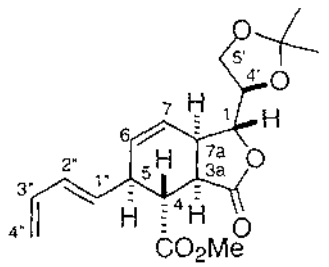


4.84

R_f = 0.43, (5:1 CH_3Cl/Et_2O). Found: M^+, 348.1571; $C_{19}H_{24}O_6$ requires 348.1573. $[\alpha]_D^{20°}$ = +258.4°, (c = 1.27, CH_2Cl_2). ^{1}H NMR δ/ppm 6.27 (1H, dt, *J* = 16.7, 10.1 Hz, H3"), 6.05 (1H, dd, *J* = 14.9, 10.6 Hz, H2"), 5.93 (1H, dt, *J* = 9.9, 1.5 Hz, H7), 5.65 (1H, ddd, *J* = 9.9, 3.7, 2.4 Hz, H6), 5.49 (1H, dd, *J* = 14.9, 9.2 Hz, H1"), 5.18 (1H, dd, *J* = 16.7, 1.7 Hz, H4"$_\alpha$), 5.08 (1H, dd, *J* = 9.9, 1.7 Hz, H4"$_\beta$), 4.37 (1H, td, *J* = 6.6, 3.5 Hz, H4'), 4.20 (1H, dd, J = 6.8, 3.5 Hz, H1), 4.13 (1H, dd, *J* = 8.6, 6.8 Hz, H5'$_\alpha$), 3.98 (1H, dd, *J* = 8.6, 6.8 Hz, H5'$_\beta$), 3.69 (3H, s, -CO_2CH_3), 3.42-3.30 (1H, m, H5), 3.05 (1H, dd, *J* = 10.9, 7.5 Hz, H4), 2.82-2.69 (2H, m, H7a, H3a), 1.43, 1.39 (6H, 2 × s, -$C(CH_3)_2$). ^{13}C NMR δ/ppm 172.4 (C3, -CO_2CH_3), 136.0 (C3"), 133.6 (C2"), 132.0 (C7), 130.9 (C1"), 123.2 (C6), 117.7 (C4"), 110.1

(-C(CH_3)$_2$), 80.1 (C1), 74.0 (C4'), 65.1 (C5'), 51.8 (-CO_2CH_3), 44.1 (C4), 41.7 (C5), 41.4, 41.3 (C3a, C7a), 26.0, 25.4 (-C(CH_3)$_2$). IR (thin film) υ_{max} 2991, 2936, 2880, 1789, 1732, 1454, 1440, 1372, 1260, 1222, 1156, 1068, 1007, 971, 902, 855, 755 and 727 cm^{-1}. *m/z* (EI, 70 eV) 348 (M$^+$, 11%), 333 (37), 216 (10), 188 (16), 129 (22), 101 (100), 91 (15), 55 (11) and 43 (27).

Methyl (1R,3aR,4R,5S,7aR)-5-((1*E*,3*E*)-1,3-butadien-1-yl)-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-1,3,3a,4,5,7a-hexahydro-4-isobenzofurancarboxylate 4.86



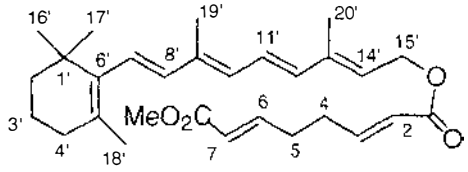
4.86

R_f = 0.53, (5:1 CH_3Cl/Et_2O). Found: M$^+$, 348.1575; $C_{19}H_{24}O_6$ requires 348.1573. $[\alpha]_D^{20°}$ = +160°, (c = 0.21, CH_2Cl_2). ^{1}H NMR δ/ppm 6.30 (1H, dt, *J* = 16.9, 10.0 Hz, H3"), 6.05 (1H, dd, *J* = 15.2, 10.3 Hz, H2"), 5.84 (1H, ddd, *J* = 10.1, 4.0, 1.5 Hz, H6), 5.75 (1H, ddd, *J* = 10.1, 3.3, 1.3 Hz, H7), 5.60 (1H, dd, *J* = 15.2, 7.3 Hz, H1"), 5.15 (1H, dd, *J* = 16.9, 1.1 Hz, H4"$_\alpha$), 5.05 (1H, dd, *J* = 10.1, 1.1 Hz, H4"$_\beta$), 4.29 (1H, td, *J* = 4.2, 2.2 Hz, H4'), 4.19 (1H, dd, *J* = 4.2, 2.2 Hz, H1), 4.11 (1H, dd, *J* = 8.5, 6.7 Hz, H5'$_\alpha$), 3.96 (1H, dd, *J* = 8.4, 7.3 Hz, H5'$_\beta$), 3.74 (3H, s, -CO_2CH_3), 3.40 (1H, dd, *J* = 9.0, 5.3 Hz, H3a), 3.35-3.30 (1H, m, H5), 3.25-3.20 (1H, m, H7a), 3.00 (1H, dd, *J* = 5.1, 4.6 Hz, H4), 1.39 (6H, s, -C(CH_3)$_2$). ^{13}C NMR δ/ppm 173.2 (-*C*O_2CH_3, C3), 136.2 (C3"), 133.7, 132.6 (C1", C2"), 129.6, 125.5 (C6, C7), 117.1 (C4"), 110.2 (-*C*(CH_3)$_2$), 81.4 (C1), 77.2 (C4'), 65.4 (C5'), 52.4 (-CO_2*C*H_3), 43.1 (C4), 39.0, 39.1 (C5, C3a), 36.5 (C7a), 25.8, 25.7 (-C(*C*H_3)$_2$). IR (thin film) υ_{max} 3054, 2988, 2953, 2930, 1775, 1735, 1436, 11382, 1373, 1266, 1154, 1065, 1006, 734 and 704 cm^{-1}. *m/z* (EI, 70 eV) 348 (M$^+$, 13%), 333 (35), 216 (16), 188 (20), 143 (21), 129 (30), 101 (100), 91 (18) and 43 (29).

6.5 Chapter Five Experiments

6.5.1 Retinyl Ester, Synthesis And Attempted TIMDA Reactions

Retinyl methyl (2*E*,6*E*)-2,6-octadienedioate 5.16

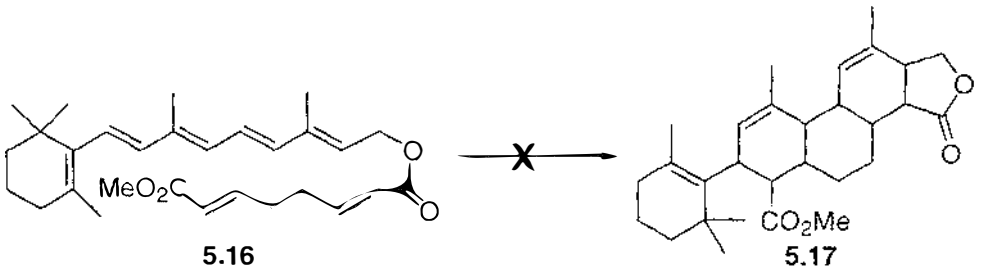


5.16

All-*trans*-retinol (50.0 mg, 0.17 mmol) **5.12** and BHT (3.80 mg, 0.02 mmol) were dissolved in CH_2Cl_2 (6 mL) at 0°C (ice/salt bath) under Ar in a darkened flask. DCC (43.2 mg, 0.21 mmol), acid **5.15** (48.2 mg, 0.26 mmol) and DMAP (4.26 mg, 0.03 mmol) were added and the reaction solution allowed to warm to RT and stirred for 15 h. Additional acid **5.15** (16.1 mg, 0.09 mmol) and DMAP (4.30 mg, 0.03 mmol) were then added. After an additional 1 h, the reaction solution was diluted with Et_2O (50 mL) and washed with 10% aqueous HCl (5 mL), saturated $NaHCO_3$ (5 mL) and H_2O (5 mL). The aqueous fractions were combined and back-extracted with Et_2O (20 mL). The combined organics were washed with saturated brine (5 mL), dried over $MgSO_4$, Na_2SO_4 and the solvent removed *in vacuo* to give an oil (229 mg). Purification by radial chromatography (2:1 Hex/Et_2O, 4 mm plate) afforded the title ester **5.16** (R_f = 0.38) as an oil (57.7 mg, 0.13 mmol, 73%). Found: M^+, 452.2904; $C_{29}H_{40}O_4$ requires 452.2927. ^1H NMR δ/ppm 6.97-6.91 (2H, m, H3, H6), 6.66 (1H, dd, *J* = 15.2, 11.3 Hz, H8'), 6.30 (1H, d, *J* = 15.2 Hz, H7'), 6.17-6.09 (3H, m, H10', H11', H12'), 5.88 (2H, dm, *J* = 15.4 Hz, H2, H7), 5.65 (1H, t, *J* = 7.2 Hz, H14'), 4.81 (2H, d, *J* = 7.2 Hz, 2 × H15'), 3.74 (3H, s, $-CO_2CH_3$), 2.40-2.38 (4H, m, 2 × H4, 2 × H5), 2.03 (2H, t, *J* = 6.2 Hz, 2 × H4'), 1.98, 1.92, 1.73 (9H, 3 × s, 3 × H16', 3 × H19', 3 × H20'), 1.67-1.58 (2H, m, 2 × H3'), 1.50-1.47 (2H, m, 2 × H2'), 1.04 (6H, s, 3 × H17', 3 × H18'). ^{13}C NMR δ/ppm 166.5, 166.0 ($-CO_2CH_3$, $-CO_2R$), 147.0 (C3, C6), 139.0, 137.7, 137.4, 136.4, 135.7, 135.6 (C5', C6', C7', C9', C11', C13') 129.8, 129.2 (C8' C12'), 126.8, 124.4, 122.0, 121.8 (C2, C7, C10', C14'), 61.2 (C15'), 51.5 ($-CO_2CH_3$), 39.6 (C4'), 34.3, 33.1, 30.5, 30.4, 29.0 (C3, C4, C1', C2', C3'), 21.8, 12.9, 12.8 (C16', C19', C20'). IR (thin film) υ_{max} 2954, 2864, 1725, 1659, 1434, 1314, 1269, 1201, 1153, 1026, 968, 861 and 756 cm^{-1}. UV λ_{max} (Et_2O) 326 nm (ε 25 966), 215 (18 069), 204 (11 803) and 195 (5 279). *m/z* (EI, 70 eV) 452 (M^+, 14%), 268 (100), 253 (25), 145 (46), 143 (36),

119 (45), 105 (45), 91 (39), 79 (53), 55 (37) and 41 (50).

6.5.1.1 Attempted TIMDA Reactions Of Retinyl methyl (2E,6E)-2,6-octadienedioate 5.16



5.16 **5.17**

All of the attempted TIMDA reactions of the retinyl ester **5.16** were performed in the absence of light by covering the reaction vessel in aluminium foil.

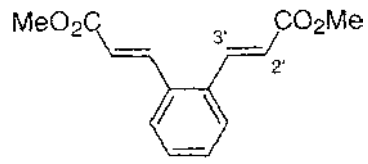
Retinyl ester **5.16** (10.4 mg, 0.02 mmol) was heated in refluxing toluene (5 mL), in the presence of BHT (1.3 mg, 0.006 mmol), for 14 h. There was no change by TLC. The ^{1}H NMR spectrum of the crude product showed changes consistent with an isomerisation of one of the alkenes in the tetraene unit. The C9' and C13' methyl peaks at 1.92 and 1.73 ppm had decreased in intensity and new peaks had appeared at 4.83 (2H, d, J = 7.0 Hz, H15'), 5.52 (1H, d, J =7.2 Hz, H2'), 6.17-6.09 (3H, m, H10', H11', H12'), 6.25 (d, J = 8.6 Hz, H7') and 6.72-6.60 (1H, m, H8') ppm.

Retinyl ester **5.16** (9.6 mg, 0.02 mmol) was heated in refluxing xylene (5 mL), in the presence of BHT (1 mg, 0.006 mmol) for 3 h. Analysis of the ^{1}H NMR spectrum showed the same result as described above.

The retinyl ester **5.16** (8.7 mg, 0.02 mmol) was stirred at RT in CH_2Cl_2 (4 mL) for 14 h in the presence of BHT (1 mg, 0.005 mmol). No reaction occurred, with TLC and ^{1}H NMR spectroscopy showing the presence of only the starting material **5.16**.

6.5.2 Phthalate-Derived Ester, Synthesis And Attempted TIMDA Reaction

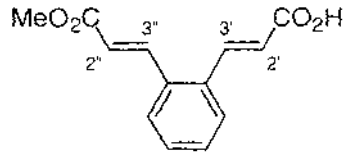
Dimethyl benzene-1,2-diacrylate 5.20



5.20

A mixture of phthalic dicarboxaldehyde (1.00 g, 7.46 mmol) and (carbomethoxymethylene)triphenylphosphorane (5.46 g, 16.3 mmol) in CH_2Cl_2 (20 mL) was stirred at RT for 3 h. Silica (10 g) was added and the CH_2Cl_2 was removed *in vacuo*. Column chromatography (4:1 Hex/EtOAc) furnished the desired *E,E*-dimethyl ester **5.20** (R_f = 0.34) as a white crystalline solid (1.74 g, 95%). Found: M^+, 246.0890; $C_{14}H_{14}O_4$ requires 246.0892. ^{1}H NMR δ/ppm 8.04 (2H, d, *J* = 15.9 Hz, 2 × H3'), 7.59-7.54 (2H, m, aryl CH), 7.40 (2H, dd, *J* = 5.8, 3.4 Hz, aryl CH), 6.36 (2H, d, *J* = 15.9 Hz, 2 × H2'), 3.83 (6H, s, 2 × $-CO_2CH_3$). ^{13}C NMR δ/ppm 166.6, ($-CO_2CH_3$), 141.3, (C3'), 134.1, 133.0, 127.5, (3 × aryl C), 121.4 (C2'), 51.9 ($-CO_2CH_3$). IR (KBr disk) υ_{max} 2998, 2951, 1733, 1637, 1473, 1440, 1319, 1188, 981 and 765 cm^{-1}. UV λ_{max} (Et_2O) 287 nm (ε 25 245), 258 (31 209), 208 (16 396). *m/z* (EI, 70 eV) 246 (M^+, 3%), 215 (14), 186 (71), 171 (16), 143 (23), 128 (100), 115 (15), 64 (14) and 59 (25).

Methyl hydrogen 1,2-benzenediacrylate 5.21

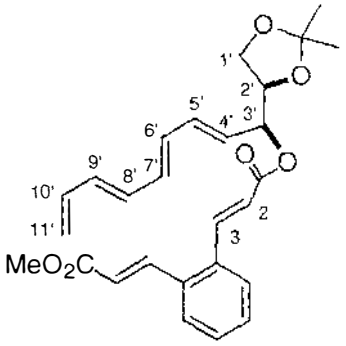


5.21

To a solution of the *E,E*-dimethyl ester **5.20** (985 mg, 4.00 mmol) in THF/H_2O (10 mL, 1:1) was added, at 30°C, a solution of LiOH.H_2O (168 mg, 4.00 mmol) in THF/H_2O (6 mL, 1:1). The resulting solution was stirred for 1 h then the solvent was removed *in vacuo*. The residue was partitioned between H_2O (20 mL) and Et_2O (3 × 20 mL). The combined Et_2O phases were dried ($MgSO_4$) and evaporated to give recovered diester (375 mg, 38%). The aqueous phase was acidified to pH 6.5 with 2 M HCl, saturated with NaCl and extracted with $CHCl_3$ (20 mL). The aqueous phase was re-adjusted to pH 6.5, saturated with NaCl and extracted with more $CHCl_3$ (20 mL). This procedure was

repeated for a total of six times, then the combined $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated to dryness to afford the monoacid **5.21** as a white amorphous solid (202 mg, 22%). Found: M^+, 246.0890; $C_{14}H_{14}O_4$ requires 246.0892. ^1H NMR δ/ppm 8.16 (1H, d, *J* = 15.6 Hz, H3'), 8.06 (1H, d, *J* = 15.8 Hz, H3"), 7.65-7.58 (2H, m, aryl CH), 7.46-7.42 (2H, m, aryl CH), 6.39 (2H, dd, *J* = 15.8, 8.1 Hz, H2', H2"), 3.85 (3H, s, $-CO_2CH_3$). ^{13}C NMR δ/ppm 171.0 ($-CO_2H$), 166.6, ($-CO_2CH_3$), 143.5, 141.2 (C3', C3"), 134.4, 133.7, 130.4, 130.0, 127.7, 127.7 (coincident peaks), (6 × aryl C), 121.7, 120.6 (C2', C2"), 51.9 ($-CO_2CH_3$). IR (KBr disk) υ_{max} 3064, 2997, 2952, 1732, 1714, 1634, 1483, 1435, 1316, 1196, 978 and 765 cm^{-1}. UV λ_{max} (Et_2O) 288 nm (ε 16 760), 257 (21 899), 208 (9 413), 204 (9 218). *m/z* (EI, 70 eV) 232 (M^+, 4%), 186 (47), 172 (40), 157 (16), 143 (11), 128 (100), 115 (19), 77 (14) and 59 (10).

(2R,3S,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-4,6,8,10-octatetraen-3-yl methyl 1,2-benzenediacrylate 5.18

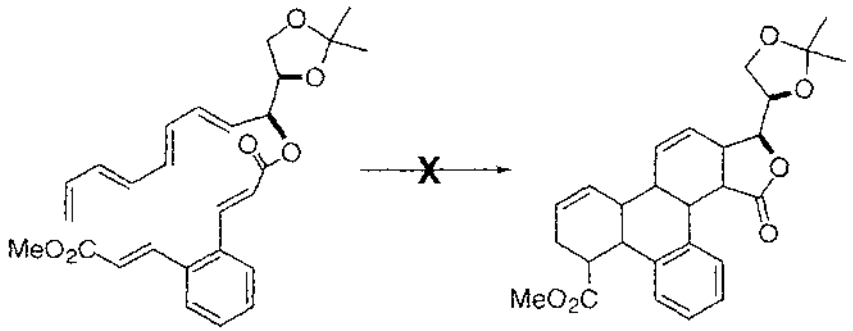


5.18

Tetraene **4.47** (59.8 mg, 0.25 mmol) was dissolved in dry CH_2Cl_2 (5 mL) under an atmosphere of Ar in the presence of BHT (6 mg, 0.03 mmol). Monoacid **5.21** (88 mg, 0.38 mmol), DCC (62.6 mg, 0.30 mmol) and DMAP (6.20 mg, 0.05 mmol) were added and the reaction solution stirred at RT for 2 h. Additional BHT (10 mg, 0.05 mmol) was added and the reaction solution diluted with Et_2O (30 mL). The organic layer was washed with 10% aqueous HCl (5 mL), saturated $NaHCO_3$ (5 mL) and H_2O (5 mL) and the combined aqueous fractions extracted with Et_2O (20 mL). The organic fractions were combined and dried ($MgSO_4/Na_2SO_4$). Removing the solvent *in vacuo* afforded a crude oil which was purified by column chromatography (4:1 Hex/EtOAc) to yield the title compound **5.18** (R_f = 0.22) as a clear, colourless oil (72.8 mg, 0.16 mmol, 65%). Found: M^+, 450.2038; $C_{27}H_{30}O_6$ requires 450.2042. $[\alpha]_D^{20^\circ} = -65^\circ$, (c = 0.95, CH_2Cl_2). ^1H NMR δ/ppm 8.04 (1H, d, *J* = 15.8, H3), 8.09 (1H, d, *J* = 15.8, H3), 7.61-7.55 (2H, m, aryl CH), 7.43-7.39 (2H, m, aryl CH), 6.46-6.25 (8H, m, 2 × H2, H5'-H10'), 5.74 (1H, dd, *J* = 14.9, 7.3 Hz, H4'), 5.53 (1H, dd, *J* = 7.3, 4.8 Hz, H3'), 5.25 (1H,

dd, J = 16.0, 1.8 Hz, H11'$_\alpha$), 5.13 (1H, dd, J = 9.9, 1.8 Hz, H11'$_\beta$), 4.33 (1H, td, J = 6.4, 4.8 Hz, H2'), 4.11 (1H, dd, J = 8.8, 6.9 Hz, H1'$_\alpha$), 3.89 (1H, dd, J = 8.6, 6.2 Hz, H1'$_\beta$), 3.83 (3H, s, -CO_2CH_3), 1.44, 1.39 (6H, 2 × s, -$C(CH_3)_2$). ^{13}C NMR δ/ppm 166.5, 165.2 (-CO_2CH_3, -CO_2R'), 142.0, 141.2 (2 × C3), 136.7, 134.8, 134.4, 134.2, 133.9, 132.7, 131.7, 130.1, 129.9, 128.2, 127.6, 127.5, 126.6 (C4'-C10', 6 × aryl C), 121.6, 121.1 (2 × C2), 117.9 (C11'), 110.0 (-$C(CH_3)_2$), 76.8, 74.2, 65.9 (C1', C2', C3'), 51.8 (-CO_2CH_3), 26.4, 25.3 (-$C(CH_3)_2$). IR (thin film) υ_{max} 3029, 2988, 2950, 1718, 1635, 1478, 1435, 1381, 1371, 1317, 1272, 1215, 1171, 1009, 978 and 759 cm^{-1}. UV λ_{max} (Et_2O) 311 nm (ε 50 718), 297 (62 649), 286 (53 886) and 207 (17 528). *m/z* (EI, 70 eV) 450 (M^+, 2%), 215 (21), 171 (13), 143 (8), 128 (28), 115 (8), 101 (100), 91 (9) and 43 (18).

6.5.2.1 Attempted TIMDA Reaction Of (2R,3S,4E,6E,8E,10E)-1,2-O-Isopropylidene-1,2-dihydroxy-4,6,8,10-octatetraen-3-yl methyl 1,2-benzenediacrylate 5.18

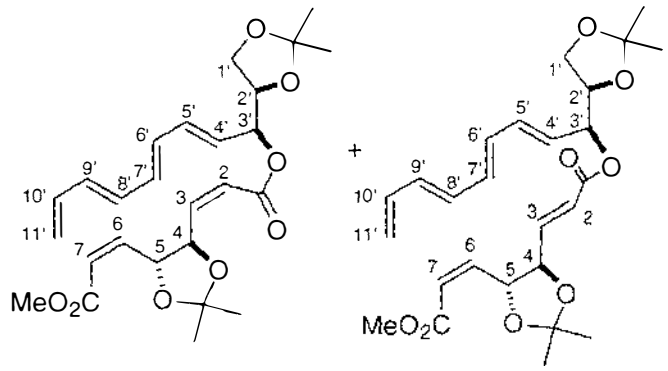


5.18 **5.22**

The benzeneacrylate derived ester **5.18** (8.6 mg, 0.02 mmol) and BHT (0.4 mg, 0.002 mmol) were dissolved in toluene (2 mL). After refluxing for 22 h, the solvent was removed *in vacuo*. Both TLC and ^{1}H NMR analysis indicated the presence of unreacted starting material **5.18** with no trace of the TIMDA adduct **5.22**.

6.5.3 *Bis*-*Z*-Dienophile Precursor, Synthesis And Attempted TIMDA Reactions

(2R,3S,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-4,6,8,10-octatetraen-3-yl methyl (2*Z*,4R,5R,6*Z*)-4,5-*O*-isopropylidene-4,5-dihydroxy-2,6-octadienedioate 5.23 and (2R,3S,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-iso-propylidene-1,2-dihydroxy-4,6,8,10-octatetraen-3-yl methyl (2*E*,4R,5R,6*Z*)-4,5-*O*-isopropylidene-4,5-dihydroxy-2,6-octadienedioate 5.25

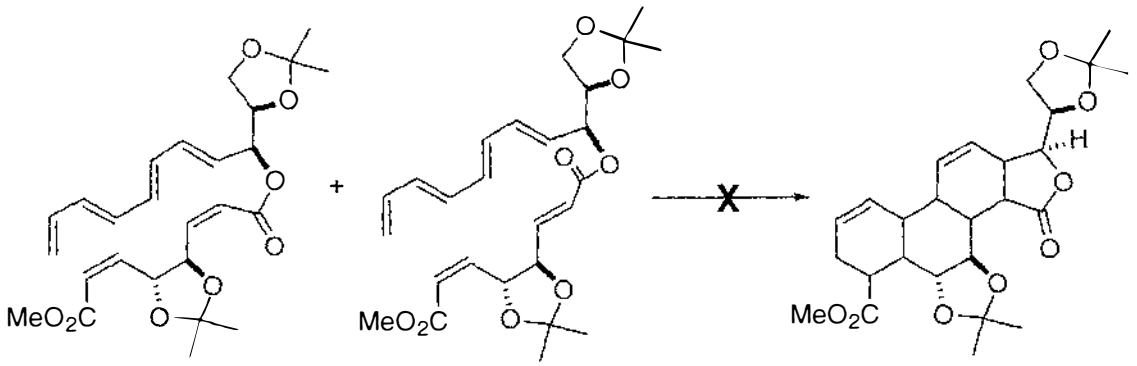


5.23, 5.25

Tetraene **4.47** (49.3 mg, 0.21 mmol) was dissolved in dry CH_2Cl_2 (9 mL) under an atmosphere of Ar with BHT (3.2 mg, 0.02 mmol) present. DCC (64.6 mg, 0.31 mmol), mono acid **5.24** (78.7 mg, 0.31 mmol) and DMAP (5.1 mg, 0.04 mmol) were added and the reaction solution stirred for 1 h. After this time, additional monoacid (31.8 mg, 0.12 mmol) and DMAP (5.1 mg, 0.04 mmol) were added and the reaction stirred for a further 1 h. Then BHT (5 mg, 0.02 mmol) was added and the reaction solution diluted with Et_2O (50 mL). The organic layer was washed with 10% aqueous HCl (2 mL), saturated $NaHCO_3$ (2 mL) and H_2O (2 mL) and the combined aqueous washings back-extracted with Et_2O (20 mL). The combined organic fractions were washed with saturated brine and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a crude oil which was purified by column chromatography (2:1 Hex/Et_2O) to yield an inseparable 3:2 mixture of esters **5.23** and **5.25** (R_f = 0.32) as an oil (71.6 mg, 0.15 mmol, 72%). Found: M-CH_3^+, 459.2392; $C_{25}H_{31}O_8$ requires 459.2383. ^{1}H NMR δ/ppm (*maj* = peaks due to major isomer, *min* = peaks due to minor isomer) 7.00 (dd, *J* = 15.6, 5.1 Hz, H3 (*min*)), 6.41-6.11 (m, H5'-H10', H6 (*maj* and *min*), H3 (*maj*), H2 (*min*)), 6.00-5.90 (m, H7 (*maj* and *min*), H2 (*maj*)), 5.68, (dd, *J* = 15.3, 7.0 Hz, H4' (*maj*)), 5.62 (dd, *J* = 15.8, 7.3 Hz, H4' (*min*)), 5.45-5.32 (m, H5, H3' (*maj* and *min*), H4 (*maj*), 5.23 (d, *J* = 16.3, H11'$_\alpha$ (*maj* and *min*), 5.10 (d, *J* = H11'$_\beta$ (*maj* and *min*)), 4.29-4.18 (m, H2' (*maj* and *min*), H4 (*min*), 4.05 (dd, *J* = 10.3, 6.8 Hz, H1'$_\alpha$ (*maj*), 4.02 (dd, *J* = 10.3, 6.6 Hz,

H1'$_{\alpha}$ (*min*)), 3.82 (dd, *J* = 8.6, 6.4 Hz, H1'$_{\beta}$ (*maj*)), 3.76 (dd, *J* = 8.6, 6.4 Hz, H1'$_{\beta}$ (*min*), 3.67 (s, -CO_2CH_3 (*maj* and *min*)), 1.47, 1.46, 1.46, 1.42, 1.40, 1.37, 1.35, 1.32 (peaks due to the -$C(CH_3)_2$ methyl groups of both major and minor isomers). ^{13}C NMR δ/ppm 165.5, 165.2, 164.5, 163.9 (-CO_2CH_3, -CO_2R - *maj* and *min*), 145.1, 144.3, 144.1, 143.9 (C3, C6 - *maj* and *min*), 136.7. 136.7, 134.6, 134.4, 134.3, 134.3, 134.2, 134.1, 132.6, 132.5, 131.7, 131.5, 126.7, 126.2, (C4'-C10' - *maj* and *min*), 123.0, 122.6, 122.4, 121.6 (C2, C7 - *maj* and *min*), 117.9, 117.8 (C11' - *maj* and *min*), 110.6, 110.3, 109.8, 109.8 (2 × -$C(CH_3)_2$ - *maj* and *min*), 79.8, 76.7, 76.6, 76.2, 75.6, 75.5, 73.9, 73.9 (C4, C5, C2', C3' - *maj* and *min*), 65.9, 65.7 (C1' - *maj* and *min*), 51.6, 51.4 (CO_2CH_3 - *maj* and *min*), 30.3, 27.1, 27.1, 26.9, 26.4, 26.3, 25.3, 25.2 (4 × -$C(CH_3)_2$ - *maj* and *min*). IR (thin film) υ_{max} 2988, 2952, 1726, 1651, 1439, 1410, 1372, 1203, 1180, 1160, 1062, 1010, 880, 854, 824 and 681 cm^{-1}. *m/z* (EI, 70 eV) 459 (M-CH_3^+, 5%), 219 (10), 181(19), 149 (14), 117 (12), 101 (100), 73 (28) and 43 (32).

6.5.3.1 Attempted TIMDA Reactions Of (2R,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6,8,10-octatetraen-3-yl methyl (2Z,4R,5R,6Z)-4,5-O-isopropylidene-4,5-dihydroxy-2,6-octadienedioate 5.23 and (2R,3S,4E,6E,8E,10E)-1,2-O-isopropylidene-1,2-dihydroxy-4,6,8,10-octatetraen-3-yl methyl (2E,4R,5R,6Z)-4,5-O-isopropylidene-4,5-dihydroxy-2,6-octadienedioate 5.25



5.23 + **5.25** → **5.26**

The mixture of tetraene esters **5.22** and **5.25** (19.9 mg, 0.04 mmol) and BHT (1 mg, 0.004 mmol) were dissolved in toluene (4 mL) in a sealed reaction vessel which was lowered into an oil bath at 175°C. After 17 h, the solvent was removed *in vacuo* to give a crude oil. The desired cycloadduct could not be identified by ^{1}H NMR spectroscopy with the crude reaction mixture showing evidence only of polymerisation.

Tetraene esters **5.23** and **5.25** (25.7 mg, 0.05 mmol) were dissolved in toluene (5 mL)

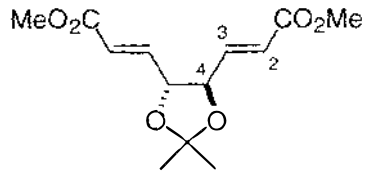
and refluxed in the presence of BHT (1 mg, 0.005 mmol) for 17 h. Analysis by TLC and ^{1}H NMR indicated the presence of starting material and no sign of the cycloadduct.

The esters **5.23** and **5.25** (26.5 mg, 0.06 mmol) were dissolved in acetonitrile (6 mL) in the presence of BHT (1 mg, 0.004 mmol) and refluxed for 36 h. TLC and ^{1}H NMR analysis showed no reaction had occurred. The reaction mixture refluxed for a further 24 h. Destruction of the starting material was observed by ^{1}H NMR spectroscopy.

The mixture of esters **5.23** and **5.25** (10 mg, 0.02 mmol) was dissolved in d_6-DMSO (1 mL) in an NMR tube under Ar. The NMR tube was sealed and heated in an oil bath at 150°C for 14 h. ^{1}H NMR analysis showed destruction of the starting material and no formation of the desired TIMDA adduct. The reaction was repeated, with the same result after only 5.5 h of heating.

6.5.4 Synthesis Of The Diketone

Dimethyl (2*E*,6*E*,4R,5R)-4,5-*O*-isopropylidene-4,5-dihydroxy-2,6-octadiene-1,8-dioate 5.30[10]

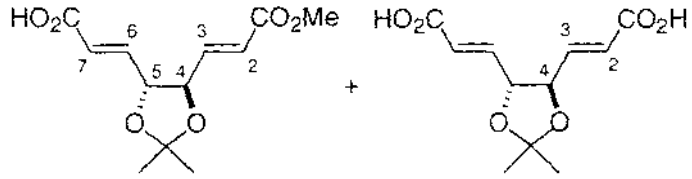


5.30

3,4-*O*-Isopropylidene-D-mannitol **5.29** (5.0 g, 22.5 mmol) was dissolved in 5% aq. $NaHCO_3$ (44 mL). A dispersion of $NaIO_4$ (14.4 g, 67.3 mmol) in H_2O (44 mL) was added slowly over 1 h. The reaction temperature was kept below 8°C with the use of an ice bath. The reaction mixture was then stirred for a further 1 h at RT. The reaction mixture was cooled to 0°C and trimethylphosphonoacetate (15 mL, 92.66 mmol) was added, followed by 5M aq. K_2CO_3 (90 mL). The reaction mixture was allowed to warm to RT and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and the aqueous fraction was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic fractions were washed with saturated brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography, using 3:2 Hex/EtOAc, gave the dimethyl ester **5.30** (R_f = 0.35) as a clear oil (5.06 g, 18.6 mmol, 82%). Found: M-CH_3^+, 255.0876; $C_{12}H_{15}O_6$ requires 255.0869. $[\alpha]_D^{20^\circ}$ = +69.5°, (c = 1.48, CH_2Cl_2). ^{1}H NMR δ/ppm 6.87 (2H, ddd, *J* = 15.6, 3.5, 1.8 Hz, H3), 6.13 (2H, d, *J* = 15.6 Hz, H2),

4.29-4.26 (2H, m, H4), 3.75 (6H, s, $-CO_2CH_3$), 1.45 (6H, s, $-C(CH_3)_2$). ^{13}C NMR δ/ppm 165.8 ($-CO_2CH_3$), 142.0 (C3), 123.1 (C2), 110.8 ($-C(CH_3)_2$), 79.6 (C4), 51.8 ($-CO_2CH_3$), 26.8 ($-C(CH_3)_2$). IR (thin film) υ_{max} 2989, 2953, 2882, 1728, 1666, 1437, 1374, 1306, 1279, 1236, 1195, 1166, 1051, 979 and 722 cm^{-1}. *m/z* (EI, 40 eV) 255 ($M-CH_3^+$, 29%), 181 (19), 156 (22), 98 (100), 83 (25), 73 (17) and 43 (30).

Methyl hydrogen (2*E*,6*E*,4R,5R)-4,5-*O*-isopropylidene-4,5-dihydroxy-2,6-octadiene-1,8-dioate 5.32 and (2*E*,6*E*,4R,5R)-4,5-*O*-isopropylidene-4,5-dihydroxy-2,6-octadiene-1,8-dioic acid 5.31



5.32, 5.31

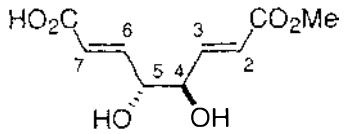
The dimethyl ester **5.30** (1.07 g, 3.96 mmol) was dissolved in a 4:1:1 mixture of THF/H_2O/MeOH (40 mL). $LiOH.H_2O$ (166 mg, 3.96 mmol) was added and the reaction mixture stirred at RT for 5.5 h. The reaction was quenched with H_2O (20 mL) and diluted with Et_2O (60 mL). The organic layer was separated and the solvent removed *in vacuo* to yield recovered starting material (296 mg, 1.10 mmol). The aqueous fraction was acidified with HCl to a pH of 5.54 and then extracted with *sec*-butanol/EtOAc (10% v/v). This was repeated 6 times. The organic fractions were combined and the solvent removed *in vacuo* to give the mono acid **5.32** (487 mg, 1.90 mmol, 48%) as a yellow oil (R_f = 0.48, 100% EtOAc).

The aqueous fraction was then acidified with HCl to a pH of 3.36 and extracted with *sec*-butanol/EtOAc (10% v/v). Removal of the solvent *in vacuo* afforded the diacid **5.31** (baseline spot, 100% EtOAc) as a white powder (230 mg, 0.95 mmol, 24%).

Monoacid 5.32 (R_f = 0.48, 100% EtOAc). Found: M^+, 256.0952; $C_{12}H_{16}O_6$ requires 256.0947. $[\alpha]_D^{20^\circ}$ = +64.0°, (c = 0.95, acetone). ^1H NMR δ/ppm 6.99 (1H, dd, *J* = 15.6, 5.2 Hz, H6), 6.90 (1H, dd, *J* = 15.6, 5.2 Hz, H3), 6.18 (2H, d, *J* = 15.6 Hz, H2, H7), 4.34-4.32 (2H, m, H4, H5), 3.78 (3H, s, $-CO_2CH_3$), 1.49 (6H, s, $-C(CH_3)_2$). ^{13}C NMR δ/ppm 170.3, ($-CO_2H$), 165.9 ($-CO_2CH_3$), 144.3, 142.0 (C3, C6), 123.2, 122.6 (C2, C7), 111.0 ($-C(CH_3)_2$), 79.6, 79.5 (C4, C5), 51.9 ($-CO_2CH_3$), 26.9 ($-C(CH_3)_2$). IR (thin film) υ_{max} 2989, 2953, 2681, 1727, 1663, 1437, 1382, 1307, 1280, 1236, 1167, 1118, 1052, 979, 869, 855 and 682 cm^{-1}. *m/z* (EI, 40 eV) 256 (M^+, 16%), 241 ($M-CH_3^+$, 54), 181, (22), 167 (24), 142 (16), 98 (60), 84 (67), 59 (56) and 43 (100).

Diacid 5.31. Found: M^+, 242.0786; $C_{11}H_{14}O_6$ requires 242.0790. $[\alpha]_D^{21^\circ}$ = +78.1° (c = 0.65, CH_2Cl_2). ^1H NMR δ/ppm 11.44 (2H, broad s, $-CO_2H$), 7.00 (2H, ddd, *J* = 15.6, 3.3, 1.8 Hz, H3), 6.18 (2H, d, *J* = 15.6 Hz, H2), 4.35-4.31 (2H, m, H4), 1.48 (3H, s, $-C(CH_3)_2$), 1.47 (3H, s, $-C(CH_3)_2$). ^{13}C NMR d/ppm 170.8 ($-CO_2H$), 144.3 (C3), 122.7 (C2), 111.1 ($-C(CH_3)_2$), 79.4, 26.8 ($-C(CH_3)_2$). IR (KBr disc) υ_{max} 3084, 2690, 2588, 1744, 1661, 1420, 1377, 1263, 1234, 1169, 1134, 979 and 944 cm^{-1}. *m/z* (EI, 40 eV) 241 ($M-H^+$, 24%), 227 (16), 167 (16), 142 (16), 98 (39), 84 (96), 73 (23), 59 (68) and 43 (100).

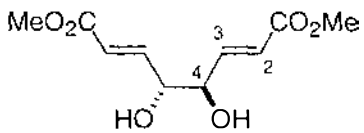
Methyl hydrogen (2*E*,6*E*,4R,5R)-4,5-dihydroxy-2,6-octadiene-1,8-dioate 5.33



5.33

The monoacid **5.32** (405 mg, 1.58 mmol) was dissolved in a 95:5 mixture of CH_3CN/H_2O (15 mL). Amberlite-118 resin (400 mg) was added and the reaction mixture heated at reflux for 1 h. The Amberlite resin was removed by filtration and the solvent removed *in vacuo*. Azeotroping with benzene removed any residual H_2O. Purification by column chromatography, using 100% EtOAc, yielded the title compound **5.33** (R_f = 0.23) as a white powder (57.2 mg, 0.26 mmol, 53%). Found: $M-OH^+$, 199.0604; $C_9H_{11}O_5$ requires 199.0606. $[\alpha]_D^{19^\circ}$ = +56.4°, (c = 0.92, acetone). ^1H NMR δ/ppm 6.93 (1H, dd, *J* = 15.6, 2.8 Hz, H6), 6.91 (1H, dd, *J* = 15.6, 2.8 Hz, H3), 6.13 (1H, dd, *J* = 15.6, 1.3 Hz, H7), 6.09 (1H, dd, *J* = 15.6, 1.3 Hz, H2), 4.25-4.19 (2H, m, H4, H5), 3.72 (3H, s, $-CO_2CH_3$), 3.16 (3H, broad s, -OH, $-CO_2H$). ^{13}C NMR δ/ppm 168.4 ($-CO_2H$), 166.9 ($-CO_2CH_3$), 146.4, 146.3 (C3, C6), 122.6, 121.9 (C2, C7), 73.3, 73.3 (C4, C5), 51.7 ($-CO_2CH_3$). IR (KBr disc) υ_{max} 3408, 2957, 1705, 1662, 1439, 1284, 1180, 1102 and 982 cm^{-1}. *m/z* (EI, 70 eV) 116 (35%), 102 (69), 84 (75), 73 (38), 55 (74) and 44 (100).

Dimethyl (2*E*,6*E*,4R,5R)-4,5-dihydroxy-2,6-octadiene-1,8-dioate 5.34

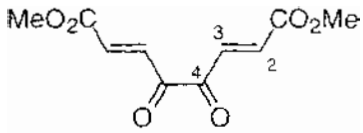


5.34

Dimethyl ester **5.30** (505 mg, 1.87 mmol) was dissolved in a 5:1 mixture of $MeOH/H_2O$

(20 mL). Amberlite-118 resin (500 mg) was added and the reaction mixture heated at reflux for 4.5 h. The Amberlite resin was removed by filtration and the solvent removed *in vacuo.* Purification by column chromatography, using a gradient elution of 1:1 Hex/EtOAc followed by 100% EtOAc, yielded the title compound **5.34** (R_f = 0.30, 100% EtOAc) as a white powder (344 mg, 1.49 mmol, 80%). Found: M-OCH_3^+, 199.0598; $C_8H_{11}O_5$ requires 199.0606. $[\alpha]_D^{20^\circ}$ = +63.3°, (c = 0.98, CH_2Cl_2). ^{1}H NMR δ/ppm 6.95 (2H, dd, *J* = 15.7, 4.5 Hz, H3), 6.20 (2H, d, *J* = 15.7 Hz, H2), 4.33-4.26 (2H, m, H4), 3.77 (6H, s, -CO_2CH_3), 2.76 (2H, d, *J* = 4.5 Hz, -OH). ^{13}C NMR δ/ppm 166.5 (-*C*O_2CH_3), 145.3 (C3), 122.6 (C2), 73.4 (C4), 51.9 (-CO_2*C*H_3). IR (KBr disc) υ_{max} 3396, 3288, 2999, 2956, 1716, 1667, 1446, 1319, 1279, 1202, 1178, 1020, 982, 931 and 782 cm^{-1}. *m/z* (EI, 40 eV) 199 (M-OCH_3^+, 1%), 167 (4), 116 (100), 101 (7), 84 (66) and 55 (40).

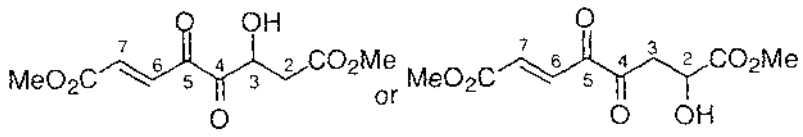
Dimethyl (2*E*,6*E*)-4,5-dioxo-octadiene-1,8-dioate 5.35



5.35

Diol **5.34** (316 mg, 1.37 mmol) was dissolved in CH_2Cl_2 (25 mL). Dess-Martin periodinane (1.40 g, 3.29 mmol) was added and the reaction mixture was stirred at RT for 2 h. The reaction was quenched with a solution of $Na_2S_2O_3$ (1g) in saturated aqueous $NaHCO_3$ (5 mL) and stirred for 5 min. The aqueous phase was extracted with Et_2O (50 mL) and the combined organic fractions combined and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a crude oil which was purified by column chromatography, using 1:8 Hex/CH_2Cl_2, to yield diketone **5.35** (R_f = 0.30, 3:1 Hex/EtOAc) as a yellow powder (187 mg, 0.83 mmol, 60%). Found: M^+, 226.0464; $C_{10}H_{10}O_6$ requires 226.0477. ^{1}H NMR δ/ppm 7.74 (2H, d, *J* = 16.0 Hz, H3), 7.00 (2H, d, *J* = 16.0 Hz, H2), 3.86 (6H, s, -CO_2*C*H_3). ^{13}C NMR δ/ppm 186.0 (C4), 164.9 (-*C*O_2CH_3), 135.4, 132.2 (C2 ,C3), 52.6 (-CO_2*C*H_3). IR (KBr disc) υ_{max} 3081, 3065, 2958, 1719, 1687, 1442, 1309, 1274, 1204, 1179, 1005, 970, 932, 780, 710 and 646 cm^{-1}. UV λ_{max} (Et_2O) 242.5 nm (ε 13 877) and 212.5 (16 737). *m/z* (EI, 40 eV) 226 (M^+, 0.5%), 195 (3), 167 (5), 113 (100), 85 (11), 59 (16) and 54 (8).

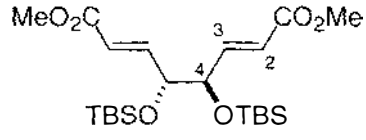
Dimethyl (6*E*)-2-hydroxy-4,5-dioxo-6-octaene-1,8-dioate or dimethyl (6*E*)-3-hydroxy-4,5-dioxo-6-octaene-1,8-dioate 5.36



5.36

Diketone **5.35** (79.9 mg, 0.35 mmol) was dissolved in a 4:1:1 mixture of THF/MeOH/H_2O (4 mL). LiOH.H_2O (14.8 mg, 0.35 mmol) was added and the reaction mixture stirred at RT for 6.5 h. The reaction was quenched with 10% aqueous HCl (10 mL) and diluted with EtOAc (20 mL). The organic fraction was removed and concentrated *in vacuo*. Any residual H_2O was removed by azeotroping with benzene (2 × 5 mL). The remaining yellow oil was purified by column chromatography, using 10% AcOH in EtOAc, to give the title compound **5.36** (R_f = 0.28) (29.5 mg, 0.12 mmol, 53% based on recovered SM). Found: M^+, 244.0584; $C_{10}H_{12}O_7$ requires 244.0583. ^{1}H NMR δ/ppm 8.16 (1H, broad s, -OH), 6.89 (2H, AB quartet, J = 25.0, 15.8 Hz, H6, H7), 3.83 (3H, s, $-CO_2CH_3$), 3.79-3.75 (1H, m, H2 or H3), 3.71 (3H, s, $-CO_2CH_3$), 2.74-2.61 (2H, m, 2 × H3 or 2 × H2). ^{13}C NMR δ/ppm 175.2, 169.8 (C4, C5), 166.7, 162.3 (2 × $-CO_2CH_3$), 132.2, 130.2 (C6, C7), 74.5 (C2), 49.8, 49.3 (2 × $-CO_2CH_3$), 26.2 (C3). IR (thin film) υ_{max} 3024, 2955, 1731, 1439, 1369, 1216, 1172, 997, 755 and 668 cm^{-1}. *m/z* (EI, 40 eV) 245 (MH^+, 26%), 244 (M^+, 23), 213 (86), 198 (68), 184 (47), 139 (46), 113 (100), 99 (77), 85 (50) and 59 (72).

Dimethyl (2*E*,6*E*,4R,5R)-4,5-di-(*tert*-butyldimethylsilyloxy-2,6-octadiene-1,8-dioate 5.37

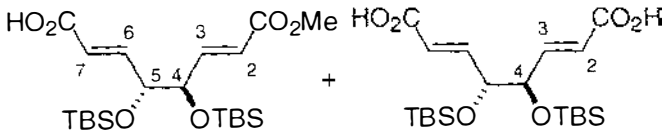


5.37

Imidazole (672 mg, 9.88 mmol), followed by *tert*-butyldimethylsilyl chloride (714 mg, 4.74 mmol) was added to a solution of diol **5.34** (455 mg, 1.98 mmol) in dry DMF (1 mL). After stirring at RT for 27 h, more imidazole (108 mg, 1.58 mmol) and *tert*-butyldimethylsilyl chloride (120 mg, 0.79 mmol) were added and the reaction stirred for a further 1 h. The reaction solution was diluted with H_2O (25 mL) and Et_2O (15 mL) and the aqueous fraction extracted with Et_2O (4 × 30 mL). The combined organic fractions were washed with saturated brine (5 mL) and dried (Na_2SO_4) and the solvent removed *in*

vacuo. The crude oil was purified by column chromatography (5:1 Hex/EtOAc) to give the disilylated compound **5.37** (R_f = 0.31) (800 mg, 1.74 mmol, 88%). Found: M^+, 458.2531; $C_{22}H_{42}O_6Si_2$ requires 458.2520. $[\alpha]_D^{20^\circ}$ = +78.9°, (c = 1.78, CH_2Cl_2). ^1H NMR δ/ppm 6.95 (2H, dd, *J* = 15.6, 3.3 Hz, H3), 5.98 (2H, dd, *J* = 15.6, 1.4 Hz, H2), 4.37 (2H, t, *J* = 1.4 Hz, H4), 3.73 (6H, s, $-CO_2CH_3$), 0.94 (18H, s, $-SiC(CH_3)_3$), 0.10 (3H, s, $-Si(CH_3)_2-$), 0.08 (3H, s, $-Si(CH_3)_2-$). ^{13}C NMR δ/ppm 166.4 ($-CO_2CH_3$), 146.3 (C3), 121.5 (C2), 74.3 (C4), 51.5 ($-CO_2CH_3$), 25.8 ($-SiC(CH_3)_3$), 18.2 ($-SiC(CH_3)_3$), -4.7, -4.8 ($-Si(CH_3)_2-$). IR (thin film) υ_{max} 2953, 2886, 2857, 1728, 1661, 1472, 1463, 1435, 1362, 1301, 1262, 1192, 1167, 1127, 836 and 778 cm^{-1}. *m/z* (EI, 40 eV) 401 ($M-{}^tBu^+$, 32%), 344 (9), 229 (100), 147 (24), 115 (14), 89 (16), 73 (87) and 57 (11).

Methyl hydrogen (2*E*,6*E*,4R,5R)-4,5-di-(*tert*-butyldimethylsilyloxy-2,6-octadiene-1,8-dioate 5.39 and (2E,6E,4R,5R)-4,5-di-(*tert*-butyldimethylsilyloxy-2,6-octadiene-1,8-dioic acid 5.38



5.39, 5.38

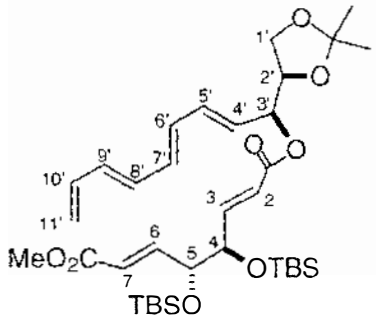
Dimethyl ester **5.37** (646 mg, 1.41 mmol) was dissolved in a 4:1:1 mixture of THF/MeOH/H_2O (20 mL). $LiOH.H_2O$ (59.1 mg, 1.41 mmol) was added and the reaction solution stirred at RT for 16 h. The reaction was quenched with H_2O (30 mL) and diluted with Et_2O (60 mL). The Et_2O fraction was removed and concentrated *in vacuo* to afford a crude mixture of the starting material **5.37** and monoacid **5.39**. The aqueous fraction was acidified to pH 6.60 and extracted with Et_2O (50 mL). Removal of the solvent *in vacuo* gave a crude mixture of the monoacid **5.39** and diacid **5.38** compounds. The crude mixtures were combined and purified by column chromatography using a gradient elution (4:1 Hex/EtOAc, 2:1 Hex/EtOAc, 100% EtOAc). (Recovered SM **5.37**, R_f = 0.53 (4:1 Hex/EtOAc), 154 mg, 24%).

Monoacid 5.39 (R_f = 0.35, 2:1 Hex/EtOAc) (199 mg, 0.45 mmol, 32%). Found: $M-CH_3^+$, 429.2156; $C_{20}H_{37}O_6Si_2$ requires 429.2129. $[\alpha]_D^{20^\circ}$ = +82.5°, (c = 0.79, CH_2Cl_2). ^1H NMR δ/ppm 7.06 (1H, dd, *J* = 15.6, 3.3 Hz, H6), 6.95 (1H, dd, *J* = 15.6, 3.3 Hz, H3), 5.99 (2H, d, *J* = 15.6, Hz, H2, H7), 4.38-4.39 (2H, m, H4, H5), 3.74 (3H, s $-CO_2CH_3$), 0.94 (18H, $-C(CH_3)_3$), 0.09 (6H, s, $-Si(CH_3)_2-$), 0.08 (6H, s, $-Si(CH_3)_2-$). ^{13}C NMR δ/ppm 170.9 ($-CO_2H$), 166.5 ($-CO_2CH_3$), 148.8, 146.2 (C3, C6), 121.6, 121.2 (C2, C7), 74.4, 74.3 (C4, C5), 51.6 ($-CO_2CH_3$), 25.9 ($-C(CH_3)_3$), 18.2 ($-C(CH_3)_3$), -4.7, -4.8 ($-Si(CH_3)_2-$). IR (thin film) υ_{max} 2957, 2987, 1738, 1732,

1714, 1694, 1682, 1651, 1644, 1634, 1470, 1434, 1258, 1122 and 836 cm^{-1}. *m/z* (EI, 40 eV) 387 (M-^{t}Bu$^+$, 20%), 30 (7), 255 (6), 229 (67), 215 (10), 147 (22), 115 (14) and 73 (100).

Diacid 5.38 (R_f = 0.22, 1:2 Hex/EtOAc) (278 mg, 0.65 mmol, 44%). Found: M^+, 430.2238; $C_{20}H_{38}O_6Si_2$ requires 430.2207. $[\alpha]_D^{19°}$ = +51.1°, (c = 1.55, acetone). ^{1}H NMR δ/ppm 7.07 (2H, d, *J* = 15.6 Hz, H3), 6.00 (2H, d, *J* = 15.6 Hz, H2), 4.14 (2H, broad s, H4), 0.95 (18H, -C(CH_3)$_3$), 0.12 (6H, s, -Si(CH_3)$_2$-), 0.11 (6H, s, -Si(CH_3)$_2$-). ^{13}C NMR δ/ppm 171.4 (-CO_2H), 148.7 (C3), 121.0 (C2), 74.2 (C4), 25.9 (-C(*C*H_3)$_3$), 18.2 (-*C*(CH_3)$_3$), -4.7, -4.8 (-Si(CH_3)$_2$-). IR (KBr disc) υ_{max} 2958, 2932, 2860, 2685, 1699, 1655, 1640, 1472, 1419, 1364, 1291, 1262, 1135, 1094, 835 and 780 cm^{-1}. *m/z* (EI, 40 eV) 373 (M-^{t}Bu$^+$, 7%), 330 (9), 241 (7), 215 (46), 147 (25), 115 (14), 73 (100) and 57 (12).

(2R,3S,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-4,6,8,10-octatetraen-3-yl methyl (2*E*,6*E*,4R,5R)-4,5-di-(*tert*-butyldimethylsilyloxy-2,6-octadiene-1,8-dioate 5.40

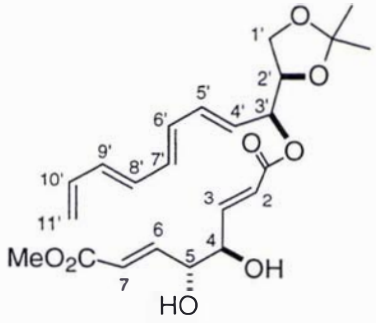


5.40

Tetraene **4.47** (53.6 mg, 0.23 mmol) was dissolved in dry CH_2Cl_2 (6 mL) under an atmosphere of Ar, in the presence of BHT (5.0 mg, 0.02 mmol). DCC (70.2 mg, 0.34 mmol), monoacid **5.39** (152.5 mg, 0.34 mmol) and DMAP (5.5 mg, 0.05 mmol) were added and the reaction solution stirred at RT. After 4 h, further mono acid **5.39** (20.4, 0.05 mmol) was added and the reaction solution stirred for a further 30 min. Additional BHT (5 mg, 0.02 mmol) was added and the reaction solution diluted with Et_2O (50 mL). The solution was washed with 10% aqueous HCl (2 mL), saturated $NaHCO_3$ (2 mL) and H_2O (2 mL) and the combined aqueous washings back-extracted with Et_2O (20 mL). The combined organic fractions were washed with saturated brine (5 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude oil was purified by column chromatography (3:1 Hex/Et_2O) to yield the title compound **5.40** (R_f = 0.23) as a clear colourless oil (68.8 mg, 0.10 mmol, 46%). Found: M+, 662.3677; $C_{35}H_{58}O_8Si_2$ requires 662.3639. $[\alpha]_D^{20°}$ = +21.5°, (c = 2.73, CH_2Cl_2). ^{1}H NMR δ/ppm 7.05-6.92 (2H, m, H3, H6), 6.40-6.21

(6H, m, H5'-H10'), 6.00 (2H, ddd, J = 15.8, 9.7, 1.3 Hz, H2, H7), 5.65 (1H, dd, J = 14.8, 6.7 Hz, H4'), 5.45 (1H, dd, J = 6.6, 5.3 Hz, H3'), 5.24 (1H, dd, J= 15.8, 1.3 Hz, H11'$_\alpha$), 5.12 (1H, dd, J = 9.8, 1.8 Hz, H11'$_\beta$), 4.42-4.35 (2H, m, H4, H5), 4.23 (1H, dd, J = 11.6, 6.2 Hz, H2'), 4.04 (1H, dd, J = 8.1, 6.6 Hz, H1'$_\alpha$), 3.84 (1H, dd, J = 8.2, 6.7 Hz, H1'$_\beta$), 3.72 (3H, s, -CO_2CH_3), 1.44, 1.39 (6H, 2 × s, -$C(CH_3)_2$), 0.94 (18H, s, 2 × -$SiC(CH_3)_3$), 0.11, 0.08 (12H, 2 × s, 2 × -$Si(CH_3)_2$-). ^{13}C NMR δ/ppm 166.3, 164.8 (C1, C8), 147.1, 146.2 (C3, C6), 136.7, 134.2, 134.1, 132.7, 131.8, 128.2, 126.9 (C4'-C10'), 121.5, 121.4 (C2, C7), 117.7 (C11'), 109.8 (-$C(CH_3)_2$), 76.9, 74.3, 74.3, 73.5, 65.7 (C4, C5, C1', C2', C3'), 51.5 (-CO_2CH_3), 26.5 (-$C(CH_3)_2$), 25.8 (2 × -$SiC(CH_3)_3$), 25.5 (-$C(CH_3)_2$), 18.2 (2 × -$SiC(CH_3)_3$), -4.7, -4.8 (2 × -$Si(CH_3)_2$-). IR (thin film) υ_{max} 2955, 2887, 2858, 1732, 1715, 1660, 1471, 1260, 1164, 1127 and 836 cm^{-1}. *m/z* (EI, 40 eV) 329 (12 %), 229 (81), 219 (13), 147 (14), 115 (14), 101 (90), 91 (15) and 73 (100).

(2R,3S,4*E*,6*E*,8*E*,10*E*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-4,6,8,10-octatetraen-3-yl methyl (2*E*,6*E*,4R,5R)-4,5-dihydroxoxy-2,6-octadiene-1,8-dioate 5.41



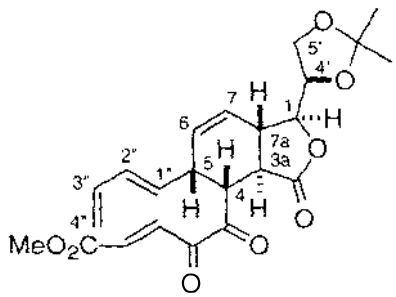
5.41

Disilylated ester **5.40** (52.4 mg, 0.08 mmol) and BHT (0.7 mg, 0.004 mmol) were dissolved in dry THF (7 mL) under Ar at 0°C (ice/salt bath). A solution of TBAF in THF (174 mL, 1.0 M, 0.17 mmol) was added and the reaction mixture stirred for 15 min. The reaction was quenched with saturated aqueous ammonium chloride (1 mL) and H_2O (1 mL) and diluted with Et_2O (50 mL). The aqueous fraction was removed and back-extracted with Et_2O (2 × 10 mL). The combined organic fractions were washed with saturated brine (5 mL) and dried ($MgSO_4$). Removing the solvent *in vacuo* gave the crude product which was then purified by column chromatography (1:1 Hex/EtOAc) to give the title compound **5.41** as an oil (R_f = 0.26, 18.4 mg, 53%). Found: M^+, 434.1948; $C_{23}H_{31}O_8$ requires 434.1941. $[\alpha]_D^{19°}$ = -12.1°, (c = 0.89, CH_2Cl_2). ^{1}H NMR δ/ppm 7.03-6.91 (2H, m, H3, H6), 6.42-6.16 (8H, m, H2, H7, H5'-H10'), 5.67 (1H, dd, J = 14.9, 7.3 Hz, H4'), 5.44 (1H, dd, J = 7.3, 4.8 Hz, H3'), 5.25 (1H, dd, J = 16.2, 1.5 Hz, H11'$_\alpha$), 5.13 (1H, dd, J = 9.8, 1.5 Hz, H11'$_\beta$), 4.30-4.23 (3H, m, H4,

H5, H2'), 4.06 (1H, dd, J = 8.6, 6.8 Hz, H1'$_\alpha$), 3.83 (1H, dd, J = 8.6, 6.2 Hz, H1'$_\beta$), 3.75 (3H, s, -CO_2CH_3), 3.02 (2H, br s, 2 × -OH), 1.41, 1.36 (6H, 2 × s, -$C(CH_3)_2$). ^{13}C NMR δ/ppm 166.3, 164.8 (C1, C8), 146.0, 145.2 (C3, C6), 136.7, 134.8, 134.5, 134.5, 132.6, 131.6, 126.4 (C4'-C10'), 122.7, 122.7 (C2, C7), 118.0 (C11'), 110.0 (-$C(CH_3)_2$), 76.7, 74.2, 73.4, 73.3, 65.8 (C4, C5, C1', C2', C3'), 51.8 (-CO_2CH_3), 26.4, 25.3 (2 × -$C(CH_3)_2$). IR (thin film) υ_{max} 3443, 2989, 2953, 1731, 1714, 1372, 1270, 1010 and 851 cm^{-1}. *m/z* (EI, 40 eV) 434 (M^+, 8%), 218 (23), 143 (16), 117 (17), 101 (100), 91 (19), 83 (24), 55 (21) and 34 (43).

6.5.4.1 Attempted TIMDA Reaction Of Bis-Ketone 5.27

(1S)-5-((1*E*,3*E*)-1,3-Butadien-1-yl)-1-((4R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(methyl, 1,2-dioxo-3-pentaenecarboxylate)-1,3,3a,4,5,7a-hexahydro-isobenzofuran-3-one 5.42



5.42

Diol **5.41** (4.7 mg, 0.02 mmol) and BHT (0.5 mg, 0.002 mmol) were dissolved in dry CH_2Cl_2 (1 mL) under Ar. Dess-Martin periodinane (11 mg, 0.03 mmol) was added and the reaction mixture was stirred at RT for 1 h. The reaction was quenched with a solution of $Na_2S_2O_3$ in saturated aqueous Na_2HCO_3 (0.5 mL) and diluted with Et_2O (5 mL). After stirring for 5 min, the aqueous phase was removed and back-extracted with Et_2O (10 mL). The combined organic fractions were washed with saturated brine (2 mL) and dried (Na_2SO_4). Removing the solvent *in vacuo* gave a crude oil which was purified by passing through a mini-column of silica to remove baseline impurities. The ^{1}H NMR spectrum of the purified product **5.42** was consistent with the structure given, that resulting from a single IMDA reaction. ^{1}H NMR δ/ppm 7.63 (1H, d, J = 16.0 Hz, H3" or H4"), 6.94 (1H, d, J = 16.2 Hz, H3" or H4"), 6.21-6.11 (2H, m, H7, H3'''), 5.90 (1H, dd, J = 15.1, 10.3 Hz, H2'''), 5.58 (1H, dt, J = 9.5, 3.1 Hz, H6), 5.32 (1H, dd, J = 14.9, 9.5 Hz, H1'''), 5.17-5.06 (2H, m, 2 × H4'''), 4.22-4.12 (2H, m, H4', H5'$_\alpha$), 4.07- 4.03 (2H, m, H1, H5'$_\beta$), 3.90 (1H, dd, J = 11.6, 7.5 Hz, H4), 3.84 (3H, s, CO_2CH_3), 3.79-3.77 (1H, m, H5), 2.95 (1H, dd, J = 13.8, 11.6 Hz, H3a), 2.79-2.63

(1H, m, H7a), 1.49, 1.39 (6H, 2 × s,-C(CH_3)$_2$).

6.6 References

(1) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1988.

(2) Roth, W.; Pigman, W. *Methods in Carbohydrate Chemistry* **1963**, *2*, 405.

(3) Lichtenhaler, F. W. *Modern Synthetic Methods* **1992**, 273-376.

(4) Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H NMR FT NMR Spectra*; 1 ed.; Aldrich Chemical Co. Ltd.: Wisconsin, 1993; Vol. 1.

(5) Perlin, A. S.; Gonzales, F.; Lesage, S. *Carbohydrate Research* **1975**, *42*, 267-274.

(6) Becher, J. *Org. Synth.* **1980**, *59*, 79-84.

(7) Becher, J. *Acta Chem. Scand.* **1972**, *26*, 3627-3635.

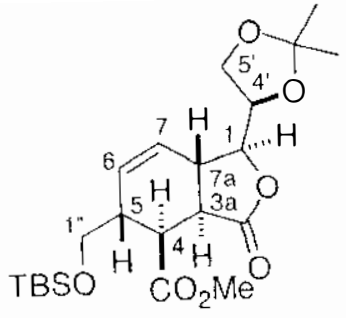
(8) Becher, J.; Nielsen, H. C.; Jacobsen, J. P.; Simonsen, O.; Clausen, H. *J. Org. Chem.* **1988**, *53*, 1862-1871.

(9) Näf, F.; Decorzant, R.; Thommen, W.; Willhalm, B.; Ohloff, G. *Helv. Chim. Acta* **1975**, *58*, 1016-1037.

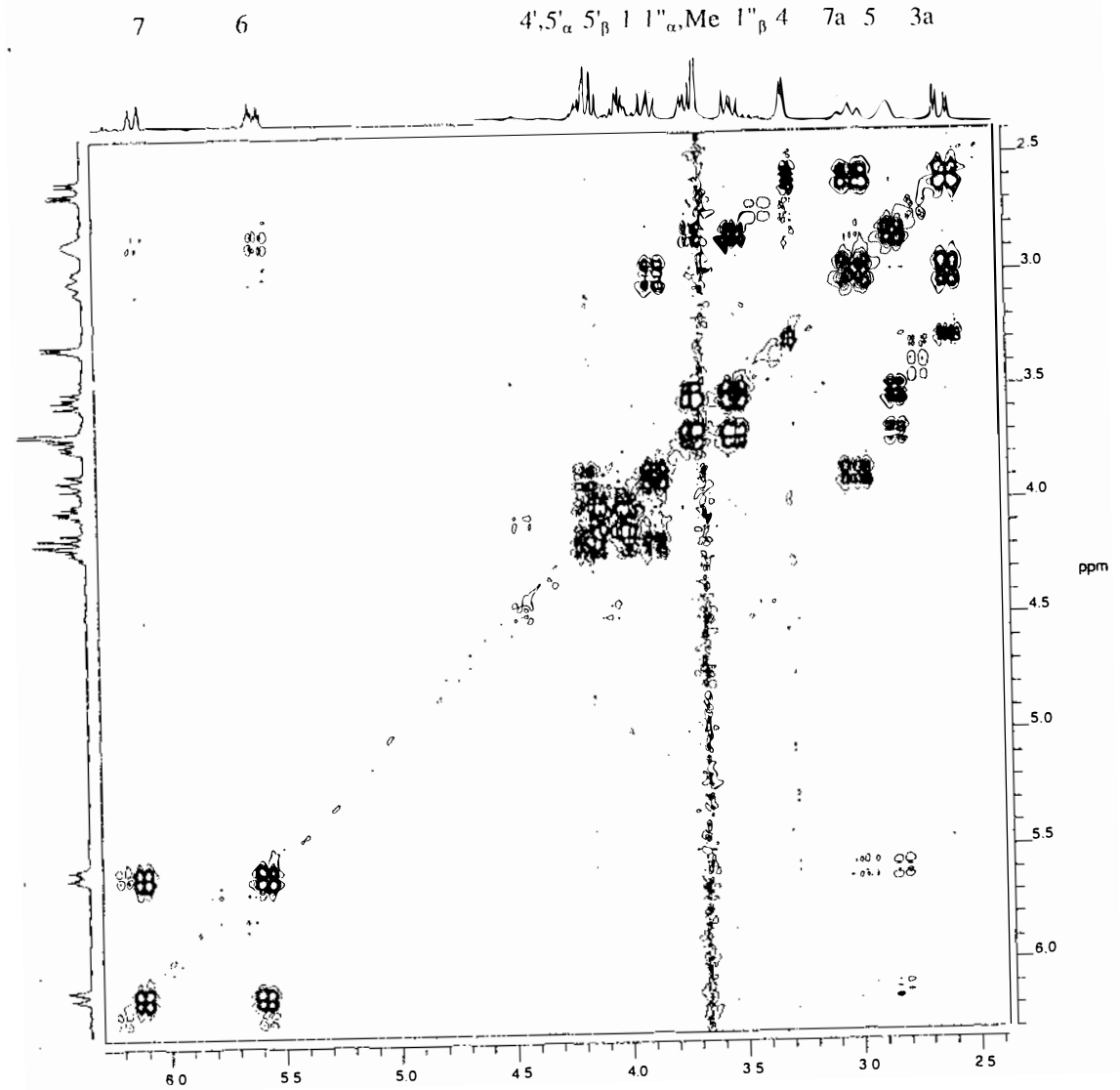
(10) Krief, A.; Dumont, W.; Pasau, P.; Lecomte, P. *Tetrahedron* **1989**, *45*, 3039-3052.

APPENDIX

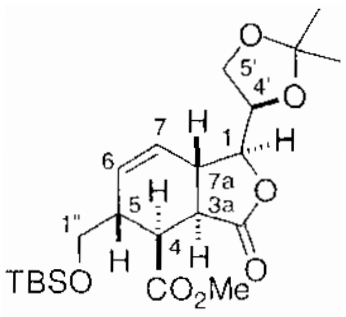
COSY Spectrum Of 2.73



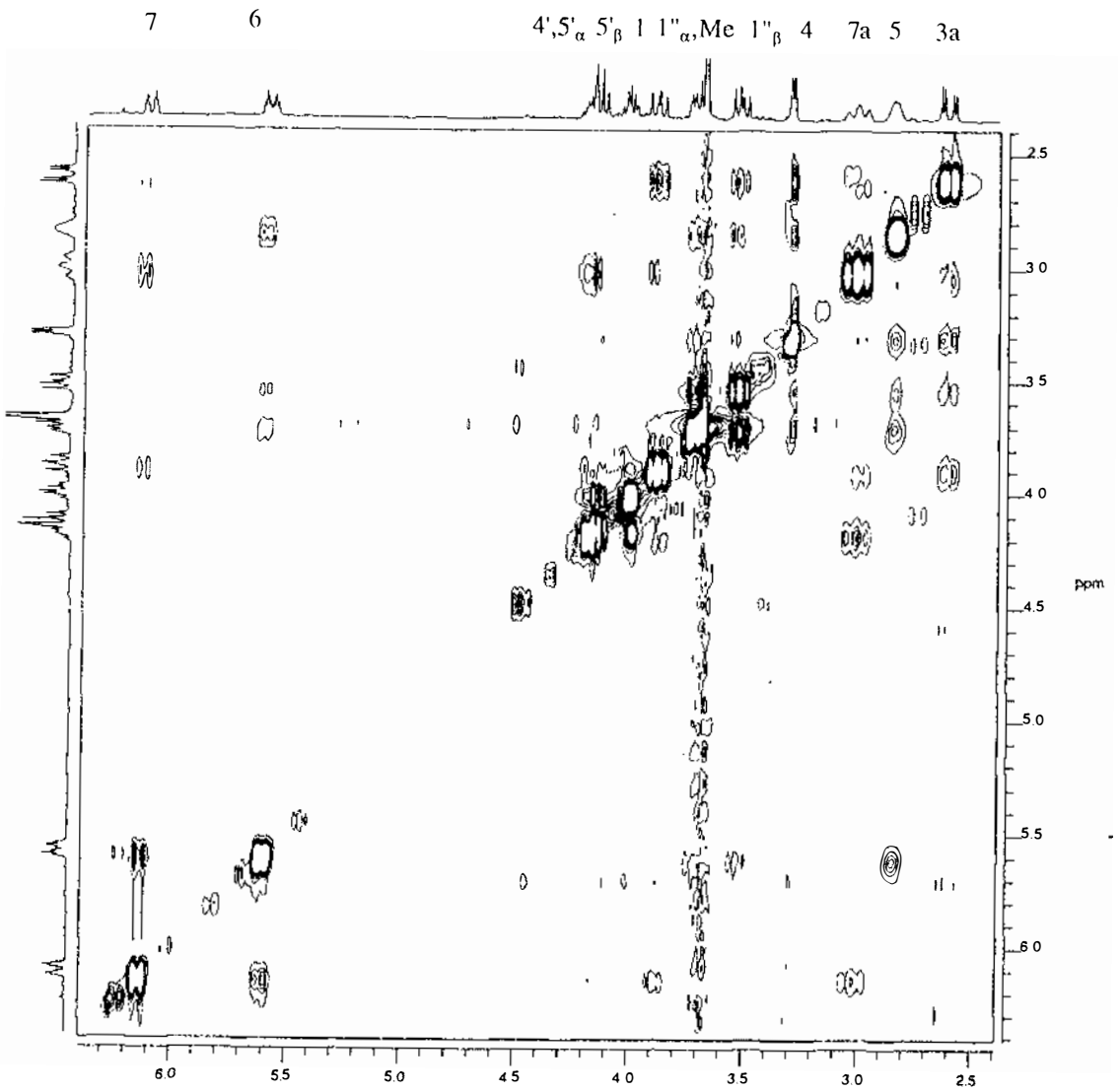
2.73



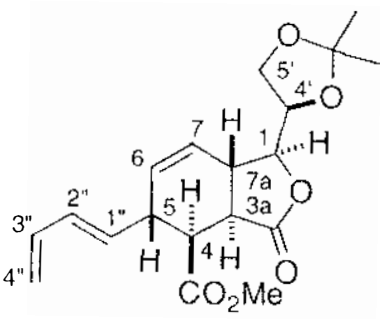
NOESY Spectrum Of 2.73



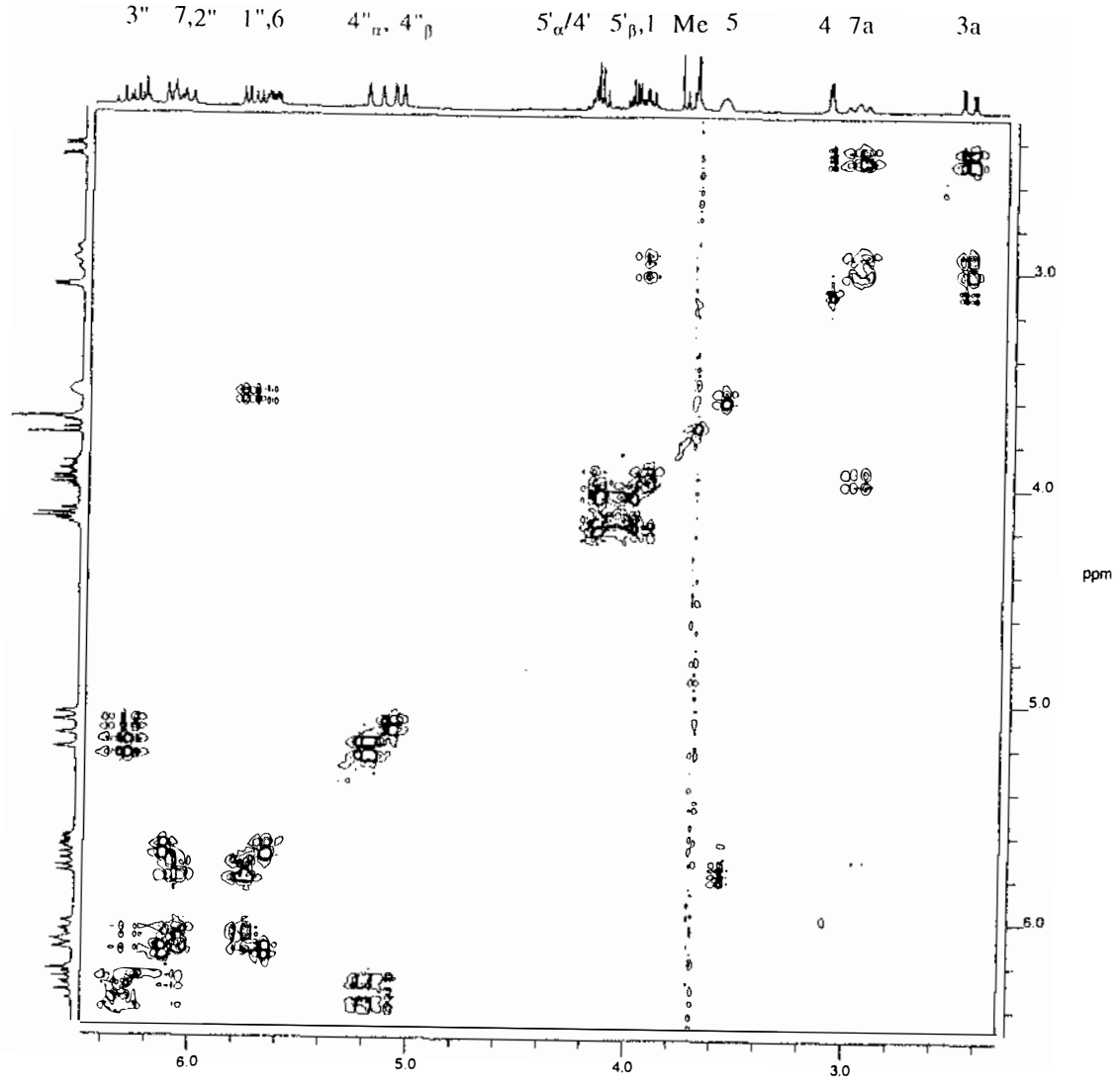
2.73



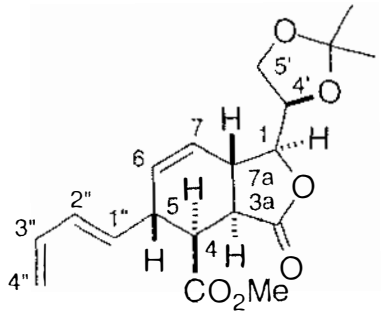
COSY Spectrum Of 4.56



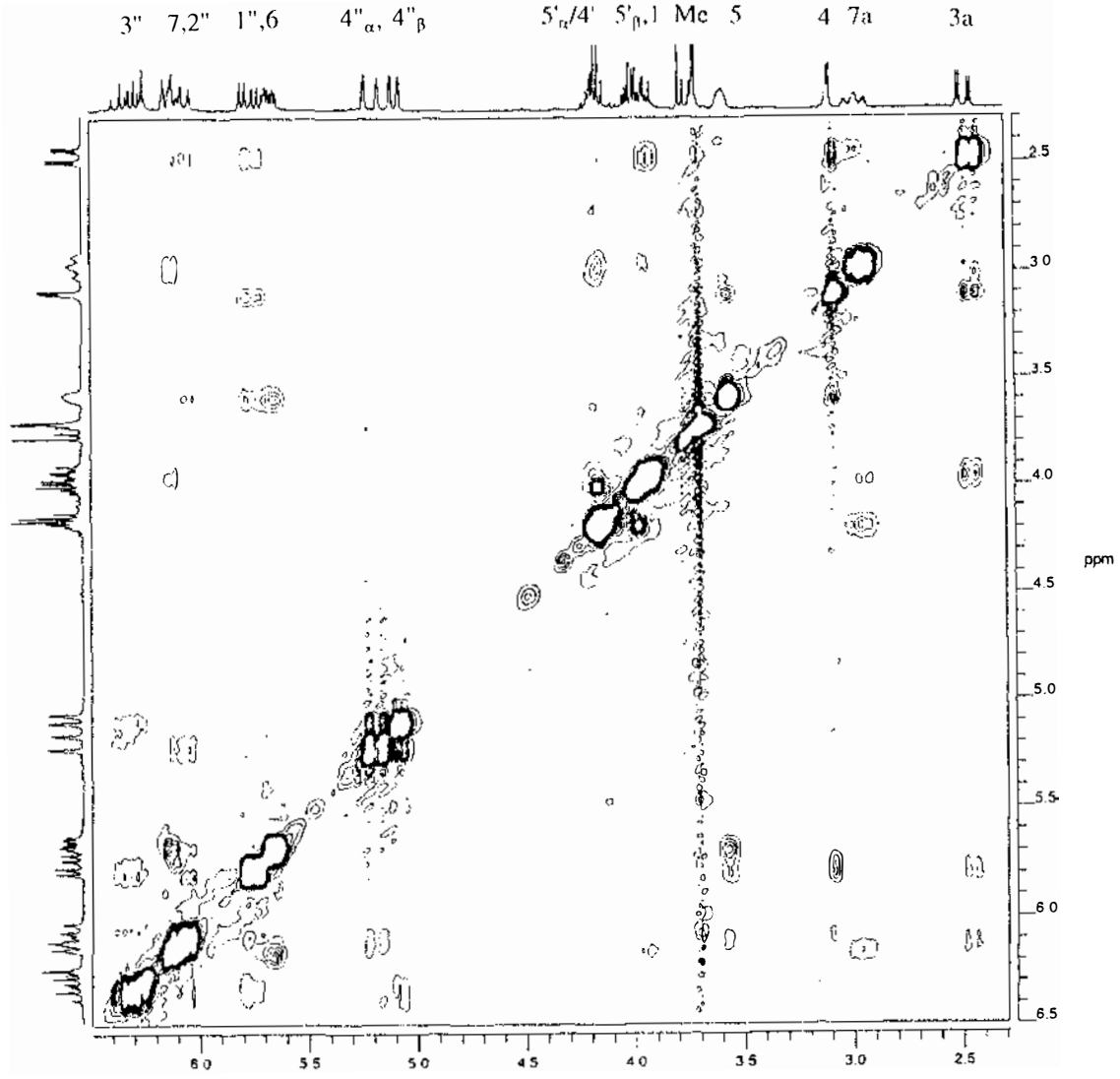
4.56



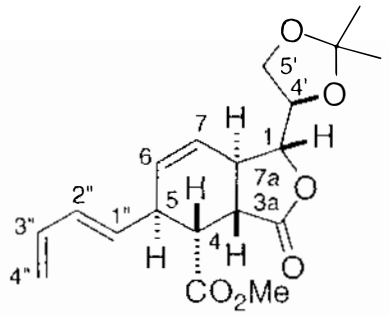
NOESY Spectrum Of 4.56



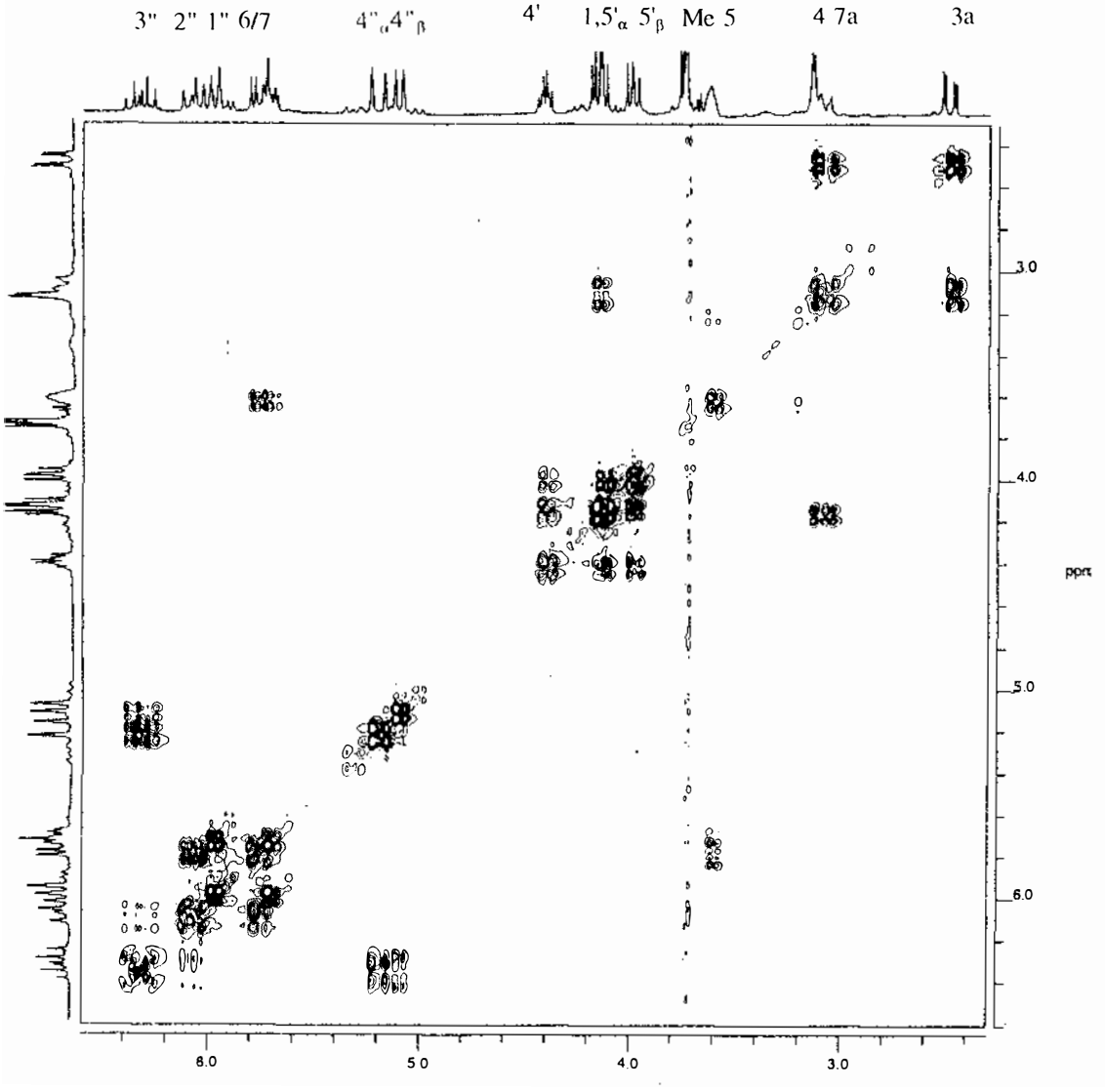
4.56



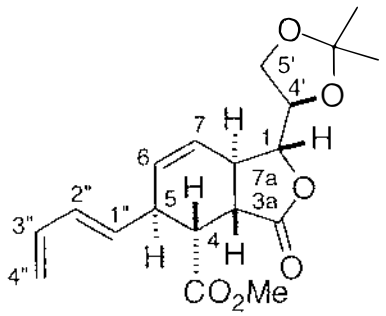
COSY Spectrum Of 4.80



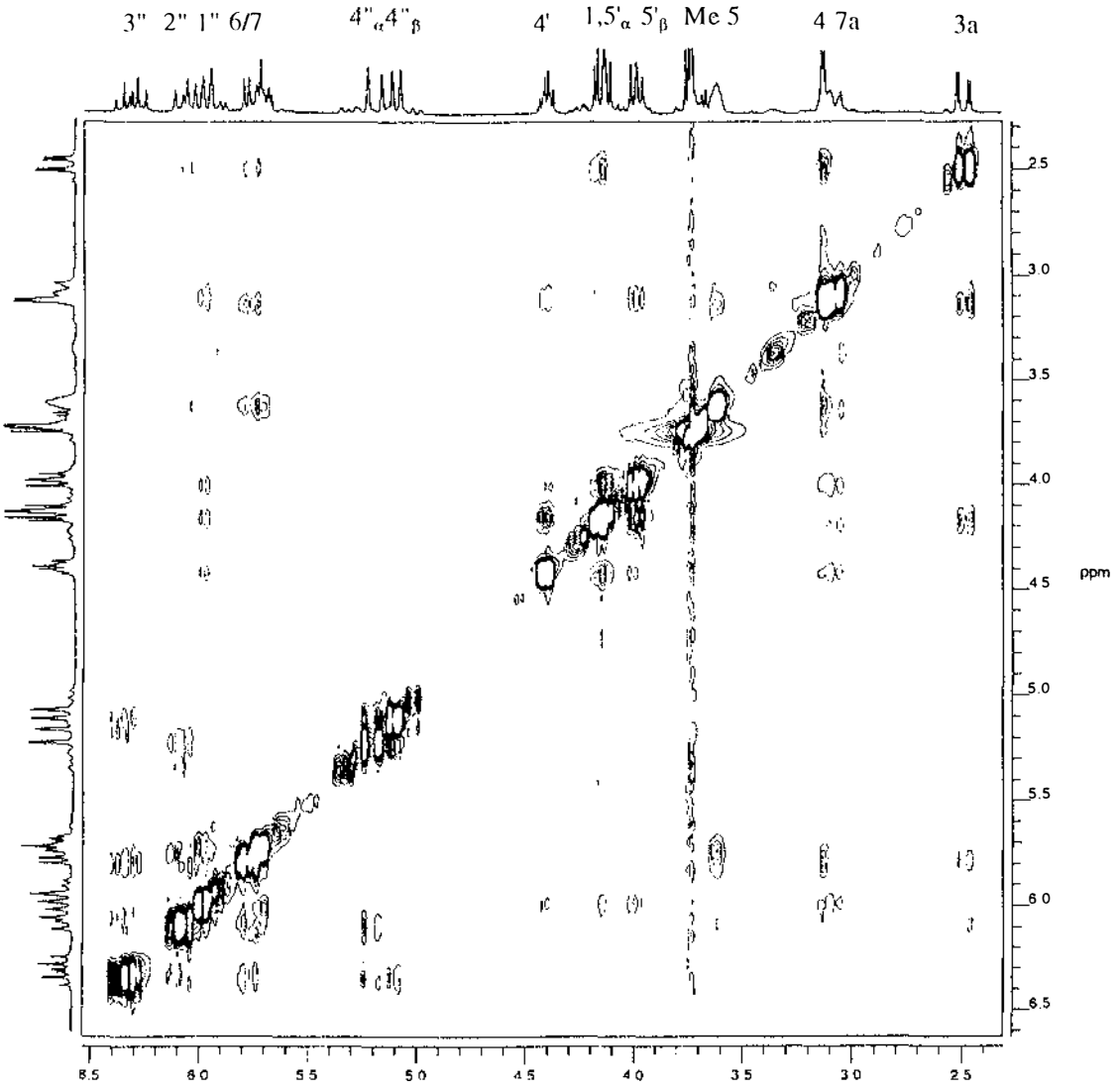
4.80



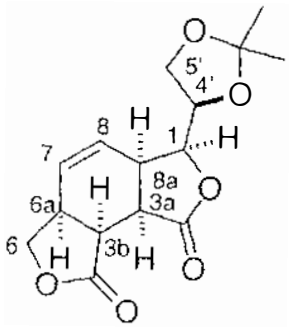
NOESY Spectrum Of 4.80



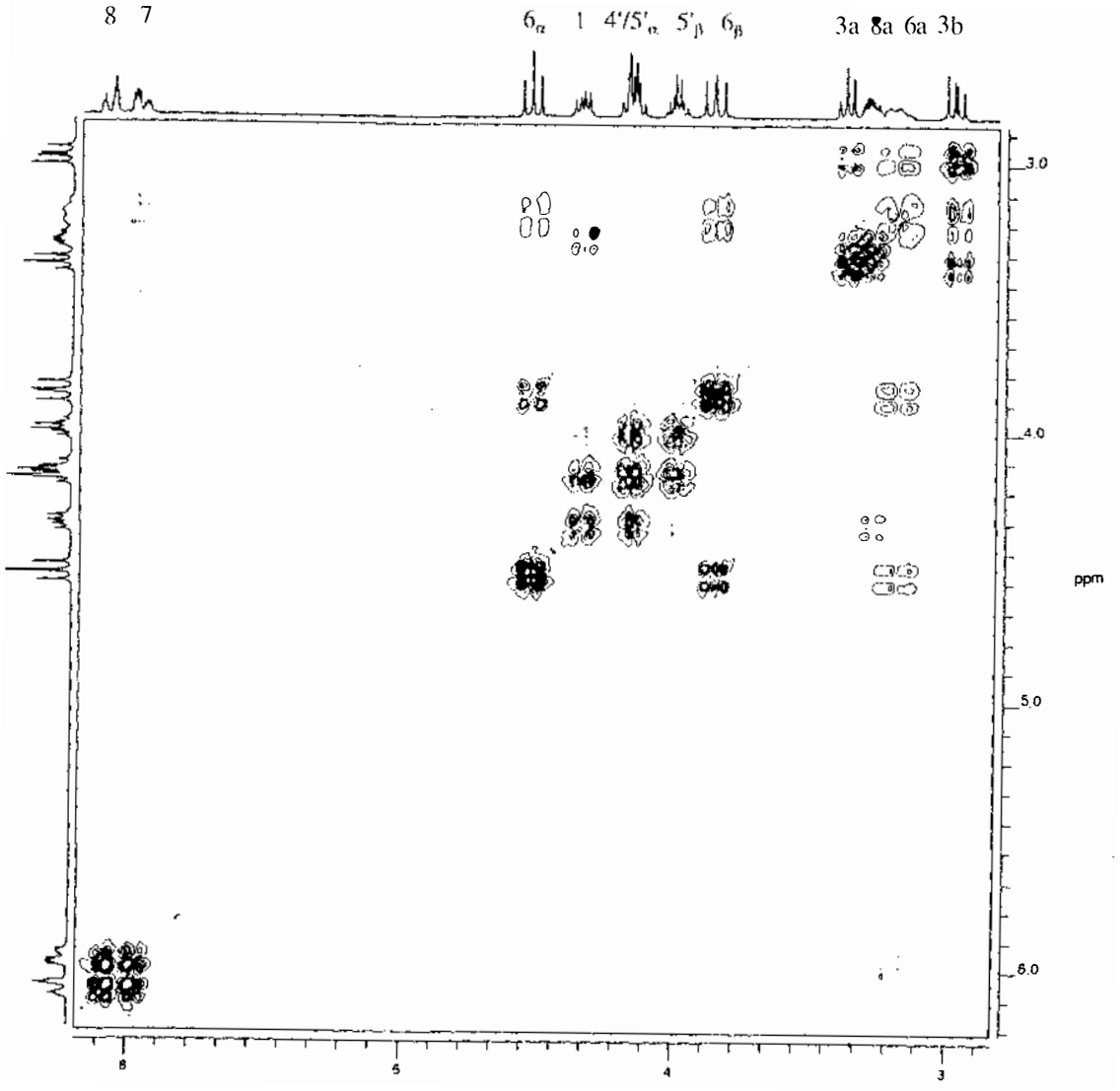
4.80



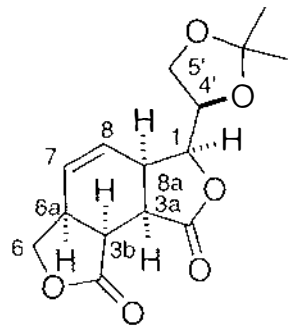
COSY Spectrum Of 3.82



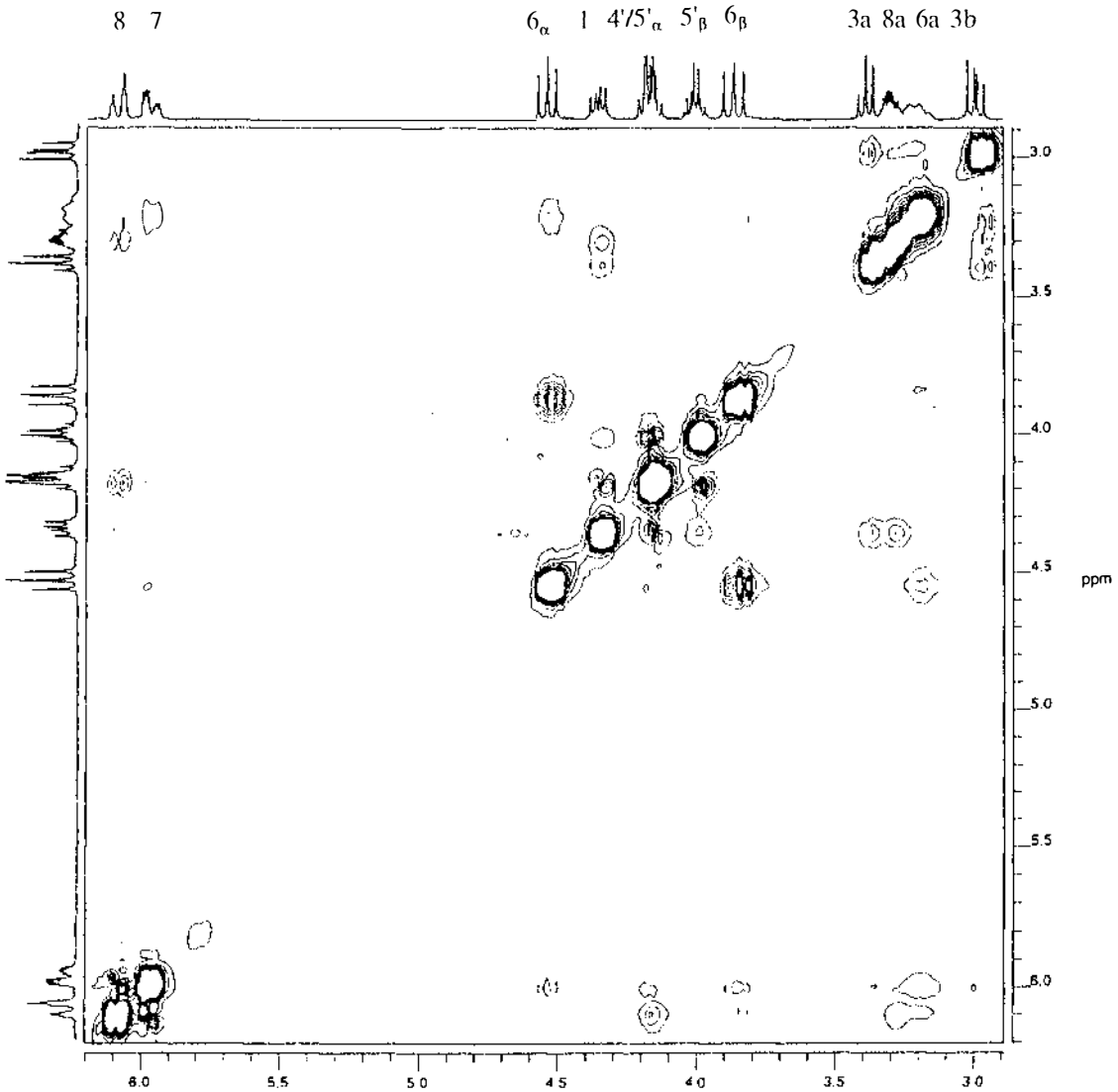
3.82



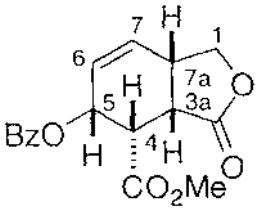
NOESY Spectrum Of 3.82



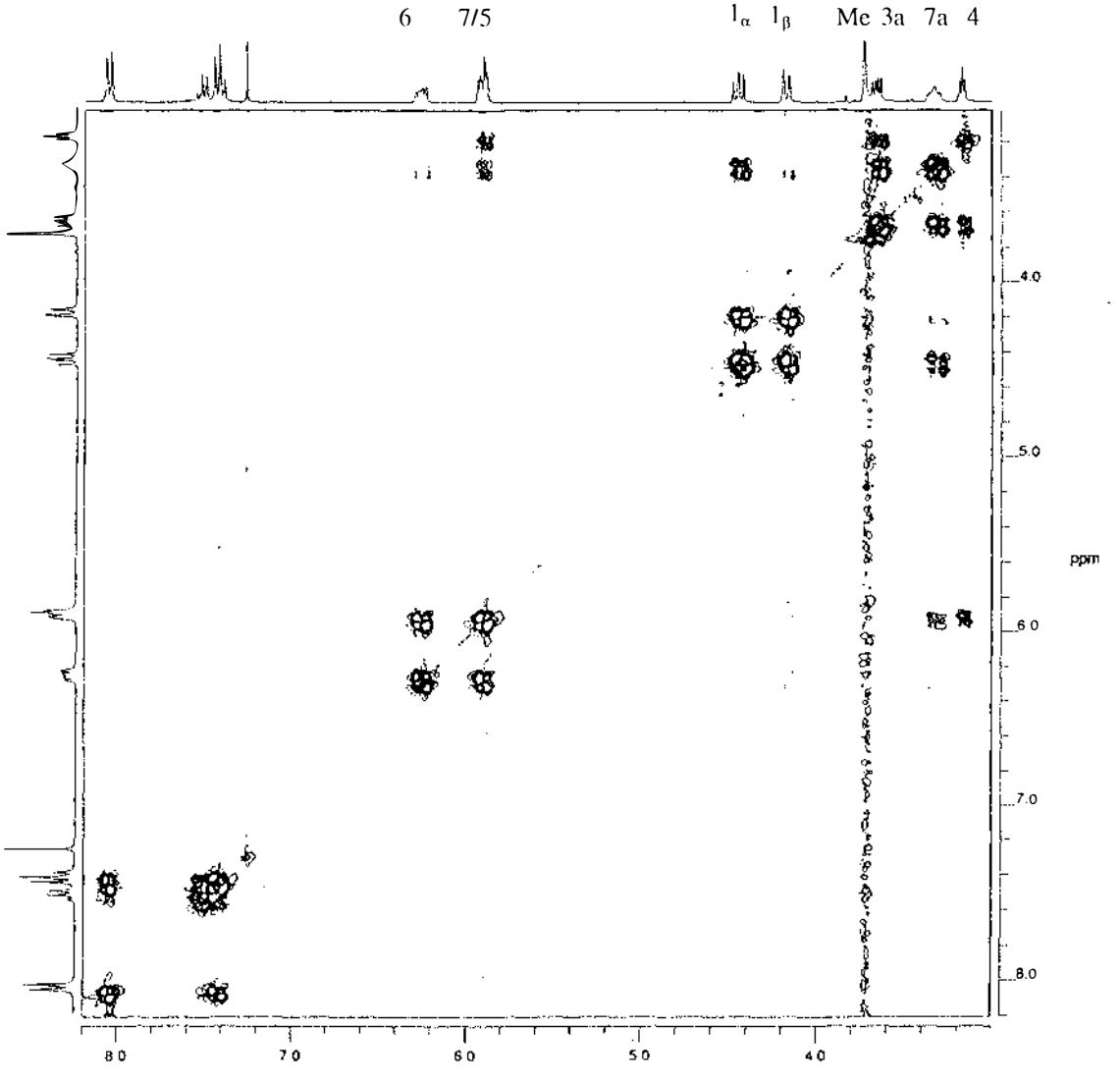
3.82



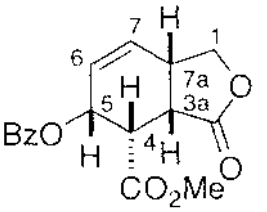
COSY Spectrum Of 3.90



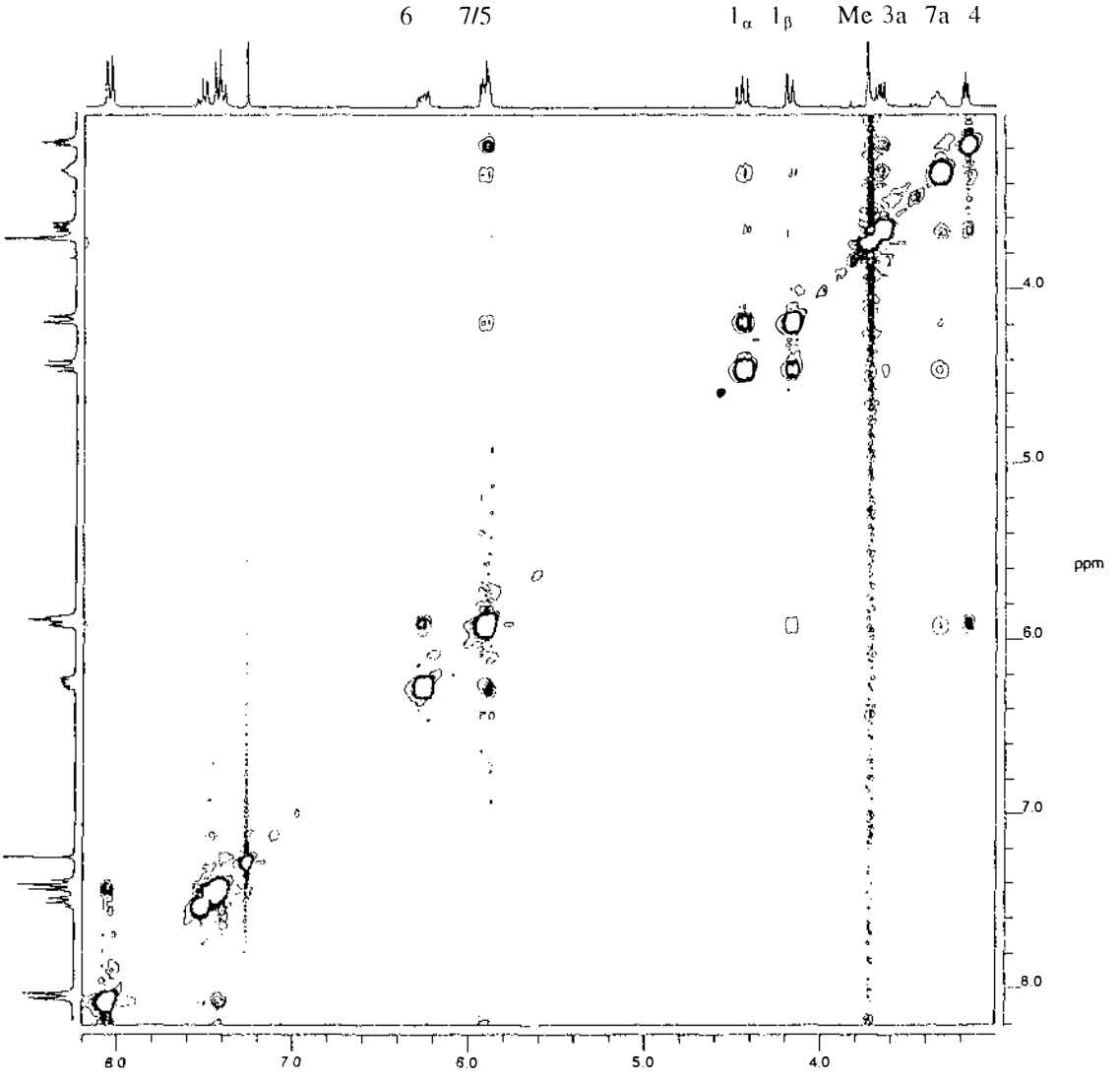
3.90



NOESY Spectrum Of 3.90



3.90



ERRATA

Page 2, line 8	Should read, "The presence of electron-donating substituents...".
Page 8, line 11	endo should be *endo*.
Page 11, Scheme 1.4	Compounds **1.40** and **1.41** should be benzyl esters, not ketones.
Page 11, line 11	Should read "...can also be controlled by including...".
Page 12, line 14	Should read "...gives a significant difference.".
Page 27, line 9	Scheme 1.25 should be **Scheme 1.25**.
Page 27, line 14	**1.142** should be **1.140**.
Page 48, line 11	Should read "...the steric bulk of the substituent...".
Pages 49, 50 and 51	Compounds **2.23** and **2.31** should have ClOC, and not ClO_2C substituents.
Page 64, line 1	Should read "...the result of dienopbile...".
Page 75, line 16	Should read "...it was conceded by...".
Page 86, line 3	Esterifiction should be esterification.
Page 117, Scheme 4.16	The diene of compound **4.39** should have an all-*E* configuration.
Page 134, Figure 4.11	The numbering on this structure is the same as that in **Figure 4.10**.
Page 153, line 4	Should read "..two doublet of doublets...".
Page 153, line 12	Should read "...for 17 hours and resulted in...".
Page 154, line 14	Should be "...both TLC analysis and...".
Page 159, line 10	"...monoacid **5.30**..." should be "...monoacid **5.28**...".
Page 176, line 10	178 μL of propiolic acid was used.
Page 214	Names of **5.20** and **5.21** should be (*E*,*E*) dimethyl benzene-1,2-diacrylate and (*E*,*E*) methyl hydrogen 1,2-benzenediacrylate respectively.
Pages 215-218	The term "octatetraen-3-yl" should read "undecatetraen-3-yl".
Pages 225 and 226	The term "octatetraen-3-yl" should read "undecatetraen-3-yl".
Page 227	In the name of compound **5.42**, "pentaenecarboxylate" should read "pentenoate".

General Corrections In Chemical Nomenclature

All chemical names with (2R,3S,4*E*,6*E*,8*E*,10*E*) descriptors should read, (2R,3S,4*E*,6*E*,8*E*).
All chemical names with (2R,3S,2*E*,4*E*,6*E*,8*E*) descriptors should read, (2R,3S,4*E*,6*E*,8*E*).
All chemical names with (2R,3R,4*E*,6*E*,8*E*,10*E*) descriptors should read, (2R,3R,4*E*,6*E*,8*E*).
All chemical names with (2R,3R,2*E*,4*E*,6*E*,8*E*) descriptors should read, (2R,3R,4*E*,6*E*,8*E*).