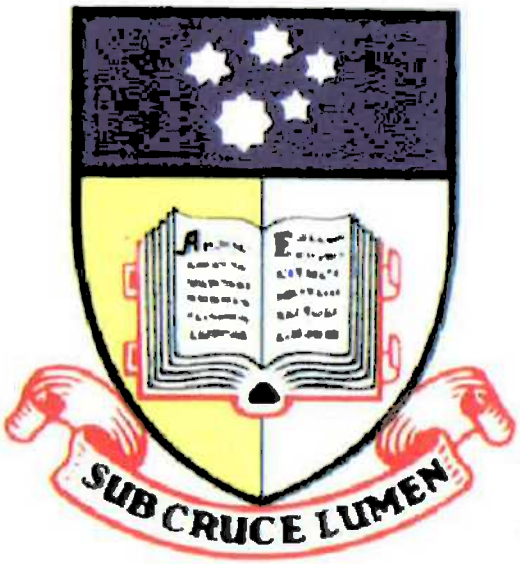
Exploitation of 1,2-Dioxines for the Synthesis of Cyclopropyl Natural Products and Novel Tetrahydropyrans and Tetrahydrofurans

A thesis submitted in fulfilment
of the requirements of the
Degree of Doctor of Philosophy

by

Julie Anne Culbert BSc. (Hons)



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Abstract

The main focus of the work discussed in this thesis was to explore the utility of 1,2-dioxines for the synthesis of selected bioactive, cyclopropyl-containing, natural products and to investigate their potential for the construction of novel oxygen heterocycles, namely tetrahydropyrans and tetrahydrofurans.

This thesis consists of six chapters. The first chapter is an introduction to (i) natural products and some natural product derivatives that have been used as therapeutics, many which still are in use today, (ii) a range of cyclopropyl natural products, which exhibit various bioactivities including those of interest, specifically, cyclopropyl steroids and fatty acids and (iii) a detailed discussion of the various methods for construction of the cyclopropyl motif including our method utilising the reactions between 1,2-dioxines, or the isomeric *trans* γ-hydroxy enones, with stabilised phosphorus ylides.

The utility of this method for the synthesis of cyclopropyl steroids and cyclopropyl fatty acids is discussed in Chapters 2 and 3, respectively. Cyclopropyl steroids of the Aragusterol series could not be synthesised by applying our methodology due to problems associated with the introduction of the methyl group *alpha* to the cyclopropyl ring. However, a method for the generation of a novel, highly substituted cyclopropyl steroid was established utilising our methodology. Unfortunately, this steroid was obtained in poor diastereomeric purity and yield. The utilisation of 1,2-dioxines and stabilised phosphorus ylides was more suited to the construction of the cyclopropyl core of the cyclopropyl fatty acid, grenadamide. Chemical modifications of the cyclopropyl substituents lead to the first total synthesis of natural grenadamide.

There are also many examples of naturally occurring tetrahydropyrans that exhibit impressive bioactivity and therefore, there is a great demand in developing methods for their synthesis. Chapter 4 briefly converses the current methods for THP construction and highlights the usefulness of 1,2-dioxines containing tethered *n*-propanol groups as precursors to *trans* and *cis* 2,3-disubstituted tetrahydropyrans. 1,2-Dioxines ring-open in the presence of base to the isomeric *cis* γ-hydroxy enones, which then undergo intramolecular 1,4-addition to generate THP's. Variation in solvent and base alters the *trans* and *cis* selectivity observed. The geometry of the γ-hydroxy enone also influences the ratio of THP's. Factors influencing the preference for cyclisation under the various

conditions are discussed. The utilisation of this methodology towards the synthesis of the natural product, Decarestrictine *L*, was also explored.

The work presented within chapter 5 highlights the utility of 1,2-dioxines containing tethered oxygen nucleophiles for the preparation of a range of compounds including tetrahydrofurans, variations in the tetrahydropyrans discussed in Chapter 4, benzodioxoles and lactones. Initial investigations towards the generation of optically-enriched tetrahydropyrans are also discussed.

Chapter 6 consists of all experimental data presented in Chapters 2-5.

Declaration

This thesis contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution. To the best of my knowledge it contains no material published or written by another person, except where due reference has been made.

I give my consent for this copy of my thesis being made available for loan and photocopying when deposited in the University Library.

Julie Anne Culbert

Acknowledgments

Firstly, I would like to thank my supervisor Assoc. Prof. Dennis K. Taylor for the opportunity to undertake a Ph.D and for the freedom to explore the direction of my studies. I am indebted to Dr. Tom Avery, Dr. Marc Kimber and Dr. Ben Greatrex for their advice, guidance and brainstorming sessions, which helped, alleviate frustrations that ultimately occur as a result of the unpredictability of research. I would also like to thank other past and present members of the Taylor group who have helped me during my postgraduate studies, in particular Natalie Jenkins, my friend and colleague, who helped me stay sane during the tough times by listening to me ramble on about my chemistry problems.

There are many people I need to thank in the Department who have contributed to the work presented in this thesis; Phil Clements for performing 600 MHz NMR; Tom Blumenthal for performing MS; Dr. Simon Pyke for help in analysing NMR data; Dr. Bruce May for chemistry advice and thesis editing; Jeff Borkent for IT assistance; Edward Tiekink for performing x-ray crystallography and John Cameron for running the 'chemistry store' so efficiently. Thankyou to everyone who has contributed, academically and/or socially, to the enjoyable times I have experienced during my time in the department.

Thanks to the departmental touch footy team and the Adelaide University Women's Soccer Team for helping me stay active during my studies. It helped me clear my mind, vent some frustrations (usually a result of my research) and gave me the opportunity to make some great friends.

To my best friends Evelyn, Nicki and Cherie, thanks for all the support over the years and for the opportunity to have a decent break from my studies by travelling to NZ and Europe with me. Most importantly I would like to thank my parents and sister for all their encouragement and emotional and financial support, as without it I would not be where I am today. Thanks for always asking me how my day was and for trying to make sense of the chemistry talk I would throw back at you. Thanks to my beautiful dog Chloe and my puppy Kiera for all the unconditional love and for the distractions that allowed me to have a break from writing this thesis. Last but not least I would like to thank God for giving me the inspiration to keep persevering no matter what.

Abbreviations

Ac	Acetyl
Anal. Calcd	analysis calculated
Ar	aromatic
Bn	benzyl
Boc	*tert*-butoxycarbonyl amide
Bu	butyl
Bu^t	*tert*-butyl
Bz	benzoyl
$Co(SALEN)_2$	*N,N'-bis*(salicyclidene)-ethylenediaminocobalt(II)
COSY	correlated spectroscopy
Δ	heat
DABCO	1,4-diazobicyclo[2.2.2]octane
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DCU	*N,N*-dichlorourethane
de	diastereomeric excess
δ	chemical shift
DEPT	Distortionless Enhancement through Polarization Transfer
DIBAL-H	di*iso*butylaluminium hydride
4-DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulphoxide
DNA	deoxynucleic acid
ee	enantiomeric excess
EI	Electron Impact
Equiv.	equivalents
Et	ethyl
eV	electron volts
EW	electron withdrawing
GC	gas chromatography
GS	ground state
HMBC	heteronuclear multiple bond connectivity
HMQC	heteronuclear multiple quantum coherence

HPLC	high performance liquid chromatography
hr	hour(s)
HRMS calcd.	high resolution mass spectrum calculated
hv	irradiation
Hz	hertz
IR	infrared
J	coupling constant
kcal/mol	kilocalories per mole
KHMDS	potassium hexamethyldisilazane
LDA	lithium di*iso*propylamine
LD_{50}	Lethal dose that killed 50% of the tested population
LHMDS	lithium hexamethyldisilazane
M	moles per litre
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
MHz	megahertz
MIRC	Michael initiated ring closure
mol	mole(s)
m.p.	melting point
MS	mass spectrum
m/z	mass to charge ratio
n-BuLi	*n*-butyl lithium
n-Pr	*n*-propyl
NMR	nuclear magnetic resonance
Nu	nucleophile
o-	*ortho*-
ortep	oak ridge thermal ellipsoid plot
p-	*para*-
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
p-TSA	*para*-toluenesulphonic acid
Ph	phenyl
ppm	parts per million

Pr^i	isopropyl
R_f	retention factor
ROESY	Rotating Frame Overhauser Effect Spectroscopy
rt	room temperature
S_N2	bimolecular nucleophilic substitution
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilane
TEA	triethylamine
TFA	trifluoroacetic acid
THF('s)	tetrahydrofuran(s)
THP('s)	tetrahydropyran(s)
TLC	thin layer chromatography
TMS	trimethylsilane
TPPO	triphenylphosphine oxide
W	watts

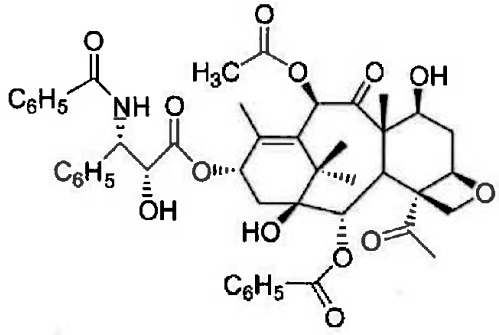
Chapter 1: Introduction

1.1 Natural Products as Therapeutics

Today, the use of natural remedies is widespread and there are numerous medicines used clinically which are based on natural products obtained from plants and fungi.[1,2] Such therapeutic agents are used as analgesic agents, anti-cancer agents, antidysrhythmic agents (for the heart) and anti-infective agents, just to name a few. Semi-synthetic derivatives of natural products also make up some of the other therapeutic drugs in clinical use today.

Morphine **1** and codeine **2** are examples of two natural products used extensively as analgesic agents.[1] Both are closely related alkaloids found in the opium poppy *(Papaver somniferum)*.[3] Use of the opium juice for pain relief dates back to ancient times when it was used by the Greeks and Romans.[3] However, it was not until the 1800's that Sertürner in Germany and Derosne and Séguin in France accomplished the isolation of the active constituent, morphine.[4] The first reported isolation of codeine from opium occurred in 1832 by French pharmacist Pierre Jean Robiquet. Today morphine is isolated from opium in large quantities (over 1000 tons per year) and a large amount of it is methylated to codeine.

1: R = H
2: R = CH_3



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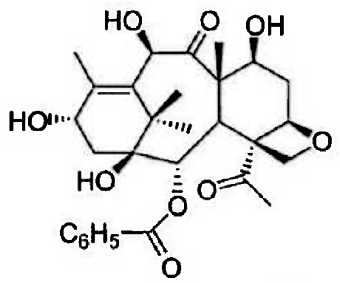
Taxol **3** (also known by its generic name Paclitaxel) is probably one of the most well known naturally occurring anti-tumour agents used clinically to treat patients suffering from breast or ovarian cancer. It was first isolated and recognised as the active ingredient of the extract from the bark of the yew tree, *Taxus Brevifolia* in 1967.[5] A few years later the structure of taxol was established by x-ray analysis of taxol derivatives.[5]

In 1979, Horwitz and co-workers reported that taxol promotes microtubule assembly *in vitro* by reducing the critical concentration of tubulin required for assembly.[6] The microtubules formed are shorter than that observed for non-taxol treated microtubules and they are resistant to depolymerisation by calcium chloride. Polymerisation and depolymerisation of cytoplasmic microtubules is important for cell migration and lack of depolymerisation therefore blocks cell migration and division. Initially, drug development of taxol was made difficult by the scarcity of its natural source.[7] The bark of a typical one hundred year old yew tree contains only 300 milligrams of taxol and its collection results in death of the tree. However, this problem was overcome by the semi-synthesis of taxol from the structurally similar 10-deacetylbaccatin III **4**, a compound present in the leaves of the European yew, *Taxus baccata*.[7,8]

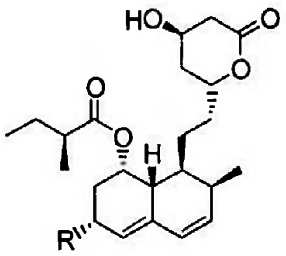


4

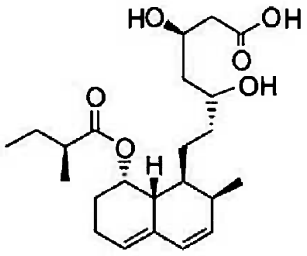
Several drug trials later, the Food and Drug Administration finally approved taxol in 1992 for the treatment of treatment-resistant ovarian cancers. Two years later the FDA also approved the use of taxol for recurrent breast cancer chemotherapy. Holton and colleagues reported the first total synthesis of taxol in 1994.[9,10] Since that time, Nicolaou and co-workers have also successfully synthesised taxol.[11-14] However, currently no total syntheses are viable for the industrial scale production of taxol.

There are many other examples of clinically used anti-cancer agents either of natural origin or originating from the semi-synthesis of natural products. For instance, pentostatin, a *Streptomyces* metabolite is used to treat patients with hairy cell leukaemia while docetaxel, an analogue of taxol, is used for second line breast cancer. Bryostatin I, squalamine and perillyl alcohol are just three examples of natural products being investigated in clinical trials as potential anti-cancer agents. There are numerous other natural product analogues currently in Phase I or Phase II clinical trials. In 1998, along with anti-infective agents, anti-tumour agents of natural origin made up 60% of the agents either available commercially or in late stage clinical trials.[2]

Digoxin, obtained from the leaves of the foxglove family, is used for the treatment of cardiac failure associated with rapid atrial fibrillation. Administration of this steroidal cardiac glycoside results in cardiac slowing and a reduction in the rate of conduction through the AV node.[15,16] However, the efficacy and safety of digoxin continues to be a topic of debate.[17] The statins are another class of natural products used for reducing the risks of hypercholesterolemia and coronary heart disease. Mevastatin **5** (also known as compactin), its hydrolytic analogue Pravastatin **6**, Lovastatin **7** and Simvastatin **8** are four examples in this class of HMG CoA reductase inhibitors.[2,18]



5: R = H
7: R = CH_3



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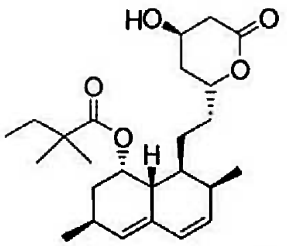

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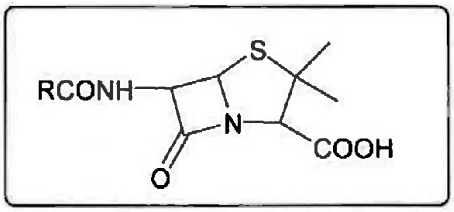
Pravastatin has been used since 1998 to reduce the risk of stroke in patients who have already suffered a heart attack but who have normal cholesterol. Simvastatin is also used clinically for the same reason as Pravastatin but is given to patients with high cholesterol.[2]

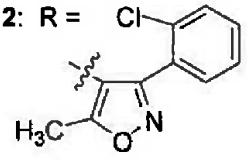
As mentioned previously, naturally occurring anti-infective agents used clinically or in late stages of clinical trials make up a large percentage of the drug market. This group of agents includes those possessing anti-bacterial, anti-parasitic and anti-fungal activity. Many of these agents originate from fungal fermentations while others are of plant origin.[2] Some examples of each are given below.

The explosion of natural antibiotics started in 1940 when Florey and Chain successfully isolated Penicillin, an active ingredient in the fermentation broth produced by *Penicillium notatum*, originally discovered by Alexander Fleming twelve years earlier.[19,20] This agent was able to kill bacteria responsible for such diseases as tetanus, diphtheria, gonorrhoea, enteric fever and typhoid. The chemical structure of benzylpenicillin **9** was later determined.[20] The general structure of the penicillin group of antibiotics is given below.



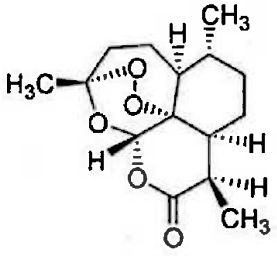
The general structure of penicillins

9: R = CH_2Ph
10: R = CH_2OPh
11: R = $CH(NH_2)Ph$
12: R =



This initial work has lead to the development of a large series of natural and semi-synthetic penicillins, many only differing structurally by the R group attached to the amide functionality (i.e. *N*-acyl derivatives of 6-aminopenicillanic acid). Along with benzylpenicillin, phenoxymethyl penicillin **10** is another example of a natural antibiotic produced by *P. notatum*.[20] However, most penicillins available on the market are semi-synthetic derivatives. Ampicillin **11** and Cloxacillin **12** are two examples of semi-synthetic antibiotics derived from fungal fermentation products.[21] In the last 60 years, more than thirty penicillins have been developed for commercial use. There are also other examples of therapeutically used natural antibiotics or their semi-synthetic derivatives such as the macrolide Erythromycin, produced by *Streptomyces erythraeus*[21-23] and the Rifamycins, a family of antibiotics derived from the fermentation products of *Streptomyces mediterranei*.[24,25]

The discovery of the natural product quinine from the bark of the *Cinchona* tree prior to World War II revolutionised the treatment of malaria.[1] This potent anti-malarial agent is still in clinical use today. The herb, *Artemisia annua*, is the source of another naturally occurring anti-malarial agent, the sesquiterpene endoperoxide artemisinin **13**. Artemisinin has been shown to be effective in the treatment of chloroquine-resistant malaria. Artemether **14**, a semi-synthetic derivative of artemisinin is also of current clinical use. It is as effective as quinine in the treatment of malaria.[2]



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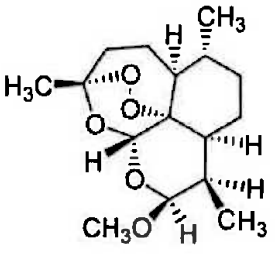

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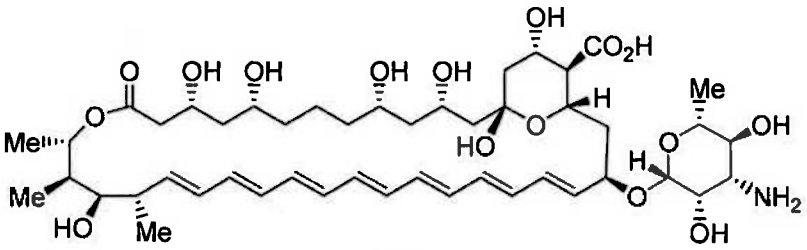
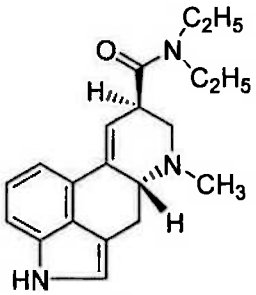
There are several examples of natural products used clinically as anti-fungal agents. Among the most effective is the polyene Amphotericin B **15**.[26] This fermentation product of *Streptomyces nodosus* has a wide spectrum of antifungal activity and is the drug of choice for many severe fungal infections including cryptococcal meningitis. Nystatin and Griseofulvin are two other examples of naturally occurring anti-fungal agents used therapeutically.



15

Natural products have also been used to treat asthma, dementia (including Alzheimer's disease), cerebrevascular disease, Parkinson's disease, male erectile dysfunction, diabetes and inflammatory and autoimmune diseases.[2]

There are many other naturally occurring compounds that are pharmacologically active but are not used clinically to treat diseases. For instance, lysergic acid diethylamide (LSD) **16** is an interesting ergot alkaloid that is most notably known as a drug of abuse due to its hallucinogenic effects. Caffeine **17** and theobromine are both stimulants found in coffee and tea and cocoa, respectively.[15] There are also many natural remedies available on the shelves at pharmacies. One such example is Blackmores Hyperiforte 1800 (St. John's Wort) which is a tablet consisting of extracts from the plant *Hypericum perforatum*. It has been found to be as effective as prescription drugs to relieve nervous tension, stress and mild anxiety.[27] Blackmores Valerian Forte sleep formula based on extracts from the plant *Valeriana officinalis* (Valerian) is another example. It has been shown to improve sleep quality.[28]



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As can be seen from this discussion, there is no doubt that the area of natural product chemistry has played an important role in the development of many useful therapeutic agents. Natural products have strongly shaped the drug industry with 6 out of the top 20 prescriptions dispensed in 1996 originating from this source.[1] In addition, over 50% of these top 20 drugs could be linked to natural product research.

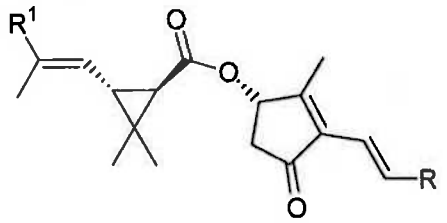
Consequently, the area of natural product chemistry continues to be one of great interest due to the possible therapeutic benefits associated with some naturally occurring bioactive species. Furthermore, there is continual search for new and improved therapeutic drugs with minimal side effects and ones that can overcome drug-resistance developed by some cancers and infective species.

1.2 Cyclopropyl-containing bioactive compounds

There are many cyclopropyl compounds, of natural or synthetic origin, that exhibit impressive biological activity. Natural sources of bioactive cyclopropanes include plants, fungi and bacteria[29] while many synthetic examples are simply derivatives of naturally occurring cyclopropanes that exhibit improved biological and chemical properties, such as the pyrethroid based insecticides. Cyclopropyl-containing compounds are present in living organisms as either intermediates or as metabolic products in their biosynthetic pathways.[29] For instance, 1-aminocyclopropane carboxylic acid (ACC) is a biosynthetic precursor of ethylene[30] while Dictyopterene A is a metabolic product derived from the breakdown of the fatty acid, arachidonic acid.[31] These two examples will be discussed in more detail later.

The biological activity observed for many cyclopropyl compounds appears to be a consequence of the conformational constrainment introduced by the presence of the rigid cyclopropane motif. This rigidity can be important for activity by providing favourable binding interactions of the substrate with the receptor.[30] In most cases the cyclopropyl moiety remains inert.[29] Improved substrate-receptor binding is often observed for conformationally constrained analogues of lead compounds.[32] Cyclopropyl compounds exhibit a diverse range of bioactivities and some interesting examples are given below.

One well-known class of cyclopropyl natural products are the commercially important pyrethroid group of insecticides. Pyrethrin I **18a** and II **18b**, cinerin I **18c** and II **18d** and jasmolin I **18e** and II **18f** are biosynthesised by the pyrethrum flowers, *Chrysanthemum cinerariaefolium*.[33-35]

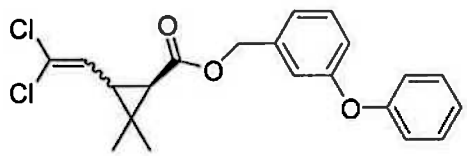


		R	R^1
18	**a :**	CH_3	$CH{=}CH_2$
	b :	CO_2CH_3	$CH{=}CH_2$
	c :	CH_3	CH_2CH_3
	d :	CO_2CH_3	CH_2CH_3
	e :	CH_3	CH_3
	f :	CO_2CH_3	CH_3

Natural Pyrethrums

The basic structural backbone of this class of compounds includes a tetra-substituted cyclopropane with *gem*-dimethyl substitution and *trans* geometry about the three

membered ring. Although the natural pyrethrins have impressive insecticidal activity, they could not be applied agriculturally due to their rapid photo-stimulated oxidative degradation.[34] However, the natural pyrethroids lead to the development of synthetic analogues with good activity and photo-stability such as the commercially used permethrin **19**, cypermethrin and deltamethrin **20**. Along with their natural analogues these synthetic derivatives exhibit low mammalian-toxicity, which is extremely important for commercialisation of these compounds.[35,36]



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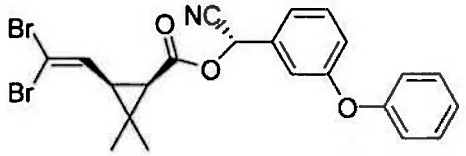

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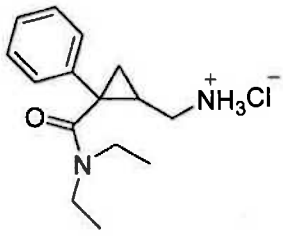
Three other important cyclopropyl compounds that are used commercially are the therapeutic agents milnacipran[37,38] **21** (previously called midalcipran), efavirenz[39-41] **22** and Abacavir[42-44] **23**.



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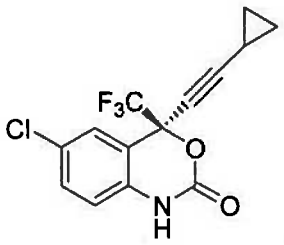

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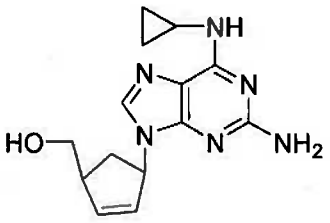


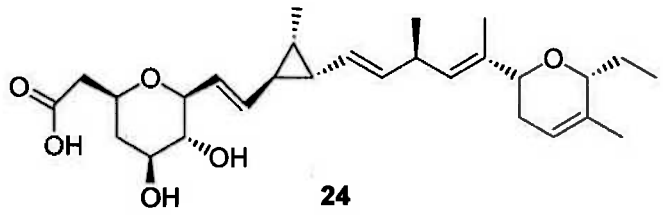
23

Milnacipran has been used as an antidepressant and possesses its action through inhibition of noradrenaline and serotonin uptake.[37,38,45,46] It has been shown to be as effective as the tricyclic antidepressants but with fewer adverse side effects.[38,45] Milnacipran is currently registered throughout Europe as an antidepressant[38] but there is also evidence that it may be effective in the treatment of bulimia nervosa.[47]

Efavirenz and Abacavir (1592U89, or Ziagen) are both potent inhibitors of the enzyme HIV-1 reverse transcriptase.[40,43] Since HIV requires this enzyme to copy its single stranded RNA into double stranded DNA,[48] these drugs therefore inhibit its replication. The Food and Drug Administration (FDA) have approved both drugs for the treatment of acquired immunodeficiency syndrome (AIDS).[40,43] Abacavir is as potent as the well-known AIDS

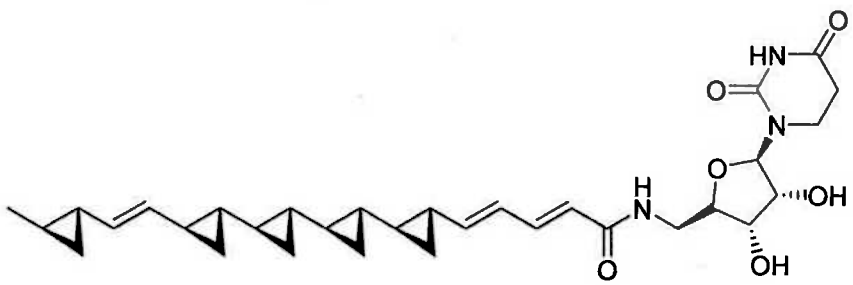
drug 3'-azido-3'-deoxythymidine (AZT)[42] while numerous studies have shown the effectiveness and durability of efavirenz in combination with other AIDS drugs.[40,41]

There are several examples of cyclopropyl compounds possessing anti-infective activity. Among them is the orally active anti-fungal antibiotic ambruticin (or W-7783) **24** produced by a *myxobaceriale Polyangium cellulosum var. fulvum.*[49] Its 5-epi isomer, also isolated from the same species, shows similar antimicrobial activity.[50]



24

FR-900848 **25**, a muti-cyclopropanated compound was isolated from *Streptoverticillium fervens* in 1990.[51] This interesting molecule possesses potent activity against filamentous fungi. Marasmic acid **26** is another naturally occurring cyclopropyl compound possessing antibacterial activity against such bacteria as *E. coli* and *Staphylococcus aureus.*[29]



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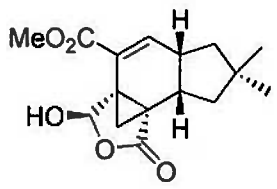
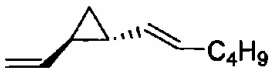


26

As mentioned earlier, cyclopropyl-containing compounds can be present in living organisms as metabolic products in their biosynthetic pathways. They may not necessarily be bioactive to humans or insects but they play important roles in the survival of the species. For instance, there are numerous sex pheromones that contain a cyclopropane ring.

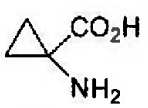
These include Dictyopterene A **27** and Dictyopterene B (or hormosirene) **28**, sperm attractants from brown algae such as *Hormosira banksii*, *Dictyoperis plagiogramma* and *D. australis*.[31,52,53] These compounds are biosynthesised by the breakdown of C_{20} fatty acids.[31]



27

28

In nature, there also exists a wide range of cyclopropyl amino acids. One of the most well known examples is 1-aminocyclopropane carboxylic acid (ACC) **29**. It was first isolated in 1957 from perry pears and cider apples but at this time its metabolic significance was unknown.[54] It was later discovered that ACC is a biosynthetic precursor of ethylene, a molecule important in the ripening process of fruit.[30] Consequently, many analogues of ACC have been synthesised with the aim to develop one that may be able to give control over the ripening process.[55] There are many other examples of naturally occurring bioactive cyclopropyl amino acids, most originating from plant species, including hypoglycine A **30**, coronamic acid, carnosadine, 3,4-methanoglutamic acid and 3,4-methanoproline.[56]



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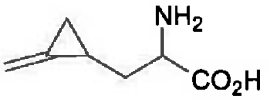
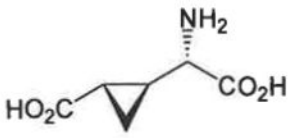


30

Cyclopropyl amino acids can also be used as peptidomimetics.[57] Peptidomimetics are molecules possessing bioactivity that are designed to mimic bioactive proteins. Since amino acids are extremely important for processing enzymes, cyclopropyl derivatives can potentially result in the reduction of enzyme activity or may cause stabilization of peptides toward enzyme cleavage. A conformationally restricted *L*-glutamate derivative, (2*S*,1'*S*,2'*S*)-2-(carboxycyclopropyl)glycine (*L*-CCG-1) **31** exhibits agonist activity towards group II metabotropic glutamate receptors.[58] Other cyclopropyl amino acids are potent NMDA receptor antagonists.[59] Peptide mimics **32a-b** have been used in peptidomimetics and are subnanomolar HIV-1 protease inhibitors.[57]



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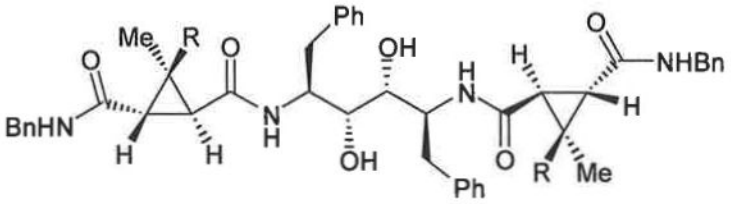


32 **a** : R = H
b : R = Me

There are many other examples of natural bioactive cyclopropyl-containing compounds including anti-miotic agents,[60] DNA polymerase inhibitors,[61,62] cholesteryl ester transfer protein inhibitors[63] and immunosuppressants.[64]

Of particular interest to our group are the cyclopropyl compounds possessing anti-tumour activity. These include the cyclopropyl marine steroids, aragusterols and the cyclopropyl fatty acids, grenadadiene, debromogrenadadiene and grenadamine. Interestingly, all compounds have been isolated from marine sponges.

1.3 Marine Species – A rich source of bioactive products

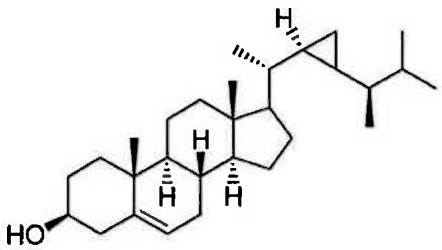
Marine species appear to be a rich source of natural products including terpenoids, sterols, cyclopropanes, quinones and fatty acid metabolites, just to name a few.[65] In addition, they possess a wide range of bioactivites from being antimalarial agents, antitumour agents, antibiotics, enzyme inhibitors to antifungal agents.[65]

One interesting group of compounds isolated from marine organisms is the naturally occurring cyclopropane containing and non-cyclopropane containing marine sterols. These sterols have been isolated from a range of marine species including sponges,[66,67] algae,[68] coelenterata,[69,70] starfish,[71,72] crustaceans and molluses.[73] The presence of these unique sterols in these marine species is unclear since they do not possess specific activity.[74] However, it has been postulated that some may be intermediates in bioalkylation processes while others may replace cholesterol as a cell-membrane constituent.[74] Of particular interest to our group are the cyclopropyl-containing aragusterols due to the cytotoxicity some of these molecules exhibit. Cyclopropyl-containing marine steroids including the aragusterol series will be discussed in more detail in section 1.4.

Another aquatic species, which is the source of other interesting cyclopropyl natural products, is the marine cyanobacterium *Lyngbya majuscula*. It is a source of bioactive cyclopropyl fatty acids, such as the cytotoxic grenadadiene.[75] Once again, these cyclopropyl-containing natural products are of interest since the presence of the rigidified cyclopropyl motif may be responsible for the bioactivities some of these molecules exhibit. Cyclopropyl fatty acids will be discussed in more detail in section 1.5.

1.4 Cyclopropyl-containing marine steroids

Gorgosterol **33** was the first of several naturally occurring marine sterols in which the presence of a cyclopropyl-containing side chain was established.[68] Its cyclopropyl motif is positioned between carbons 22 and 23.[76] There are many other relatives of gorgosterol which contain a cyclopropane at the same position. A few examples include dihydroxygorgost-5-en,[77] 4-methyl gorgosterol and 23-dimethyl gorgosterol.[70] Other commonly known cyclopropane-containing sterols include petrosterol **34**, hebesterol **35** and dihydrocalysterol **36** which possess their cyclopropane motif in various positions in their side chain.[78] However, none of these sterols have been reported to possess bioactivity.



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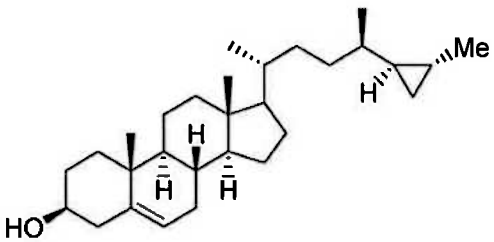

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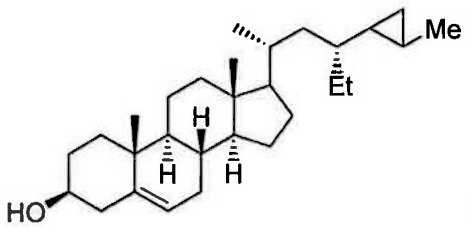

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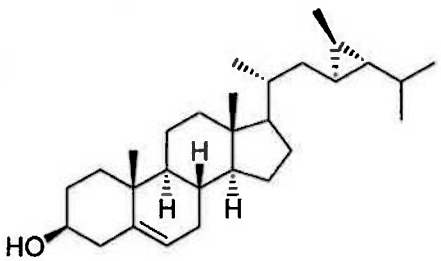


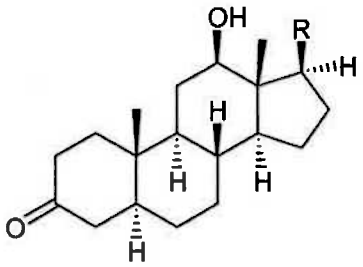
36

Aragusterols A-H **37-44**, isolated from the Okinawan marine sponge *Xestospongia* **(Figure 1.1)**, are fascinating examples of C_{25}-C_{27} cyclopropane-containing sterols. They are of particular interest since initial pharmacological studies on these unusual C_{29} sterols found that some have anti-tumour activity. For instance, aragusterols A and C were found to strongly inhibit the proliferation of KB cells at an IC_{50} of 0.042 and 0.041μg/mL, respectively.[79] In addition, these two aragusterols were found to express potent *in vivo* antitumor activity against L1210 leukaemia in mice (T/C 220% and 257%, at 1.6 mg/kg). Consequently, they have potential therapeutic application. However, while aragusterols A-D have been tested for bioactivity the others have yet to be tested due to the lack of sufficient quantities available from the natural source. This is a common problem since

extraction of large quantities of marine species may result in only milligrams of a natural product being obtained. Therefore, large quantities of these steroids are needed for further biological evaluation.

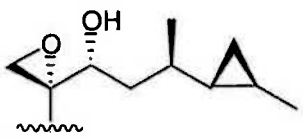
Figure 1.1: An example of a sea sponge from the *Xestospongia sp.* family.

Even though more than 120 sterols have been isolated and their structures determined,[80] few have been synthesised to date. The semi-total synthesis of aragusterols A-D has only been recently achieved but involves a multi-step sequence. We therefore are seeking to develop a new versatile synthetic protocol which will allow for quick access to these steroids and related steroids. In addition, our new methodology must be able to allow for the synthesis of both enantiomers of the cyclopropyl motif as well as allowing for the incorporation of additional functionality around the cyclopropane ring. This will allow for a thorough investigation of whether the cyclopropyl motif is necessary for bioactivity.

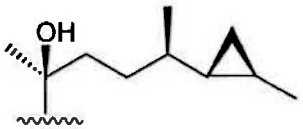


Base structure for Aragusterols A-E

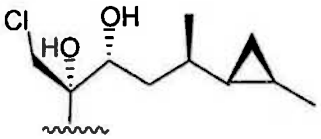
Where R =



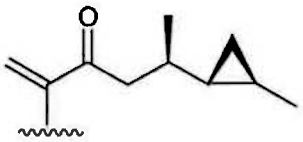
Aragusterol A **37**



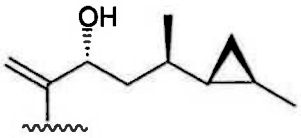
Aragusterol B **38**



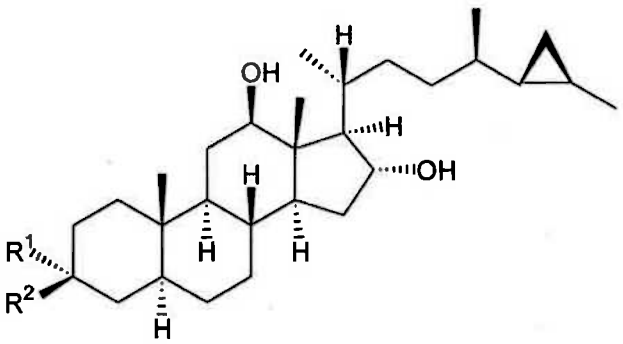
Aragusterol C **39**



Aragusterol D **40**



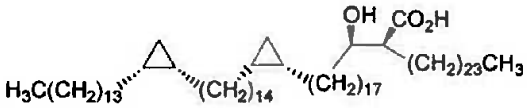
Aragusterol E **41**



Aragusterol F **42**: R^1, R^2 = =O
Aragusterol G **43**: R^1 = OH, R^2 = H
Aragusterol H **44**: R^1 = H, R^2 = OH

1.5 Cyclopropyl fatty acids

Cyclopropyl fatty acids are another interesting class of cyclopropyl natural products. There are very few molecules of this type, either natural or synthetic, reported in the literature. Some examples include the mycolic acid **45**,[81] cepaciamide A **46**[82-84] and the unsaturated C_{20} cyclopropane-containing fatty acid **47**.[85] Most cyclopropyl fatty acids originate from bacterial sources.



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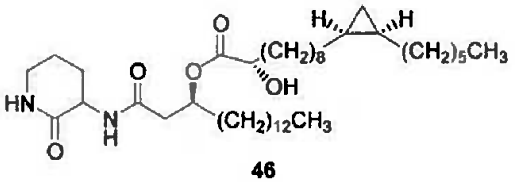

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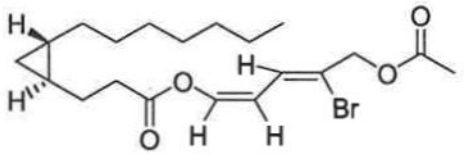
47

The presence of these unusual compounds in natural products is not fully understood but they are believed to be involved in the organism's defensive mechanisms. For instance, the cyclopropyl-containing mycolic acids are found in the cell wall of human tuberculosis bacilli (*Mycobacterium tuberculosis*) and most likely protect the bacilli from its environment and from chemical therapies used to combat it.[81] Cepaciamide A is a fungitoxic lipid isolated from *Pseudomonas cepacia* D-202,[82] while fatty acid **47** isolated from the digestive gland of the sea hare *Bursatella leachii* is believed to originate from cyanobacteria ingested as part of the hare's algal diet.[85]

The marine cyanobacterium *Lyngbya majuscula*, is another source of three other interesting cyclopropyl fatty acids. These include grenadadiene **48**, debromogrenadadiene **49** and grenadamide **50**.[75] Grenadadiene has been shown to exhibit cytotoxicity against an *in vitro* NCI60 cell line[75] and has also been found to inhibit fatty acid amide hydrolase, an enzyme that catalyses the hydrolysis of fatty acid amides and esters.[86] Grenadamide exhibits brine shrimp toxicity (LD_{50}=5 μg/mL) and cannabinoid receptor binding activity.[75]



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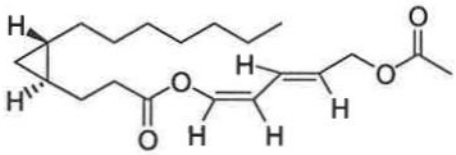

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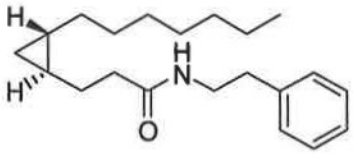

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These cyclopropyl fatty acids are attractive synthetic targets due to the bioactivies they exhibit. In addition, there is a limited supply of these compounds from the natural source therefore limiting thorough biological testing of them. To date, none have been synthesised. However, a recent paper published during the writing of this thesis reported the absolute stereochemistry of grenadamide as being the 2*R*,1*R*-enantiomer, based on the equal but opposite optical rotation observed for its synthetic 2*S*,1*S*-enantiomer.[87]

1.6 Strategies for the construction of the cyclopropyl motif

As a consequence of the abundance and diverse range of naturally occurring compounds possessing the cyclopropyl motif there has been a great interest in the development of synthetic strategies towards cyclopropanes. In particular, it is important to generate cyclopropanes diastereoselectively and with high enantioselectivity, since natural products are often optically pure compounds. Furthermore, usually only one enantiomer of a compound will exhibit biological activity.

Cyclopropanation can be achieved via numerous pathways, however, only the most common four methods will be discussed here. These include (i) carbene transfer to olefins, (ii) 1,3-elimination of heteroatoms, (iii) nitrogen extrusion from pyrazolines and (iv) Michael induced ring closure (MIRC). Other methods for cyclopropane construction include ring contraction[88,89] and conversion from epoxide precursors.[90,91] However, utilisation of these two methods is not as common.

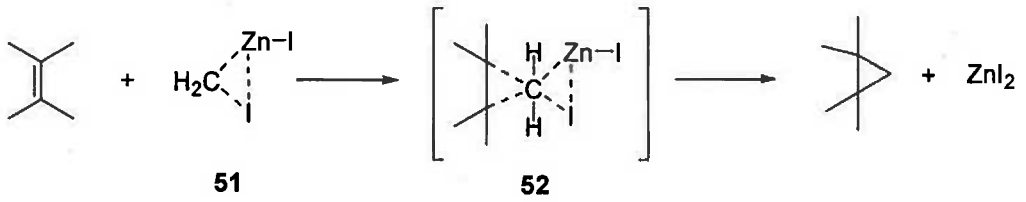
As mentioned above, asymmetric synthesis of cyclopropanes is extremely important for natural product synthesis. The efficient synthesis of diastereomerically and enantiomerically-pure cyclopropanes is a considerable synthetic challenge for the organic chemist. However, over the last five decades there has been significant advances in asymmetric cyclopropane synthesis and these will be discussed in regards to the above methods.

1.6.1 Carbene Transfer to Olefins

One of the most widely utilised reactions for the construction of cyclopropanes is the addition of a carbenoid species to an olefin. The delivery of methylene or higher analogues to an olefin can be achieved via three ways. Firstly, carbene transfer to olefins can proceed via utilisation of the Simmons-Smith reagent, secondly, via the decomposition of diazo compounds and thirdly via the use of transition metal-carbene complexes.

In 1958, Simmons and Smith[92] discovered that cyclopropanes were the sole products of reactions involving alkenes and diiodomethane in the presence of a zinc-copper couple. The reaction was versatile to a range of alkenes with various functional groups giving their corresponding cyclopropanes in 10-70% yield. The reactive intermediate, iodomethylzinc iodide **51**, possesses enhanced electrophilic character similar to that of carbenes.[93]

Simmons and Smith proposed that the addition of methylene to the olefin probably occurs through a three centre transition state[93] **52**, as illustrated in **Scheme 1.1**



51 **52**

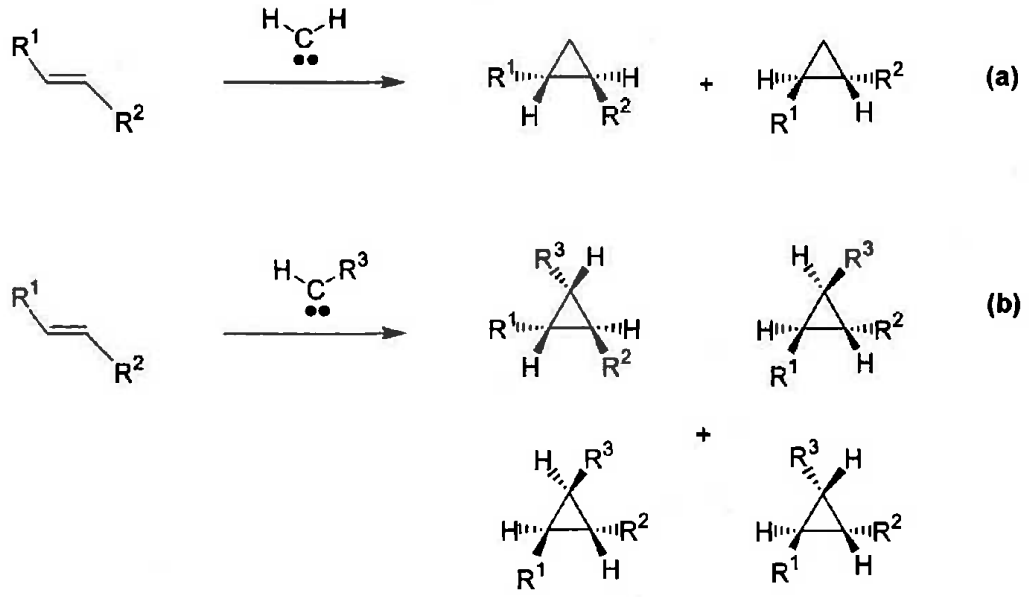
Scheme 1.1

Following this research, alternative methods for the generation of the classical Simmons-Smith reagent ($IZnCH_2I$) have been discovered including the reaction between (i) zinc-silver couple and diiodomethane,[94,95] (ii) a zinc(II) salt and a diazoalkane developed by Wittig and colleagues[96] and (iii) ethylzinc iodide and diiodomethane developed by Charette and co-workers.[97] Furthermore, other related reactive carbenoids of the type $RMCH_2I$ have been developed. These include the formation of $EtZnCH_2I$ via the reaction of diethylzinc and dihaloalkane, known as the Furukawa procedure.[98] In addition, Molander and Harring[99] have reported that replacement of zinc with samarium in the Simmons-Smith reagent (i.e. formation of $XSmCH_2I$, where X = I or Cl) also facilitates cyclopropanation of alkenes. All these procedures for generating a reactive carbene-like species are summarised in **Table 1.1**.

Table 1.1 Summary of the various procedures for the generation of the reactive carbene species used in the Simmons-Smith cyclopropanation reaction.

	Reagents	Reactive Carbene Species
Classical Simmons-Smith reaction[92]	Zn (Cu or Ag) + CH_2I_2	$IZnCH_2I$
Other Simmons-Smith reactions Reference		
Charette and co-workers (1996)[97]	$EtZnI + CH_2I_2$	$IZnCH_2I$
Wittig and Schwarzenbach (1959)[96]	$ZnI_2 + CH_2N_2$	$IZnCH_2I$
Furukawa and co-workers (1966)[98]	$Et_2Zn + CH_2I_2$	$EtZnCH_2I$
Molander and Harring (1989)[99]	$Sm(Hg) + CH_2X_2$	$XSmCH_2X$

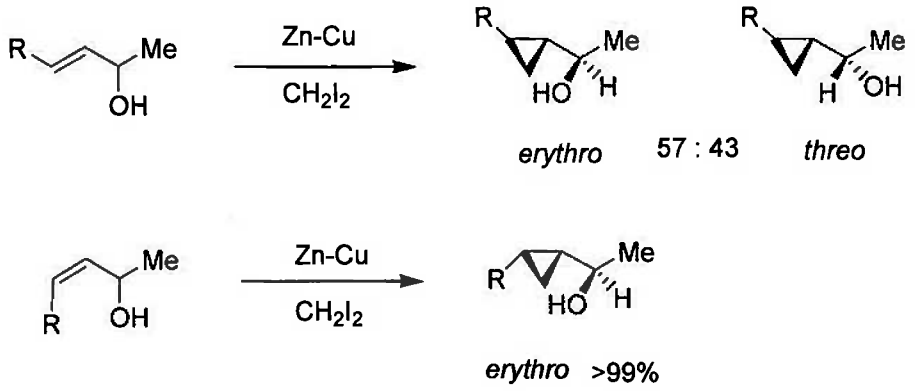
The delivery of methylene or higher analogues to alkenes to afford cyclopropanes may occur on either face of the alkene. Consequently, various cyclopropyl isomers can be formed. The majority of Simmons-Smith reactions involve the addition of methylene to olefins and therefore only one enantiomeric pair is generated (**Scheme 1.2 (a)**). However, the addition of higher carbene analogues to alkenes possessing 1,2-disubstitution (where $R^1 \neq R^2$) may result in the formation of two enantiomeric pairs (**Scheme 1.2 (b)**). Therefore, for this process to be efficient it is important to be able to exert some stereocontrol in these reactions in order to obtain cyclopropanes of high *de* and/or high *ee*.



Scheme 1.2

An important advancement towards asymmetric synthesis of cyclopropanes via the Simmons-Smith procedure was the observation that the presence of proximal oxygen atoms strongly directs the cyclopropanation of allylic alcohols.[94,100,101] Stereocontrol is achieved through coordination[95] of the allylic alcohol oxygen to the zinc of the reactive carbenoid species.[100] Ratier and colleagues found that the Simmons-Smith reaction of *cis*-allylic alcohols was highly stereospecific giving the *cis-erythro*-cyclopropyl alcohols in greater than 99% *de*.[102] However, the reactions of the corresponding *trans*-allylic alcohols were not stereospecific giving the *trans*-cyclopropyl alcohols as mixtures of their *threo*- and *erythro*-isomers **(Scheme 1.3)**. Without going into great detail, these observations are a consequence of the transition states. When utilising the *cis*-alcohols only one transition state is favoured and that transition state results solely in formation of the *erythro*-isomer. The case is more complicated for the *trans*-alcohols since their cyclopropanation can

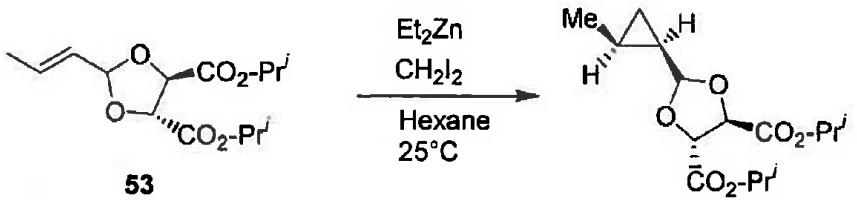
proceed via three separate transition states.[102] Subsequently, selectivity is not observed when using the *trans*-alcohols. Charette and co-workers discovered almost twenty years later that stereocontrol could be achieved in the cyclopropanation of *trans*-allylic alcohols if chiral allylic alcohols are used.[97]



Scheme 1.3

The presence of allylic oxygen atoms in the form of ethers,[103] esters[104] and acetals[105] rather than as free hydroxyl groups can also exhibit some diastereocontrol in the cyclopropanation of olefins. Fukuyama and co-workers successfully synthesised the bicyclic sesquiterpene, (+)-bicyclohumulenone, by utilising a stereoselective Simmons-Smith cyclopropanation on an olefin containing both an allylic ether and acetal to introduce the cyclopropyl moiety.[106] Despite the high diastereoselectivity observed in this case, diastereomeric ratios observed for other substrates can vary dramatically depending on the reaction conditions and the steric influences of the olefins used.[101]

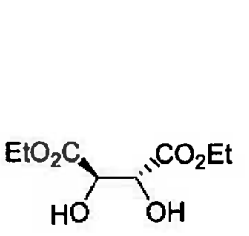
More significant advances in the Simmons-Smith asymmetric synthesis of cyclopropanes have occurred with the exploitation of chiral auxiliaries or reagents. Chiral auxiliaries such as (*R*,*R*) or (*S*,*S*)-tartaric acid esters, attached to the reacting olefin, are able to facilitate enantioselective cyclopropanation.[95] For example, as depicted in **Scheme 1.4** the Simmons-Smith cyclopropanation of acetal **53** proceeded in 90% yield to give cyclopropane **54** in 94% diastereomeric excess.[95] Other chiral auxiliaries that have been utilised to synthesis chiral olefins include 1,4-di-*O*-benzyl-*L*-threitol and (*S*,*S*)-hydrobenzoin.[95]



53 54

Scheme 1.4

The observation that the presence of a chiral auxiliary enhances enantioselectivity of the Simmons-Smith cyclopropanation reaction stimulated the idea that the presence of a chiral reagent not attached to the reacting substrate may also have the same effect. This was first proven to be the case in 1992 when Ukaji and co-workers reported that moderate to high ee could be achieved in the Simmons-Smith cyclopropanation of allylic alcohols in the presence of a stoichiometric amount of (+)-(*R*,*R*)-diethyl tartrate (DET) **55**.[107] Since that time, many other chiral reagents either required catalytically or stoichiometrically, have been identified as promoters of *ee* in this reaction. These include dioxaborolane **56**[108,109] and titanium catalyst **57** designed by Charette and co-workers,[110] the chiral disulfonamides **58** used extensively by Denmark and co-workers,[111,112] Takahashi and co-workers[113] and Imai and co-workers[114] and the binaphthyl carboxamides **59** developed by Kitajima and co-workers.[115] The success of these reagents depends on their ability to complex to the halomethylzinc reagent and alkene simultaneously. For this to occur, the chiral reagent must possess a Lewis acidic site for accepting the allylic alcohol and a second site for coordination of the iodomethylzinc.[115]



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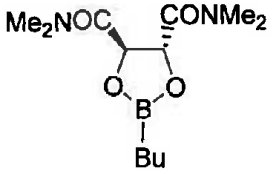

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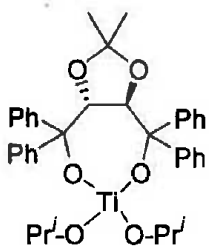

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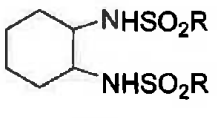

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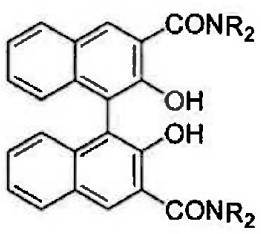


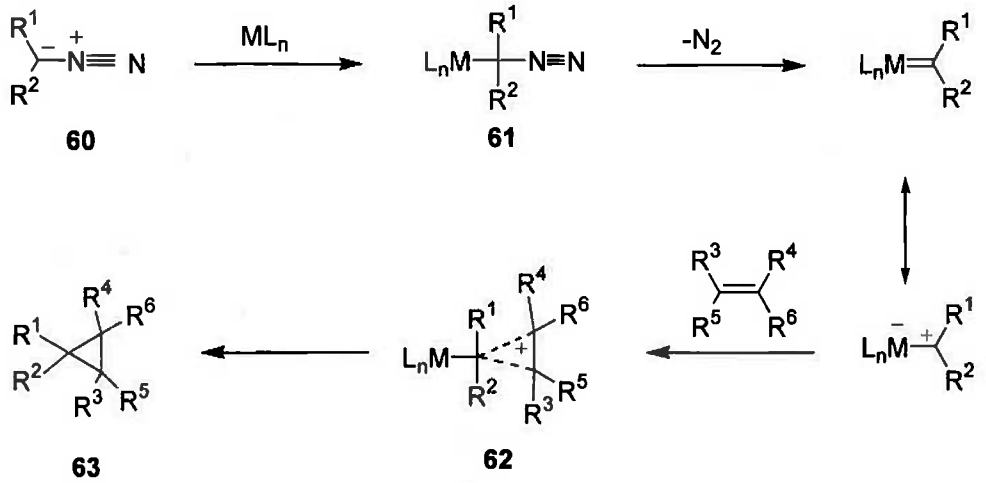
59

Table 1.2 Range of %*ee*'s obtained for the cyclopropanations of various olefins in the presence of one of the above chiral reagents.

Reagent used	Reference	% *ee*
55	Ukaji and co-workers (1993)[107]	34-92
56	Charette and co-workers (1994)[108]	91-94
57	Charette and co-workers (1995)[110]	60-90
58	Takahashi and co-workers (1992)[113]	13-82
58	Denmark and co-workers (1995)[112]	0-80
58	Denmark and co-workers (1996)[111]	3-89
58	Imai and co-workers (1994)[114]	59-86
59	Kitajima and co-workers (1997)[115]	14-94

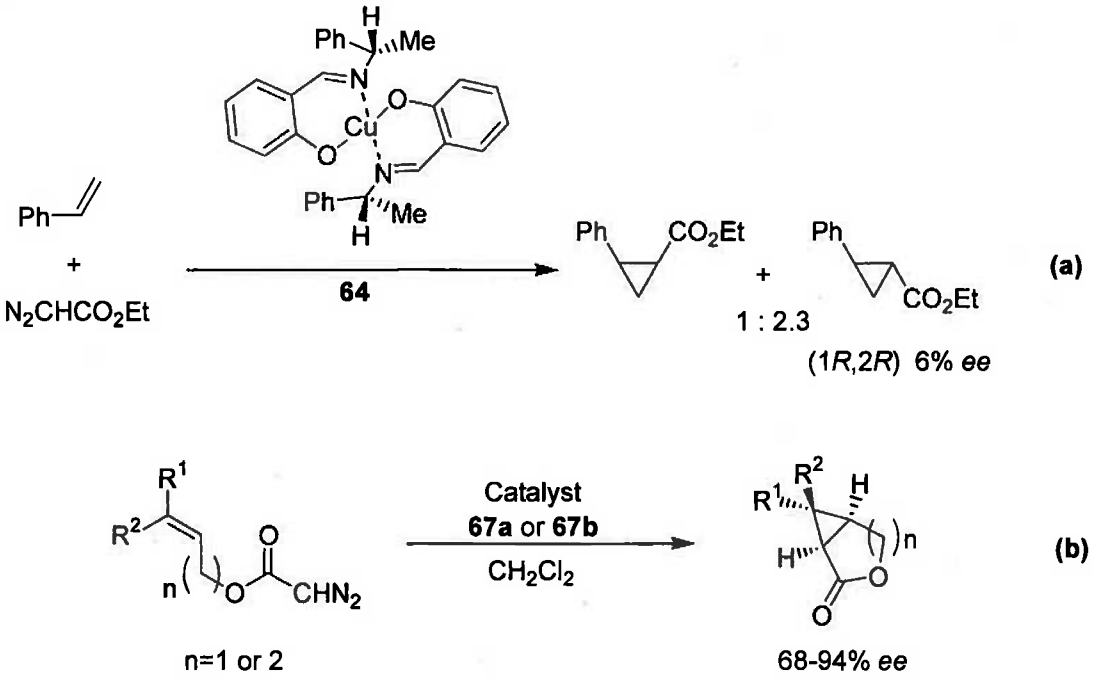
As can be seen in **Table 1.2**, the enantio-control observed for each catalyst can vary greatly. This variation is a result of the steric and electronic influences of both the reacting olefin and catalyst. For instance, the cyclopropanation of 3-methyl-2-buten-1-ol in the presence of titanium catalyst **57** gives the corresponding cyclopropane in 30% less *ee* compared to the same reaction with cinnamyl alcohol.[110] Variation in the R groups of catalysts **58** and **59** can also have a dramatic effect on *ee* incorporation. For example, simply changing the R group in catalyst **59** from a methyl to an ethyl, dramatically increases the enantioselectivity in the cyclopropanation of cinnamyl alcohol from 14% *ee* to 94% *ee*.[115] The potent antifungal agent FR-900848, mentioned previously in **section 1.2**, and the structurally related U-106305 (a cholesterol ester transferase protein inhibitor) have both been successfully synthesised via exploitation of chiral reagent **56**.[116,117]

A second procedure for the cyclopropanation of olefins using carbenoids involves metal-catalysed carbene transfer from diazo precursors. The reacting diazo compounds are most commonly diazoalkenes,[118] diazoacetates,[119-121] diazoacetamides[121] and diazoketones[122] and usually copper, ruthenium or rhodium catalysts are used (For a review see Doyle and Protopopova[122]). These reactions proceed via coordination of the diazo precursor **60** to the metal-catalyst (ML_n), followed by loss of nitrogen[123] from compound **61** and finally transfer of the resulting carbenoid species from the metal-catalyst to the alkene via transition state **62** to give cyclopropanes of type **63 (Scheme 1.5)**.



Scheme 1.5

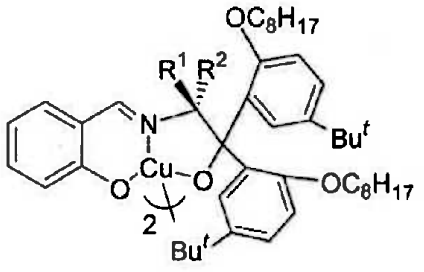
Cyclopropanation of alkenes via this method can proceed either intermolecularly or intramolecularly depending on whether the diazo and alkene functionalities are located on separate molecules (**Scheme 1.6 (a)**) or on the same molecule, respectively (**Scheme 1.6 (b)**).



Scheme 1.6

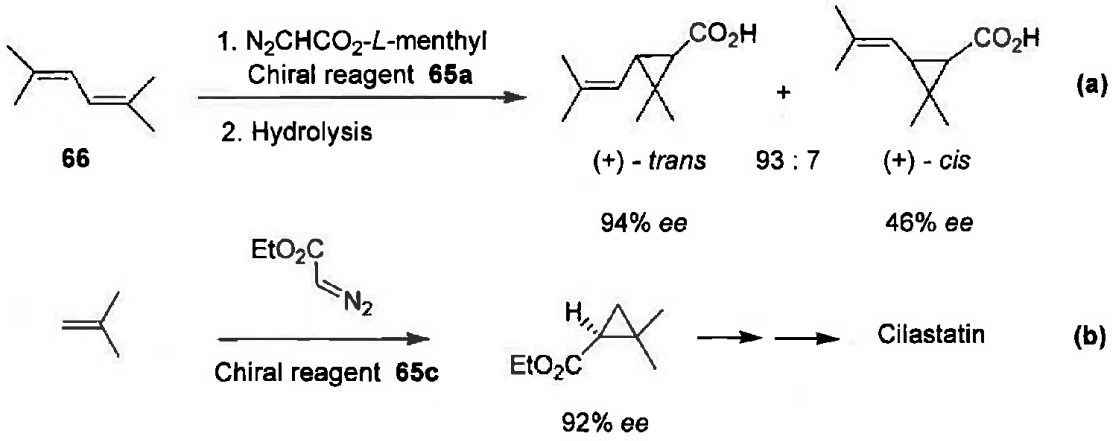
The reaction of styrene and ethyl diazoacetate in the presence of *bis*(acetylacetonato)copper(II) **64**, depicted in **Scheme 1.6 (a)**, was reported in 1966 by Nozaki and co-workers.[123] This reaction was the first example of asymmetric induction of cyclopropanes using a chiral catalyst. Even though the *ee* of this reaction was poor (only

6%) this research stimulated further research into the development of salicyladimine catalysts.[122] For instance, Aratani went on to develop several important salicyladimine copper catalysts **65a-c**, that have been used for the commercial synthesis of some pyrethroid insecticides along with cilastatin, a dehydropeptidase I inhibitor.[124]



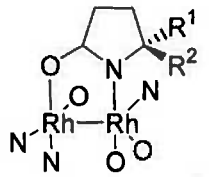
65 **a** : R^1 = H, R^2 = CH_3
b : R^1 = CH_3, R^2 = H
c : R^1 = H, R^2 = CH_2Ph

As depicted in **Scheme 1.7 (a)**, (+)-*trans*-chrysanthemic acid was synthesised in high diastereoselectivity and enantioselectivity from the chiral copper catalysed reaction of l-menthyl diazoacetate with olefin **66**, followed by ester hydrolysis. Preferential formation of the (+)-*trans* isomer only occurred with exploitation of a bulkier alkyl diazoacetate and with use of copper catalyst **65a**. In contrast, the reaction of ethyl diazoacetate with 2-methyl-5,5,5-trichloro-2-pentene in the presence of copper catalyst **65b**, the (*S*)-isomer of **65a**, resulted in high diastereo- and enantio-selectivity of the corresponding (+)-*cis* cyclopropyl isomer. Consequently, (+)-*cis*-permethrinic acid was successfully synthesised via this pathway. Therefore, the chirality of the catalyst used strongly influences the selectivity observed in these reactions. Utilisation of the (*R*)-copper catalyst **65c** in the reaction between isobutylene and ethyl diazoacetate, generated (+)-1*S*-2,2-dimethyl-cyclopropanecarboxylic acid, an important precursor to cilastatin, in 92% *ee*[124] (**Scheme 1.7 (b)**).

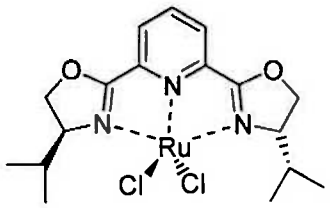


Scheme 1.7

In addition to chiral copper catalysts, chiral dirhodium (II) catalysts[121,125,126] and ruthenium catalysts[118,120] have been successful in the asymmetric cyclopropanation of olefins using diazo-precursors. Two examples of dirhodium catalysts are the chiral dirhodium (II) carboxamides **67a-b** used to catalyse the intramolecular reactions depicted in **Scheme 1.6 (b)**.[118] Compound **68** is just one example of a ruthenium catalyst used in the carbene transfer of diazo precursors to olefins.[120]



For ease only one lactam ring has been drawn



67 a : R^1 = H, R^2 = CO_2Me
b : R^1 = CO_2Me, R^2 = H

68

There have been numerous catalysts with either copper or rhodium metal centres attached to *bis*-oxazoline ligands. The copper catalysts are usually more effective at inducing enantioselectivity than the rhodium catalysts. Similarly, copper catalysts are more effective at carbene transfer than ruthenium catalysts even though the latter make more stable carbene complexes. In addition, there is limited application with ruthenium catalysts since good yields are usually only observed with conjugated alkenes.[122]

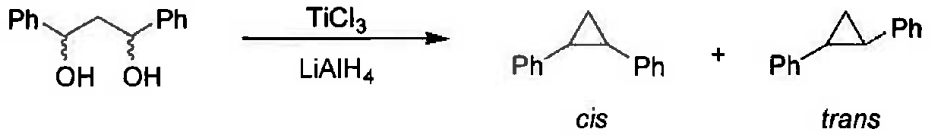
Despite great advances in the asymmetric synthesis of cyclopropanes via carbene transfer to olefins, only a handful of reactions have been able to achieve greater than 95% *ee*.[122] Enantioselectivity of these reactions is influenced by a number of factors including the ligand size and transition metal of the catalyst, the bulkiness of the carbene species and the nature of the olefin. Consequently, a given catalyst may induce high *ee* into a specific substrate but variations of this substrate can dramatically reduce ee. Generally, these reactions work best with mono-substituted alkenes.

The intermediacy of transition-metal-carbene complexes in various catalytic processes, including the previously mentioned metal-catalysed carbene transfer reactions using diazo-precursors, increased interest in these types of complexes. Subsequently, various transition metal carbene complexes of type L_nM=CRR', have been successfully used in the formation of cyclopropanes from olefins (see Review by Brookhard and Studabaker[127]). The transition metals (M) most commonly used are chromium, iron, tungsten, nickel and

molybdenum. These metal-catalysed carbene transfer reactions do not involve the use of diazo-compounds for the generation of the metal-carbene complex. Most commonly, these metal-carbene complexes are formed by ionisation of a leaving group that is located alpha to the metal-alkyl complex. The stereoselectivity observed for these reactions depends greatly on the reagent and solvent used. Some stereo-control can be achieved by variation of the metal and ligand. However, the enantioselectivities reported for these types of reactions are poor to moderate (10-38%). Therefore, this method is not very efficient for the asymmetric synthesis of cyclopropanes.

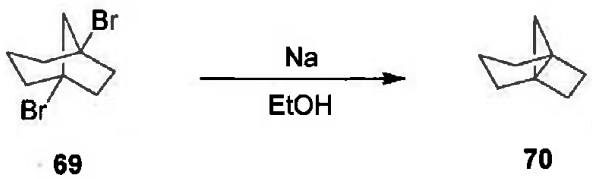
1.6.2 1,3-Elimination of heteroatoms

Although not as common as the carbene transfer reactions previously mentioned, 1,3-elimination of heteroatoms is another procedure that has been successfully used for the formation of cyclopropanes. As depicted in **Scheme 1.8**, Baumstark and co-workers found that treatment of 1,3-diphenyl-1,3-propanediol with the reagent prepared from titanium trichloride and lithium aluminium hydride gave *cis* and *trans*-1,3-diphenylcyclopropanes.[128] This reaction is believed to occur via the ring-closure of a diradical formed after thermal decomposition of the titanium (II) dialkoxide complex formed originally between the diol and the titanium species.



Scheme 1.8

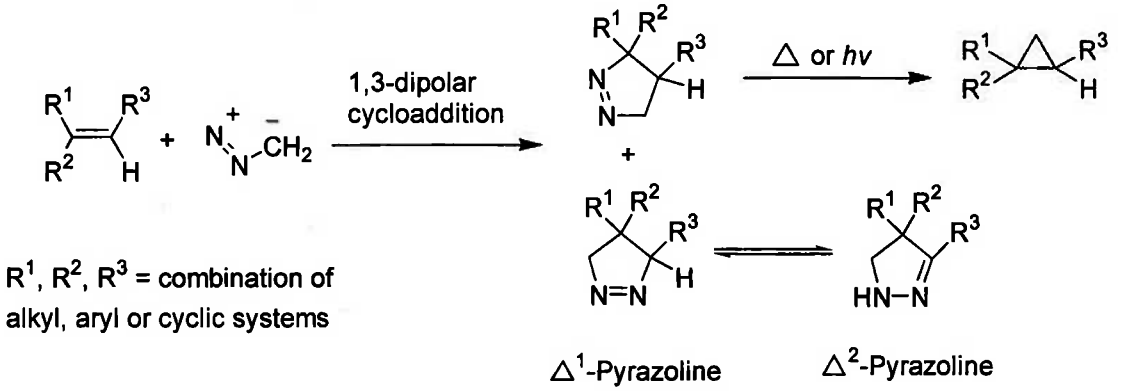
Tricyclic compound **70** has been successfully synthesised via a dissolving metal reduction on dibromide **69** that results in 1,3-dibromide elimination[129] **(Scheme 1.9)**. Similarly, 1,3-diiodide elimination of *bis*-diiodides via lithium aluminium hydride, sodium in liquid ammonia or Raney nickel reductions affords *bis*-cyclopropanes.[130]



Scheme 1.9

1.6.3 Nitrogen Extrusion from Pyrazolines

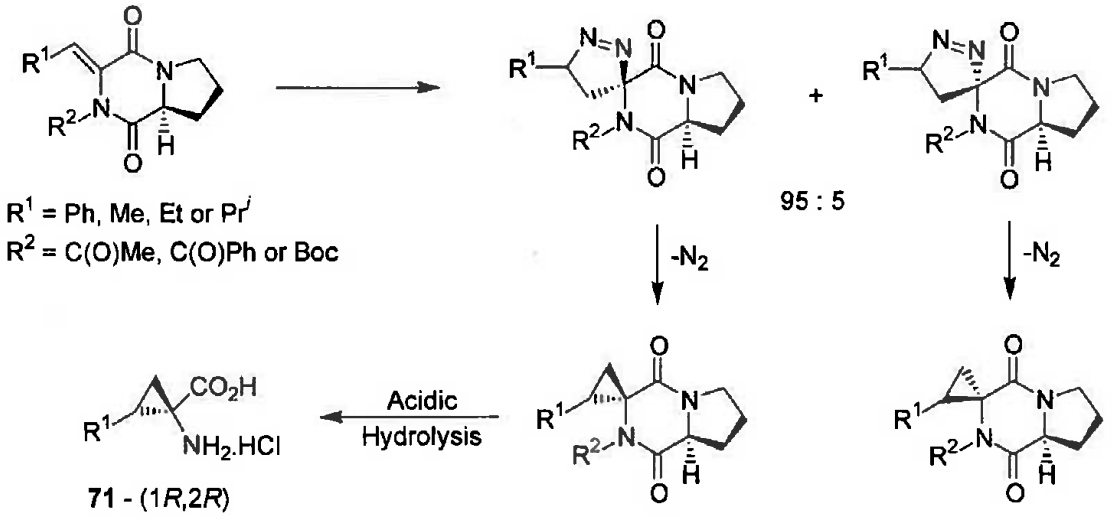
Another common procedure for the asymmetric synthesis of cyclopropanes involves the extrusion of nitrogen from Δ^1-Pyrazolines. Δ^1-Pyrazolines are generated via 1,3-cycloaddition of diazoalkanes to alkenes[131] and their subsequent loss of nitrogen as a result of photo-induced decomposition[132] affords cyclopropanes **(Scheme 1.10)**.



Scheme 1.10

There are several ways to introduce asymmetry in these reactions. These include the use of chiral alkenes, the use of 1,3-dipoles and chiral dipolarophiles and finally the use of intramolecular reactions.[133] Most commonly, chiral alkenes are utilised in order to guide the addition of the diazoalkane to the less hindered face of the alkene. For instance, diazomethane preferentially attacks chiral 3-substituted furanones on the π-face opposite to the substituent.[131,132] Therefore, attack on the less hindered face of these furanones results in the preferential formation of anti adducts. However, in contrast, syn adducts are favoured when chiral 4-alkoxy pentenoates are used since these open-chain structures possess more conformational freedom.[131]

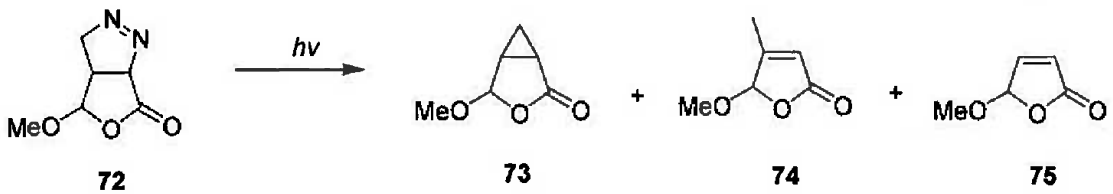
Alcaraz and co-workers have synthesised ACC derivatives **71** in up to 90% *de* by exploitation of diketopyperazines.[134] The rigid diketopyperazine moiety promotes cycloaddition of the diazo-compound to the less hindered face **(Scheme 1.11)**.



Scheme 1.11

Cycloadditions of diazo compounds to enantiomerically pure 5-(*R*)-menthyloxy-2(5*H*)-furanones has also introduced some *de* into the corresponding pyrazolines, but only to a maximum of 44%.[133] Spiropyrazolines and hence spirocyclopropanes have also been stereoselectively synthesised via cycloadditions to chiral 5-alkylidene-1,3-dioxan-4-ones and 3-benzylidene-β-lactones.[135]

The major disadvantage with this method is the formation of side products. Firstly, Δ^1-pyrazolines can undergo tautomerisation to their more stable Δ^2-pyrazolines[133,136] (see **Scheme 1.10**). However, like Δ^1-pyrazolines, Δ^2-pyrazolines afford cyclopropanes upon heating or upon irradiation with photons. The most common side products that can be formed during photolysis of the pyrazolines are the corresponding methyl-substituted derivatives or the regenerated starting material via cycloreversion[133] **(Scheme 1.12)**.



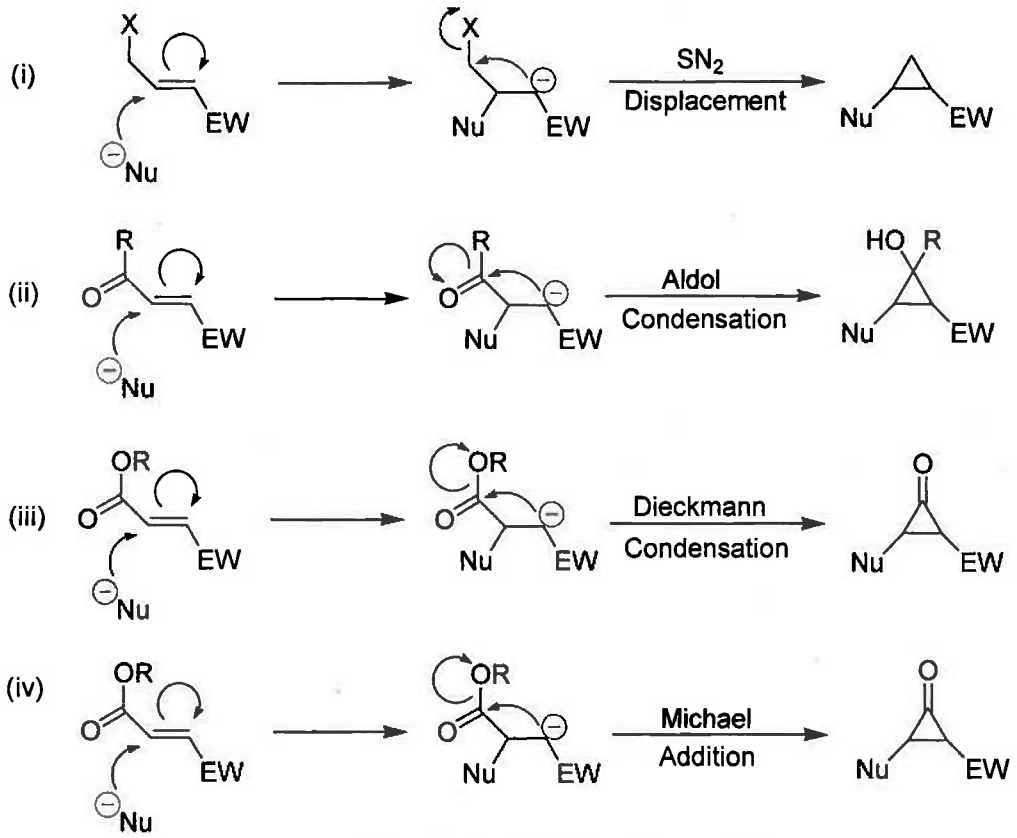
Scheme 1.12

The ratio of products **73-75** formed during photolysis of pyrazoline **72** is influenced by the solvent and sensitiser used. Therefore, in some cases the formation of the cyclopropyl product can be controlled.

1.6.4 Michael-Initiated Ring Closure (MIRC) Reactions

The formation of cyclopropanes can proceed via a two step process initiated by Michael addition to an α,β-unsaturated carbonyl compound followed by intramolecular ring-closure of the resulting enolate. Not surprisingly, these types of reactions are known as Michael-Initiated Ring Closure (MIRC) reactions.[137]

Most commonly, the nucleophilic conjugate addition to an α,β-unsaturated carbonyl compound involves the use of sulfonium, sulfoxonium or phosphonium ylides.[138] However, there are some cases where the reacting nucleophile is an enolate rather than an ylide.[139,140] Ring-closure to afford the desired cyclopropyl motif can occur via several methods as illustrated in **Scheme 1.13**. These include (i) SN_2 displacement, (ii) Aldol condensation, (iii) Dieckmann condensation and (iv) Michael addition.[141]

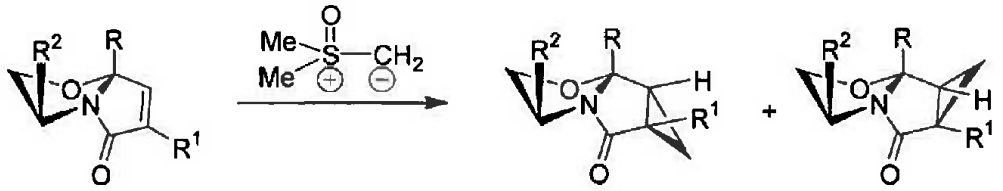


Scheme 1.13

Asymmetric cyclopropanation via MIRC reactions is possible through the utilisation of either chiral ylides or chiral α,β-unsaturated compounds.[138] If chiral ylides are used the

reaction is reagent-controlled but if chiral α,β-unsaturated compounds are used the reaction is substrate-controlled. Reagent-controlled asymmetric cyclopropanations have occurred via the reactions of achiral α,β-unsaturated compounds with either chiral aminosulfoxonium, sulfonium, sulfoxonium or arsonium ylides.[138] Although some reactions of aminosulfoxonium or sulfonium ylides proceed to give cyclopropanes in high optical purity, generally these reagent-controlled asymmetric syntheses proceed with poor stereocontrol giving cyclopropanes of low *ee* and moderate diastereoselectivies.

Asymmetric cyclopropanation via MIRC reactions has been more successful with substrate-controlled reactions of achiral phosphonium, sulfoxonium or sulfonium ylides with chiral α,β-unsaturated substrates. The use of α,β-unsaturated bicyclic γ-lactams **76a-g**, also known as 'Meyer's lactams', are excellent examples of the use of chiral substrates that undergo stereospecific cyclopropanation.[142-145] Meyers and co-workers allowed various α,β-unsaturated bicyclic γ-lactams to react with dimethylsulfoxonium methylide to generate the corresponding *endo* **77** or *exo* **78** cyclopropanated lactams in greater than 90% *de*[142] **(Scheme 1.14)**. The nature of the R groups attached to the lactams strongly influences the *endo-exo* selectivity. For instance, reaction of lactam **76a** with the sulphur ylide predominately affords the *endo* cyclopropyl product in 98% *de*, while the same reaction with lactam **76b** (where R changes from methyl to hydrogen) predominately affords the *exo* cyclopropyl product in greater than 93% *de*.



76 *endo* **77** *exo* **78**

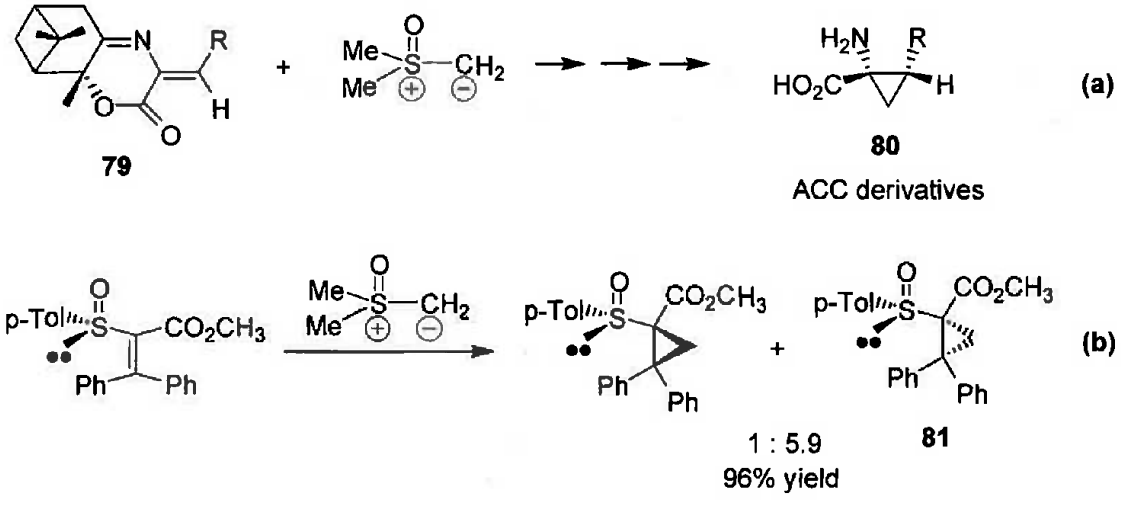
76	R	R^1	R^2	*endo/exo*	*de*%
a	Me	CO_2Me	Pr^i	100/1	98
b	H	CO_2Me	Pr^i	<1/30	>93
c	Me	H	Bu^t	19/1	90
d	Me	S(O)Me	Pr^i	>19/1	>90
e	H	S(O)Me	Pr^i	<1/19	>90
f	Me	H	Pr^i	40/1	95
g	Me	Ph	Pr^i	>29/1	93

Scheme 1.14

Subsequent hydrolysis of the cyclopropyl lactams gives the corresponding chiral cyclopropyl keto esters in high *ee*. Chemical manipulations of the cyclopropanes generated from this methodology has been successful in synthesising some biologically important molecules including *cis*-(1*S*,3*R*)-deltamethrinic acid, a precursor to the pyrethroid insecticide deltamethrin, and dictyopterene C and C', the latter being a potent seaweed sperm attractant.[142] In addition, Meyers and co-workers have extended this methodology to the formation of enantiomerically-pure 1,2,3-tri-substituted cyclopropanes.[144]

The synthesis of cyclopropyl precursors of pyrethroid insecticides has also been successfully achieved in high *ee* from the reactions of *L*-tartaric acid derived α,β-unsaturated esters and either phosphonium or sulfonium isopropylide. In general, sulfonium isopropylide possesses marginally better stereocontrol than the phosphonium equivalent.[138]

There are also several other chiral auxiliaries that have been used for substrate-controlled asymmetric cyclopropanation. For instance, cyclopropanation of rigid 1,4-oxazinones **79**, derived from (1*R*,2*R*,5*R*)-2-hydroxy pinan-3-one, and their subsequent hydrolysis resulted in the formation of optically pure 1-amino 2-alkyl cyclopropane carboxylic acids **80** (ACC derivatives)[146] (**Scheme 1.15 (a)**).



Scheme 1.15

As illustrated in **Scheme 1.15 (b)**, the reaction of dimethyl sulfoxonium methylide with optically pure methyl α-(p-tolyl sulfinyl) acrylate (a Michael acceptor) gave the

corresponding *R,S* cyclopropyl isomer **81** in 82% yield and 98% *de*, after chromatographic purification and subsequent recrystallisation.[147]

As can be seen from discussion of the various methods of cyclopropanation, there is not one type of reaction that is versatile to a range of substrates. Variation in the olefinic substrate used or changes to the R groups of the reacting Simmons-Smith reagent, diazo-species or ylide can have dramatic effects on the diastereoselectivity and/or the enantioselectivity observed for the cyclopropyl product. Furthermore, some catalysts that have shown impressive stereocontrol in the cyclopropanation of select olefins by carbene transfer, do not exhibit universal control. Once again, variation in the olefinic substrate and the carbene reagent utilised strongly influences the success of a given catalyst.

In regards to asymmetric cyclopropanation, the efficient synthesis of distereomercially and enantiomerically-pure cyclopropanes still remains a considerable challenge. There is also a deficiency in methods for the construction of diversely functionalised cyclopropanes that contain greater than di-substitution. However, as will be discussed shortly (Section 1.8), a recent methodology developed by our group at The University of Adelaide allows for the preparation of both tri- and di-substituted diastereomerically-pure cyclopropanes. Furthermore, the exploitation of chiral cobalt catalysts has also allowed for the preparation of enantio-enriched tri-substituted cyclopropanes.

1.7 Methods for resolution of cyclopropanes

As illustrated in the research already presented, optically pure cyclopropanes are very rarely obtained directly by the various cyclopropanation reactions. Although some reactions incorporate high *ee*, purification methods are still required in order to obtain optically pure compounds by the removal of the unwanted enantiomer.

Since enantiomers possess very similar physical properties it is usually impossible to separate them by conventional methods such as column chromatography or recrystallisation.[148] However, in some cyclopropanation reactions where chiral substrates have been used and the chiral centre is retained in the product, the resulting diastereomers can be easily separated by these methods prior to cleavage of the chiral auxiliary to give the pure enantiomers.

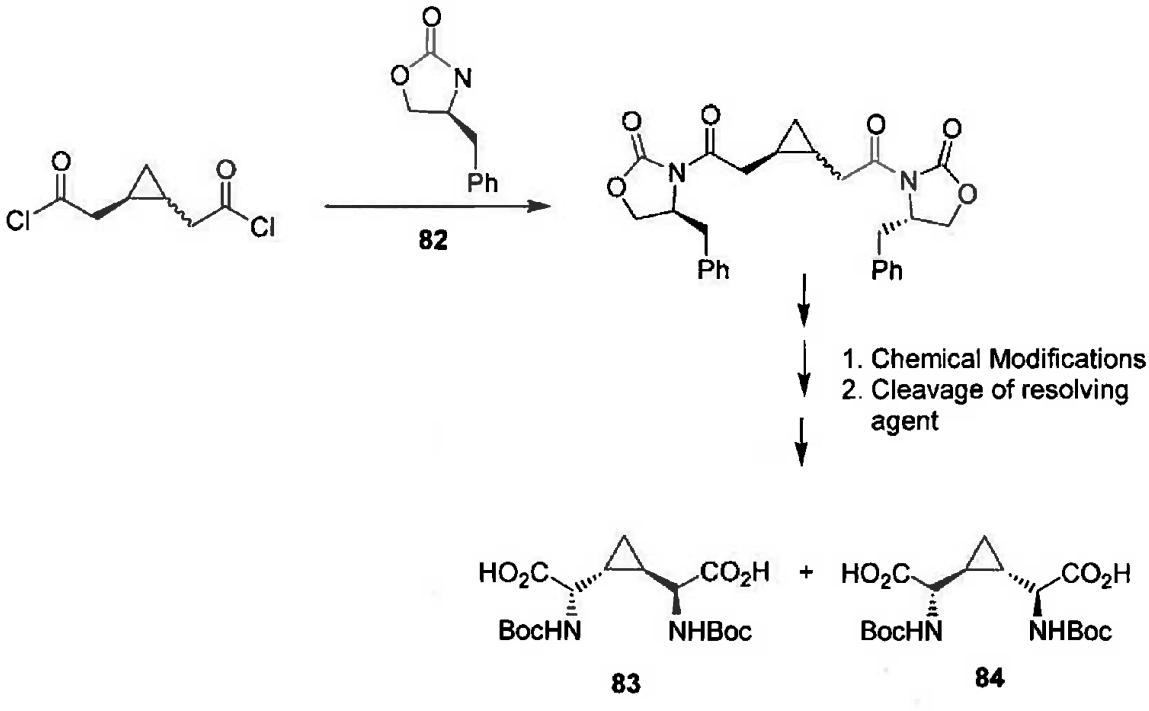
Resolution of enantiomers can be achieved by one of three ways. These include manual separation, chemical resolution or enantiomeric discrimination using micro-organisms.[148] Manual separation of enantiomers can only occur if the enantiomers undergo spontaneous separation into enantiomeric crystals upon recrystallisation. If this process occurs and the crystals appear physically different then separation can be achieved via the use of lens and tweezers. This method of resolution is not common since the enantiomers must be crystalline and even if they are crystalline very few form enantiomeric crystals.[136,148]

Chemical resolution of enantiomers can be achieved by either direct[149] or indirect[150] methods. Direct methods include resolution by paper, column, thin-layer, gas or liquid chromatography while indirect methods involve the conversion of enantiomers to more easily separable diastereomers.[136]

The use of gas chromatography (GC) or high performance liquid chromatography (HPLC) involves the exploitation of an optically active stationary phase. Most commonly separation of enantiomers occurs due to differences in attractive forces (i.e. hydrogen bonding / hydrophobic interactions) of the two enantiomers with the chiral stationary phase or due to selective formation of inclusion complexes of one enantiomer with the chiral selector.[149,151] These direct methods of resolution may not be suitable for all compounds. For instance, the use of GC is restricted to substrates with hydrogen donor or acceptor sites and/or substrates with sufficient volatility.[149] In addition, some chiral GC and HPLC columns are expensive, have relatively short life spans and/or have insufficient

sensitivity.[150] Therefore in some situations it may be more appropriate to use indirect chemical resolution.

Conversion of enantiomers to diastereomers via the use of a chiral resolving agent is one of the most fundamental methods of enantiomeric separation.[136] Since diastereomers have different physical properties they can be separated by recrystallisation or normal (i.e. non-chiral) chromatography. After the diastereomers have been separated the enantiomers can be regenerated by cleavage of the resolving agent. Carboxylic acids or amines can be converted to diastereomeric salts that can be separated by fractional recrystallisation.[152] Historically, Pasteur successfully separated the enantiomers of tartaric acid by using this method.[148] However, the process of fractional recrystallisation can be long and tedious[136] and therefore, it can be more beneficial to form neutral compounds that can be separated by chromatography. One such method that was used for the separation of cyclopropyl enantiomers and is discussed later in this thesis involves the use of (*S*)-(-)-4-benzyl 2-oxazolidinone. Neset and colleagues used (*S*)-(-)-4-benzyl 2-oxazolidinone **82** to resolve *bis*-cyclopropyl precursors of cyclopropane-1,2-*bis*(glycine) derivatives **83** and **84**,[153] as illustrated in **Scheme 1.16**. There are numerous other resolving agents available for indirect chemical resolution of enantiomers.



Scheme 1.16

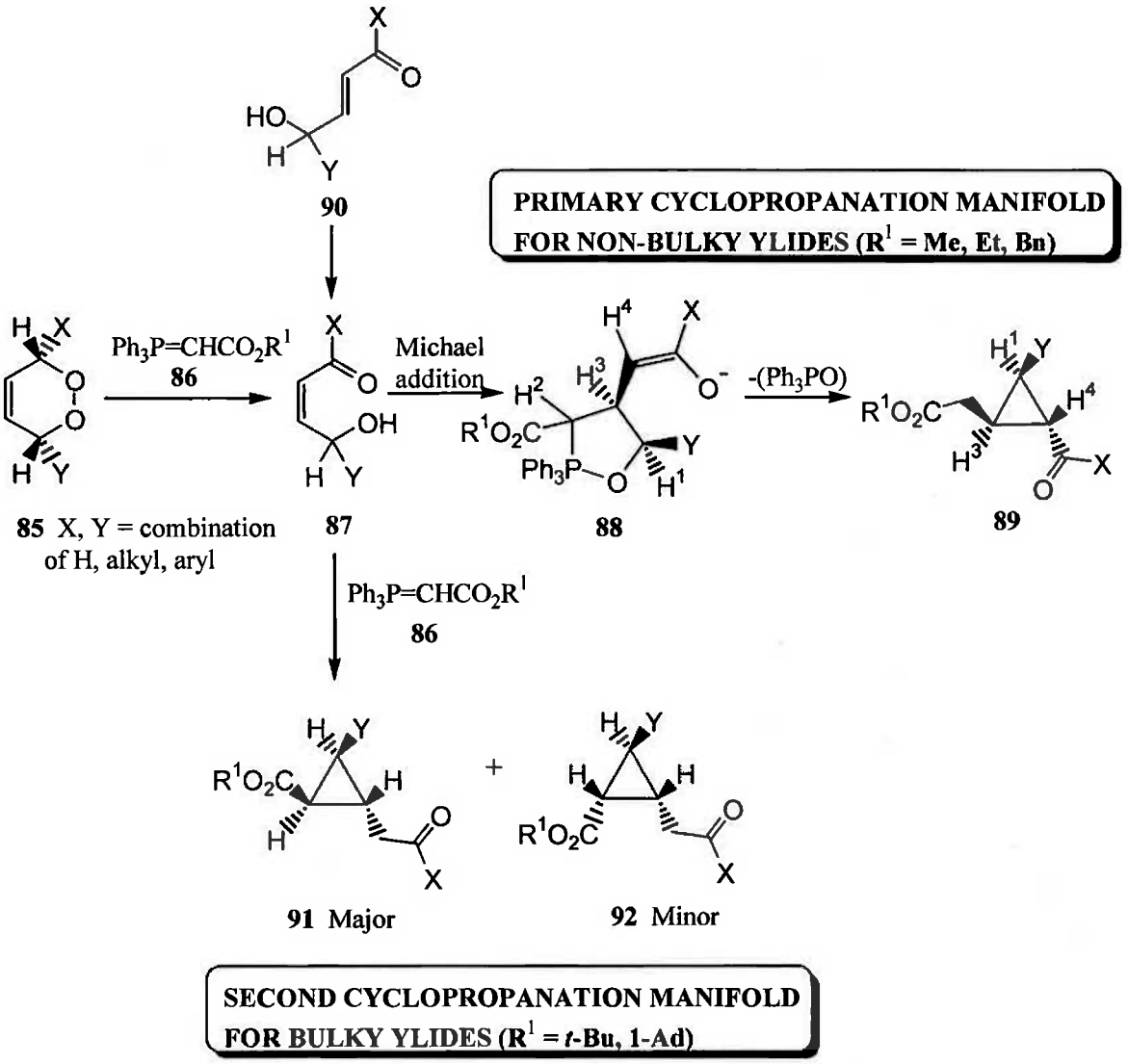
Enantiomer discrimination by micro-organisms is another method employed for the separation of enantiomers. This method relies on the micro-organisms enzymes selectively metabolising only one enantiomer.[148] For instance, *S* amido acids are selectively hydrolysed by the enzyme carboxypeptidase while *R* amido acids are not. Therefore, the resulting *S* amino acid can now be separated from the unreacted *R* amido acid.[152] Another interesting chemoenzymatic process for the formation of chiral cyclopropanes utilises the microbially derived *cis*-1,2-dihydrocatechols. Banwell and Forman have successfully used this methodology for the synthesis of an enantiopure (1*R*)-*cis*-pyrethroid precursor.[154] Therefore, microbial discrimination can be used in the resolution of enantiomers directly, or be used to generate chiral starting materials of importance in asymmetric synthesis.

1.8 Exploitation of 1,2-dioxines for cyclopropane construction

Our approach to diasteromerically-pure or enantiopure diversely functionalised cyclopropanes utilises the MIRC reaction between either 3,6-disubstituted 1,2-dioxines[155] or their isomeric *trans* γ-hydroxy enones with stabilised phosphorus ylides.[156] This method avoids the use of potentially explosive diazo precursors and gives rise to diversely functionalised cyclopropanes in high yield and diastereomeric excess.[155,157] The first step of this primary cyclopropanation manifold **(Scheme 1.17)** involves induced ring-opening of the 1,2-dioxine **85** to its isomeric *cis* γ-hydroxy enone **87** by the mildly basic ylide **86**. Subsequent Michael addition of the ylide to the enone and attachment of the electrophilic phosphorus pole of the ylide to the hydroxyl moiety affords the intermediate 1-2λ^5-oxaphospholanes **88** and sets up the *cis* stereochemistry between H^1 and H^3. Cyclisation of the resultant enolate, expulsion of triphenylphosphine oxide and proton transfer from the reaction manifold gives rise to the observed cyclopropanes **89**. This cyclopropanation pathway provides for a range of substituents at the 3- and 6-positions of the 1,2-dioxine, hence affording a range of both di- and tri-substituted cyclopropanes. In addition, this primary cyclopropanation manifold may be entered utilizing the related *trans* γ-hydroxy enones **90**.

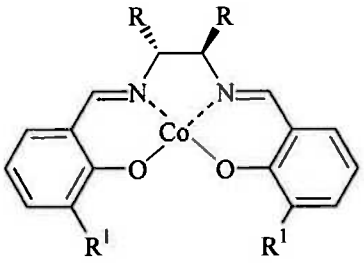
The utilization of bulky ester stabilised phosphorus ylides favours the formation of a completely different cyclopropyl series[158] **(Scheme 1.17)**. However, the use of sterically bulky ester ylides under concentrated conditions and/or elevated temperatures favours the primary cyclopropanation pathway while dilute conditions and/or sub-ambient temperatures favours the formation of cyclopropanes **91** and **92** via the second cyclopropanantion manifold. Likewise, the addition of lithium bromide in the presence of both bulky and non-bulky ester ylides favours the second cyclopropanation manifold.[159] For instance, reaction of dioxine **85** (X = Y = Ph) with both *tert*-butyl ester ylide **86** (R^1 = *tert*-butyl) and 1-adamantyl ylide (R^1 = 1-Ad) without added lithium bromide results in approximately an equal mixture of cyclopropane **89**, originating from the primary manifold, as compared to cyclopropanes **91** and **92**, originating from the second manifold. However, in the presence of lithium bromide formation of cyclopropanes **91** and **92** is dramatically favoured over formation of cyclopropane **89**.[159] Furthermore, utilisation of non-bulky ylides, such as the benzyl ester ylide **86** ($R^1 = CH_2Ph$) in the presence of lithium bromide exclusively forms cyclopropanes **91** and **92**, of which none is formed in the absence of the lithium salt.[159] The effect of lithium bromide on reaction outcome is

attributed to stabilisation of enolate **88**, resulting in the situation where intramolecular quenching of the enolate is favoured over intramolecular cyclisation to afford cyclopropane **89**. Exploitation of these different experimental conditions can give rise to a diverse range of cyclopropanes.



Scheme 1.17

Recently, this methodology has been extended to the synthesis of enantio-enriched cyclopropanes by the utilisation of cobalt (II) catalysts of type **93-96**.[160,161] Formation of enantio-enriched cyclopropanes of type **99** was achieved via reaction of benzyl ester ylide with *cis* γ-hydroxy enones **98a-e** obtained from ring-opening of the corresponding 1,2-dioxines **97a-e** in the presence of a chiral cobalt (II) catalyst **(Scheme 1.18)**.



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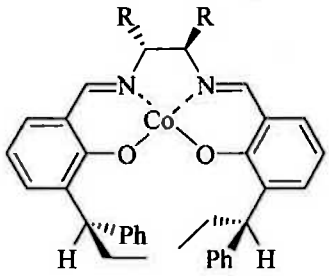

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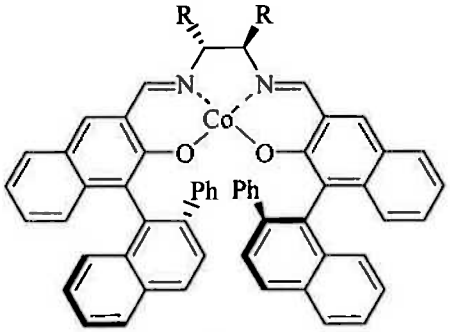

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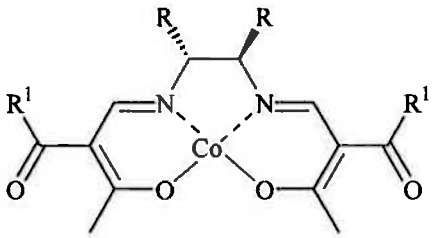

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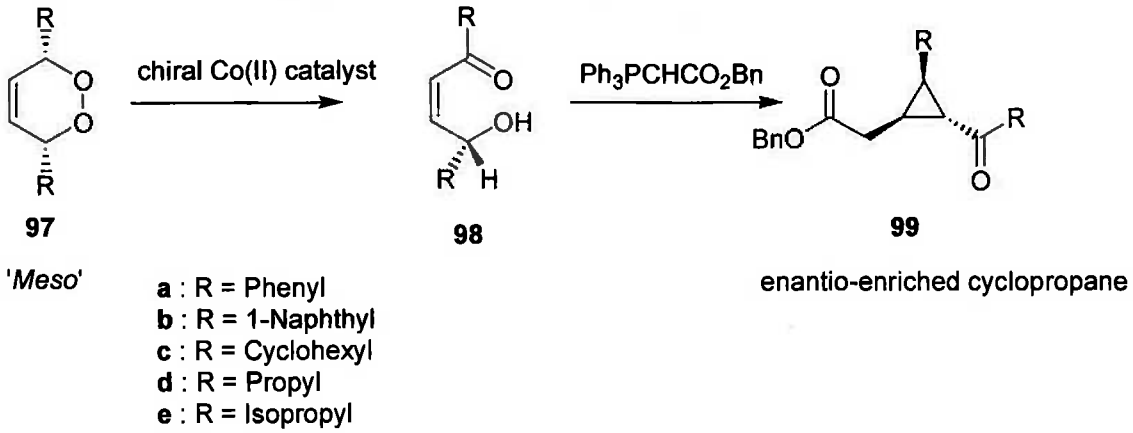


Scheme 1.18

The %*ee* incorporated into cyclopropane **99** was found to be dependent on the catalyst, the catalyst concentration and the temperature and solvent used. Optimal *ee* incorporation was achieved when the reaction was performed with 7.5 mol% of catalyst in THF at –15 °C. Up to 76 % *ee* was obtained for cyclopropane **99a** when 3,6-diphenyl-3,6-dihydro-1,2-dioxine **97a** was ring-opened with catalyst **96** (where R = Ph, R^1 = (-)-Bornoxy (*S,S* isomer)) and the resulting enone consumed by benzyl ester ylide.[160,161]

1.9 Aims

The subsequent two chapters of this thesis discusses methodological studies towards the synthesis of novel cyclopropyl steroids and cyclopropyl fatty acids by the exploitation of the aforementioned reaction of 3,6-disubstitued 1,2-dioxines with ester stabilised ylides. The ultimate aim of this research is to employ these strategies for the synthesis of diversely functionalised biologically active cyclopropyl containing steroids and fatty acids, previously discussed in section 1.4 and 1.5, respectively. This has been a considerable challenge and the difficulties encountered towards these natural product syntheses will be discussed.

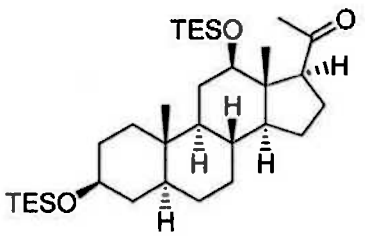
Exploitation of 1,2-dioxines for the synthesis of other important core components of natural products, such as tetrahydropyrans and tetrahydrofurans, were the focus of investigations discussed in Chapters 4 and 5. Similarly to cyclopropane construction, new methodologies for the construction of THP and THF ring systems are desirable.

Chapter 2: Cyclopropyl Steroids

2.1 Introduction

It is pertinent to investigate and synthesise a range of cyclopropyl-containing steroids of similar structure to the aragusterol series, in order to determine their potential therapeutic use as cytotoxic agents. Cyclopropane construction by exploitation of 1,2-dioxines and stabilised phosphorus ylides is advantageous over other methods as it allows for the preparation of highly substituted *cis* and/or *trans* derivatives in high yield and diastereomeric purity. The suitability of this methodology towards the synthesis of cyclopropyl-containing steroids was therefore investigated.

Previously, Aragusterol B has been synthesised via the stereoselective coupling of the cyclopropane side chain **101** with the protected keto-sterol **100** using lithium naphthalenide, followed by deprotection of the triethylsilyl (TES) ether and finally regioselective Oppenauer oxidation of the hydroxyl group at C_3.[79] The protected keto-sterol **100** was prepared from (+)-hecogenin acetate in 6 steps while the desired cyclopropane **101** was generated in 13 steps. Therefore, the overall synthesis of aragusterol B contained 22 steps. The synthesis of aragusterol A, C and D was successfully achieved via chemical modifications of the side chain of aragusterol B.[79] As mentioned previously, we are seeking to develop a new versatile synthetic protocol that will allow for quick access to not only these steroids but also to others in the aragusterol series.



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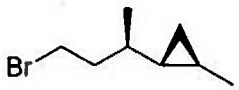


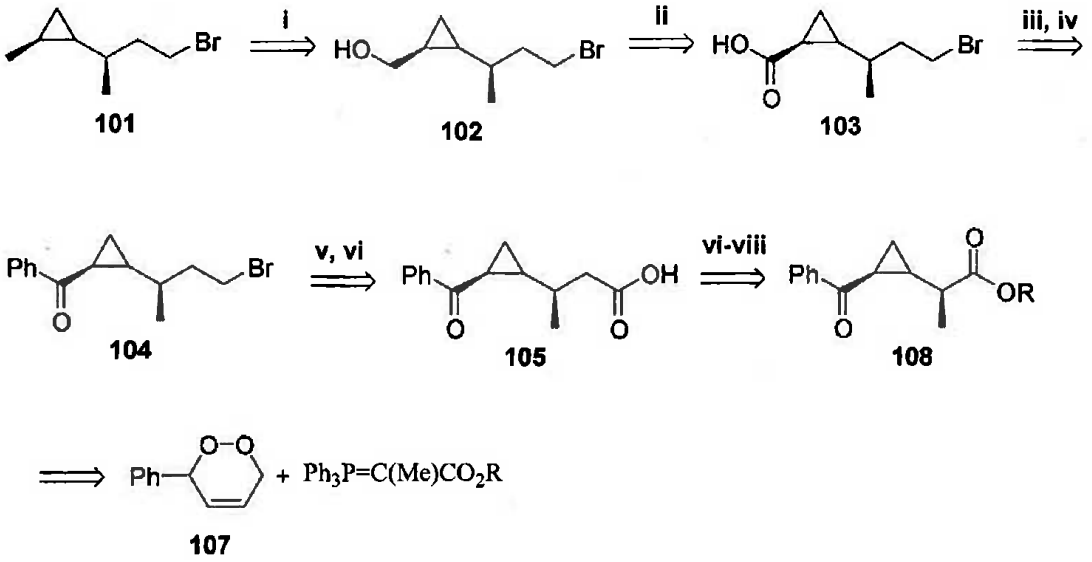
101

2.2 Results and Discussion

2.2.1 Investigations into the Generation of the Cyclopropyl Side Chain of the Aragusterol Series : Pathway 1.

Since the protected keto-sterol **100** can be prepared from the breakdown of (+)-hecogenin acetate in six steps,[79] the major focus was towards the development of a versatile synthetic protocol for generation of the cyclopropyl-containing side chain **101** and other related cyclopropanes.

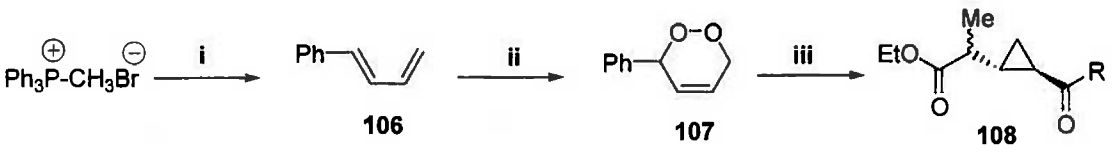
Retrosynthetic analysis envisaged that **101** could be prepared by deoxygenation of **102**, which should result from reduction of the carboxylic acid **103**. The latter may be accessible via ester hydrolysis of the Baeyer-Villiger oxidation product of the phenyl ketone **104**. Bromination of the alcohol obtained from chemoselective reduction of the cyclopropyl acid **105** should give the phenyl ketone **104**. The acid **105** could be furnished by hydrolysis of **108**, followed by Ardnt-Eistert homologation and enantiomeric resolution. The reaction of the 1,2-dioxine **107** with (carbethoxyethylidene)triphenylphosphorane and diastereomeric separation of the resulting cyclopropyl products should give the cyclopropane **108** and set up the desired *trans* stereochemistry about the cyclopropyl ring (**Scheme 2.1**).



Scheme 2.1 (i) Dehydration. (ii) Reduction. (iii) Baeyer-Villiger oxidation. (iv) Hydrolysis. (v) Chemoselective reduction. (vi) Halogenation. (vii) Hydrolysis followed by enantiomeric separation. (viii) Ardnt-Eistert homologation.

The 1,2-dioxine **107** was prepared by photo-oxidation of the 1,3-butadiene **106** in the presence of Rose Bengal *bis*(triethylammonium) salt and under irradiation from three

500W halogen lamps in moderate yield. The 1,3-butadiene **106** was synthesised by a Wittig reaction of *trans*-cinnamaldehyde and methylene(triphenyl)phosphonium, methodology previously established for this compound (**Scheme 2.2**).[155]



Scheme 2.2 (i) KOBu^t, diethyl ether, 0°C (30 min), *trans*-cinnamaldehyde, 0°C → rt (16 hr), 67%. (ii) Rose Bengal *bis*(triethylammonium) salt, DCM, O_2, *hv*, 6 hr, 52%. (iii) $Ph_3P{=}C(Me)CO_2CH_3$, DCM, 14 days, 30%.

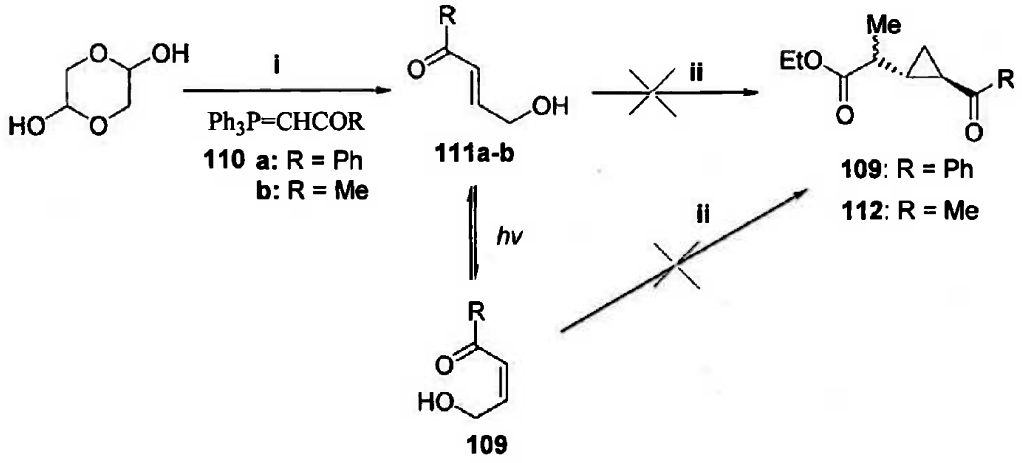
The reaction between the 1,2-dioxine **107** and (carbethoxyethylidene)triphenylphosphorane proceeded in poor yield (30%) and gave a mixture of three isomeric cyclopropanes of type **108**. Apart from expulsion of triphenylphosphine oxide, these cyclopropanes were the only products observed in this reaction. Their characterisation and hence stereochemical elucidation could not be established due to inefficient separation by flash chromatography. Several solvent systems were used to effect separation, including 5% diethyl ether in benzene (which gave the best separation by TLC), but only partial separation of one isomer could be achieved. Use of all available techniques to separate the components of the mixture failed and it was decided that further attempts at purification of the mixture would be futile.

It was investigated whether the ratio of isomeric cyclopropanes formed could be influenced in order to effect better separation. The ability of reaction temperature to control the products formed in a reaction has been documented previously,[136] hence in a first attempt to influence the ratio of products formed, the reaction temperature was altered. The reaction of the 1,2-dioxine **107** and (carbethoxyethylidene)triphenylphosphorane was repeated at –25°C, however, at this temperature the thermodynamic energy required to enable the reaction to proceed was unavailable. Even at slightly higher temperatures (0-5°C), the energy available was inadequate for the reaction to proceed.

Cyclopropanation of 1,2-dioxines proceeds via ring-opening of the 1,2-dioxine in the presence of ylide, generating *cis* γ-hydroxy enones of type **109** (**Scheme 2.3**). Subsequent 1,4-Michael addition of the ylide to the *cis* γ-hydroxy enone, followed by cyclisation of the resulting enolate and expulsion of triphenylphosphine oxide affords cyclopropane.[155] It has been shown that cyclopropane formation also occurs between stabilised phosphorus ester

ylides and *trans* γ-hydroxy enones.[155,156] Therefore, in a second attempt to influence the ratio of products formed, the *cis* γ-hydroxy enone **109** was replaced with the *trans* counterpart **111** in the aforementioned reaction.

Generation of *trans* γ-hydroxy enones can occur either by isomerization of their *cis* counterparts[155,162] or by their synthesis from simple starting materials.[156,162] Both methods have previously been used successfully in our group. Palmer and Taylor synthesised several *trans* γ-hydroxy enones, both optically active and racemic, towards investigations into the synthesis of optically pure cyclopropanes.[156] Following their method, the *trans* γ-hydroxy enones **111a-b** were prepared by Wittig reactions of glycoaldehyde dimer with either the phenyl or methyl keto ylides **110a-b** in good yield, respectively (**Scheme 2.3**).



Scheme 2.3 (i) DCM, **110a** or **110b**, reflux, 4 hr. (ii) $Ph_3P=C(Me)CO_2Et$, DCM, Benzophenone (10 mol %), *hv*, rt, 30-72 hr, 0%.

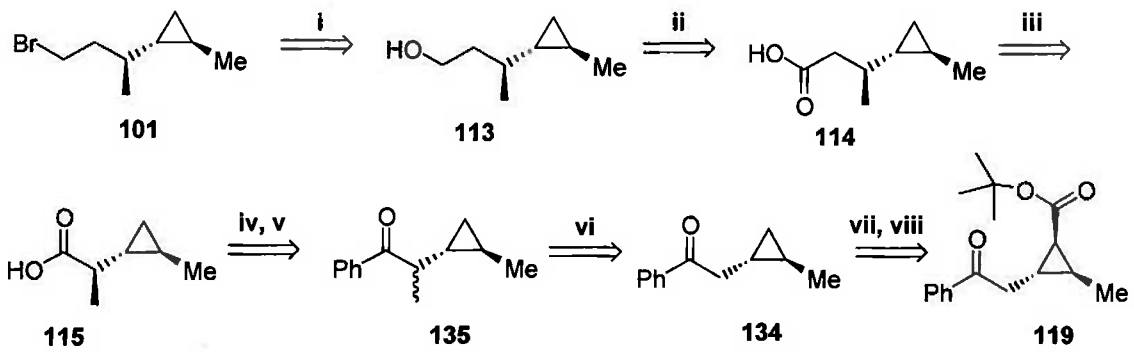
In previous investigations into the formation of cyclopropanes derived from *trans* γ-hydroxy enones and stabilised phosphorus ylides, Palmer and Taylor found that in most cases cyclopropane formation occurred under both thermal and photolytic conditions. However, under thermal conditions (where the *cis-trans* γ-hydroxy enone equilibrium favours the thermodynamically more stable *trans* isomers) cyclopropane formation is slower and yields are poorer in comparison to the same reactions performed under photolytic conditions (irradiation with 2 x 300W sun lamps in the presence of 10 mol% benzophenone).[156]

Therefore, the reactions of (carbethoxyethylidene)triphenylphosphorane and the *trans* γ-hydroxy enones **111a-b** were first investigated under photolytic conditions. In the presence of 10 mol% benzophenone and (carbethoxyethylidene)triphenylphosphorane, the enones

111a and **111b** were fully consumed after irradiation with two 300W sun lamps for 30 and 72 hours, respectively. Despite consumption of the enones, analysis of the reaction mixtures by ^{1}H NMR indicated that complex mixtures of decomposition products had formed. All reported reactions of *trans* γ-hydroxy enones by Palmer and Taylor proceeded under photolytic conditions. There was only one reported example where a complex mixture of decomposition products was observed and this occurred under thermal conditions. Consequently, if the reaction of (carbethoxyethylidene)triphenylphosphorane and the enones **111a-b** were unsuccessful photolytically, it was unlikely to succeed thermally. Therefore they were not attempted.[156]

2.2.2 Investigations into the Generation of the Cyclopropyl Side Chain of the Aragusterol Series : Pathway 2.

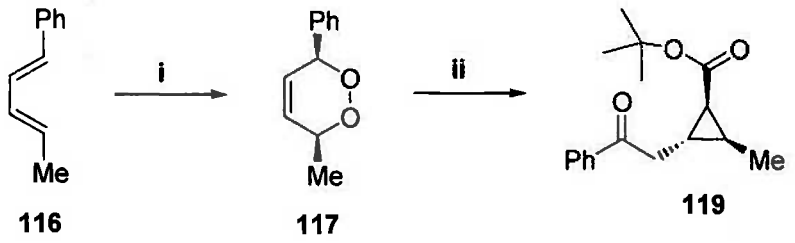
An alternative pathway was proposed towards the formation of the cyclopropane **101** (**Scheme 2.4**). This synthetic route involves the incorporation of the α-methyl group by methylation of **134** rather than through the utilisation of (carbethoxyethylidene)triphenyl-phosphorane. Important features of this pathway include the direct incorporation of a methyl group *trans* to the phenyl keto moiety, hydrolysis and decarboxylation of **119** and subsequent methylation of cyclopropane **134** to afford cyclopropane **135**.



Scheme 2.4 (i) Halogenation. (ii) Reduction. (iii) Arndt-Eistert homologation. (iv) Baeyer-Villiger oxidation. (v) Hydrolysis, followed by diastereomeric separation;. (vi) Methylation. (vii) Hydrolysis. (viii) Barton decarboxylation.

The 3,6-disubstituted 1,2-dioxine **117** was prepared by photo-oxidation of the 1,3-butadiene **116**, prepared by the Wittig reaction of either crotonaldehyde and benzyl phosphonium ylide or cinnamaldehyde and ethyl phosphonium ylide.[155] The cyclopropyl keto-ester **119** was synthesised in excellent yield from the reaction of the 1,2-dioxine **117**

and the *tert*-butyl ester ylide **118** in the presence of lithium bromide at ambient temperature (**Scheme 2.5**).[159]

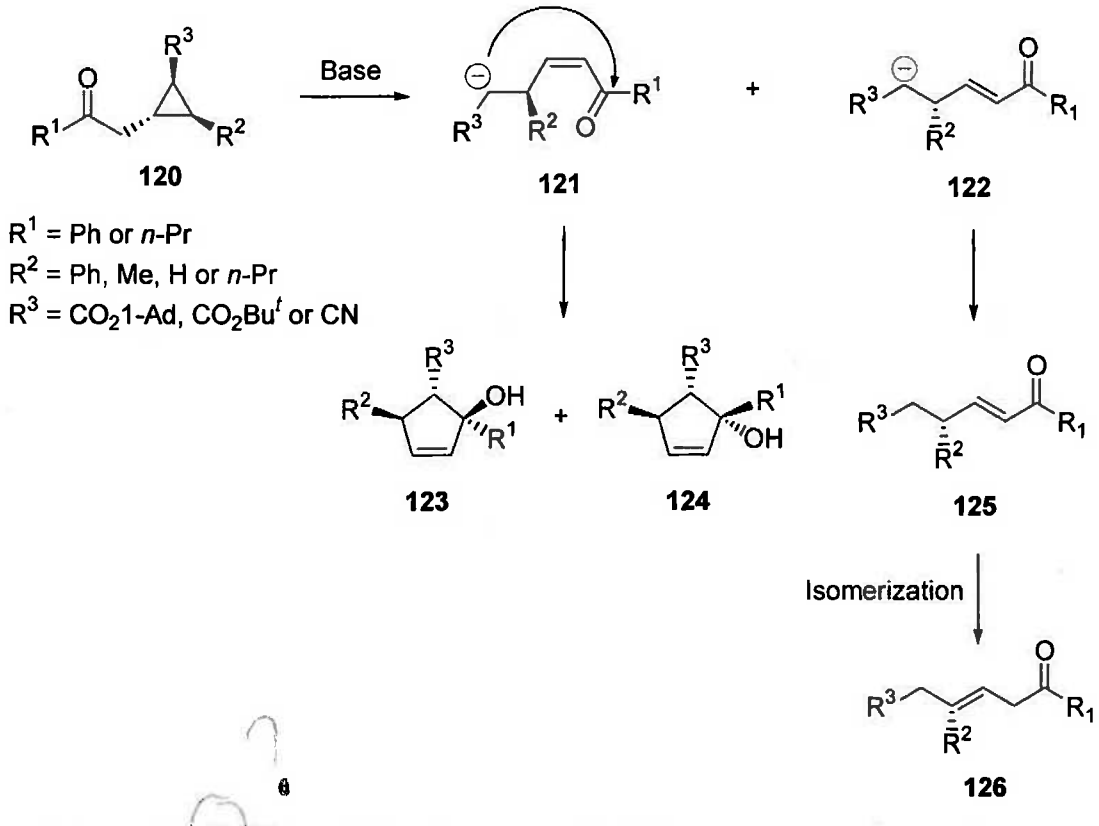


116 **117** **119**

Scheme 2.5 (i) Rose Bengal *bis*(triethylammonium) salt, DCM, O_2, *hv*, 6 hr, 55%. (ii) $Ph_3P{=}CHCO_2Bu^t$ **118**, DCM, LiBr, rt, 3.5 days, 80%.

At this stage, investigation into whether cyclopropane **119** could be methylated prior to its hydrolysis and decarboxylation was undertaken. Using the method of Still and Galynker[163], the cyclopropane **119** was added to a solution of lithium diisopropylamine (LDA), which was prepared *in situ* by the addition of butyllithium to diisopropylamine, followed by the addition of the methylating agent, iodomethane. Under these conditions no methylated cyclopropane was obtained due to its base induced ring-opening. Utilisation of potassium *bis*(trimethylsilyl)amide for proton extraction also resulted in cyclopropane ring-opening. However, the product obtained was significantly different to that observed when methylation was attempted using LDA (as indicated by ^{1}H NMR).

Greatrex and co-workers found that *β*–ketocyclopropanes of type **120** ring-open in the presence of base to give the corresponding *cis* or *trans* anionic *α,β*-unsaturated ketones **121** and **122**, which either cyclised to form diastereomeric cyclopentenols **123** and **124** or were protonated to give the corresponding neutral compound **125**, respectively (**Scheme 2.6**). In some cases, *α,β*-unsaturated ketones **125** underwent 1,3-hydrogen shifts to give *β,γ*-unsaturated ketones **126**.[164]



Scheme 2.6 (i) THF or diethyl ether, Base (1.5-2.0 equiv.), temp between -78°C and 110°C, 15 min.

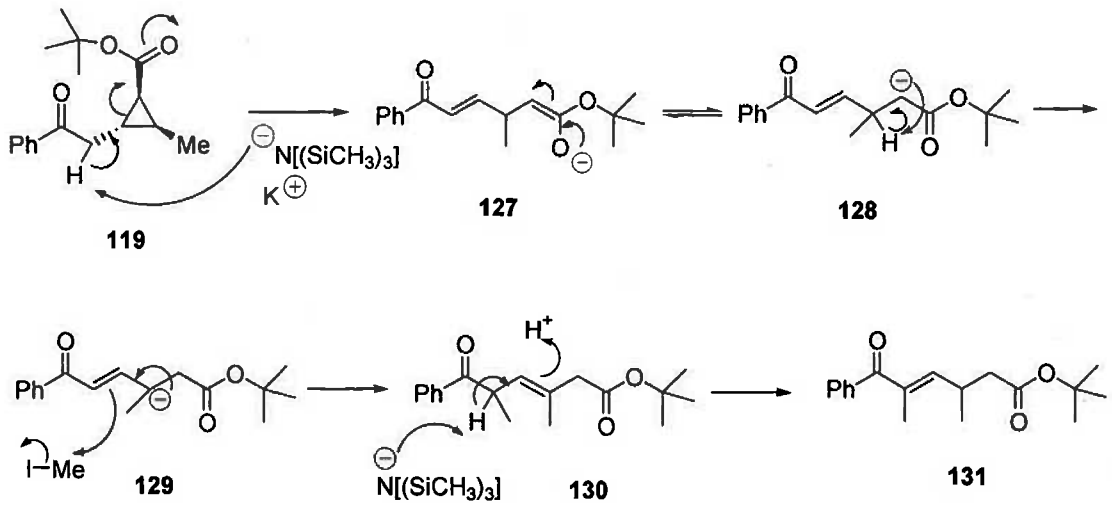
Table 2.1: Ratio of products, **123-126**, obtained when β-ketocyclopropane **120** is treated with various bases.

R^1	R^2	R^3	Base	Temp	Ratio of 123:124:125:126
Ph	Me	CO_2Bu^t	NaH	rt	23:0:0:77
Ph	Me	CO_2Bu^t	LHMDS	-78°C	6:0:0:94
Ph	Me	CO_2Bu^t	LHMDS	rt	100:0:0:0
Ph	Me	CO_2Bu^t	KHMDS	rt	86:14:0:0

Table 2.1 summarises the results obtained by Greatrex and co-workers[164] for the reaction of various bases with the same cyclopropane that methylation was performed on (i.e. cyclopropane **119**). Ring-opening of this cyclopropane occurred in the presence of NaH, LHMDS and KHMDS. However, the major reaction product varied between compounds **123** and **126** depending on the base utilised and the reaction temperature. The ^{1}H NMR spectrum of the product isolated from attempted methylation of cyclopropane **119** using LDA was consistent with that obtained by Greatrex and co-workers[164] for cyclopentanol **123**, where R^1 = Ph, R^2 = Me, R^3 = Bu^t (n.b. ^{1}H NMR data for this compound in the

supplementary data signal incorrectly quoted at δ2.41 instead of δ1.41 (*tert*-butyl protons) and signal at δ2.65 is due to one proton not three).

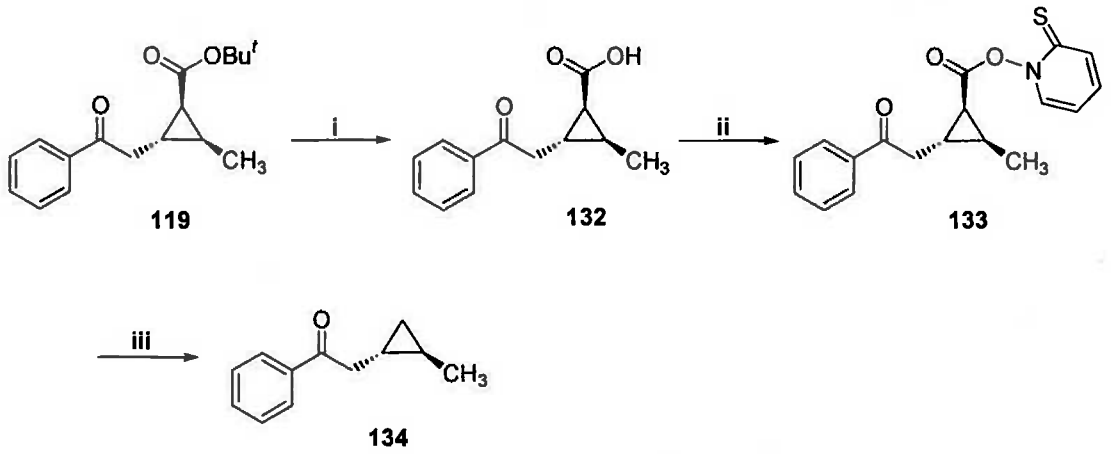
The structure of the major product obtained by methylation of **119** in the presence of potassium *bis*(trimethylsilyl)amide and iodomethane was determined to be the *α,β*-unsaturated aryl ketone **131**. This was determined through a combination of ^{1}H, ^{13}C, COSY, HMBC, HMQC and ROESY NMR experiments. The presence of the *E* double bond is clearly evident by the large coupling constant of 17.4 Hz between the vinylic protons. A feasible mechanism for its formation, via the ketone intermediate **128** proposed by Greatrex and co-workers[164], is depicted in **Scheme 2.7**. The reaction sequence is initiated by base extraction of one of the *α*-keto acidic protons of cyclopropane **119**, which results in its ring-opening to generate *α,β*-unsaturated aryl ketone **127**. Compound **127** undergoes a 1,2-proton shift to give **128**, which is then methylated to afford compound **129**. In the presence of excess base, compound **130** undergoes base catalysed 1,3-hydrogen migration to afford the observed methylated *α,β*-unsaturated aryl ketone **131**.



Scheme 2.7

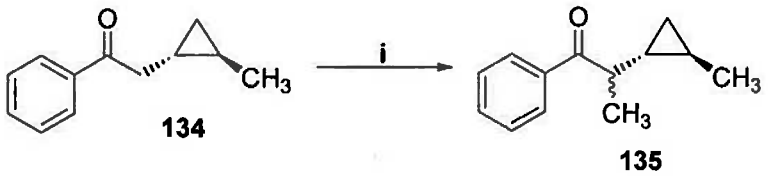
The use of milder bases by Greatrex and co-workers[164] could not prevent ring-opening of a wide range of *β*-ketocyclopropanes of type **120**, suggesting that methylation of these types of systems, without destruction of the cyclopropyl moiety, is improbable. However, methylation of decarboxylated cyclopropane **134** is more likely due to the absence of the electron withdrawing *tert*-butyl ester group, which aids in ring-opening of the aforementioned *β*-ketocyclopropanes. Therefore, we were interested in exploring this possibility.

Decarboxylation of cyclopropane **119** was achieved by its conversion to cyclopropyl acid **132** via acidic hydrolysis in the presence of trifluoroacetic acid, followed by photolytic mercaptan reduction[165] of 'Barton ester' **133**, formed by the coupling of cyclopropyl acid **132** with 2-mercaptopyridine *N*-oxide in the presence of DCC[165] (**Scheme 2.8**). Disubstituted cyclopropane **134** was obtained in 50% yield over these three steps.



Scheme 2.8 (i) TFA, DCM, rt, 8 hr, 77%. (ii) 2-mercaptopyridine *N*-oxide, DCC, DCM, rt, N_2, 3 hr. (iii) *tert*-butylthiol, C_6H_6, *hv*, 2 hr, 65% (2 steps).

Treatment of *β*-ketocyclopropane **134** with one equivalent of LDA followed by excess iodomethane gave methylated cyclopropane **135** as a 1:1 mixture of diastereomers in 80% yield (**Scheme 2.9**).



Scheme 2.9 (i) LDA, MeI, -78°C, 80%.

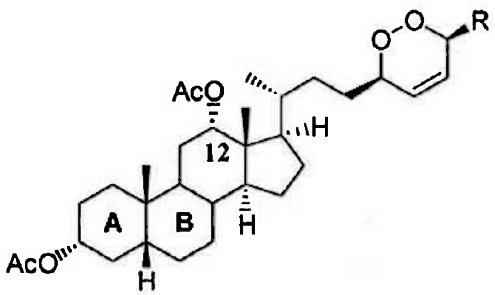
The issue of the separation of the diastereomers was again a problem. The diastereomeric cyclopropanes **135** could not be separated by flash chromatography. Synthesis towards the desired product was consequently stopped at this point. Although the generation of cyclopropanes by the reaction of 1,2-dioxines and stabilised phosphorus ylides allows for the preparation of highly substituted *cis* and/or *trans* derivatives in high yield and diastereomeric purity, this methodology is inadequate for the preparation of cyclopropanes of type **101**, possessing a chiral centre beyond the ring system. This methodology is more

suited to the synthesis of compounds possessing chirality around the cyclopropyl ring only, as is shown by the synthesis of natural grenadamide by this methodology in Chapter 3.

2.3 Preparation and Reactions of Novel Steroid containing Ylides, 1,3-Butadienes and 1,2-Dioxines

2.3.1 Introduction

Given the difficulties encountered towards the synthesis of the desired cyclopropyl portion of aragusterol B mentioned above, the synthesis of some other novel cyclopropyl steroids was undertaken. We have previously shown that 3,6-disubstituted 1,2-dioxines and stabilised phosphorus ylides react to generate diastereometrically-pure di- or tri-substituted cyclopropanes.[155,157] The reaction of a steroid possessing a 1,2-dioxine in its side chain with a phosphorus ylide should generate a cyclopropyl-containing steroid. The 1,2-dioxines **136a-c** were targeted for examination of this methodology.



136 **a:** R = Ph
b: R = Me
c: R = H

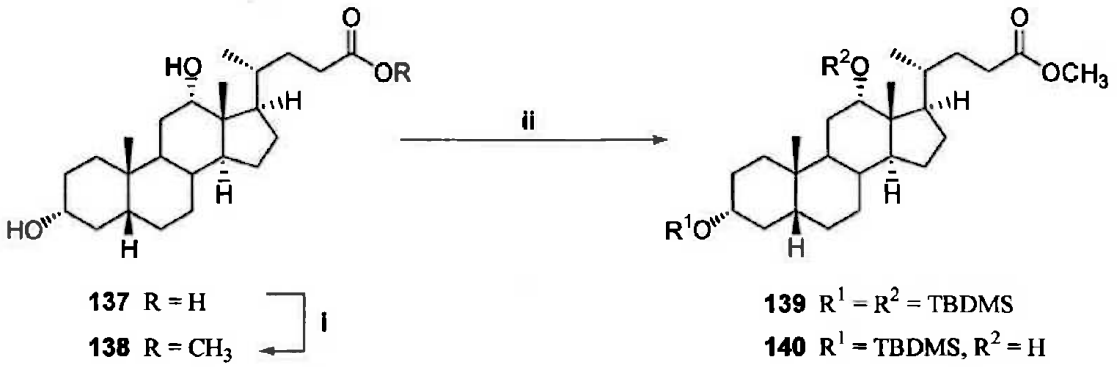
2.3.2 Synthesis of Steroid Containing 1,3-Butadienes

The 1,2-dioxines **136a-c** should be obtainable by photo-oxidation of the corresponding 1,3-butadienes. Steroids with the desired functionality to undergo Wittig reactions to form these 1,3-butadienes were the initial targets, namely steroid aldehydes and/or phosphonium salts.

Deoxycholic acid was chosen as the starting material for the synthesis of the above steroid 1,2-dioxines as it is a relative inexpensive and commercially available chiral auxiliary. The stereochemistry of deoxycholic acid differs to that of the aragusterol series by possessing a *cis* A/B ring junction and inverted stereochemistry at C_{12}.

The first pathway explored involved the attempted synthesis of the *tert*-butyldimethylsilyl (TBDMS) di-protected methyl ester **139** from deoxycholic acid **137**

(**Scheme 2.10**). It was anticipated that subsequent DIBAL-H reduction of the ester **139** would lead to the formation of the desired aldehyde required for 1,3-butadiene formation by Wittig chemistry.



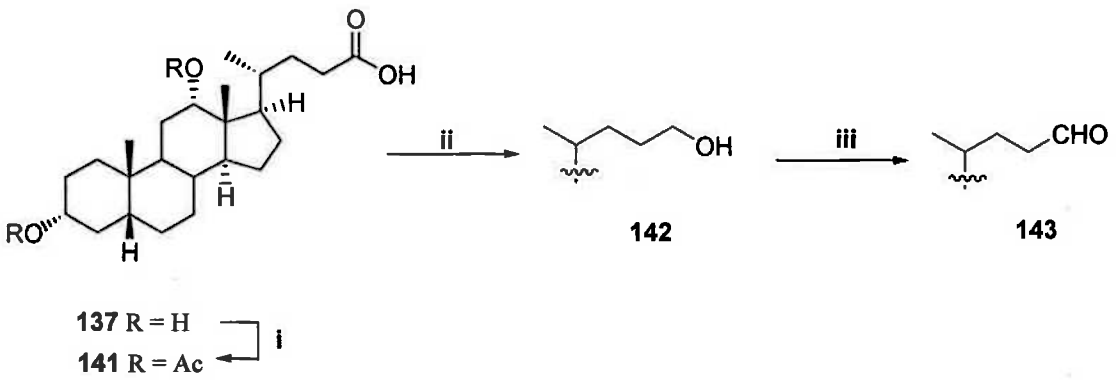
Scheme 2.10 (i) MeOH, DOWEX-H^+, reflux, 16 hr, 94%. (ii) DMF, TBDMSCl (2.4 equiv.), Imidazole (5 equiv.), rt, 16 hr.

Esterification of deoxycholic acid **137** in the presence of methanol and DOWEX-H^+ gave the methyl ester **138** in 94% yield. The di-protected steroid **139** could not be formed under the standard procedure for protection of alcohols by TBDMS.[166] Instead only mono-protected sterol was formed when the methyl ester **138** was treated with excess *tert*-butyldimethylsilyl chloride and imidazole in DMF. Given that the mono-protected sterol precipitated out of solution upon formation, heating to 35°C was required for the product to redissolve. Despite heating to temperatures of up to 65°C the di-protected steroid **139** did not form.

Most likely, the mono-protected sterol **140** formed during this reaction as the hydroxyl group at C_3 is less sterically hindered than that at C_{12}. Furthermore, steroids containing a TBDMS protected alcohol at C_3 have been reported in the literature, but no experimental data was available for comparison of these compounds to that obtained.[167] This result is interesting since it allows for the regioselective protection of one secondary alcohol over another. Consequently, stereochemical inversion and/or chemical modifications of the C_{12} hydroxyl group can be performed without chemical modification of the protected hydroxyl group at C_3.

At this stage the mono-protected sterol **140** could have been further protected at C_{12} using a less bulky TMS or acetate group, followed by reduction of its methyl ester to give the desired aldehyde. However, an easier approach was devised in which the aldehyde moiety of **143** was obtained from oxidation of the corresponding alcohol **142**, which was

prepared by reduction of deoxycholic acid diacetate **141** (**Scheme 2.11**). This two-step approach eliminates the possibility of obtaining mixtures of the desired aldehyde with fully reduced alcohol and non-reduced ester, which most likely would occur on reduction of the ester moiety with one equivalent of DIBAL-H. Furthermore, the steroid alcohol **142** was found to be an important precursor in the synthesis of steroid phosphonium salt **148** (**Scheme 2.13**).



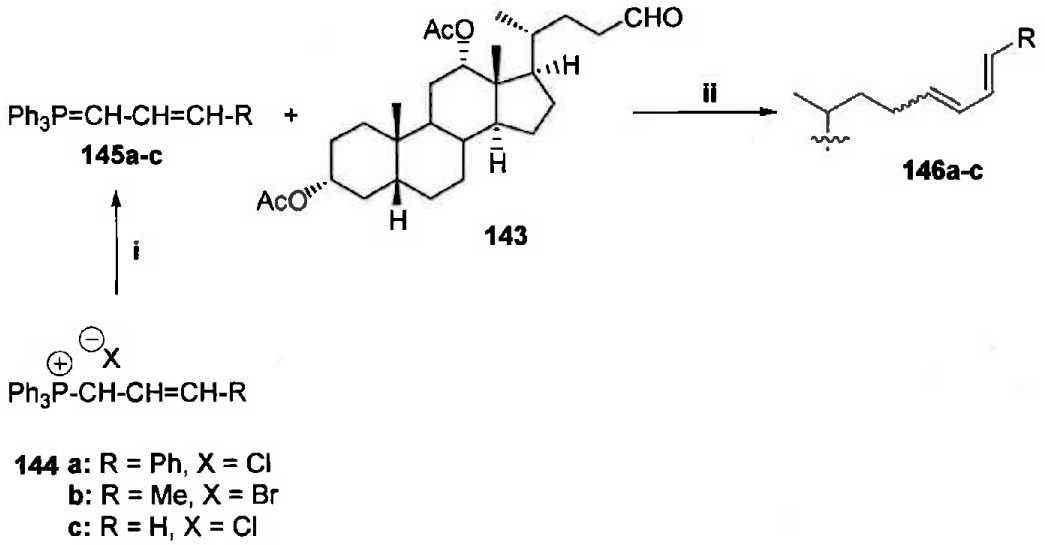
Scheme 2.11 (i) Ac_2O, pyridine, 4-DMAP, rt, 3.5 hr, 97%. (ii) BH_3.THF (1M), THF, rt, 16 hr, 86%. (iii) PCC (2.2 equiv.), DCM, rt, 2 hr, 78% or DMSO (4 equiv.), oxalyl chloride (2 equiv.), -78°C, 0.5 hr, 78%.

Deoxycholic acid **137** was quantitatively converted to its diacetate **141** in the presence of pyridine, acetic anhydride and 4-dimethylaminopyridinium (4-DMAP) at ambient temperature. The same procedure has been used in the literature for the acetylation of cholic acid,[168] which differs from deoxycholic acid by possessing an extra hydroxyl group at C_7. Deoxycholic acid diacetate was cleanly and selectively reduced to the alcohol **142** using a solution of BH_3 in THF.[169] This reagent was utilised in order to minimise the possibility of reducing the acetate protecting groups, which may occur with a stronger reducing agent such as lithium aluminium hydride. After workup, the alcohol **142** was sufficiently pure to be oxidised to the aldehyde **143** without further purification.

Oxidation of primary alcohols can be achieved by a large number of reagents such as potassium permanganate ($KMnO_4$), chromium (VI) oxide (CrO_3) and sodium dichromate ($Na_2Cr_2O_7$).[152] However, one of the best methods to convert alcohols to aldehydes, without their further oxidation to carboxylic acids, involves the utilisation of pyridinium chlorochromate (PCC).[152] Since PCC is a mild oxidising agent and facilitates oxidation at ambient temperatures, it is an ideal reagent for the oxidation of a wide range of alcohols.[152] PCC is easily prepared by the addition of pyridine to chromium (VI) oxide dissolved in

hydrochloric acid.[170] Gargiulo and colleagues[168] successfully used an excess of PCC in dichloromethane to convert a primary steroidal alcohol (similar to **142**) to the corresponding aldehyde in 85% yield. Following their method, oxidation of the steroid alcohol **142** gave the desired aldehyde **143** in 78% yield. Likewise, oxidation of **142** under Swern conditions[171] gave **143** in 78% yield after chromatographic purification.

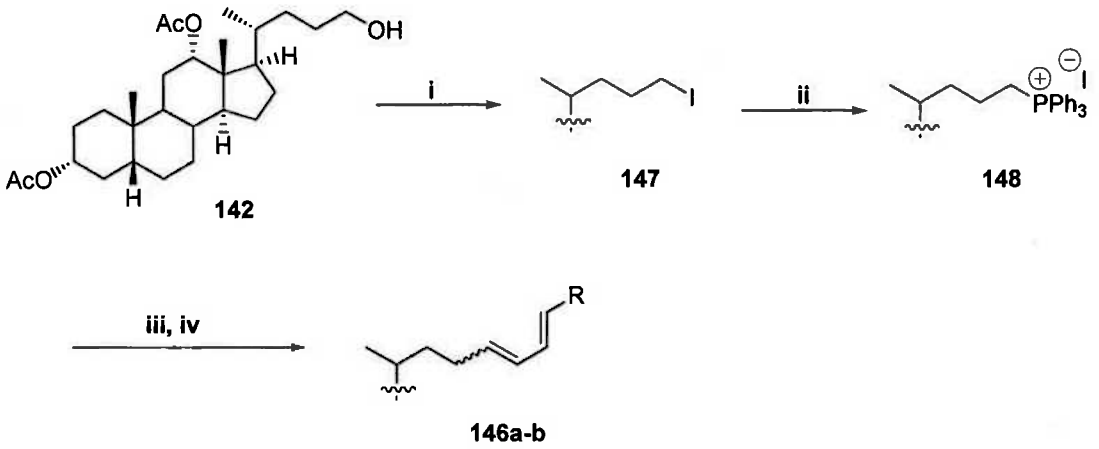
With the desired steroid aldehyde in hand, formation of 1,3-butadienes **146a-c** was achieved via Wittig reactions involving the aldehyde **143** and the phosphoranes **145a-c** (**Scheme 2.12**). The phosphonium salts **144a-c** were prepared by the reaction of triphenylphosphine with cinnamyl chloride, crotyl bromide and ally chloride, respectively. Wittig reactions involving **143** proceeded in poor to moderate yields, with 66%, 36% and 37% yields for the 1,3-butadienes **146a**, **146b** and **146c**, respectively. The low yields obtained are most likely a consequence of self-condensation of the reacting α,β-unsaturated phosphoranes, which was more pronounced for the ylides **145b** and **145c**.



Scheme 2.12 (i) **144a, b or c**, THF, KOBu^t, 10 min, **143**. (ii) rt, 16hr, 36-66%.

Alternatively, the 1,3-butadienes **146a-b** were generated by the reaction of the ylide obtained from steroid phosphonium salt **148** with either *trans*-cinnamaldehyde or crotonaldehyde, in 35% and 32% yield, respectively (**Scheme 2.13**). The steroid phosphonium salt **148** was synthesised in two steps from the alcohol **142**. The alcohol **142** was a suitable precursor to **148** as phosphonium salts are classically formed by the reaction of triphenylphosphine and an alkyl halide, the latter being commonly formed from their corresponding alcohols. The iodo derivative **147** was targeted as iodo phosphonium salts

are more readily formed compared to the bromo and chloro derivatives and have enhanced reactivity.



Scheme 2.13 (i) DCM, PPh_3 (1.25 equiv.), imidazole (1.25 equiv.), I_2 (1.25 equiv.), 0°C (15 min) → rt (16 hr), 58%. (ii) PPh_3 (4 equiv.), neat, 130°C, 1.5 hr, 81%. (iii) THF, $KOBu^t$, rt, 15 min. (iv) *trans*-cinnamaldehyde or crotonaldehyde, 0°C (5 min) → rt (16 hr), 32-35% (two steps).

Primary alcohols can be converted to alkyl iodides by treatment with triphenylphosphine, imidazole and iodine in dichloromethane[172] or tetrahydrofuran.[173] The reaction is driven to completion by the formation of the thermodynamically stable triphenylphosphine oxide. The steroid alcohol **142** was converted to the iodo species **147** by this method, under the conditions described by Neef and co-workers.[173] Although good conversion of the alcohol was observed, the iodide **147** was isolated in only 62% yield. This was a consequence of partial hydrolysis of the iodo species during purification by flash chromatography. Nevertheless, complete removal of triphenylphosphine oxide was only possible by this method.

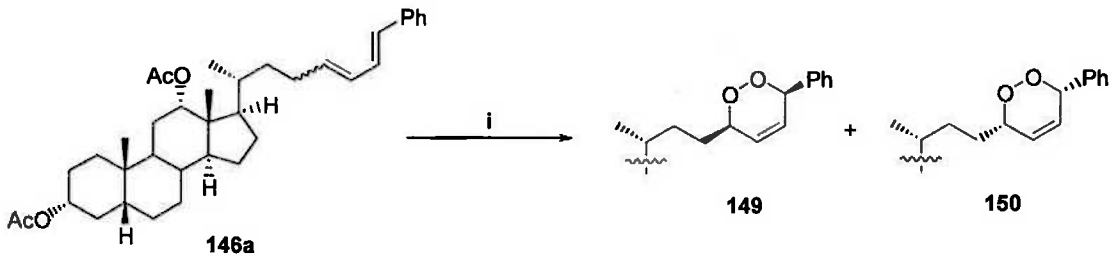
As mentioned above, phosphonium salts are formed by halogen displacement of an alkyl halide by triphenylphosphine. Commonly, these reactions are carried out under reflux in toluene[174] with precipitation of the salt allowing for easy isolation by filtration. However, utilisation of toluene in the formation of steroid phosphonium salt **148** was found to be inadequate for two reasons. Firstly and most importantly, the reaction proceeded in only 52% yield and secondly, the solubility of the steroid phosphonium salt in toluene made it impossible to visualise the progress of its formation via precipitation and furthermore, made its isolation time consuming. It was found that melting **147** neat with 4 equivalents of triphenylphosphine[174] for 1.5 hours at 130°C gave the desired sterol phosphonium salt **148** in high yield (>80%) after trituration with diethyl ether to remove excess

triphenylphosphine. Reduced yields of 44% and 65% were observed when 1.05 and 2 equivalents of triphenylphosphine were utilised, respectively.

Although yields of the 1,3-butadienes **146a-b** were very poor using the ylide obtained from the steroid phosphonium salt **148**, these reactions gave cleaner products and were regioselective towards the formation of the *E,Z* isomers over their geometric *E,E* isomers in a ratio of approximately 5:1. However, enhanced *E,Z* formation does not offer any benefit as only *E,E* dienes can undergo photo-oxidation, and therefore, the former must undergo isomerization before oxygen addition can occur.

2.3.3 Preparation and Reaction of a Steroid Containing 1,2-Dioxine

Photo-oxidation of the 1,3-butadiene **146a** in the presence of Rose Bengal *bis*(triethylammonium) salt and under irradiation from one 500W halogen lamp afforded the diastereomeric 1,2-dioxines **149** and **150** in a 1:1 ratio with a combined yield of 67% (**Scheme 2.14**). The moderate yield observed for this NMR scale reaction (51 mg) was not reproducible, with only 35% yield obtained for additional larger scale reactions. Reasons for this reduced yield may include the reaction being performed at lower concentration and a lower radiation flux penetrating the reacting solution over the same time period.

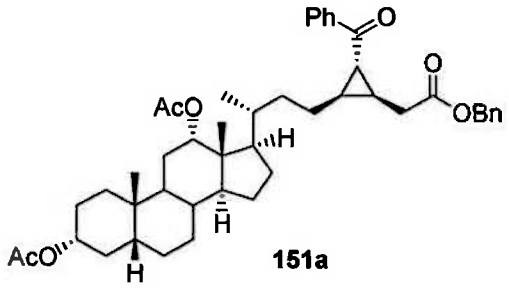


Scheme 2.14 (i) DCM or $CDCl_3$, Rose Bengal *bis*(triethylammonium) salt, O_2, *hv*, 6 hr, 37-65%.

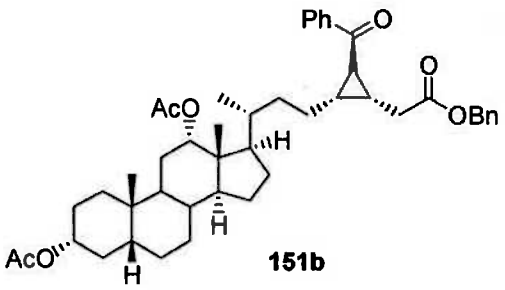
As oxygen addition occurs on both faces of the 1,3-butadiene **146a** and chirality exists within the steroidal unit of this compound, its photo-oxidation has resulted in diastereomers being formed. These diastereomers were inseparable and so cyclopropanation was performed on the mixture. Cyclopropanation was achieved by treatment of the diastereomers **149** and **150** with the benzyl ester ylide, benzyl(triphenylphosphoranylidene) acetate, in dichloromethane at 35-40°C. The reaction was sluggish, requiring 21 days to go to completion even at slightly higher temperatures

than normally employed for this type of reaction. Furthermore, cyclopropanation proceeded in a poor yield of 35%, perhaps a consequence of 1,2-dioxine **149** and **150** degradation at elevated temperatures.

Analysis of the proton spectrum of the cyclopropanation product indicated the presence of two diastereomers, most likely compounds **151a** and **151b**, based on the cyclopropyl stereochemistry previously observed, by the Taylor group, for cyclopropanations of 1,2-dioxines in the presence of non-bulky stabilised phosphorus ylides.[155]



151a



151b

These diastereomers were non-separable by flash chromatography. It was difficult to analyse the cyclopropyl portion of these isomers due to the proton signals being hidden under the overwhelming steroidal alkane proton signals between δ 0.6 and 2.1 ppm in the spectrum. However, the methylene protons *alpha* to the cyclopropyl ring were visible around δ 2.48 and 2.64 ppm, which is consistent with other substituted cyclopropanes of this type (c.f. δ 2.52 and 2.61 ppm when alkyl steroid portion is replaced by a methyl group in the above structure.[155] It was through analysis of these two signals that the presence of two diastereomers was evident. When diastereomerically pure, each of these methylene proton signals appear as a doublet of doublets. However, in the proton spectrum of cyclopropyl steroid **151**, there were two overlapping doublet of doublets at δ 2.47 and 2.48 ppm and δ 2.64 and 2.65 ppm (**Figure 2.1**). Hence, one diastereomer was responsible for the doublet of doublets at δ 2.47 (J = 8.1, 15.9 Hz) and 2.64 ppm (J = 6.9, 15.9 Hz), and the second diastereomer responsible for the doublet of doublets at δ 2.48 (J = 8.1, 15.9 Hz) and 2.65 ppm (J = 6.6, 15.9 Hz).

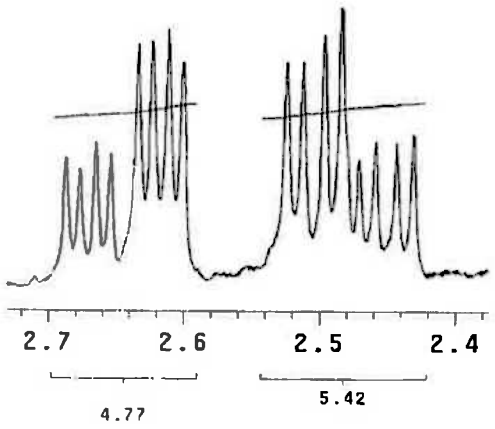
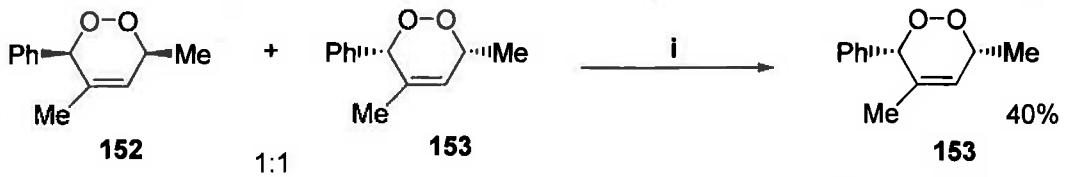


Figure 2.1 Proton spectrum of compound **151** between δ 2.40 and 2.70 ppm, which highlights the presence of two diastereomers due to overlapping doublet of doublets at δ 2.47 and 2.48 ppm and δ 2.64 and 2.65 ppm.

Cyclopropanation of **149** and **150** afforded only two diastereomers in a 1:1 ratio (reflecting the ratio of starting diastereomeric 1,2-dioxines) suggesting that the reaction of each isomer may be diastereoselective, giving only one of the two isomers observed. Consequently, if the 1,2-dioxines **149** and **150** could be separated prior to cyclopropanation, diastereomerically-pure cyclopropane would result. However, as mentioned above separation was not possible via flash chromatography. Previously, within our group, the diastereomeric 1,2-dioxines **152** and **153** were kinetically resolved on treatment with a cobalt salen catalyst. The 1,2-dioxine **152** was consumed in preference to **153**, leaving the latter as optically-pure dioxine (**Scheme 2.15**).



Scheme 2.15 (i) $CHCl_3$, $Co(SALEN)_2$.

However, kinetic resolution of the steroid 1,2-dioxines **149** and **150** was not possible as both diastereomers were consumed at similar rates in the presence of cobalt salen, as determined by a ^{13}C NMR study. Likewise, the utilisation of the *S,S* Bornyl cobalt catalyst of Jenkins,[161] consumed the two diastereomeric 1,2-dioxines **149** and **150** at similar rates. Consequently, this area was not pursued any further. Along with the formation of non-separable cyclopropyl diastereomers, poor yields of precursors were also an issue with this pathway. The 1,2-dioxines **136b** and **136c** were not synthesised as, due to a lack of an

acidic proton *alpha* to the dioxygen linkage, ring-opening in the presence of ylide would be problematic.[155] Cleavage of the dioxygen linkage, in these methyl and hydrogen dioxine derivatives, could occur via utilisation of a cobalt catalyst. However, since these dioxines are non-symmetrical, two *cis* γ-hydroxy enones could form for each diastereomer, which would result in a complex mixture of reaction products upon cyclopropanation. Therefore these examples were not investigated further.

2.4 Summary and Conclusions

It appears unlikely that steroids of the Aragusterol series can be synthesised by applying our methodology. Many factors have prevented their synthesis by this method, in particular the enantioselective induction of the methyl group *alpha* to the cyclopropyl ring. Methods explored for the incorporation of this methyl group have resulted in the formation of non-separable (by flash chromatography) diastereomeric cyclopropanes. Unfortunately, preparative HPLC was not available as a possible means for separation of the diastereomers but may be pursued in the future.

β-Ketocyclopropanes possessing *tert*-butyl ester substitution undergo ring-opening in the presence of base, a phenomenon explored in more detail by Greatrex and co-workers.[164] However, in the absence of the electron withdrawing ester group, β-ketocyclopropanes undergo non-diastereoselective α-keto alkylation in the presence of base and an alkylating source.

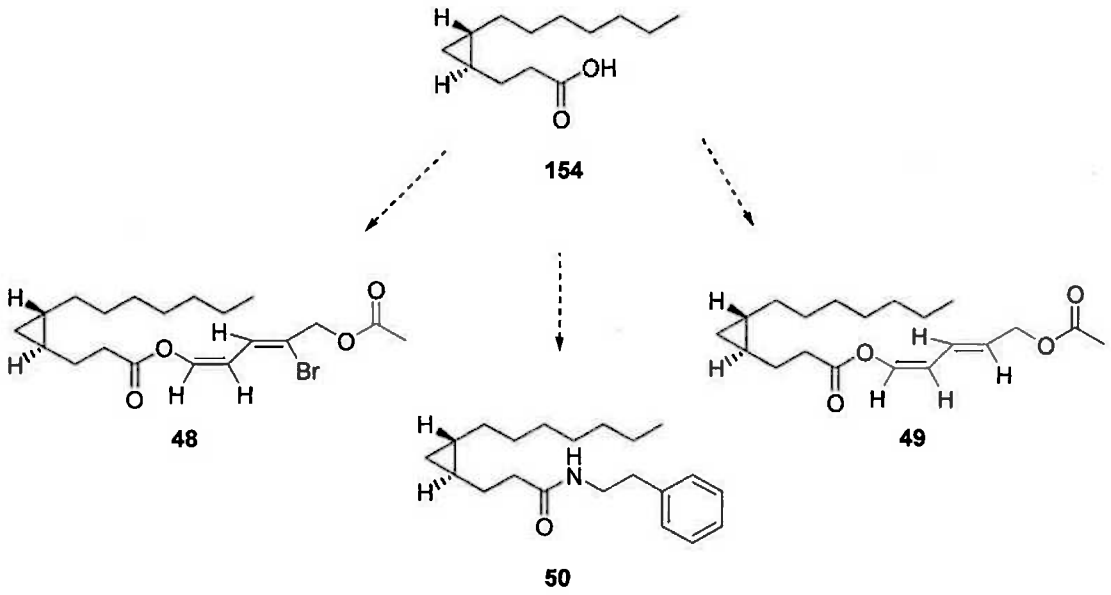
During our investigations, novel steroid containing ylides, 1,3-butadienes and 1,2-dioxines have been formed. A method for the generation of a novel highly substituted cyclopropyl steroid has been established. Unfortunately, this steroid was obtained in poor diastereomeric purity and yield.

Chapter 3: Synthesis of Cyclopropyl Fatty Acids : The First Total Synthesis of Natural Grenadamide

3.1 Results and Discussion

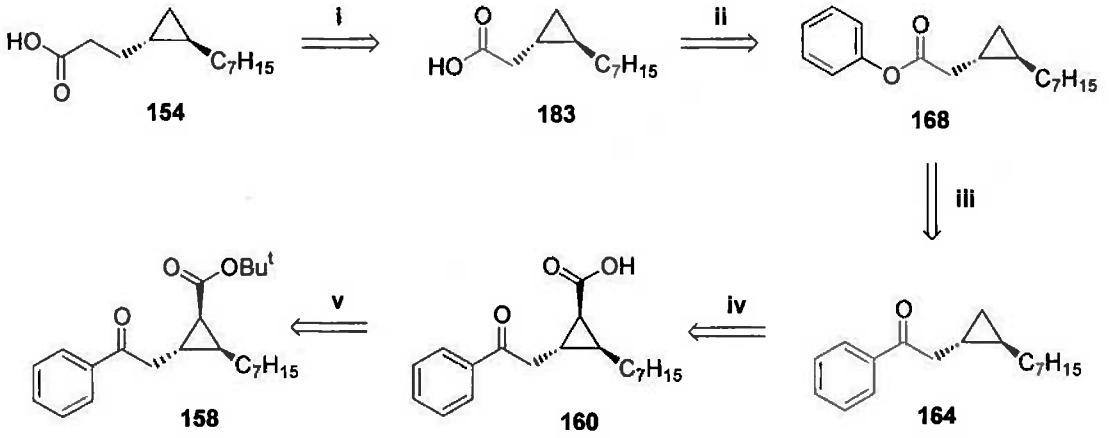
3.1.1 Retrosynthetic analysis and formation of the required 1,2-dioxine

The approach taken towards the synthesis of the natural products, grenadadiene **48**, debromogrenadadiene **49** and grenadamide **50** (previously discussed in section 1.5) focused on the development of synthetic strategies for the construction of the cyclopropyl fatty acid **154**. This compound is an important core component in all three naturally occurring cyclopropyl fatty acids depicted below (**Scheme 3.1**).



Scheme 3.1

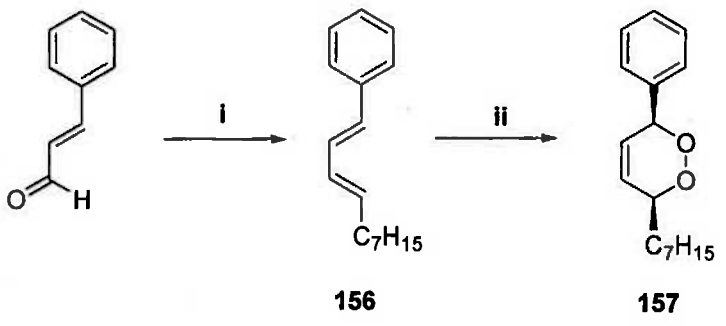
Retrosynthetic analysis of cyclopropyl acid **154** suggests that it could be obtained by chain elongation of the cyclopropane **183**, which in turn could be generated by hydrolysis of the cyclopropyl ester **168**. This ester could be synthesised by Baeyer-Villiger oxidation of the ketone **164**. Decarboxylation of cyclopropane **160** would give the desired disubstituted cyclopropane **164**, of which the former cyclopropane may be obtained by hydrolysis of the *t*-butyl ester **158** (**Scheme 3.2**).



Scheme 3.2 (i) Arndt-Eistert homologation. (ii) Hydrolysis. (iii) Baeyer-Villiger oxidation. (iv) Barton Decarboxylation. (v) Acidic hydrolysis.

Analogous to the reactions previously discussed in chapters 1 and 2, cyclopropanation to give compound **158** can occur by exploitation of MIRC reactions between 3,6-disubstituted 1,2-dioxines and stabilised phosphorus ester ylides.[159] However, since in most cases these reactions are not enantioselective (unless a chiral cobalt catalyst is used with a symmetrical dioxine[160,161]), enantiomeric resolution during this synthesis must be considered. Suitable synthetic targets for enantiomeric resolution include compounds **160** and **183** as carboxylic acids can be easily converted to diastereomeric neutral compounds or salts upon treatment with optically pure resolving agents.[136]

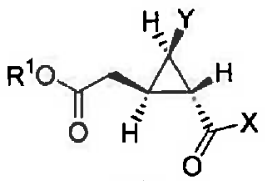
The 1,2-dioxine **157**, possessing heptyl substitution, is required for incorporation of the C_7 hydrocarbon chain observed in the targeted cyclopropyl fatty acids. This 1,2-dioxine was obtained by photo-oxidation of the corresponding 1,3-butadiene **156**, which was prepared by a Wittig reaction of *trans*-cinnamaldehyde and the ylide generated from the octyl phosphonium salt **155** (**Scheme 3.3**).



Scheme 3.3 (i) $[Ph_3P\text{-}CH_2\text{-}C_7H_{15}]^+ I^-$ **155**, KOBu^t, THF, 0°C (15 min) → 20°C (16 hr), 67%. (ii) Rose Bengal *bis*(triethylammonium) salt, DCM, O_2, *hv*, 6 hr, 59%.

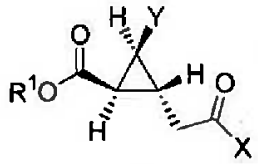
3.1.2 Formation of the cyclopropyl core and functional group modifications

As discussed in Chapter 1, reactions of 3,6-disubstituted 1,2-dioxines with stabilised phosphorus ylides can proceed to give cyclopropanes of type **89** and/or **91**, depending on the steric nature of the ylide used and whether the reaction is performed in the presence or absence of a coordinating salt such as lithium bromide.[155,159]



89

R^1 = non-bulky group



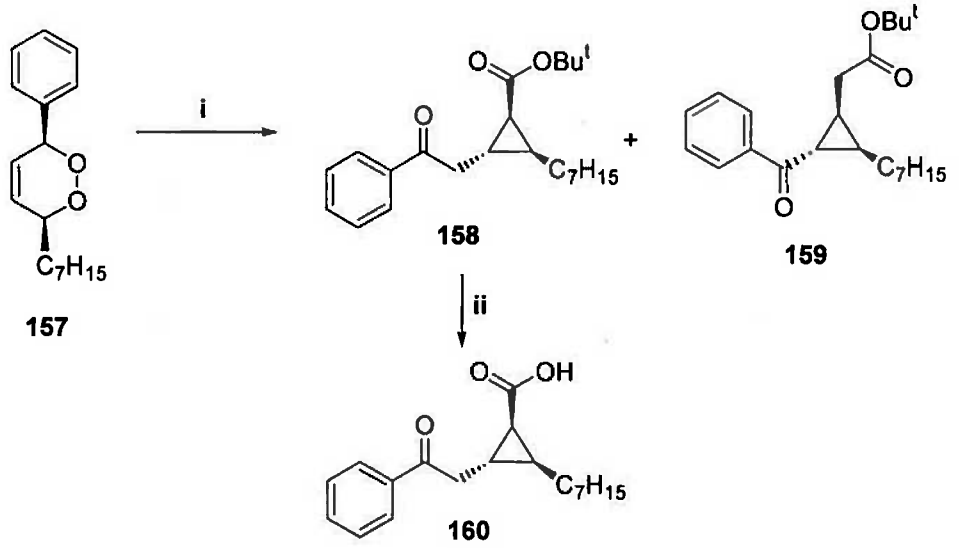
91

R^1 = bulky group

X, Y = combination of H, alkyl, aryl

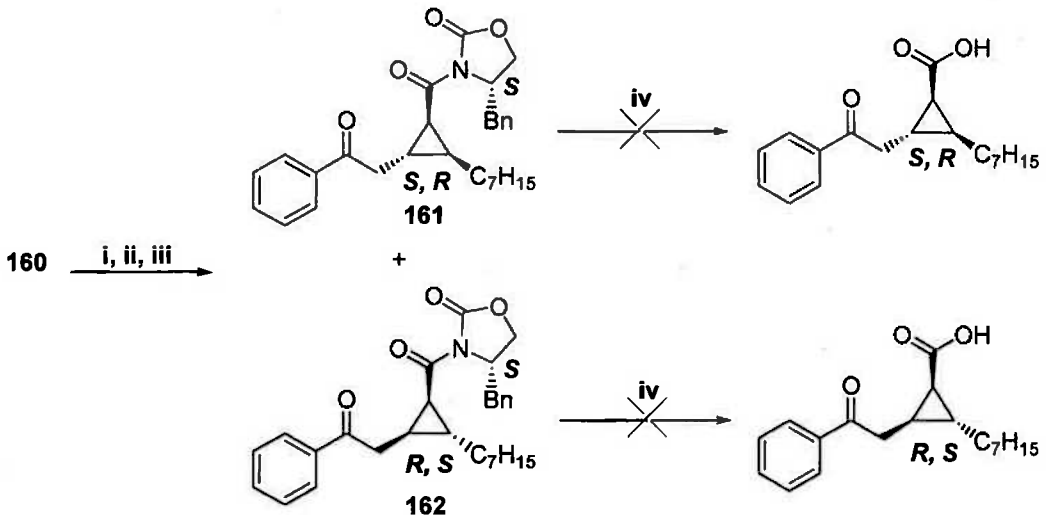
As can be seen from the above structures, the two types of cyclopropanes only differ by the location of the methylene group. Therefore, either the keto group or ester moiety can be directly attached to the cyclopropane ring as in **89** and **91**, respectively. As the targeted cyclopropyl fatty acid **154** is di-substituted, generation of the above cyclopropanes (where Y = C_7H_{15}) requires removal of either the keto or ester functionalities. Removal of the keto group of cyclopropane **89** would leave the remaining functionalities in a *cis* relationship. Hence, cyclopropanes of type **91** were targeted as removal of the ester moiety maintains the *trans* stereochemistry required for cyclopropyl fatty acid **154**.

Cyclopropanes of this type are favoured when bulky ester ylides are allowed to react with 1,2-dioxines in the presence of lithium bromide. Therefore, the 1,2-dioxine **157** was treated with the *tert*-butyl ester ylide **118** in the presence of lithium bromide to afford the tri-substituted cyclopropane **158** as the major product (**Scheme 3.4**). The isomeric cyclopropane **159** was also observed in the ^{1}H NMR of the crude reaction mixture as the minor product but it was not isolated.



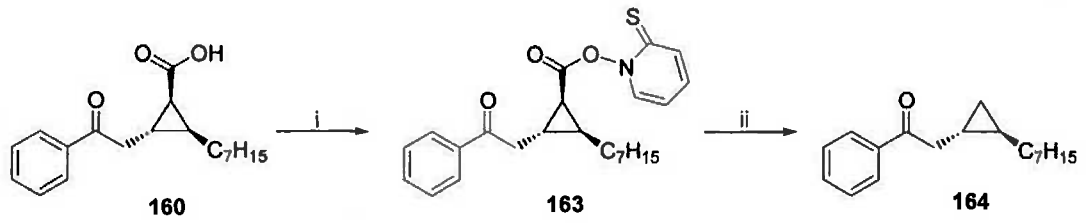
Scheme 3.4 (i) $Ph_3P{=}CHCO_2Bu^t$ **118**, DCM, LiBr, rt, 5 days, 52% of **158**. (ii) TFA, DCM (1:1), rt, 16 hr, 70% (recrystallised yield).

The cyclopropyl ester **158** was cleanly converted to the corresponding cyclopropyl acid **160** upon treatment with trifluoroacetic acid in dichloromethane.[175] Optical resolution of the cyclopropyl acid **160** was achieved by conversion of this enantiomeric pair to the diastereomers **161** and **162** using (*S*)-(-)-4-benzyl-2-oxazolidinone (**Scheme 3.5**).[153] Unfortunately, this method was inaccessible to the free enantiomeric acids of **160** as the conditions required for removal of the resolving agent were incompatible with the keto moiety present in **161** and **162**, resulting in Baeyer-Villiger oxidation of this group. Therefore, enantiomeric separation had to be revisited further down the track.



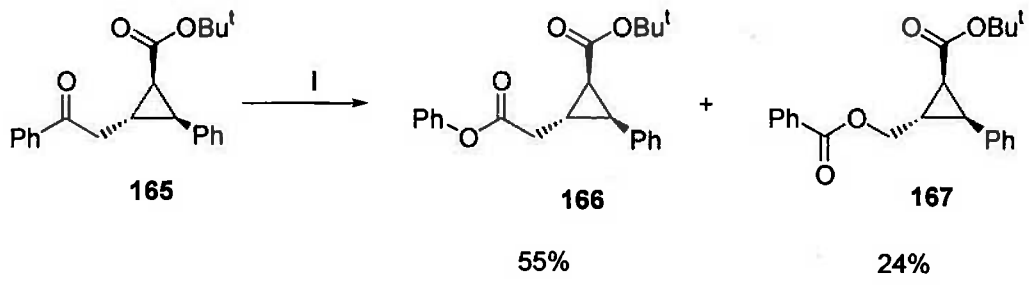
Scheme 3.5 (i) oxalyl chloride (3 equiv.), DMF (cat.), DCM, 0°C (2 hr) → rt (1 hr), (ii) (*S*)-(-)-4-benzyl-2-oxazolidinone (1 equiv.), THF, -78°C, 4 hr,. (iii) chromatographic separation, 33% of **161** and 24% of **162**. (iv) LiOH (4 equiv.), H_2O_2 30% (8 equiv.), H_2O, THF, 0°C, 0.5 hr.

Decarboxylation of cyclopropane **160** was achieved by the method of Barton and co-workers.[165] This procedure involved the esterification of acid **160** using 2-mercaptopyridine *N*-oxide and DCC to give the intermediate 'Barton ester' **163,** which upon irradiation with light in the presence of a reducing agent underwent radical decomposition to the decarboxylated cyclopropane **164 (Scheme 3.6)**. Initially, tributyltin hydride was utilised as the reducing agent in the decarboxylation of cyclopropane acid **160**. However, the yield of product was low (34-50%), a consequence of excessive purification due to the difficulty of removing tin. The problems of poor yield and purification were overcome by the replacement of tributyltin hydride with *tert*-butylthiol[165] in subsequent decarboxylations.



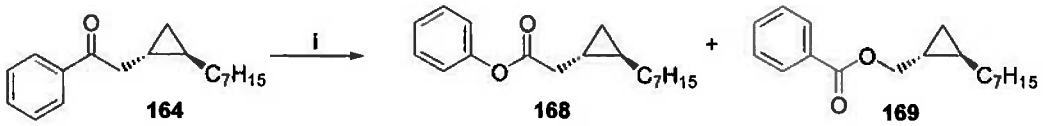
Scheme 3.6 (i) 2-mercaptopyridine *N*-oxide, DCC, DCM, rt, N_2, 3 hr. (ii) tributyltin hydride or *tert*-butylthiol, C_6H_6, *hv*, 2 hr, 65%.

With the disubstituted cyclopropane **164** in hand, conversion to the phenyl ester **168** by Baeyer-Villiger oxidation was attempted. However, treatment of cyclopropane **164** with *m*-CPBA did not favour formation of the desired phenyl ester **168 (Scheme 3.8)**. A reasonable proportion of this phenyl ester was expected since previously Avery and co-workers[159] observed a 2.3:1 mixture of compounds **166** and **167** when cyclopropane **165** was treated with *m*-CPBA **(Scheme 3.7)**. The corresponding *cis* derivative gave similar results when treated under identical conditions.



Scheme 3.7 (i) 70% *m*-CPBA (1.5 equiv.), DCM, 5 days.

In contrast to these results, the reaction of the cyclopropane **164** strongly favoured formation of the methylene migratory product **169** in a ratio of 85:15 (determined by ^{1}H NMR). The difference observed for these two cyclopropanes is most likely a consequence of the different electronic environments of the migratory carbons, due to the presence or absence of the electron withdrawing ester group.



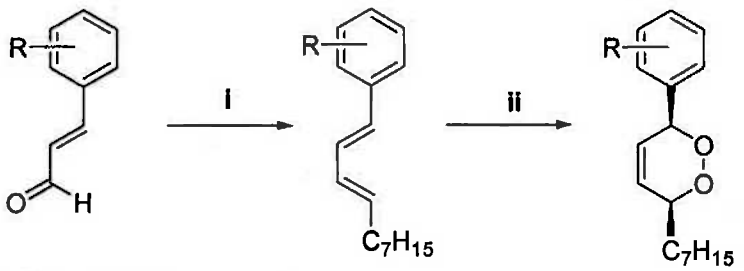
164 **168** **169**

Scheme 3.8 (i) 70% *m*-CPBA (2.15 equiv.), DCM, rt, 2 days, 80% (combined).

Due to the results observed for functional group migration in **164**, the migrating ability of the phenyl group had to be increased in order to favour its migration over the methylene group. As electron donating groups are known to increase the migrating ability of aryl substituents,[136] the methoxy group was chosen as a suitable electron donor.

3.1.3. Synthesis of *para*-methoxy phenyl and *ortho*-methoxy phenyl derivatives

The 1,2-dioxines **172a-b**, possessing *para*-methoxy phenyl and *ortho*-methoxy phenyl substitution, respectively, were prepared analogous to the method employed for the synthesis of the 1,2-dioxine **156** (**Scheme 3.9**).



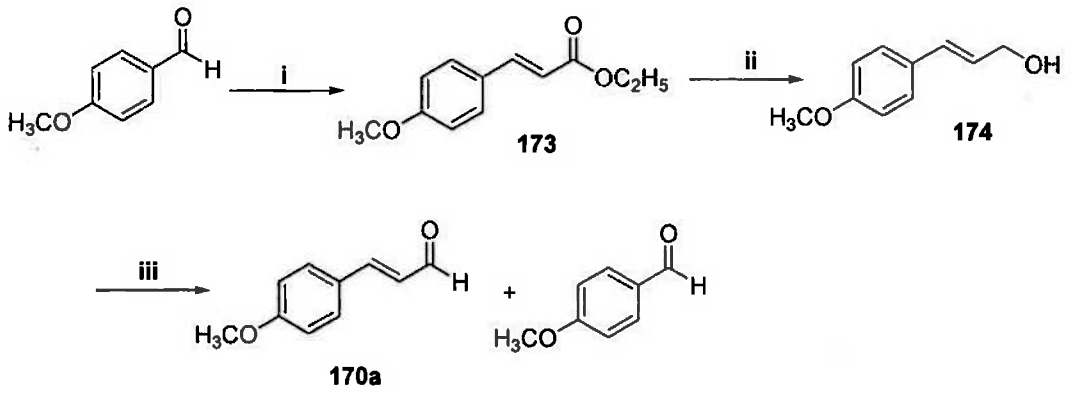
170 **a** : R = *p*-OCH_3
b : R = *o*-OCH_3

171a-b **172a-b**

Scheme 3.9 (i) $[Ph_3P\text{-}CH_2\text{-}C_7H_{15}]^+ I^-$ **155**, $KOBu^t$, THF, 0°C (15 min) → 20°C (16 hr), 77-90%. (ii) Rose Bengal *bis*(triethylammonium) salt, DCM, O_2, *hv*, 6 hr, 37-39%.

The *α,β*-unsaturated aldehyde **170a** was synthesised by a three step pathway originating from anisaldehyde (**Scheme 3.10**). This multi-step pathway involved well-known chemical transformations, of which most are known to be high yielding. The *α,β*-unsaturated ethyl

ester **173** was obtained quantitatively from a Wittig reaction of anisaldehyde and (carbethoxymethylene)triphenylphosphorane.[176] The ethyl ester **173** was reduced in the presence of lithium aluminium hydride and aluminium chloride[177] to the corresponding alcohol **174** in 94% yield, which subsequently was reoxidised to the desired *α,β*-unsaturated aldehyde **170a**. Although aldehydes can be formed in one step from their esters using such reagents as diisobutylaluminium hydride (DIBAL-H), it is difficult to prevent their complete reduction to their alcohols even when only one equivalent of reducing agent is used. Consequently, the two-step approach was taken.



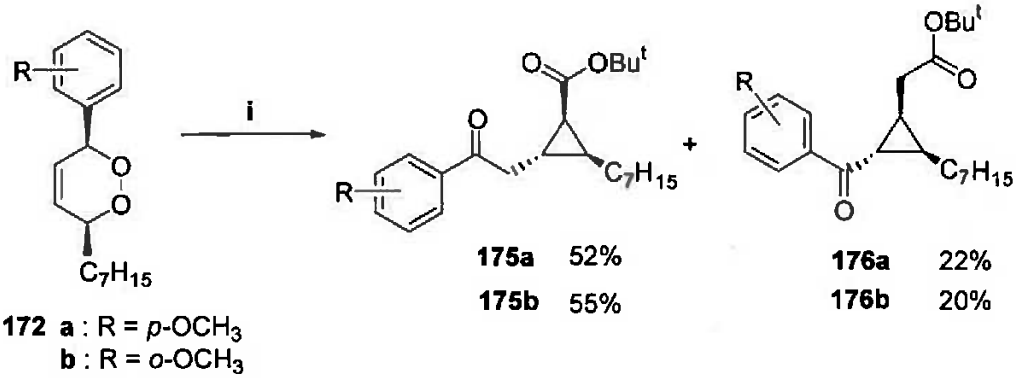
Scheme 3.10 (i) $Ph_3P{=}CH\text{-}CO_2C_2H_5$, DCM, rt, 24 hr, 100%. (ii) $AlCl_3$, $LiAlH_4$, diethyl ether, 0°C → rt, 94%. (iii) PDC (2.5 equiv.), DCM, rt, 24 hr, 55% or DMSO (4 equiv.), oxalyl chloride (2 equiv.), DCM, -78°C, 1.5 hr, 63%.

Oxidation of the *α,β*-unsaturated alcohol **174** was performed using both Swern[171] and PDC[178] oxidations. Unfortunately under both conditions, only a moderate yield (55-63%) of the desired aldehyde was obtained. The reduced yield was a consequence of carbon-carbon double bond oxidation of the *α,β*-unsaturated alcohol **174** and/or the over oxidation of aldehyde **170b**, which resulted in the regeneration of anisaldehyde. Anisaldehyde represented a 20% impurity in the product obtained after workup, as indicated by ^{1}H NMR analysis. The crude aldehyde mixture was carried through to the next step, as separation by flash chromatography was futile due to similar R_f values of the two aldehydes. **Table 3.1** summarises the yields obtained for the Wittig reactions and photo-oxidations of *trans*-cinnamaldehyde and the *α,β*-unsaturated aldehydes **170a-b** and the 1,3-butadienes **156** and **171a-b**, respectively.

Table 3.1 Percentage yields obtained for 1,3-butadienes **156** and **171a-b** and 1,2-dioxines **157** and **172a-b**.

Aldehyde	% yield of 1,3-butadiene	% yield of 1,2-dioxine
***trans*-cinnamaldehyde**	70	59
170a	77	37
170b	90	39

The 1,2-dioxines **172a-b** were treated with the *tert*-butyl ester ylide **118** in the presence of lithium bromide to afford the tri-substituted cyclopropanes **175a-b** as the major product in similar yields as for cyclopropane **158** (**Scheme 3.11**). The isomeric cyclopropanes **176a-b** were also observed in these reactions as minor products.



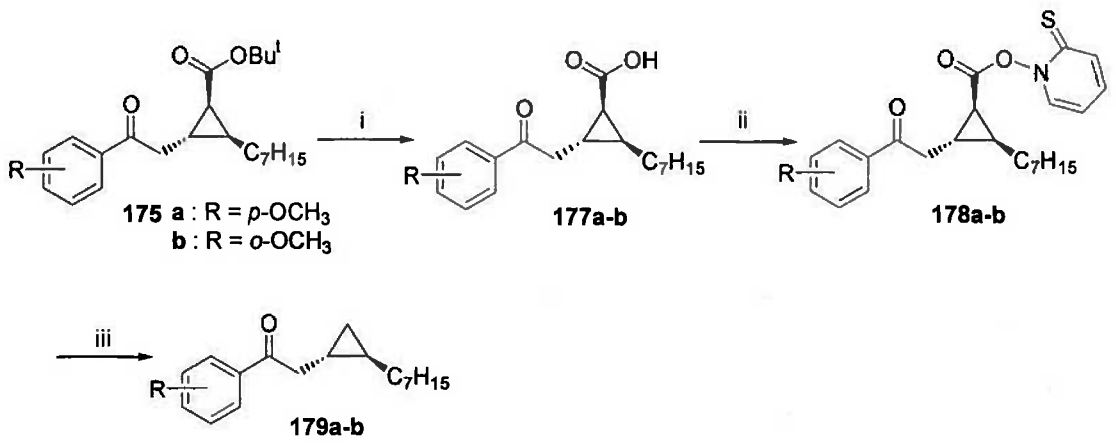
172 **a** : R = *p*-OCH_3
b : R = *o*-OCH_3

175a 52%
175b 55%

176a 22%
176b 20%

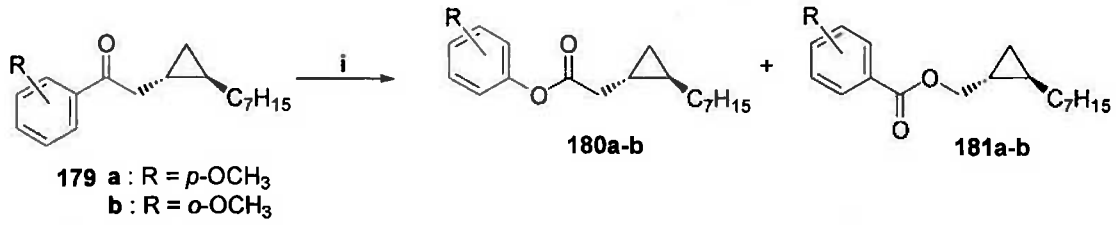
Scheme 3.11 (i) $Ph_3P{=}CHCO_2Bu^t$ **118**, DCM, LiBr, rt, 12-15 days.

The cyclopropyl esters **175a-b** were converted to the corresponding cyclopropyl acids **177a-b** upon treatment with 99% formic acid.[179] As for the phenyl cyclopropyl acid **160**, cyclopropyl acids **177a-b** were converted to the intermediary 'Barton esters' **178a-b** which upon irradiation with light in the presence of *tert*-butylthiol underwent radical decomposition to the decarboxylated cyclopropanes **179a-b** in high yield (**Scheme 3.12**).[165]



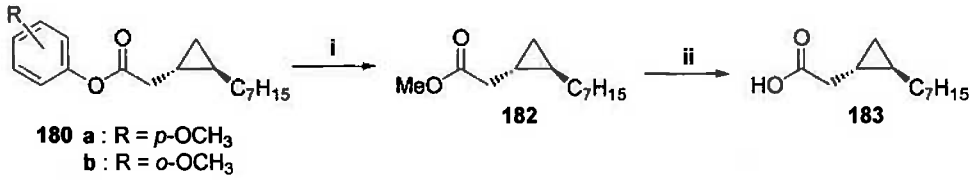
Scheme 3.12 (i) 99% Formic acid, rt, 3 hr, 89-97%. (ii) 2-mercaptopyridine *N*-oxide, DCC, DCM, rt, N_2, 3 hr. (iii) tributyltin hydride or *tert*-butylthiol, C_6H_6, *hv*, 2 hr, 76-86%.

Baeyer-Villiger oxidation of cyclopropanes **179a** and **179b** exhibited excellent selectivity towards aryl migration to give the desired phenolic esters **180a** and **180b** in yields of 91% and 77%, respectively. Formation of phenol ester **180a** was highly selective with no **181a** observed, while formation of phenol ester **180b** was favoured over cyclopropane **181b** in a ratio of ~15:1 (**Scheme 3.13**).



Scheme 3.13 (i) 70% *m*-CPBA (2.15 equiv.), DCM, rt, 2 days, 91% (**180a**), 0% (**181a**); 77% (**180b**), 5% (**181b**).

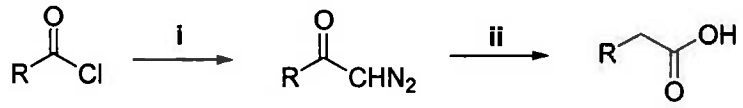
The next step in the synthetic sequence involved the generation of cyclopropyl fatty acid **183**, possessing one less methylene group than the desired cyclopropyl acid **154**. Phenol esters **180a-b** were firstly transesterified to methyl ester **182** prior to base-catalysed ester hydrolysis to afford cyclopropyl acid **183** (**Scheme 3.14**).[159] The reason for avoiding direct hydrolysis of the phenol esters was that it would result in formation of phenols, which has previously been found by our group to make purification of the acid difficult. Transesterification and ester hydrolysis proceeded in 86% overall yield.



Scheme 3.14 (i) MeOH, H_2SO_4, reflux, 16 hr, 93%. (ii) KOH (2M), MeOH, H_2O, rt, 6 hr, 93%.

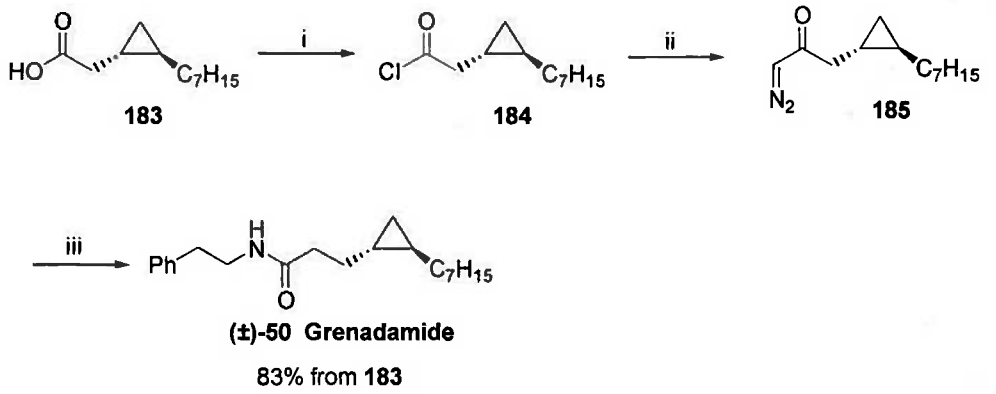
3.1.4. Arndt-Eistert Homologation and Natural Grenadamide Synthesis

With cyclopropyl acid **183** in hand, the next step involved homologation to increase its carbon chain by one. The Arndt-Eistert synthesis is the best method for conversion of a carboxylic acid to one containing an additional carbon.[136] It has been used in the homologation of α-amino acids to β-amino acids.[180] The Arndt-Eistert synthesis involves conversion of an acyl halide, which is readily available from the parent acid, to the higher carboxylic acid homolog via a diazoketone intermediate (**Scheme 3.15**).[136]



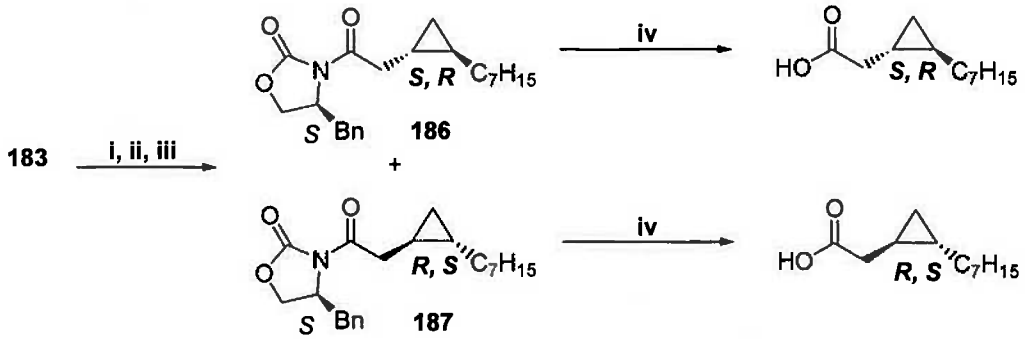
Scheme 3.15 (i) CH_2N_2 (ii) Ag_2O, H_2O or $C_6H_6CO_2Ag$, $N(C_2H_5)_3$.

Treatment of the diazoketone with water and silver oxide or triethylamine and silver benzoate affords the carboxylic acid via a Wolff rearrangement. Alternatively, direct isolation of esters or amides (rather than the carboxylic acid) can occur by treatment of the diazoketone intermediate with an alcohol or amine, respectively, instead of water.[136] Consequently, one-pot Arndt-Eistert homologation/amidation[181] of cyclopropyl fatty acid **183** proceeded cleanly to give racemic grenadamide in 83% yield, through acid chloride[153] **184** and diazoketone[182] **185** intermediates (**Scheme 3.16**).



Scheme 3.16 (i) oxalyl chloride (3 equiv.), DMF (cat.), DCM, 0°C (2 hr) → rt (1 hr). (ii) CH_2N_2 (1.5 equiv.), triethylamine (1.5 equiv.), diethyl ether, 0°C, 0.5 hr. (iii) $PhCO_2Ag$ (1.1 equiv.), phenethylamine (4 equiv.), THF, triethylamine, -15°C → rt (16 hr), 83% (3 steps).

With the synthesis of racemic grenadamide established, the synthesis of its two enantiomers was achieved by separation of the enantiomers of the cyclopropyl fatty acid **183** prior to Arndt-Eistert homologation/amidation. The cyclopropyl fatty acid **183** was resolved by conversion of its enantiomeric pair to chromatographically separable diastereomers **186** and **187** via its coupling to Evan's auxiliary (**Scheme 3.17**).[153] Auxiliary cleavage was achieved by treatment of the separated diastereomers **186** and **187** with lithium hydroxide and hydrogen peroxide in aqueous THF.



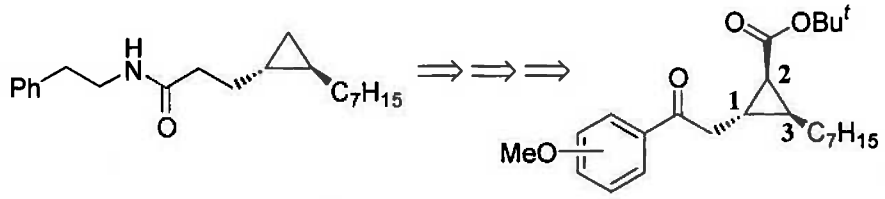
Scheme 3.17 (i) oxalyl chloride (3 equiv.), DMF (cat.), DCM, 0°C (2 hr) → rt (1 hr). (ii) (*S*)-(-)-4-benzyl-2-oxazolidinone (1 equiv.), THF, -78°C, 4 hr. (iii) chromatographic separation. (iv) LiOH (4 equiv.), H_2O_2 30% (8 equiv.), H_2O, THF, 0°C, 0.5 hr.

The enantiomerically pure fatty acids were subjected to the Arndt-Eistert protocol to give (-)- and (+)-grenadamide from (-)- and (+)-**183,** respectively. Non-natural (+)-grenadamide gave an optical rotation $[\alpha_D]^{20.5}$ +12.0° ($CHCl_3$, c = 0.005) corresponding to that recently synthesized by Baird and co-workers[87] ($[\alpha_D]^{22}$ +12.6° ($CHCl_3$, c = 0.84)) with natural (-)-grenadamide exhibiting an equal and opposite rotation $[\alpha_D]^{20.5}$ -12.0° ($CHCl_3$, c

= 0.005) which corresponds to that of the natural grenadamide isolated by Sitachitta and Grewick ($[\alpha_D]^{20.5}$ –11.0° ($CHCl_3$, c = 0.1)).[75]

3.2 Summary and Conclusion

The work described within this chapter outlines the first total synthesis of (+)-grenadamide. This route lends itself to the easy synthesis of grenadamide derivatives. Variation at carbon 3 of the cyclopropyl ring can be achieved through the use of different phosphonium salts in the generation of the 1,3-butadiene for photo-oxidation. Modification of carbon 2 of the cyclopropyl ring can be achieved by manipulation of the ester functional group.



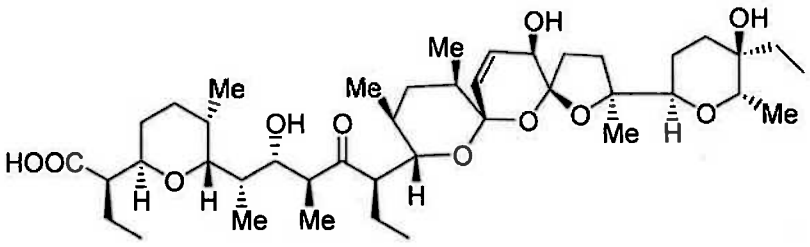
At this stage, grenadadiene and debromogrenadadiene have not been synthesised. However, since they were both isolated from the same bacterium as grenadamide, we speculate that they have the same absolute configuration as grenadamide. If this is the case, the synthesis of the cyclopropyl core of these two compounds has been established. Although, carboxylic fatty acid **154** was not isolated, it should be obtainable by treatment of diazoketone **185** with water and silver oxide in the Arndt-Eistert homologation of cyclopropyl acid **183**.

Chapter 4: Synthesis of Novel Tetrahydropyrans from 1,2-Dioxines Containing Tethered Hydroxyl Groups

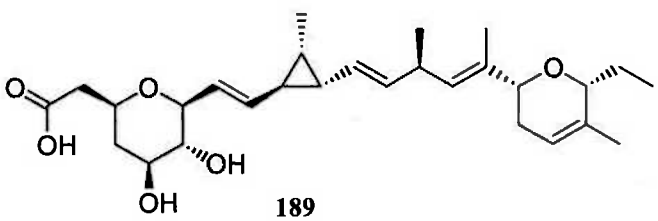
4.1 Introduction

Tetrahydropyrans (THP's) are 6-membered heterocyclic compounds containing a single oxygen atom which possess saturation about the ring. They include the extremely important blood group sugars such as β-D-glucose and β-D-galactopyranose, which exist almost exclusively in their pyran form.[183] There are many other examples of naturally occurring tetrahydropyrans, such as polyether antibiotics,[184] marine toxins,[185,186] macrolides,[187,188] annonaceous acetogenins[189] and decarestrictines.[190] Many of these are of interest as they exhibit impressive bioactivity including antibiotic,[184,191] cytotoxic,[187-189,192] antimalarial,[189] neurotoxic,[185] pesticidal[189] and antiviral.[193]

As the name suggests, polyether antibiotics are molecules containing multiple cyclic ethers that exhibit antimicrobial activity. Salinomycin **188** is one example of a polyether antibiotic that has been isolated from a strain of *Streptomyces albus*. This highly functionalised compound is effective against mycobacteria, Gram-positive bacteria and fungi.[184] The myxobacterium *Polyangium cellulosum fulvum* is another natural source of a THP-containing antimicrobial agent, ambruticin **189**.[191] Although very structurally different to the polyether salinomycin, ambruticin is a very potent antifungal agent.

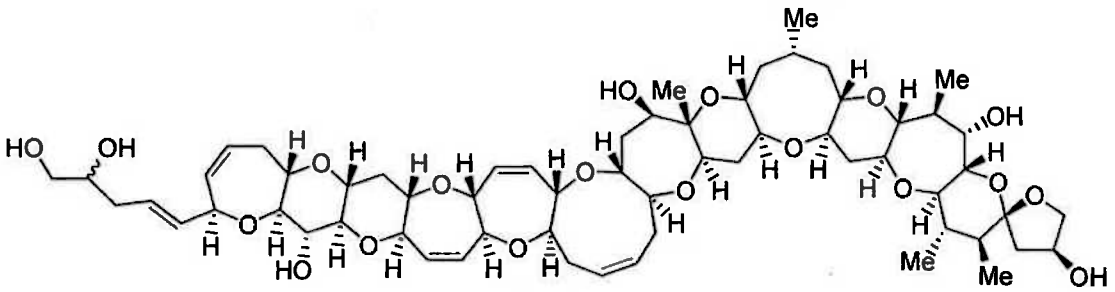


188

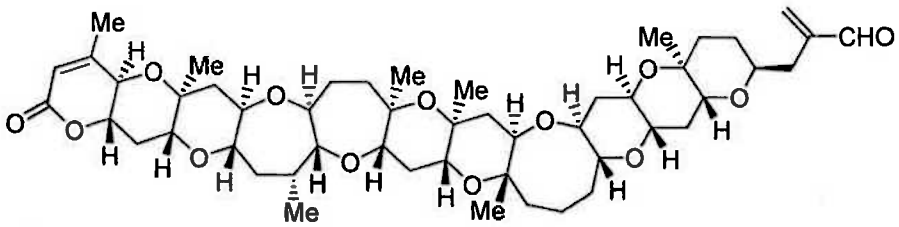


189

Some of the most interesting THP-containing natural products, for public health reasons, are the marine toxins, which include ciguatoxin[185,186] **190** and brevetoxin B[194] **191**. These highly complex molecules are responsible for human seafood poisoning and mass fish deaths caused by blooms of dinoflagellates. Ciguatoxin is produced by the dinoflagellate *Gambierdiscus toxicus* while brevetoxin B is produced by *Ptychodiscus brevis* Davis, also a dinoflagellate. Fish can become toxic through transference of these marine toxins in their diet and subsequently humans become exposed further along the food chain. These brevetoxins along with others are believed to exert their toxic effects through altering the gating mechanism of sodium channels. This is most likely a result of the conformational freedom around the centrally located 7, 8 or 9 membered rings allowing them to 'flip'.[186] Okadaic acid[192] and gambieric acids[195,196] are other interesting marine toxins which are inhibitors of dephosphorylation of proteins and antifungal agents, respectively.

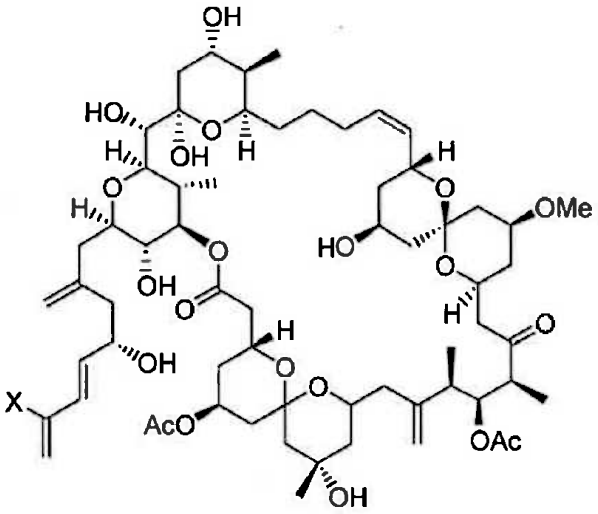


190



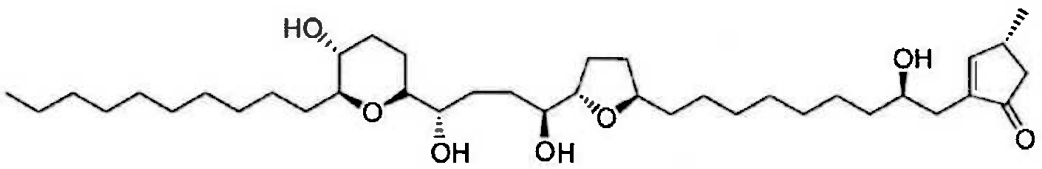
191

Within their architectural complexity, Spongistatin 1, **192a** and 2, **192b** each consist of six THP units.[187,197] Isolated from marine sponges, these unique *bis*-spiroketal macrolides along with others[188,198] exhibit cytoxicity against a range of human cancer cell lines.



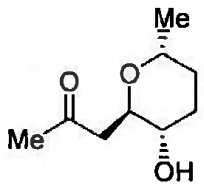
192 **a** X = Cl
b X = H

Annonaceous acetogenins, isolated from the tropical plant family Annonaceae, are sources of several THP-containing bioactive products. Most commonly, these C_{32} or C_{34} fatty acid derivatives are antitumor or pesticidal agents.[189] Mucocin **193** is one example of an annonaceous acetogenin that exhibits selective inhibition against certain lung and pancreatic cancer cell lines.[199]



193

Although most naturally occurring bioactive pyranyl compounds are structurally complex molecules, there are a selective few that are simple molecules. Decarestrictine L **194** is one such example. This structurally simple THP acts biologically by inhibiting cholesterol biosynthesis.[190]



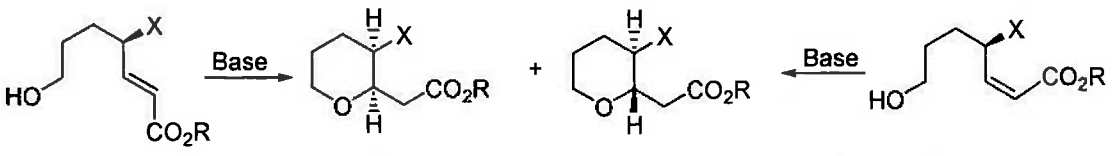
194

Subsequently, there is a great deal of interest in generating substituted tetrahydropyrans as building blocks towards the synthesis of many biologically active natural products.

4.2 Synthese of Tetrahydropyrans

There are numerous ways of synthesising tetrahydropyrans, some of the most common methods include the intramolecular 1,4-addition of alcohols to α,β-unsaturated esters or ketones, the ring-closure of α-hydroxy epoxides, the condensation of olefins with aldehydes (Prins reaction), [4+2] cycloaddition reactions and ring-closing metathesis.

Treatment of α,β-unsaturated esters containing a δ-hydroxy group with base results in ring-closure to form THP's via an intramolecular Michael addition. Diastereoselectivity of the final products is influenced by a number of factors including the nature of the reacting alkene, the base used to induce cyclisation and the solvent and equivalents of base used. For instance, (*E*)-Unsaturated esters of type **195** yield predominately the *cis*-2,3-disubstituted THP's **196**, while (*Z*)-unsaturated esters of type **198** yield predominately the *trans* counterparts **197** (**Scheme 4.1**).[200,201] However, there are reported cases where this trend is not observed. For instance, studies by Gung and Francis (1993) found that (*E*)-unsaturated esters could give predominately *cis* or *trans*-2,3-disubstituted THP's depending on the nature of the X group located on the α,β-unsaturated ester **195**. Under identical reaction conditions (toluene, KHMDS (0.1 equiv.), 22-23°C), replacement of this X group from the bulky OTBDMS to the smaller methoxy group results in the usual preference of the *cis* THP formation being diminished from 76% to 52%. Preference for *cis* formation is entirely reversed by altering the solvent, base and reaction temperature. *Trans* THP formation is optimised by performing these reactions in toluene with non-catalytic amounts of sodium bases at low temperatures. Similarly, other studies have found that the nature of the solvent and base used influences the ratio of products of type **196** and **197** obtained.[200]



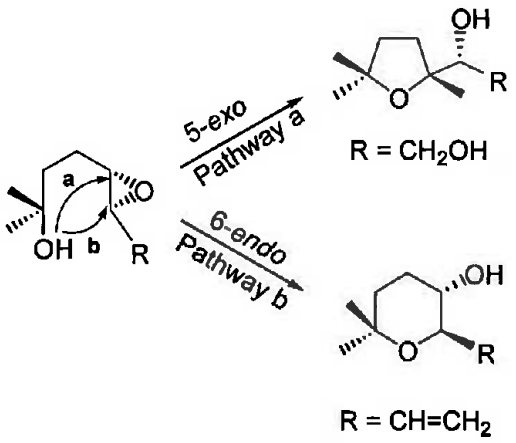
195 **196** **197** **198**

R = Me
X = OBz, Cl, Br

Scheme 4.1

This method of tetrahydropyran synthesis has been successfully used towards the synthesis of both the C_1-C_{15} and C_{27}-C_{38} segments of halichondrin.[202,203]

Another common method that affords tetrahydropyrans involves intramolecular hydroxy epoxide openings. However, in this situation an epoxide possessing a γ-hydroxy group may either undergo *exo* ring-closure to generate a tetrahydrofuran or *endo* ring-closure to generate a tetrahydropyran (**Scheme 4.2**).[204]

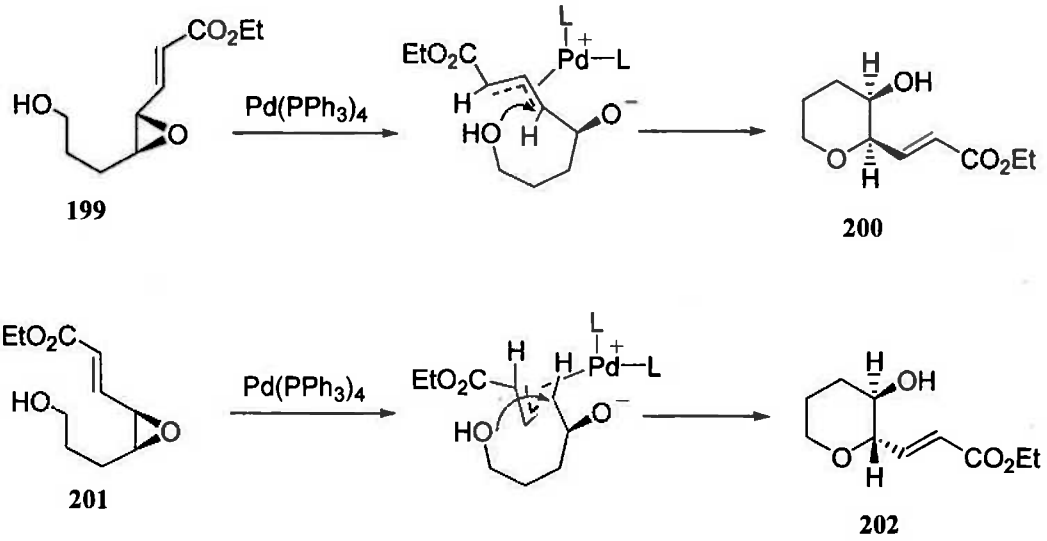


Scheme 4.2

Generally, 5-*exo* ring closure is favoured. However, Nicolaou and collegues[204] found, while investigating the acid-catalysed cyclization of various *cis* and *trans* epoxides, that THP formation is favoured when *trans* epoxides possessing a double bond such as that depicted in **Scheme 4.2** (where R = $CH{=}CH_2$) are used. Under these conditions the 6-*endo* hydroxy epoxide opening is favoured as the presence of a π-orbital adjacent to the epoxide moiety activates the C-O bond adjacent to the double bond. In addition, during the transition state the π-orbital stabilises the electron deficient carbon orbital by electron donation. Despite the presence of the π-orbital in the corresponding *cis* epoxides, 5-*exo* ring-closure is favoured in the majority of cases. This may be a consequence of steric interactions and the inability for the transition state to adopt favourable arrangements required to proceed via this pathway. In the absence of a π-orbital, tetrahydrofuran formation is also favoured, whether the reaction proceeds from the *cis* or *trans* epoxides.

Even though the work of Nicolaou and collegues[204] guided the way for the selective synthesis of *trans* 2,3-disubstitued THP's, an efficient strategy for the generation of the *cis* THP's was elusive until the later work of Suzuki and co-workers.[205] They found that palladium-catalysed cyclization of hydroxy vinyl epoxides generates predominately either

cis or *trans* THP's with regio- and stereo-control achieved by utilisation of either *cis* or *trans* epoxides.

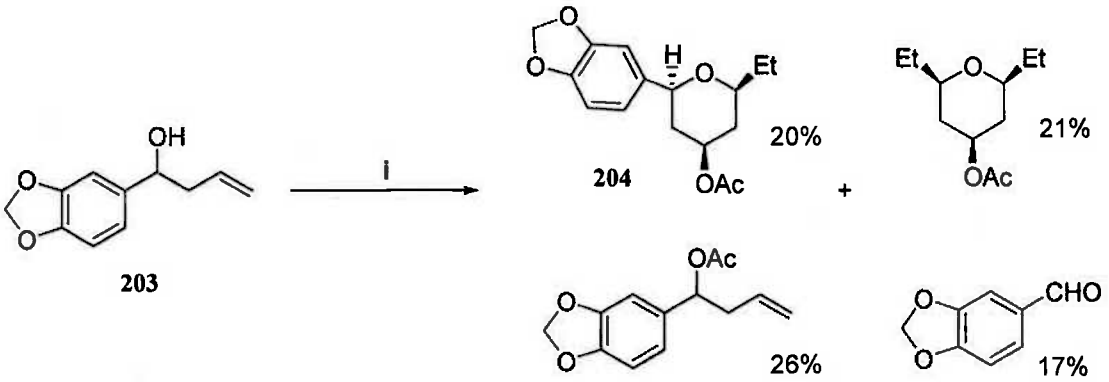


Scheme 4.3

In the presence of acetonitrile, dichloromethane or chloroform treatment of the *trans* epoxide **199** with palladium generates >99% of the *cis* THP **200**. Under the same conditions the corresponding *cis* epoxide **201** generates ≥97% of the *trans* THP **202** (**Scheme 4.3**).

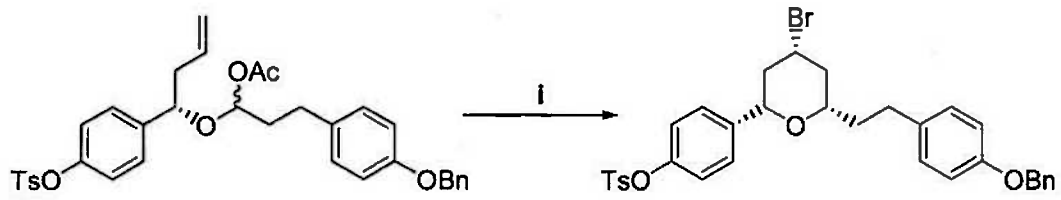
Investigations by Mukai and Collegues found that the mode of ring-closure of acetylenic epoxides when treated with the Lewis acid, boron trifluoride diethyl etherate, was dependent on the nature of the group located on the acetylenic terminus. [206] THP formation was favoured when an electron donating group such as phenyl or *p*-tolyl was positioned at the acetylenic terminus while the presence of an electron withdrawing group favoured THF formation. However, THP's were formed exclusively regardless of whether the acetylenic terminus possessed an electron withdrawing or donating substituent if the epoxides were complexed with cobalt prior to acid catalysed cyclisation.[207] Another difference observed with the pre-treatment of these epoxides with dicobalt octacarbonyl was that the *trans* epoxides no longer afforded predominately *trans* THP's but gave ≥91% of the corresponding *cis* isomers. Similarly, the *cis* epoxides now afforded ≥97% of the *trans* THP's. These results agree with the observations of Suzuki and co-workers previously discussed.

The synthesis of THP's can also be achieved by a Prins reaction between a homoallylic alcohol and an aldehyde.[208,209] One disadvantage of using this method for the generation of THP's is that it suffers from competing side reactions such as side chain exchange, racemization by reversible 2-oxonia Cope rearrangement and ene reactions that result in dihydropyran formation. For instance, optimal formation of the THP **204** from the allylic alcohol **203** and propionaldehyde is hindered by the formation of three other products (**Scheme 4.4**).[210]



Scheme 4.4 (i) EtCHO, $BF_3.OEt_2$, AcOH, TMSOAc.

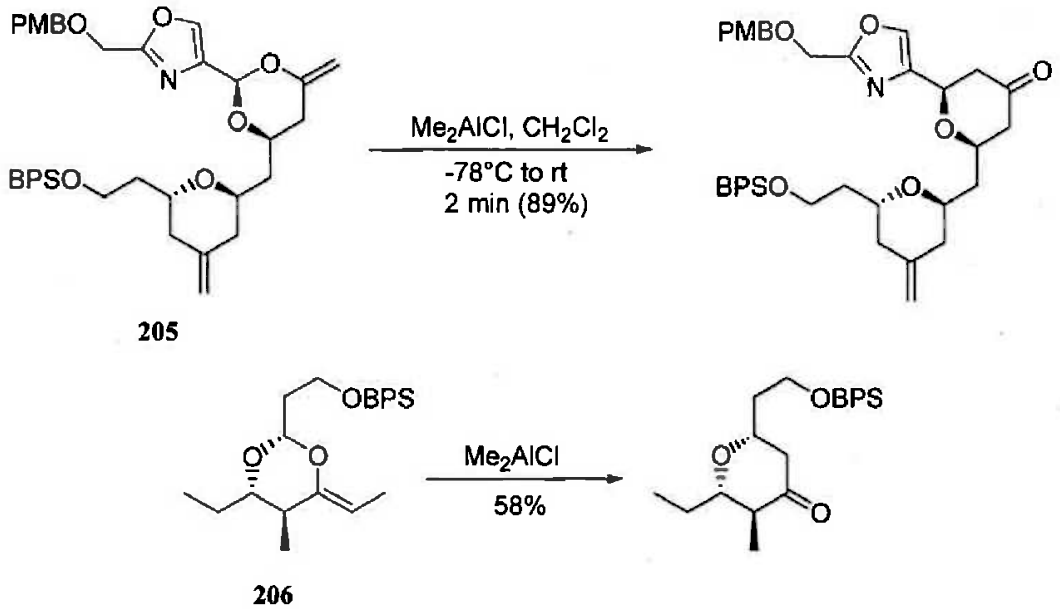
By-product formation can be overcome in the aforementioned reaction by replacement of the aldehyde with a mixed acetal in the so-called segment coupled Prins cyclisation.[211-213] Similarly, to the reaction between allylic alcohols and aldehydes, mixed acetals are able to generate oxacarbenium ions, which are believed to be the intermediate species in these reactions. Mixed acetals have been used for the assembly of both the C_1-C_{15} *bis*-THP fragment of the natural products phorboxazole A and B[213] and the pyranyl moiety of (-)-centrolobine[211] (**Scheme 4.5**). Enantio-enriched THP's have been prepared with this strategy by exploitation of enantio-enriched mixed acetals.



Scheme 4.5 (i) $SnBr_4$, DCM, -78°C.

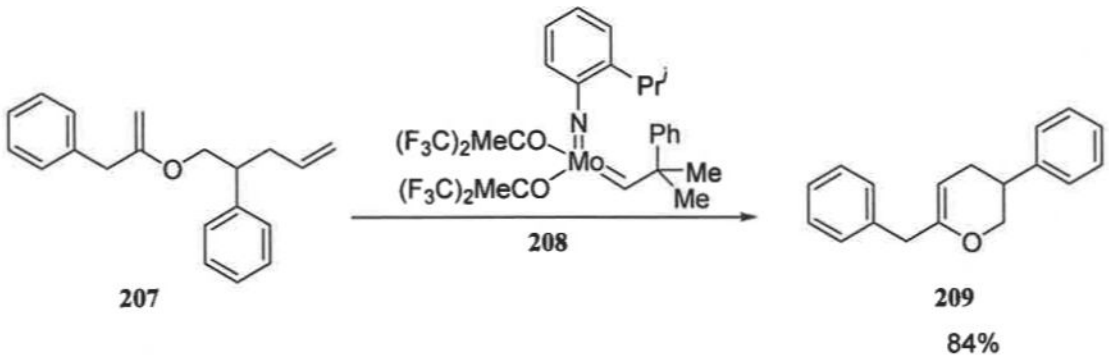
The Petasis-Ferrier rearrangement has been used recently and quite extensively by the Smith group for construction of the tetrahydropyranyl unit.[214] This method involves the rearrangement of enol acetals analogous to that reported by Petasis and Lu[215] in 1996 and

closely related enol ether rearrangements of Ferrier and Middleton[216] in 1993. In the total synthesis of (+)-phorboxazole A, Smith and co-workers[214,217], utilised the Petasis-Ferrier rearrangements of compounds **205** and **206** to construct both the C_{11}-C_{15} and C_{22}-C_{26} *cis* THP rings, respectively (**Scheme 4.6**). The same method has also been used in the assembly of the pyranyl moiety of the cytotoxic macrolide (+)-zampanolide.[218] Enantio-control is observed in these reactions if optically active precursors are used.



Scheme 4.6

Ring-closure metathesis is another method that can be utilised for the formation of THP's via the construction and subsequent hydrogenation of dihydropyrans (DHP's). Fujimura and co-workers[219] utilised the intramolecular metathesis of alkenes with enol ethers in the presence of a molybdenum catalyst for the construction of dihydrofurans and dihydropyrans. Catalytic ring-closing metathesis of the acyclic olefinic enol ether **207** in the presence of the molybdenum catalyst **208** generates the 2,5-disubstituted dihydropyran **209** in high yield (**Scheme 4.7**). This methodology has been used by Clark and Kettle[220], in the preparation of fused bicyclic enol ethers, which upon hydroboration result in *trans*-fused bicyclic ether units of the type found in many marine polyether natural products including gambierol and brevetoxin B.



207 208 209

84%

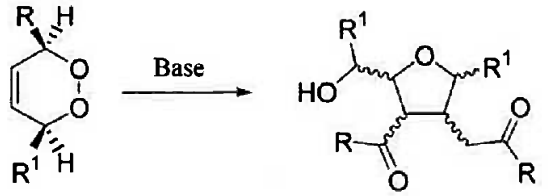
Scheme 4.7

As can be seen from this brief discussion, there are many useful ways to construct the tetrahydropyranyl unit. However, there is still great demand to improve their synthesis in regards to stereocontrol and in the diversifying their functionality.

4.3 Tetrahydropyran Synthesis Though Exploitation of 1,2-Dioxines Containing Tethered Hydroxy Groups

4.3.1 1,2-Dioxines as Suitable Tetrahydropyran Precursors : The Hypothesis

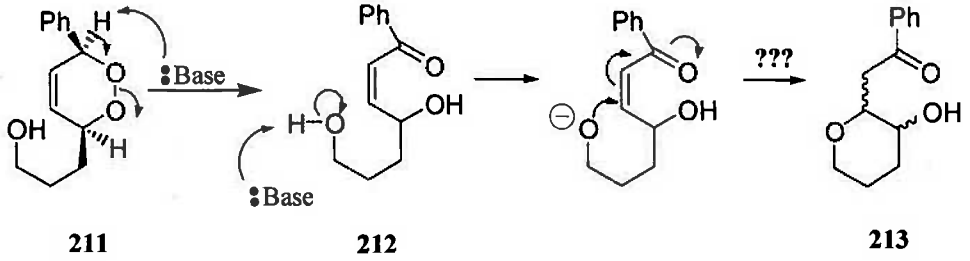
1,2-Dioxines react with numerous nucleophiles to generate a versatile range of novel compounds. This is possible since 1,2-dioxines can be regarded as masked *cis* γ-hydroxy enones, which can undergo nucleophilic 1,4-Michael addition.[221] *Cis* γ-hydroxy enones undergo 1,4-Michael attack by carbon nucleophiles, followed by ring-closure, to generate cyclopropanes[155,157-159] or lactones.[221] More recently it was found that *cis* γ-hydroxy enones undergo self-condensation in the presence of base to generate tetrahydrofurans of type **210**.[162] This occurs when one molecule of enone undergoes 1,4-nucleophilic attack by a second molecule of enone, which acts as an oxygen nucleophile, followed by intramolecular ring-closure.



R, R^1 = Combination of Ph, Me, H or *n*-Pr

210

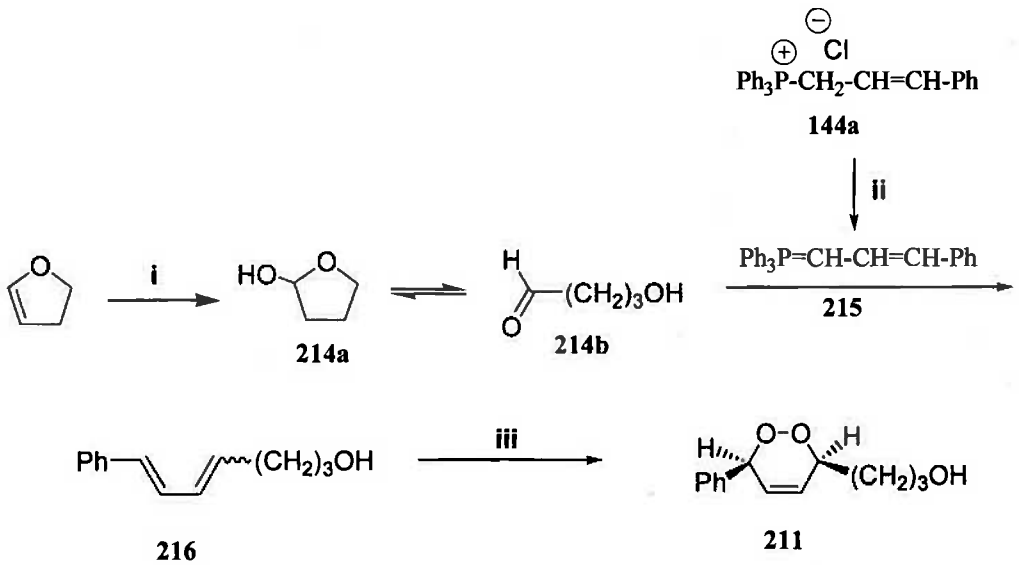
Since *cis* γ-hydroxy enones undergo nucleophilic 1,4-Michael attack by intermolecular oxygen it was envisaged that the presence of an intramolecular oxygen nucleophile would result in intramolecular ring-closure to generate a novel series of oxygen-containing heterocycles. To investigate this theory, the 1,2-dioxine **211**, containing a tethered hydroxy group, was prepared. The reason for utilising this 1,2-dioxine was two-fold. Firstly, the presence of the phenyl group is desirable to facilitate ring-opening of the 1,2-dioxine in the presence of base to give the *cis* γ-hydroxy enone **212**. Secondly, the three carbon tethered hydroxy group results in the formation of the most thermodynamically stable 6-membered tetrahydropyran **213** (**Scheme 4.8**).



Scheme 4.8

4.3.2 Synthesis of the 1,2-Dioxine 211

1,2-Dioxine **211** was obtained via several methodologies, but the most successful, in terms of yield, ease and economic efficiency, is that outlined in **Scheme 4.9**. This pathway eliminates the need for starting materials which require lengthy preparation and poor yielding hydroxy ylides (discussed in **Section 4.4.1**) which alternative Wittig reactions entail.



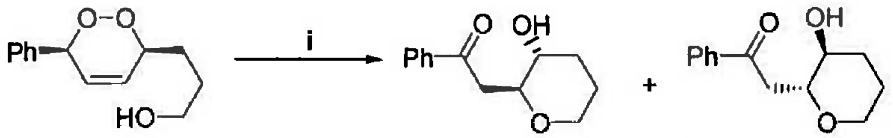
Scheme 4.9 (i) aq. HCl (1M), 0°C, 30 min, 68%. (ii) **144a**, KOBu^t, THF, rt, 15 min, **214a-b** (1.25 equiv.), 0°C (10 min) → rt (16 hr), 64%. (iii) Rose Bengal *bis*(triethylammonium) salt, DCM, O_2, *hv*, 6 hr, 43%.

The 1,3-butadiene **216** was prepared in moderate yield by the Wittig reaction of the cinnamyl ylide **215**, generated *in situ* from the chloride salt **144a**, and 4-hydroxy-1-butanal **214b**, which exists in equilibrium with its hemi-acetal, γ-butyrolactol **214a**. The cinnamyl phosphonium salt **144a** was synthesised in good yield from chloride displacement of cinnamyl chloride by triphenylphosphine. γ-Butyrolactol was prepared by hydration of 2,3-dihydrofuran using the method of Kodato and co-workers.[222] The yield of 1,3-butadiene

216 was increased when excess γ-butyrolactol was utilised, perhaps a result of reducing the amount of ylide **144a** reacting with itself, which was found to occur in the absence of an aldehyde. Photo-oxidation of **216** in the presence of rose bengal, bis(triethylammonium) salt, afforded the 1,2-dioxine **211** in moderate yield .

4.3.3 Tetrahydropyran Synthesis and Structure Determination

Treatment of the 1,2-dioxine **211** with lithium hydroxide at ambient temperature resulted in the formation of the tetrahydropyrans **217** and **218** in a ratio of 64:36, as determined by ^{1}H NMR, and with a combined yield of 82% (**Scheme 4.10**).

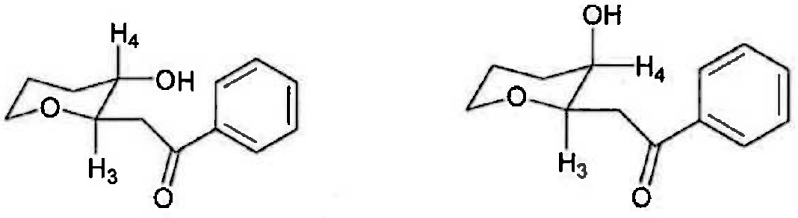


211 **217** **218**

Scheme 4.10 (i) LiOH (1 equiv.), THF, rt, 16 hr.

The structure and relative stereochemistry of each tetrahydropyran was determined through a combination of ^{1}H, ^{13}C, COSY, HMBC, HMQC and ROESY NMR experiments. In some instances, the relative stereochemistry was confirmed by X-ray crystallography.

As can be seen in **Figure 4.1**, the vicinal coupling constant between H_3 and H_4 gives important information about the relative stereochemistry of the molecule. For vicinal protons, the magnitude of the coupling constant is influenced by several factors including dihedral angle, electronegativity, angle strain and bond length.[223,224]



trans
Large dihedral angle
Larger $^3J_{3,4}$

cis
Small dihedral angle
Smaller $^3J_{3,4}$

Figure 4.1

The relationship between the vicinal coupling constant (^3J) and the dihedral angle is approximated by the Karplus equation. This theoretically derived equation predicts that ^3J will be zero when the vicinal protons are at right angles, largest when the vicinal protons are *trans* coplanar and slightly smaller than $^3J_{trans}$ when they are *cis* coplanar.[224] However, the Karplus equation has its limitations. Even though it can be used to predict the diaxial, axial-equatorial and diequatorial coupling constants in a cyclohexane chair conformation, it does not take into account the effect caused by the introduction of electronegative atoms whether they are present as a substituent or in the ring system itself. For instance, the introduction of an electronegative group directly attached to the same carbon as a vicinally coupled proton, such as observed for both H_3 and H_4, results in reduction of the ^3J value.[223,224] The reduction of ^3J is largest when the electronegative group is located in a *trans* coplanar orientation relative to one of the vicinal coupled protons.[224]

In the case of tetrahydropyran, the substitution of one of the carbons of cyclohexane with an oxygen atom results in ring contraction. This occurs since the bond length of a C-O bond is slightly less than that of a C-C bond (1.41 A and 1.54 A, respectively).[225] Therefore, this slight flattening of the tetrahydropyran ring will influence the vicinal coupling constant relative to that observed for a cyclohexane as the dihedral angle between adjacent equatorial and axial protons is reduced by approximately 3°. Another factor influencing the coupling constants in solvated 6-membered ring systems is the possibility that several contributing conformers may exist in dynamic equilibrium, such as ring flipped chair conformers and boat conformers.

Unfortunately, there are not many studies in the literature that have investigated the vicinal coupling constants of protons in 2,3-disubstituted tetrahydropyrans. In 1976 Canuel and St-Jacques[225] investigated the stereo-dependent effect of oxygen on vicinal coupling constants in selectively deutrated derivatives of tetrahydropyran. They found that the couplings of vicinal axial-equatorial (2a3e), equatorial-equatorial and axial-axial protons all slightly decreased relative to those of cyclohexane-d_8 by 1.7, 1.5 and 0.7 Hz, respectively, while that of 2e3a slightly increased by 0.8 Hz. Even though the magnitude of vicinal coupling constants can be influenced by many factors, those involving di-axial interactions (i.e. *trans* coplanar) are always larger than those for the corresponding *cis* coplanar couplings. For instance, Gung and Francis[226] observed a ^3J coupling constant of 10.6 and 2.6 Hz for protons arranged in a 2,3-disubstituted *trans* and *cis* configuration around a tetrahydropyran ring, respectively. Likewise, Nicolaou and co-workers[204]

observed higher ^3J coupling constants in *trans* bi-cyclic ethers relative to their *cis* derivatives (8.5 Hz to 5.9 Hz). Therefore, analysis of the vicinal coupling constants between H_3 and H_4 (**Figure 4.1**) should result in differentiation of the *trans* and *cis* THP's since the *trans* ^3J coupling constant should be larger.

The reaction of the 1,2-dioxine **211** and lithium hydroxide (**Scheme 4.10**) gave the *trans* THP **217** as the major product as the ^3J coupling constant between H_3 and H_4 for this product was 9.0 Hz. The ROSEY NMR spectrum for this compound was inconclusive as three proton signals were partially overlapped and therefore the spatial arrangement of H_3 and H_4 could not be confirmed by this method. X-ray crystallography gave conclusive evidence that this isomer was the *trans* tetrahydropyran **217** (**Figure 4.2**). Interestingly, the crystal structure is chiral, possessing *S* configuration about C_{22} and *R* configuration about C_{23}. This induced chirality must be a result of spontaneous resolution upon recrystallisation as a chiral synthesis was not employed. Unfortunately there was insufficient sample to perform an optical rotation.

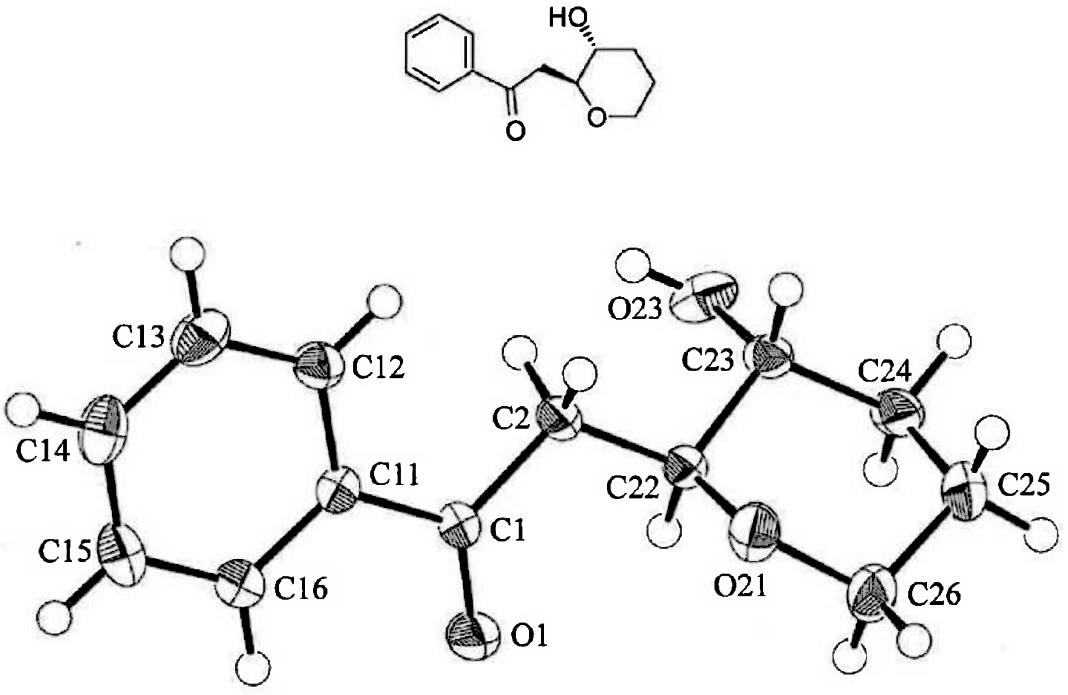


Figure 4.2 Crystal structure for the *trans* THP **217**.

The structure of the minor product was elucidated, by NMR techniques, to be the *cis* THP **218**. The vicinal coupling constant between H_3 and H_4 was 6.6 Hz, suggesting *cis* arrangement of these two protons. Furthermore, there existed a through space interaction

between H_3 and H_4 in the ROSEY NMR spectrum of this compound (**Figure 4.3**), which would only occur if the protons are located *cis* to one another.

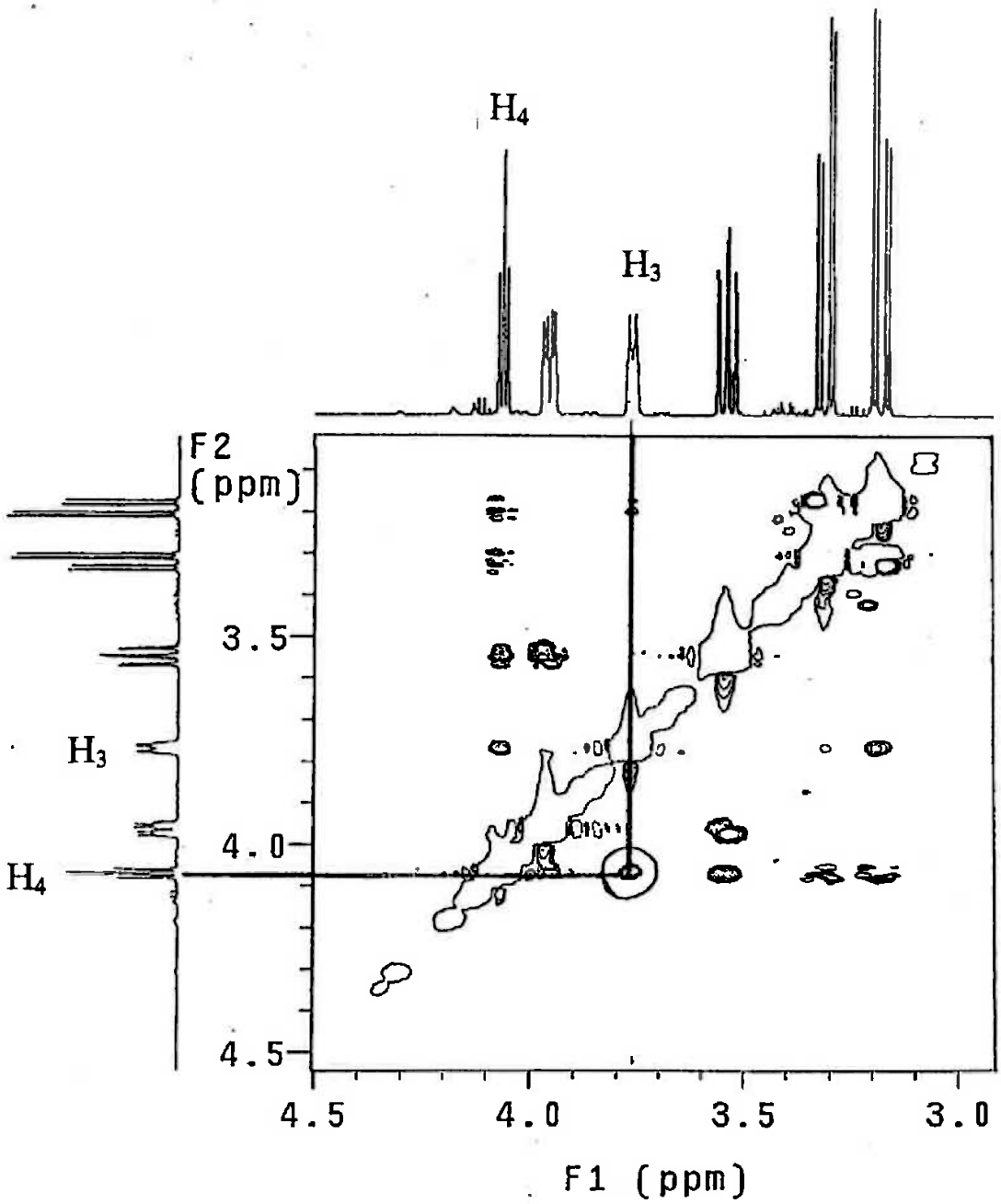


Figure 4.3 ROSEY spectrum for the *cis* THP **218** showing the cross peak between H_3 and H_4.

Therefore, treatment of the 1,2-dioxine **211** with lithium hydroxide successfully resulted in tetrahydropyran formation, with the *trans* isomer **217** predominating over the *cis* counterpart **218** under these conditions.

4.3.4 Effect of Temperature, Solvent, Base and *Trans* γ-Hydroxy Enone on THP Synthesis

With the initial hypothesis proven, attention now focused on whether the ratio of products formed could be influenced by altering the experimental conditions. It was found that treatment of the 1,2-dioxine **211** with LiOH at elevated temperatures, favoured formation of the *trans* THP **217** while treatment at lower temperatures increased the formation of the *cis* THP **218** at the expense of the *trans* isomer (**Table 4.1**). As expected the reaction rates increased as reaction temperature increased. The results of these temperature studies suggest that the *trans* THP **217** is the thermodynamic product and the *cis* THP **218** is the kinetic product. However, this is not the case as treatment of the *cis* THP under the reaction conditions that favour *trans* formation does not result in its conversion to the *trans* THP. The ratio of products formed is most likely a reflection of the populations of *cis* and *trans* γ-hydroxy enones, with higher temperatures resulting in greater conversion of the *cis* enone to its *trans* form and consequently increased *trans* THP formation. The ratio of products formed would also be dependent on the relative stabilities of the transition states leading to *cis* and *trans* THP's, which will be discussed further in **Section 4.5**.

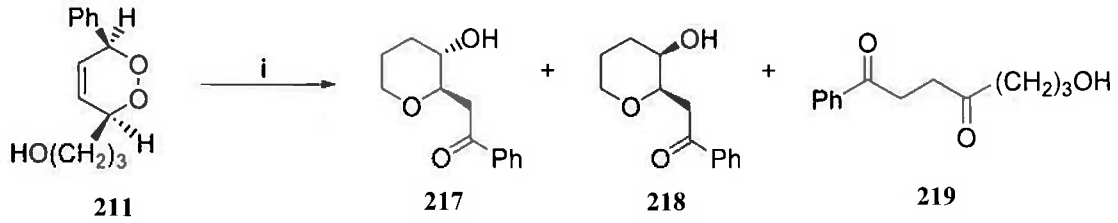
Table 4.1 Ratio of *trans* to *cis* tetrahydropyrans formed when a solution of dioxine **211** (0.1M) in THF is treated with LiOH (1 equiv.) at various temperatures.

Temperature (°C)	Reaction Time	Ratio 217 : 218[a]
0	3 days	50:50
22	16 hrs	64:36
45	16 hrs	74:26

[a]Ratio determined by ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures with crude yields of >75%.

Interestingly, exposure of the 1,2-dioxine **211** to a more hindered amine base such as DABCO, in chloroform, resulted in the *cis* THP being predominantly formed in 56% yield.

Under these conditions only 6% of the *trans* THP was formed, while the 1,4-diketone **219** was observed as a third product in 38% (**Scheme 4.11**).

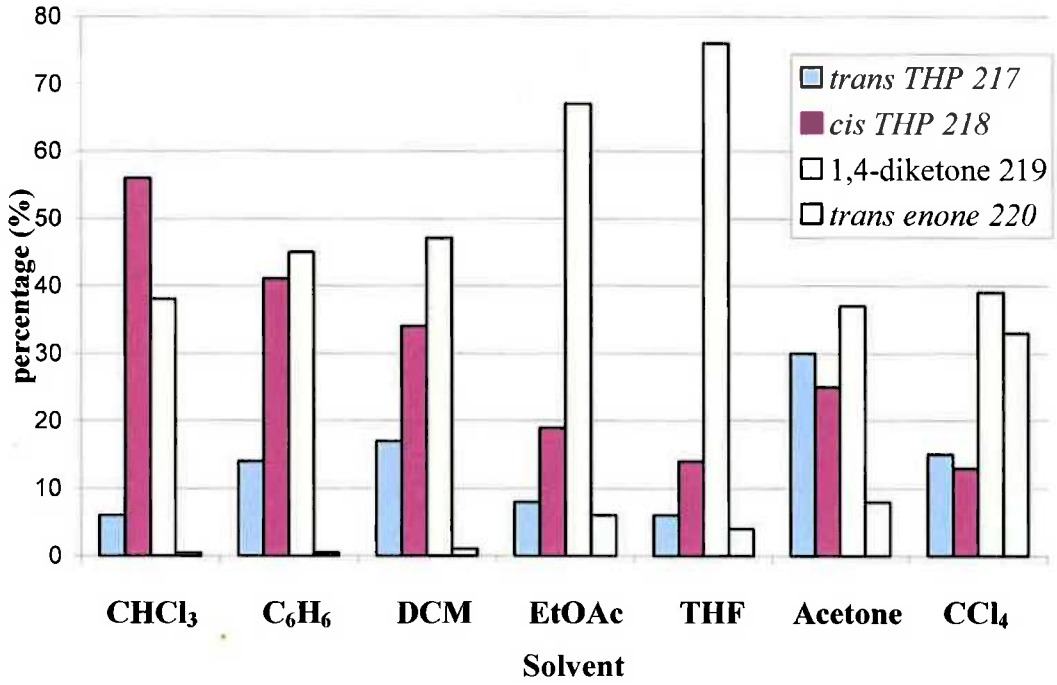


211 **217** **218** **219**

Scheme 4.11 (i) DABCO (0.4 equiv.), $CHCl_3$, rt, 16 hr, isolated yields of 58% (**218**) and 24% (**219**).

As *cis* γ-hydroxy enones are susceptible to rearrangement to their isomeric 1,4-diketones when exposed to amine bases, it was not surprising that the 1,4-diketone **219** was observed in the aforementioned reaction.[155,227] The reaction of the 1,2-dioxine **211** with DABCO was found to be solvent dependent (**Chart 4.1**). THP formation was optimised and 1,4-diketone formation minimised using chloroform as the reaction solvent. The utilisation of THF as solvent resulted in predominant 1,4-diketone formation.

Chart 4.1 Percentage of products **217-220** formed when 1,2-dioxine **211** is reacted with DABCO (0.4 equiv.) at ambient temperature for 16 hours in various solvents.



Analogous to the temperature studies performed with LiOH, the reaction of the 1,2-dioxine **211** and DABCO was investigated at 0, 22 and 45°C. In contrast to the observations when LiOH is the base, the product ratios of the reactions of **211** with

DABCO were not significantly influenced by temperature, as illustrated in **Table 4.2**. This suggests that there other factors influencing the cyclisation besides the populations of *cis* and *trans* γ-hydroxy enones.

Table 4.2 Ratio of the *trans* and *cis* tetrahydropyrans **217** and **218** and the 1,4-diketone **219** formed when a solution of dioxine **211** (0.1M) in chloroform is treated with DABCO (0.4 equiv.) at various temperatures

Temperature (°C)	Reaction Time	Ratio 217:218:219[a]
0	3 days	10:57:33
22	16 hrs	6:56:38
45	16 hrs	10:50:40

[a]Ratio determined by ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures with crude yields of >75%.

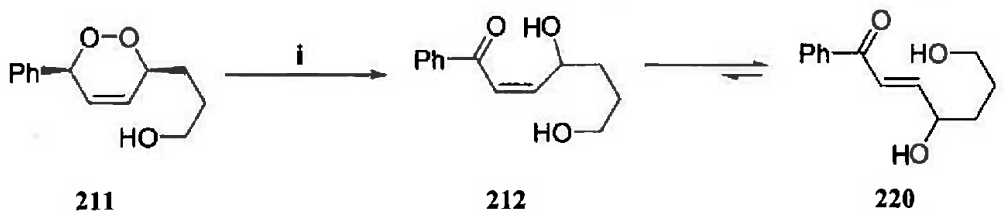
The base catalysed formation of the *trans* THP **217**, the *cis* THP **218** and the 1,4-diketone **219** from the 1,2-dioxine **211** was further investigated using various equivalents of DABCO. Although there was little influence on the ratio of the products formed when 0.1-1.0 equivalents of DABCO was utilised, a slight increase in 1,4-diketone formation at the expense of the *cis* THP was observed when the reaction was performed with 5 equivalents of base. An increase in 1,4-diketone was also observed when the reaction was performed in the absence of added solvent. Two other bases, triethylamine and potassium *tert*-butoxide were also investigated in this base catalysed reaction. Potassium *tert*-butoxide gave similar results as those observed for lithium hydroxide, while treatment of the 1,2-dioxine **211** with triethylamine gave predominately the *trans* γ-hydroxy enone **220**, which reacted slowly over seven days to afford **217**, **218** and **219**, in a final ratio of 39:22:39. These results are summarised in **Table 4.3**.

Table 4.3 Ratio of the *trans* THP **217**, the *cis* THP **218**, the 1,4-diketone **219** and the *trans* γ-hydroxy enone **220** formed when 1,2-dioxine **211** is treated with various concentrations of base at ambient temperature (22°C) for 16 hours.

Base	Equiv.	Solvent	Conc. (M)	Ratio of products[a] 217:218:219:220
DABCO	0.1	$CDCl_3$	0.1	8:58:34:0
DABCO	0.4	$CHCl_3$	0.1	6:56:37:1
DABCO	1	$CHCl_3$	0.1	10:57:33:0
DABCO	5	$CHCl_3$	0.1	12:42:46:0
DABCO	0.1	no solvent	N/A	15:25:60:0
TEA	0.4	$CDCl_3$	0.1	21:16:25:38
KOBut	1	THF	0.1	68:32:0:0

[a]Ratio determined by ^1H NMR spectra (300 MHz) of the crude reaction mixtures

Further studies revealed that *trans* and *cis* THP formation is influenced by the nature of the reacting enone. Exposure of lithium hydroxide to the *trans* γ-hydroxy enone **220**, rather than the *cis* γ-hydroxy enone **212** (which arises from ring opening of the 1,2-dioxine **211**) resulted in increased formation of the *trans* THP **217**, at the expense of the *cis* isomer **218**, from 64% to 82%. This observation suggests that **217** forms preferentially from the *trans* γ-hydroxy enone **220**, with the transition state leading to the *trans* THP being more stable than that leading to the *cis* THP. The *trans* γ-hydroxy enone **220** was obtained by treatment of the parent 1,2-dioxine with triethylamine and triphenylphosphine in acetone (**Scheme 4.12**). The *trans* γ-hydroxy enone **220** was purified by chromatography prior to treatment with lithium hydroxide or DABCO in the appropriate solvents. The ratio of products formed was not influenced by the presence or absence of triphenylphosphine during the cyclisation of the *trans* enone. The ratio maybe influenced by having triphenylphosphine present when treating the 1,2-dioxine with LiOH or DABCO, as this would enhance the isomerization of the *cis* enone to the *trans*, but this was not investigated.



211 **212** **220**

Scheme 4.12 (i) Triethylamine, acetone, PPh_3, rt, 2 hr, 84% (of **220**).

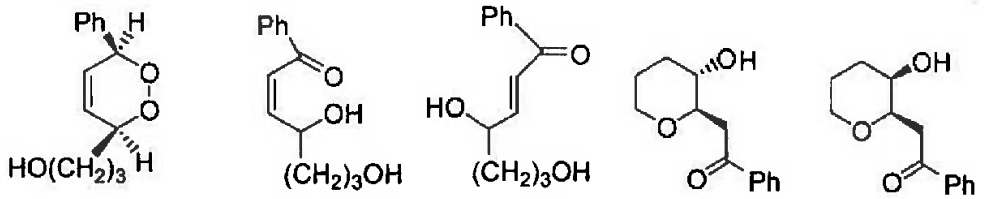
Further evidence that the *trans* THP **217** is formed preferentially from *trans* γ-hydroxy enone **220** is supported by the increased *trans* THP formation observed when this enone is exposed to DABCO (**Table 4.4**). (compare entry 2, Table 4.3)

Table 4.4 Ratio of the *trans* THP **217**, the *cis* THP **218** and the 1,4-diketone **219** formed when the *trans* γ-hydroxy enone **220** is treated with base at ambient temperature (22°C).

Base	Equiv.	Solvent	Reaction Time	Conc. (M)	Ratio of products[a] 217:218:219
LiOH	1	THF	16 hrs	0.1	82:18:0
LiOH / PPh_3	1	THF	16 hrs	0.1	80:20:0
DABCO	0.4	$CHCl_3$	11 days	0.1	51:31:18

[a]Ratio determined by ^1H NMR spectra (300 MHz) of the crude reaction mixtures

Not surprisingly, computational studies[228] found the energy for the *trans* isomer **217** to be 0.541 kcal/mol lower than that for the corresponding *cis* isomer **218**. Likewise, the *trans* γ-hydroxy enone **220** was found to be more stable than the *cis* derivative **212**, and both enones were considerably lower in energy than the corresponding 1,2-dioxine **211** (**Figure 4.3**).

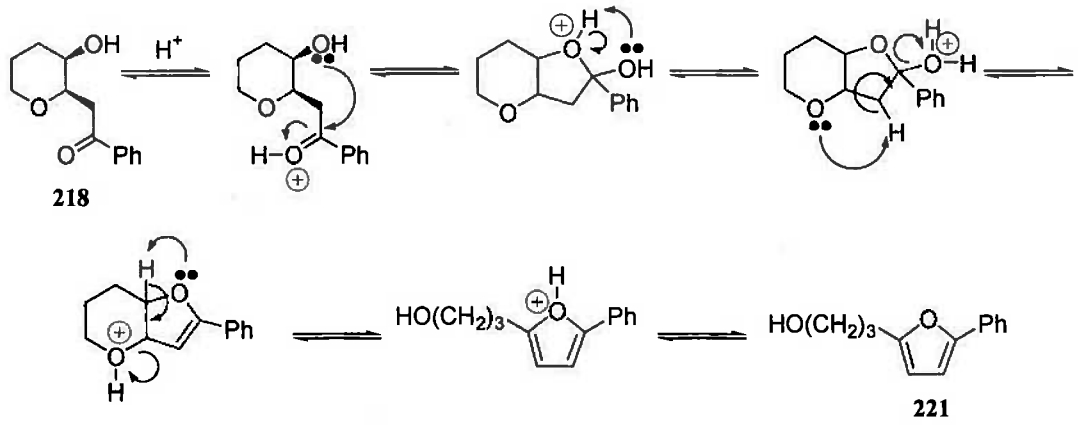


211 **212** **220** **217** **218**

-35.543 kcal/mol **-107.767** kcal/mol **-109.231** kcal/mol **-115.612** kcal/mol **-115.071** kcal/mol

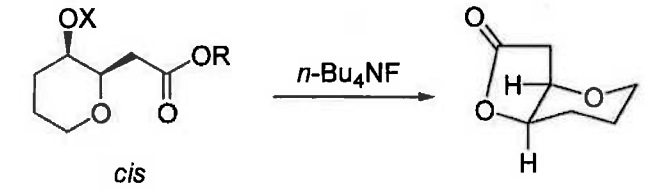
Figure 4.4

Complete characterization of the *cis* THP **218** was made difficult, as it was very acid sensitive, undergoing facile rearrangement to give the furan **221**. As proposed in **Scheme 4.13**, furanisation is initiated *via* intramolecular hemiacetal formation followed by dehydration and pyran ring scission.



Scheme 4.13

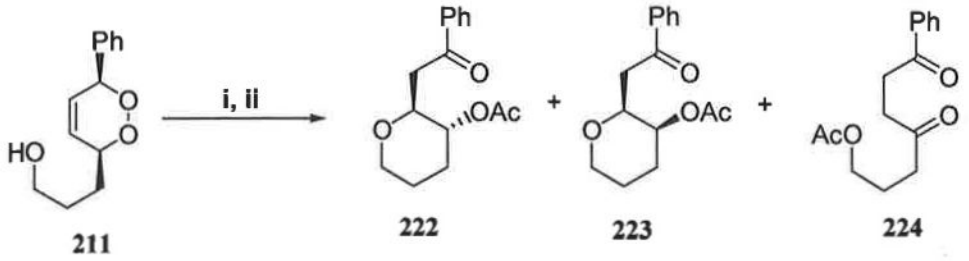
Similarly, Gung and Francis[226] found that their *cis* 2,3-disubstituted THP's underwent intramolecular cyclisation upon treatment with tetrabutylammonium fluoride to afford lactones (**Scheme 4.14**). These *cis* THP's undergo intramolecular cyclisation since the nucleophile and electrophile are in close spatial proximity to allow for their cyclisation. However, the *trans* THP **217** also decomposed to the furan **221** through active treatment with acid.



X = TBDMS or Me
R = Me or Et

Scheme 4.14

Protection of the hydroxyl moiety was necessary to prevent furanisation of the THP products, particularly for the *cis* isomers, which were found to be highly acid sensitive compared to their relatively stable *trans* counterparts. In addition, 1,4-diketone **219** was not very stable. Several protecting groups were investigated including TBDMS ethers, benzyl esters and acetates. Protection of the reaction products using excess pyridine and acetic anhydride in the presence of 4-DMAP proceeded in excellent yield, inhibited furanisation and gave clean acetylated products **222**, **223** and **224** in good combined yield (64-70%) over two steps (**Scheme 4.15**). Acetylating the reaction products was also advantageous as chromatographic separation of the acetates **222** and **223** was enhanced and the proton NMR spectra were easier to interpret, as there was less signal overlap.



211 222 223 224

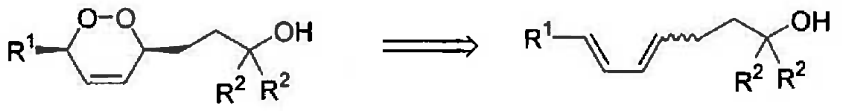
Scheme 4.15 (i) LiOH (1 equiv.), THF or DABCO (0.4 equiv.), $CHCl_3$, rt, 16 hr. (ii) Acetic anhydride, pyridine, 4-DMAP, rt, 3 hr.

With stabilisation of the reaction products established and optimal conditions for their formation identified, extension of this methodology to other hydroxy dioxines was of interest.

4.4 Extension of Methodology for the Synthesis of Other Tetrahydropyrans

4.4.1 Synthesis of other 1,2-Dioxines Containing Tethered Hydroxy Groups

The 1,2-dioxines **235a-e** were targeted as suitable substrates for tetrahydropyran synthesis by the methodology previously established for the model 1,2-dioxine **211**. Since the presence of an aryl group is important for ring-opening of 1,2-dioxines[155], the precursor 1,3-butadienes **231a-e** were designed with either phenyl, 2-naphthyl, *p*-methoxy phenyl or *p*-bromo phenyl substitution.



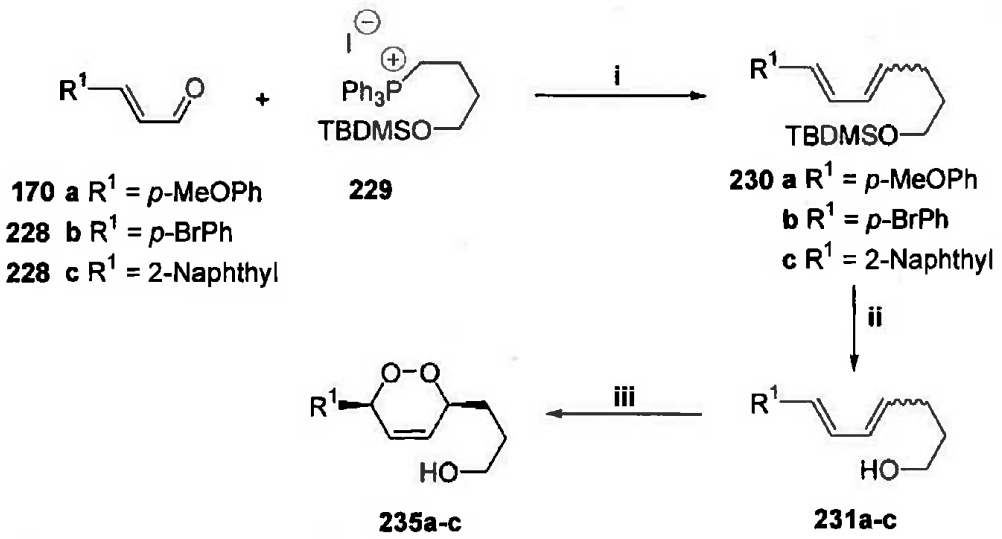
211 R^1 = Ph, R^2 = H

235 **a** R^1 = *p*-MeOPh, R^2 = H
b R^1 = *p*-BrPh, R^2 = H
c R^1 = 2-Naphthyl, R^2 = H
d R^1 = Ph, R^2 = Me
e R^1 = Ph, R^2 = Ph

216 R^1 = Ph, R^2 = H

231a-e

The methodology used for the preparation of the 1,3-butadiene **216** (**Scheme 4.9**) was inappropriate for the generation of the novel 1,3-butadienes **231a-c** as the corresponding phosphonium salts required for their preparation were not readily available. Therefore, the 1,2-dioxines **235a-c** were synthesised by the method outlined in **Scheme 4.16**.



170 **a** R^1 = *p*-MeOPh
228 **b** R^1 = *p*-BrPh
228 **c** R^1 = 2-Naphthyl

229

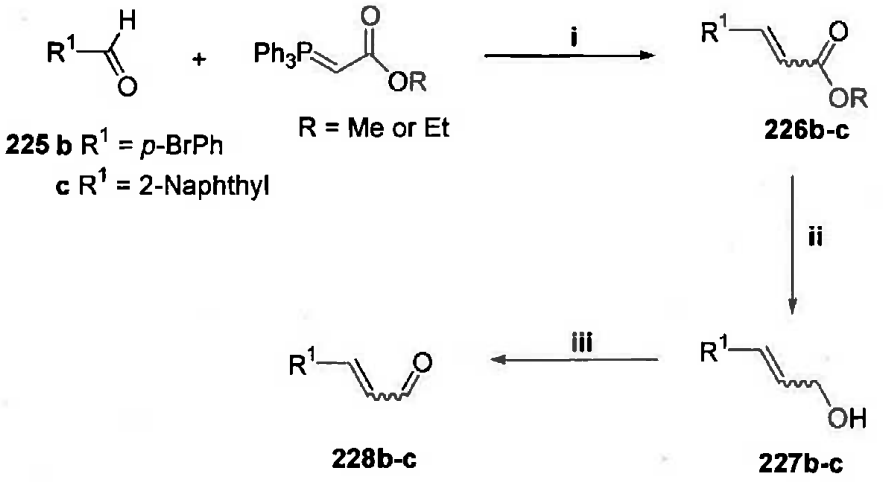
230 **a** R^1 = *p*-MeOPh
b R^1 = *p*-BrPh
c R^1 = 2-Naphthyl

231a-c

235a-c

Scheme 4.16 (i) **229**, *n*-BuLi, THF, -10°C, 30 min, **228**, -10°C (10 min) → rt (16 hr), 70-86%. (ii) TBAF (2.5 equiv.), THF, rt, 4-16 hr, 50-98%. (iii) Rose Bengal *bis*(triethylammonium) salt, DCM, O_2, *hv*, 6 hr, 23-54%.

Prior to the synthesis of the 1,2-dioxines **235a-c** by the above method, α,β-unsaturated aldehydes **228b-c** were prepared in three steps from *p*-bromobenzaldehyde and 2-naphthaldehyde, respectively, using the procedure as for the preparation of **170a** (**Chapter 3**), (**Scheme 4.17**). The α,β-unsaturated esters **226b-c** were obtained quantitatively by treatment of *p*-bromobenzaldehyde and 2-naphthaldehyde with (carbethoxymethylene)-triphenylphosphorane or (carbmethoxymethylene) triphenylphosphorane, respectively.[176] The esters **226b-c** were reduced to the alcohols **227b-c** using DIBAL-H[176], which were subsequently reoxidised to the desired α,β-unsaturated aldehydes **228b-c** by PDC oxidation.[178] The competing double bond oxidation previously observed for **174** (**Chapter 3**) was not observed for the alcohols **227b-c** resulting in high yields for the aldehydes **228b-c**.

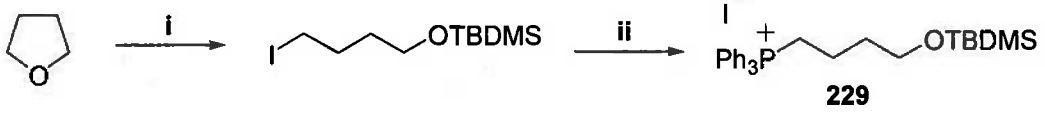


Scheme 4.17 (i) DCM, rt, 16 hr, ≥99%. (ii) DIBAL-H (2.1 equiv.), DCM, -78°C, 1.5 hr, 94-98%. (iii) PDC (1.5 equiv.), DCM, rt, 24 hr, 82-92%.

With the α,β-unsaturated aldehydes **228a-c** in hand, synthesis of the desired 1,2-dioxines **235a-c** proceeded as outlined in **Scheme 4.16**. Despite the successful use of δ-hydroxy phosphonium salt by some researchers[229,230], the corresponding TBDMS protected δ-hydroxy phosphonium salt **229** was utilised to give 1,3-butadienes **230a-c** in high yield using the α,β-unsaturated aldehydes **170a** and **228b-c**. This was a consequence of the initial investigations into the application of the δ-hydroxy phosphonium ylide in the preparation of the 1,3-butadiene **216**, which found the reaction of this ylide with cinnamaldehyde proceeded in poor yield.

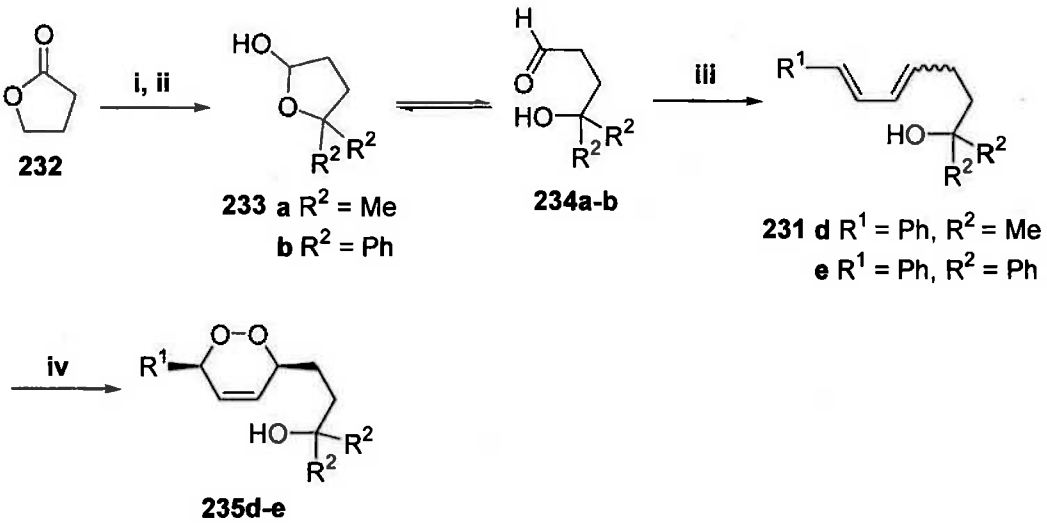
Despite the additional steps involved in protecting and deprotecting with TBDMS the overall yield of these two steps was much higher and hence more beneficial to employ than

the low yielding one step Wittig reaction involving the ylide derived from δ-hydroxy phosphonium salt. The TBDMS phosphonium salt **229** was obtained in 84% by melting triphenylphosphine with 1-[(*tert*-butyldimethylsilyl)oxy]-4-iodobutane at 90°C. 1-[(*Tert*-butyldimethylsilyl)oxy]-4-iodobutane was prepared by the method of Sodeoka and co-workers[231] involving cleavage of tetrahydrofuran in the presence of *tert*-butyldimethylsilyl chloride and sodium iodide (**Scheme 4.18**). Desilylation[166] of compounds **230a-c** proceeded in high yield to give the 1,3-butadienes **231a-c**, which were subsequently photolysed to give the desired 1,2-dioxines **235a-c**.



Scheme 4.18 (i) NaI (1 equiv.), $CaCO_3$ (0.1 equiv.), TBDMSCl (1 equiv.), reflux, 64 hr, 83%. (ii) Ph_3P (1.3 equiv.), 90°C, 3 hr, 84%.

The 1,2-dioxines **235d-e** were synthesised similarly to **211** using the aldehydes **234a** and **234b** (which exist in equilibrium with their hemi-acetal forms **233a-b**) derived from γ-butryolactone[232] **232** (**Scheme 4.19**).



Scheme 4.19 (i) PhMgBr or MeMgBr (3 equiv.), diethyl ether, rt, 6 hr, 67-71%. (ii) DMSO (4 equiv.), oxalyl chloride (2 equiv.), DCM, -78°C, 1.5 hr. (iii) $[Ph_3P\text{-}CH_2\text{-}CH{=}CH\text{-}Ph]^+ Cl^-$ **144a** (1.1 equiv.), $KOBu^t$ (1.05 equiv.), rt (15 min) → 0°C, **234a-b**, rt, 48 hr, 22-34% (2 steps). (iv) Rose Bengal *bis*(triethylammonium) salt, DCM, O_2, *hv*, 6 hr, 46-49%.

Overall, this method was not very high yielding, a consequence of the poor yielding Wittig reactions. This low yield is most likely a result of aldehyde degradation, an

increased proportion of the hemi-acetal forms **233a** and **233b** and competing elimination reactions, which can occur with tertiary alcohols. **Table 4.5** summarises the yields obtained for all six synthesised 1,2-dioxines and their precursor 1,3-butadienes.

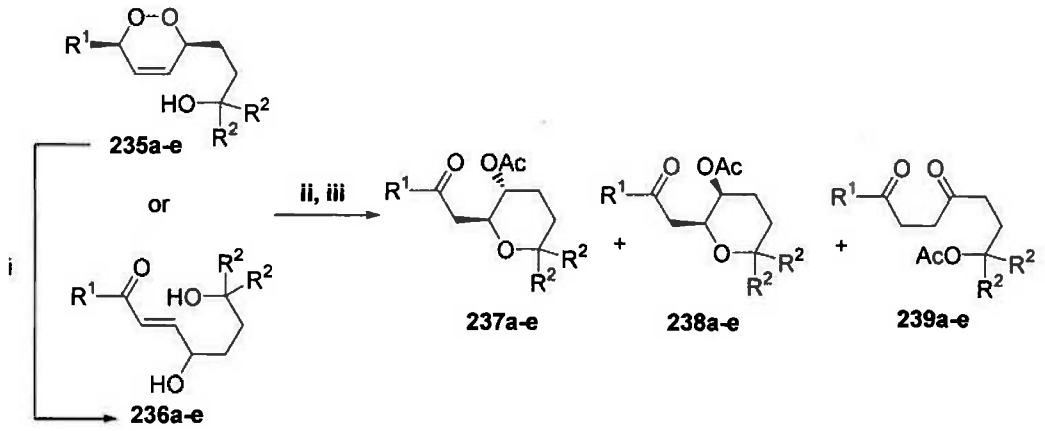
Table 4.5 Summary of yields obtained for the 1,3-butadienes **230** and **231** and the 1,2-dioxines **235**.

Aldehyde	% Isolated yield of 1,3-butadiene **230**	% Isolated yield of 1,3-butadiene **231**	% Isolated yield of 1,2-dioxine **235**
***trans*-cinnamaldehyde**	N/A	64[a,b]	43[a]
170a	79	100	23
228b	86	50	54
228c	70	88	40
234a	N/A	22[c]	46
234b	N/A	34[c]	49

[a] Where R^1 = Ph, R^2 = H; [b] Using 1.25 equiv. of *trans*-cinnamaldehyde; [c] Isolated yield over two steps from γ-butyrolactone

4.4.2 Tetrahydropyran Synthesis

Base treatment of the 1,2-dioxines **235a-e** or the *trans* γ-hydroxy enones **236a-e**, followed by acetylation of the reaction products, resulted in a combination of the THP's **237a-e** and **238a-e** and/or the 1,4-diketones **239a-e** depending on whether lithium hydroxide or DABCO was utilised (**Scheme 4.20**).



a R^1 = *p*-MeOPh, R^2 = H
b R^1 = *p*-BrPh, R^2 = H
c R^1 = 2-Naphthyl, R^2 = H
d R^1 = Ph, R^2 = Me
e R^1 = Ph, R^2 = Ph

Scheme 4.20 (i) Triethylamine, PPh_3, acetone, rt, 2 hr, 55-84%. (ii) LiOH (1 equiv.), THF or DABCO (0.4 equiv.), $CHCl_3$, rt, 16 hr. (iii) Acetic anhydride, pyridine, 4-DMAP, rt, 3 hr.

Treatment of the 1,2-dioxines **235a-e** with LiOH, followed by acetylation, resulted in the formation of the THP's **237a-e** and **238a-e** in good to moderate combined yield over two steps. The results of these reactions are summarised in **Table 4.6** and are compared to the same reaction involving the model 1,2-dioxine **211**.

Table 4.6 Formation of the THP's **237** and **238** from the treatment of the 1,2–dioxines **235** with LiOH.

1,2-Dioxine	Product ratio **237**:**238**[a] (% isolated yield)[b]
211	64(46):36(18)
235a	71(41):29(11)
235b	73(55):27(21)
235c	36(17):64(40)
235d	74(38):26(14)
235e	40:60[c]

[a]Ratio determined by ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures. [b]Reactions performed in THF using 1 equivalent of LiOH at 0.1M. [c]Pyrans unable to be separated by flash chromatography.

Cyclisations involving the 1,2-dioxines **235a**, **235b** and **235d** followed the same trend previously observed for the 1,2-dioxine **211**, in that formation of the *trans* THP's **237** are favoured over the corresponding *cis* isomers **238** (**Table 4.6**). In fact, *trans* cyclisation is slightly enhanced in these examples than for that observed for the model 1,2-dioxine **211**. However, contrary to these findings, treatment of 1,2-dioxines **235c** and **235e** shifted the preference towards the *cis* THP formation. However, this result can be reversed by starting from the corresponding *trans* γ-hydroxy enones **236c** and **236e** (**Table 4.7**) suggesting that the *cis* γ-hydroxy enones obtained from ring-opening of the 1,2-dioxines **235c** and **235e** do not readily isomerize to their *trans* form, therefore reducing *trans* pyran formation when starting from these 1,2-dioxines. Other reasons for possible anomalies in these two examples will be further discussed in **Section 4.5**.

Another interesting finding was observed upon X-ray crystallographic examination of the crystals obtained for the 2-naphthyl *cis* THP isomer **238c**. As illustrated by the ortep structures in **Figures 4.5** and **4.6**, the 2-naphthyl *cis* THP **238c** exists as two independent molecules that differ quite substantially in the relative orientations of the six membered

rings. These structures are simply enantiomers of one another, suggesting spontaneous resolution occurs upon recrystallisation, as was observed with the *trans* THP **217**. An X-ray structure was also obtained for the 1,4-diketone **239c** (**Figure 4.7**).

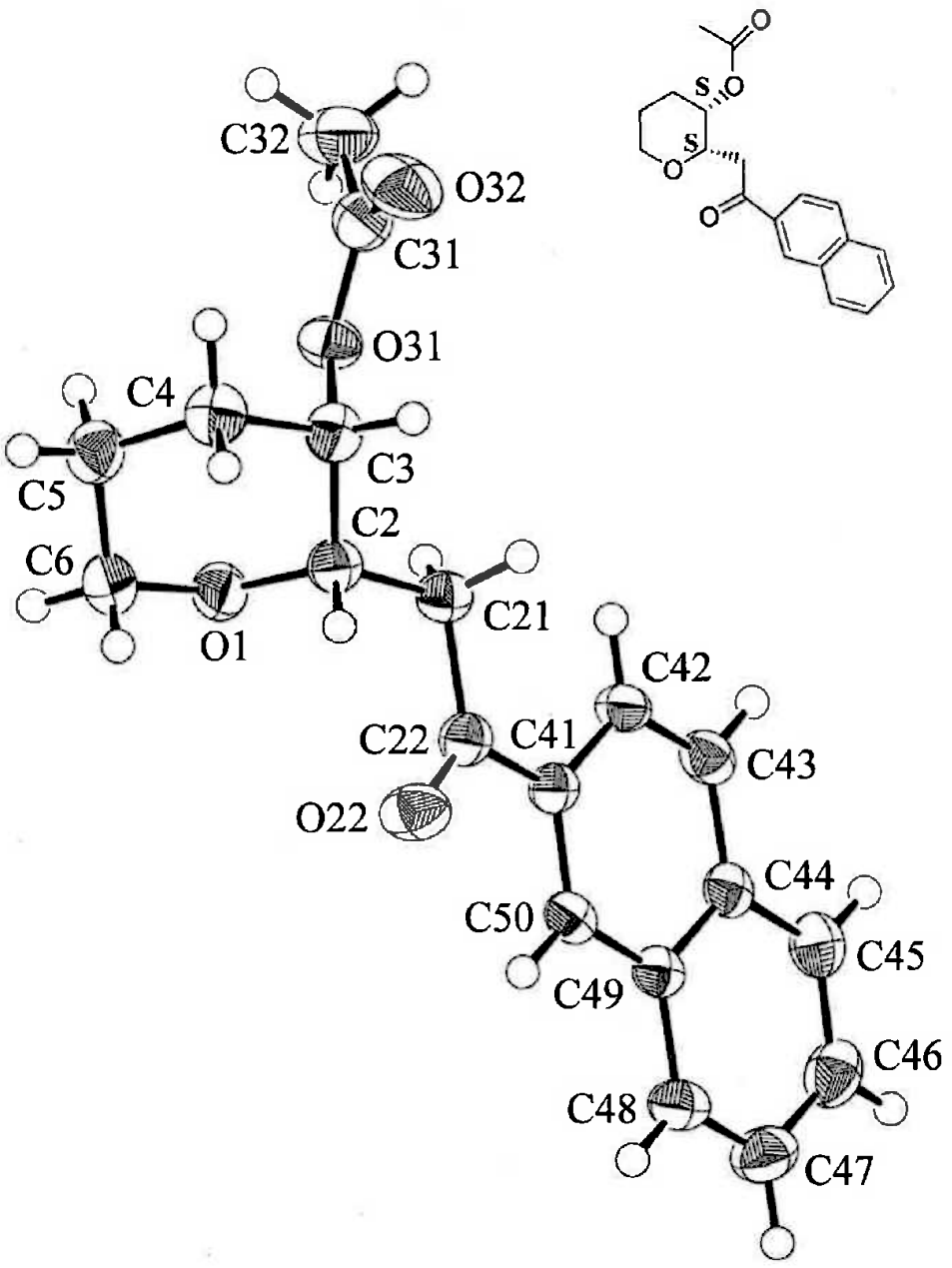


Figure 4.5 Crystal structures for the *cis* THP **238c** showing the crystallographic numbering scheme employed – first independent molecule.

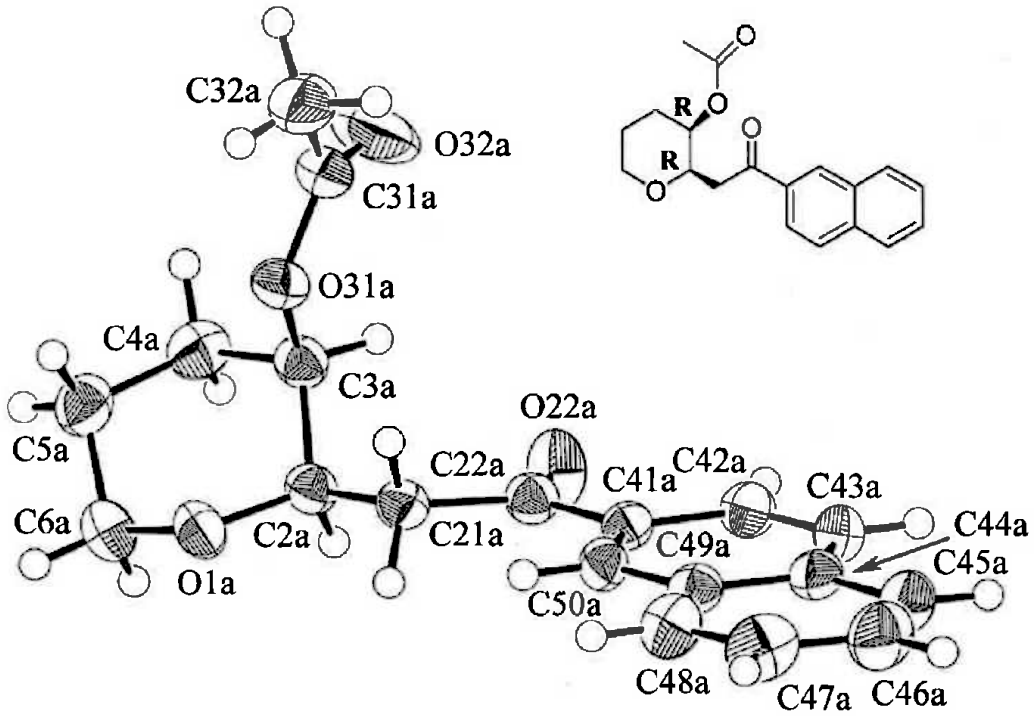


Figure 4.6 Crystal structures for the *cis* THP **238c** showing the crystallographic numbering scheme employed – second independent molecule.

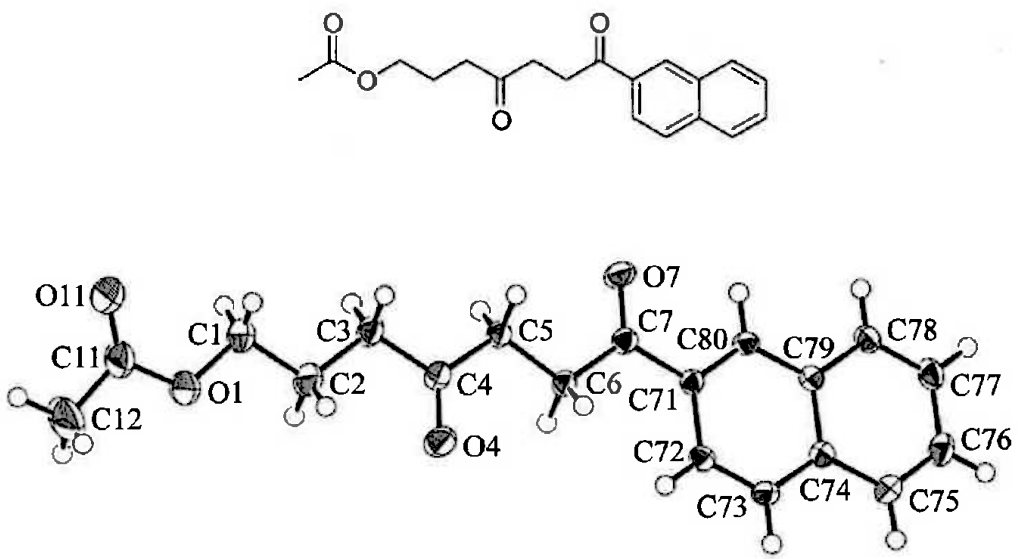


Figure 4.7 Crystal structures for the 1,4-diketone **239c** showing the crystallographic numbering scheme employed.

Analogous to the reactions of the *trans* γ-hydroxy enones **236c** and **236e** mentioned previously, treatment of the *trans* γ-hydroxy enones **236a-b** and **236d** with lithium hydroxide also resulted in increased formation of the *trans* THP's **237** relative to the *cis* in a ratio of ~4:1 for all (**Table 4.7**). This further supports the previous assumption that the *trans* THP is preferentially formed via the *trans* γ-hydroxy enone.

Table 4.7 Formation of the THP's **237** and **238** from treatment of the *trans* γ-hydroxy enones **236** with lithium hydroxide.

1,2-Dioxine	% Isolated yield of *trans* γ-hydroxy enones **236**	Product ratio **237**:**238**[a] (% isolated yield)[b]
211	84	82:18
235a	84	86(66):14(10)
235b	58	81(54):19(15)
235c	83	80(46):20(7)
235d	80	79:21
235e	55	80:20

[a]Ratio determined by ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures. [b]Reactions performed in THF using 1 equivalent of LiOH at 0.1M.

Treatment of the 1,2-dioxines **235a-e** with DABCO followed by acetylation resulted in a combination of the THP's **237a-e** and **238a-e** and the 1,4-diketones **239a-e** in good to moderate combined yield over two steps **(Scheme 4.20)**. The results of these reactions are summarised in **Table 4.8** and compared to the same reaction with the model 1,2-dioxine **211**.

Table 4.8 Formation of the products **237**, **238** and **239** from the treatment of the 1,2–dioxines **235** with DABCO.

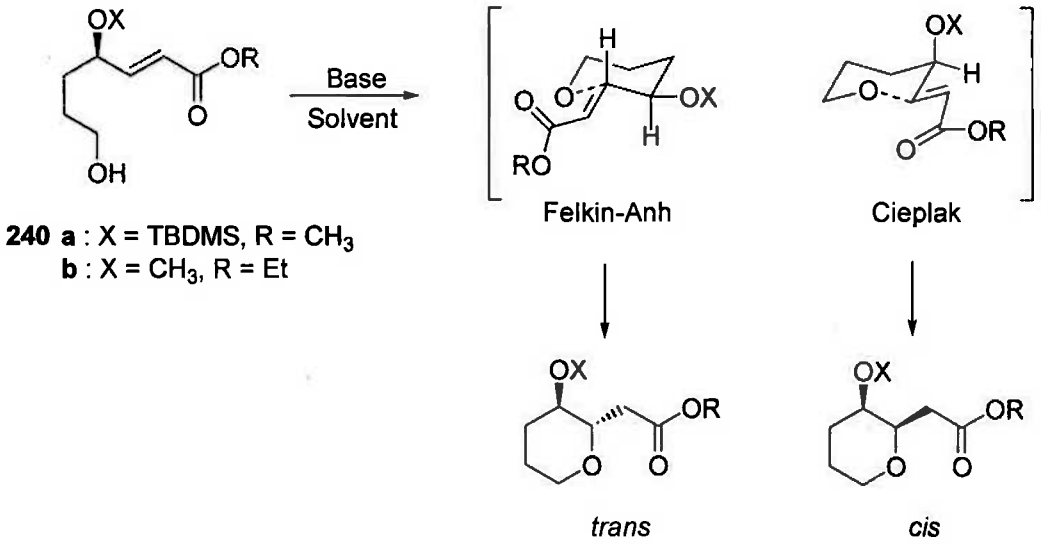
1,2-Dioxine	Product ratio **237**:**238**:**239**[a] (% isolated yield)[b]
211	6:56:38
235a	2(1):55(22):43(25)
235b	4(3):67(39):29(17)
235c	>1%:63(47):37(24)
235d	0:6:94
235e	0:19:81

[a]Ratio determined by ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures. [b]Reactions performed in chloroform using 0.4 equivalents of DABCO at 0.1M.

The results obtained for the reaction of DABCO with the 1,2-dioxines **235a-c** were very similar to that obtained for the model 1,2-dioxine **211**. The *cis* THP's **238** was the major product with moderate and small amounts of the 1,4-diketones **239** and the *trans* THP's **237** also formed, respectively. Not surprisingly, the 1,4-diketones **239d** and **239e** became the major products when the 1,2-dioxines **235d** and **235e** were treated with DABCO. Under these conditions, cyclisation of the tertiary alcohols must be disfavoured due to steric interactions of the di-methyl and di-phenyl groups within the transition states. These diketones were not fully characterised, as they were not clean after chromatography and somewhat unstable.

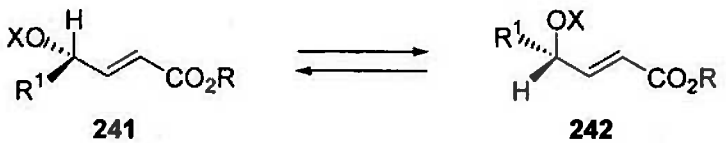
4.5 Mechanism of Reaction

At this stage, the mechanism involved in favouring one tetrahydropyran over the other is not fully understood. However, increased *trans* THP formation observed when the *trans* γ-hydroxy enones are treated with lithium hydroxide suggests that the *trans* THP is formed preferentially from the *trans* enone. Previously, Gung and Francis[226] proposed that cyclisations of the protected *trans* γ-hydroxy α,β-unsaturated esters **240a-b** may proceed via two transition states, based on Felkin Anh and Cieplak models, which result in the formation of *trans* and *cis* 2,3-disubstituted tetrahydropyrans, respectively (**Scheme 4.21**).



Scheme 4.21

In the presence of a TBDMS protecting group, polar solvents and a large cation (i.e. K^+) these cyclisations favour *cis* formation while in the presence of a smaller methoxy group, cyclisation predominately affords *trans* product, even under polar solvent and large cation conditions. These results are consistent with the ground state (GS) conformational preferences of **240a** and **240b** being reflected in the transition states for cyclisation to the THP's. For instance, the C-O eclipsed conformer **242**, which leads to the *cis* product, is favoured when X = TBDMS while the C-H eclipsed conformer **241**, which leads to the *trans* product, is favoured when X = CH_3.[226]



However, enhanced *trans* selectivity observed when **240a** and **240b** are treated with small cations in non-polar solvents, was not consistent with the GS conformational preferences being reflected in the transition state for cyclisation as mentioned above. Gung and Francis[226] proposed that the use of tighter binding (smaller) cations and non-polar solvents increase the activation energy required for cyclisation by lowering the HOMO of the nucleophile through coordination, thus, rendering the GS conformational preferences insignificant due to the activation energy being higher than that required for rotamer interconversion.

As the C-O eclipsed rotamer is preferred in the case of *trans* γ-hydroxy α,β-unsaturated esters,[233] we suggest that this can be extrapolated to cis / *trans* γ-hydroxy enones due to similarity in electronics. Therefore with the C-O eclipsed rotamer predominating we would expect the *cis* tetrahydropyrans to dominate in the absence of small highly coordinating cations. Indeed we observe in the majority of cases *cis* THP formation dominating when 1,2-dioxines are treated with DABCO in chloroform, with the exception of 1,2-dioxines **235d-e**, that afford predominantly 1,4-diketone (**Table 4.8**). *Cis* THP's most likely form via transition state **243** and possibly transition state **244** if any of the *cis* γ-hydroxy enone, generated from ring-opening of the 1,2-dioxine, interconverts to its *trans* form. The lack of preference for the C-H eclipsed conformer is evident by ≤6% of *trans* THP formation, which would most likely form via transition state **245** (**Figure 4.8**).

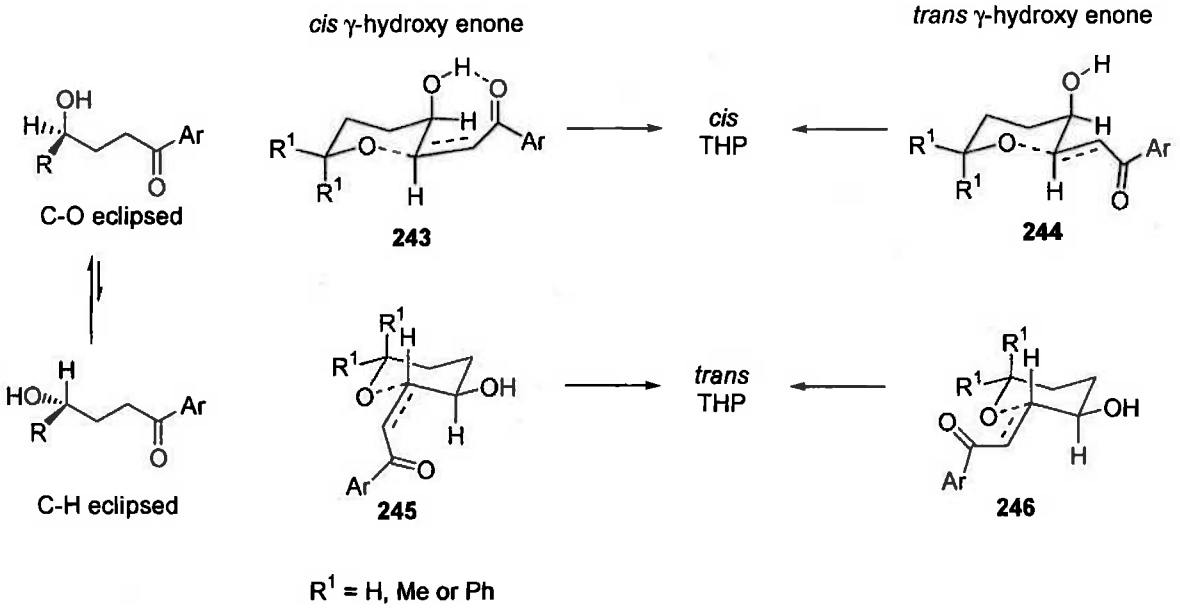


Figure 4.8

Exploration of more polar solvents, such as THF, in order to alter the ratio of THP's formed when 1,2-dioxines are treated with DABCO, results in increased 1,4-diketone at the expense of the *cis* THP. This suggests that utilisation of a more polar solvent changes the preference of the transition states for cyclisation, so that the GS conformational preferences have become insignificant. Likewise, the ratio of THP's formed when the *trans* γ-hydroxy enone **220** was treated with DABCO in $CHCl_3$ does not reflect the GS conformational preferences as increased formation of *trans* THP **217** was observed, which most likely forms via transition state **246**. The current argument does not explain this result, otherwise THP formation under these conditions would favour the *cis* THP and therefore reflect the GS conformational preferences. This result supports the theory that *trans* THP forms preferentially from the *trans* enone and therefore the populations of *cis* and *trans* enones influence the preference for cyclisation, but to what extent is unknown.

In the presence of the highly coordinating cation of LiOH and THF we observe, in most cases, a shift to *trans* THP dominance (**Table 4.6**). This is due to coordination of the oxygen nucleophile by the lithium cation, which renders the GS conformational preference insignificant. The *trans* THP's are formed preferentially in the presence of lithium hydroxide regardless of the geometry of the starting γ-hydroxy enone. However, increased *trans* THP is observed when starting from the *trans* γ-hydroxy enones (compare **Table 4.6** to **Table 4.7**). We propose that the increased proportion of *cis* THP and indeed its predominance in such polar solvent and small cation conditions (when 1,2-dioxines **235c** and **235e** are treated with LiOH in THF) is due to increased THP formation from the C-O eclipsed *cis* γ-hydroxy enone. This variation is attributed to the stabilizing effect of hydrogen bonding between the γ-hydroxy group and the aromatic ketone (transition state **243, Figure 4.8**). This interaction may also be stabilized by cation coordination. However, there is likely to be an additional factor influencing the cyclisation preference in these two examples, such as increased steric bulk or changes in the electronics of these systems, as we would expect this stabilizing effect to influence all cases.

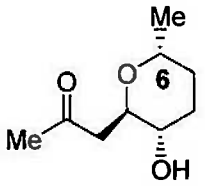
Our results are complicated by a number of currently unquantified factors, firstly it is difficult to quantify the amount of THP generated from *cis* γ-hydroxy enone when starting from 1,2-dioxines, but it is clear that it has an effect on the THP ratio. When using 1,2-dioxines **211** or **235a-e** as starting material, *cis* γ-hydroxy enone is generated primarily with *trans* γ-hydroxy enone forming through reversible Michael addition of hydroxide.[162] It is possible that the influence of base on this equilibrium contributes to the preference of

one tetrahydropyranyl isomer forming over the other. For instance, the presence of LiOH promotes isomerization of the *cis* enone to the *trans* enone, which would enhance *trans* THP formation. Secondly, the *cis* γ-hydroxy enones generated also exist in equilibrium with their hemiacetal forms[155] which may also be substrates for THP formation. Additionally, we have a free hydroxyl group in the γ position which is able to be deprotonated and coordinate with cations. Our assumption that the electronic structure variation when comparing our keto systems with the ester systems of Gung and co-workers is insignificant may be flawed.

In summary, the selectively observed in these base-catalysed cyclisation reactions appear to be influenced by several factors. These include the nature of the base and solvent influencing whether the GS conformational preferences are reflected in the transition states for cyclisation and the geometry of the starting γ-hydroxy enone. Other factors such as sterics, electronics and/or additional stabilizing effects, such as hydrogen bonding, in the transition states may also influence the THP ratios.

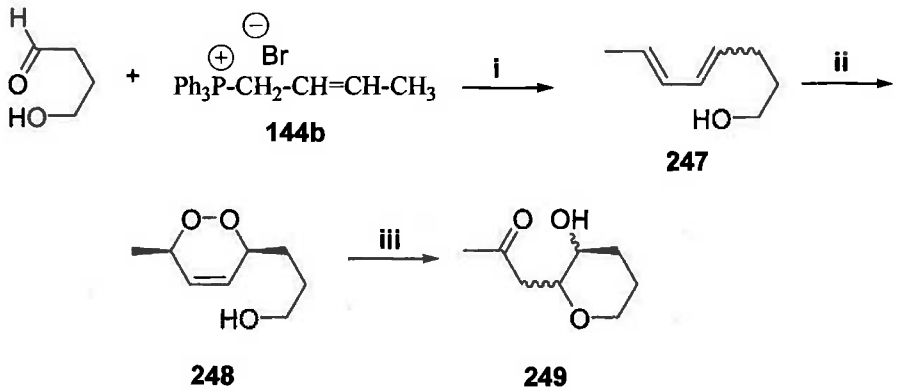
4.6 Studies into Decarestrictine L Synthesis

The tetrahydropyrans formed from base-induced cyclisation of γ-hydroxy enones are structurally related to Decarestrictine *L* **194**.[190] We were interested in examining whether this methodology could be utilised to synthesis this natural product or other closely related derivatives. The two differences between the THP's generated from this methodology and Decarestrictine *L*[190] is that the latter possesses a methyl ketone, rather than an aryl ketone, along with an additional chiral centre due to a methyl substituent at C_6 of the pyran ring.



194

Previously, only 1,2-dioxines with aryl substitution have been used due to the reliance of an acidic proton to aid in ring-opening of the dioxine. In the absence of an acidic proton, cobalt catalysts are required for ring-opening of the dioxine.[155,159] However, there has been one reported case where a 1,2-dioxine containing dipropyl substitution successfully reacted to generate lactones in the absence of a cobalt catalyst.[221] Therefore, direct incorporation of the methyl ketone in tetrahydropyran **249** was attempted using the methyl substituted 1,2-dioxine **248** which was synthesised as outlined in **Scheme 4.22**.

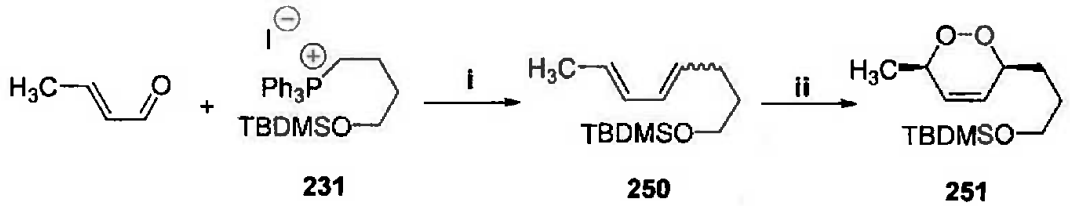


Scheme 4.22 (i) KOBu^t, THF, 0°C (15 min) → rt (16 hr), 72%. (ii) Rose Bengal *bis*(triethylammonium) salt, DCM, O_2, *hv*, 6 hr, 68%. (iii) LiOH (1 equiv.), THF, reflux, 48 hr, 12% (obtained as a mixture consisting of a further 4% of compound **253**).

The 1,3-butadiene **247** was synthesised according to the procedure developed for the corresponding phenyl derivative, but crotyl phosphonium salt **144b** was used rather than the cinnamyl equivalent. Photo-oxidation of the 1,3-butadiene **247** gave the desired 1,2-

dioxine **248**. The reaction of **248** with lithium hydroxide in THF only proceeded at elevated temperatures. However, despite complete consumption of the dioxine after heating the reaction mixture under reflux for 48 hours, only 16% of a mixture of two products consisting of 70% THP **249** was obtained. It was later discovered, based on the results obtained from reactions of 1,2-dioxine **251**, that the second product was 1,4-diketone **253**. Decomposition of the 1,2-dioxine at elevated temperatures was most likely the reason for the poor yield of **249**. In an attempt to improve the efficiency of this reaction, ring-opening of 1,2-dioxine **248** was then undertaken using Jacobsen's catalyst. Upon complete ring-opening, lithium hydroxide was added in order to induce cyclisation. However, this only resulted in the generation of unidentified decomposition products.

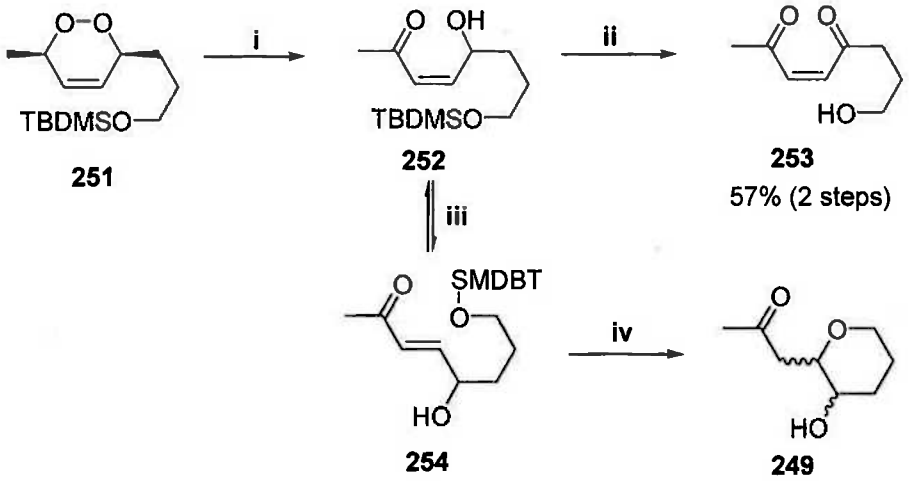
One reason for the possible failure of the above method was attributed to binding of the cobalt catalyst to the free hydroxy group. To test out this theory, the corresponding protected 1,2-dioxine **251** was synthesised (**Scheme 4.23**).



231 **250** **251**

Scheme 4.23 (i) *n*-BuLi (1 equiv.), THF, -10°C (30 min) → rt (16 hr), 58%. (ii) Rose Bengal *bis*(triethylammonium) salt, DCM, O_2, *hv*, 6 hr, 57%.

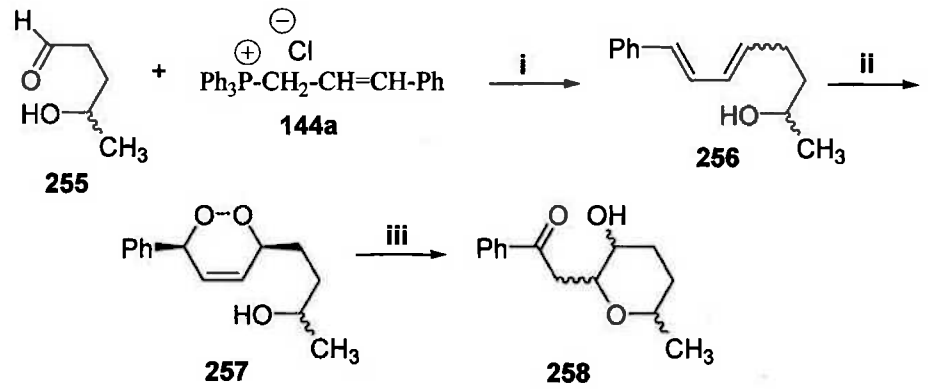
Treatment of **251** with Jacobsen's catalyst gave the *cis* γ-hydroxy enone **252**, which was partially purified by the removal of the cobalt catalyst prior to its treatment with TBAF. It was anticipated that desilylation of the enone using TBAF would subsequently induce cyclisation, a phenomenon which has been reported in the literature.[234,235] However, ^{1}H and ^{13}C NMR analysis of the major product obtained suggested it was the unsaturated 1,4-diketone **253** (**Scheme 4.24**). Complete characterisation of this compound could not be performed due to its decomposition in $CDCl_3$. As the literature examples[234,235] involved deprotection and subsequent cyclisation of *trans* enones, 1,2-dioxine **251** was treated with Jacobsen's catalyst in the presence of triphenylphosphine to afford the *trans* γ-hydroxy enone **254**. Treatment of purified **254** with TBAF resulted in the formation of the THP **249** but in only 5% yield.



Scheme 4.24 (i) $Co(SALEN)_2$ (7.5 mol %), THF, rt, 4 hr, 80%. (ii) TBAF (2.5 equiv.), THF, rt, 16 hr, 72%. (iii) PPh_3, 81% from **251**. (iv) TBAF (2.5 equiv.), THF, 16 hr, 5%.

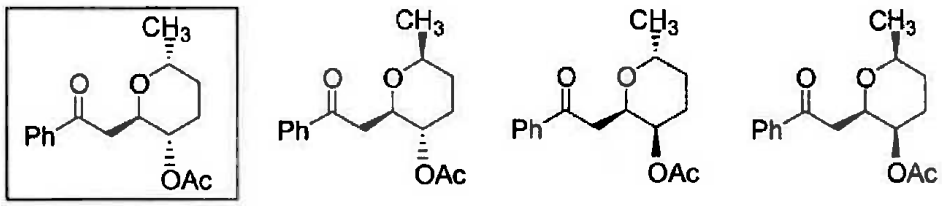
Direct incorporation of the methyl ketone found in Decarestrictine *L* is therefore not viable by this methodology. However, the phenyl ketones incorporated by this methodology would be more conveniently converted to the corresponding methyl derivative using known literature procedures. For instance, Esumi and co-workers[236] successfully incorporated the methyl ketone in Decarestrictine *L* by transformation of an ethanol substituent. This ethanol substituent could be obtained from our phenyl ketones in two steps involving Baeyer-Villiger oxidation and ester reduction, which can then be carried through to the methyl ketone using the method of Esumi and co-workers.[236]

The incorporation of an additional methyl group at the C_6 position of the tetrahydropyran ring was achieved by exploitation of the 1,2-dioxine **257**, which was synthesised according to the procedure outlined in **Scheme 4.25**.



Scheme 4.25 (i) KOBu^t, diethyl ether, 0°C (15 min) → rt (16 hr), 53%. (ii) Rose Bengal *bis*(triethylammonium) salt, DCM, O_2, *hv*, 6 hr, 70%. (iii) LiOH (1 equiv.), THF, rt, 16 hr.

The methodology employed was analogous to that originally utilised for the synthesis of the model 1,2-dioxine **212**. However, in this case, the hydroxy aldehyde **255** was obtained from DIBAL-H reduction of γ-valerolactone using the procedure of Castonguay and Brassard.[237] Not surprisingly, photolysis of the 1,3-butadiene **256** resulted in the formation of two diastereomeric 1,2-dioxines **257**, which possessed identical polarities. Treatment of this mixture with lithium hydroxide in THF followed by acetylation resulted in the formation of four tetrahydropyranyl products **258a-d** (**Figure 4.9**), the structures of which were determined through a combination of ^{1}H, ^{13}C, COSY, HMBC, HMQC and ROESY NMR experiments.



258a **258b** **258c** **258d**

8% **29%** **2%** **41%**

Figure 4.9

As illustrated above, these four diastereomers were obtained as two major and two minor products, with, unfortunately the THP possessing the analogous stereochemistry found in Decarestrictine *L* being isolated in only 8% yield. Despite manipulation of experimental conditions the yield of the desired THP **258a** could not be significantly increased (**Table 4.9**).

Table 4.9 Formation of the THP's **258**, from base treatment of the 1,2–dioxine **257** or its *trans* γ-hydroxy enone.

Reagent	Base	Solvent	Ratio of 258a:258b:258c:258d[a] (% isolated yield)
1,2-dioxine	LiOH	THF	8(8):37(29):1(2):54(41)
trans enone	LiOH	THF	13:28:5:54
1,2-dioxine	DABCO	$CHCl_3$	23:8:1:68
trans enone	DABCO	$CHCl_3$	20:26:38:16

[a]Ratio determined by ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures.

This pathway is therefore not viable for the generation of Decarestrictine *L*. However, it does allow for the synthesis of several diastereomers, of which, all can be investigated for bioactivity. It may be possible that another diastereomer may exhibit enhanced bioactivity compared to that of Decarestrictine *L*.

4.7 Summary

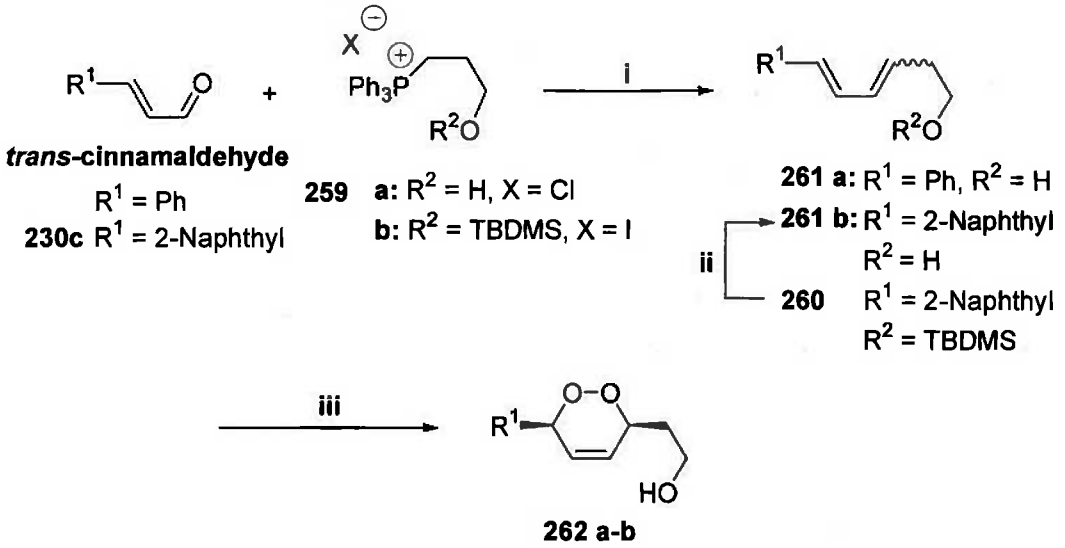
1,2-Dioxines containing tethered *n*-propanol groups are suitable precursors to *trans* and *cis* 2,3-disubstituted tetrahydropyrans of type **237** and **238**, respectively. Variation in solvent and base alters the ratio of THP's. In the majority of cases, *trans* THP's predominate when the parent dioxines are treated with lithium hydroxide in THF. This is due to coordination of the oxygen nucleophile by the lithium cation, which renders the GS conformational preference insignificant. In contrast, the corresponding *cis* THP's are predominately formed when the same 1,2-dioxines are treated with DABCO in chloroform, due to the GS conformational preferences being reflected in the transition states for cyclisation. However, by using a more polar solvent, such as THF, 1,4-diketone of type **239** can become the predominant species formed. Utilisation of *trans* γ-hydroxy enones instead of their *cis* counterparts, which are formed from ring-opening of the 1,2-dioxines, enhances *trans* THP formation. This result suggests that the populations of *cis* and *trans* enones also influence the preferences for cyclisation.

Utilisation of this methodology towards the synthesis of Decarestrictine *L* **194** was investigated. Direct incorporation of the methyl ketone of this natural product was not readily achievable by this method due to problems associated with ring-opening of 1,2-dioxine **248** and **251** in the absence of an acidic proton and enone decomposition and/or 1,4-diketone formation when a cobalt catalyst was employed for ring-opening. Incorporation of a C_6 methyl substituent on the THP ring, corresponding to that observed in Decarestrictine *L*, was achieved by exploitation of 1,2-dioxine **257**. However, despite exploring various reaction conditions, formation of the THP with identical stereochemistry to that of the natural product (i.e. **258a**) could not be enhanced beyond 23% due to competing formation of THP's **258b-d**.

Chapter 5: Synthesis of Tetrahydrofurans and Other Cyclisation Reactions of 1,2-Dioxines Containing Tethered Oxygen Nucleophiles

5.1 Tetrahydrofurans

The methodology for the generation of THP's from 1,2-dioxines containing tethered hydroxy groups can be extended to include the formation of tetrahydrofurans. This can be achieved by the utilisation of 1,2-dioxines of type **262**, which contain one less carbon than those used to construct the corresponding THP's. The 1,2-dioxines **262a-b** were prepared by the method outlined in **Scheme 5.1**. This strategy is analogous to that employed for the synthesis of the 1,2-dioxines **235a-c** previously outlined in chapter 4. However, the preparation of **262a-b** utilised either the protected or the non-protected γ-hydroxy phosphonium salts **259a** or **259b**, which possess one less carbon than the ylide used in the preparation of **235a-c**.

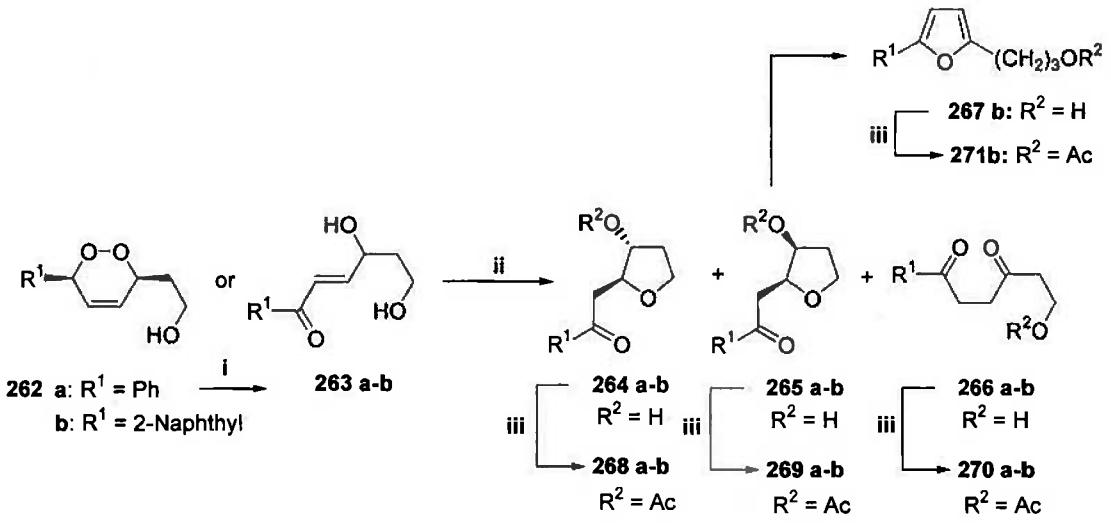


Scheme 5.1 (i) *n*-BuLi, THF, O°C (30 min) → rt (16 hr), 32-40%. (ii) TBAF (2.5 equiv.), THF, 5 hr, rt, 84%. (iii) DCM, Rose Bengal *bis*(triethylammonium) salt, O_2, *hv*, 6 hr, 48%.

Even though the 1,3-butadiene **261a** was obtained only in 32% yield, from the Wittig reaction of *trans*-cinnamaldehyde and the hydroxy phosphonium salt **259a**, this yield was sufficient over one step as it utilised cheap and readily available starting materials. On the other hand, a poor yielding Wittig reaction utilising hydroxy phosphonium salt **259a** was inefficient for the preparation of the 1,3-butadiene **261b** as multiple steps were required to prepare the 2-Naphthyl α,β-unsaturated aldehyde **228c** (as discussed in Chapter 4).

Therefore, the TBDMS protected γ-hydroxy phosphonium salt **259b** was used in preparation of **261b**. Despite this, the protected 1,3-butadiene **260** was only obtained in 40% yield from this reaction.

Treatment of the 1,2-dioxines **262a-b** with lithium hydroxide resulted in the formation of the THF's **264a-b** and **265a-b**, which were immediately acetylated to give the acetates **268a-b** and **269a** (**Scheme 5.2**). The *cis* acetate **269b** was not obtained due to rapid furanisation of the *cis* tetrahydrofuranol **265b** to **267b**. Consequently only the acetylated furan **271b** was obtained.



Scheme 5.2 (i) Acetone, TEA, PPh_3, 2 hr, rt. (ii) LiOH (1 equiv.), THF or DABCO (0.4 equiv.), $CHCl_3$, 16 hr, rt. (iii) Acetic anhydride, pyridine, 4-DMAP, 3 hr, rt.

Contrary to the trend observed for THP formation, treatment of the 1,2-dioxines **262a-b** with lithium hydroxide in THF favours formation of the *cis* isomers **265a-b** over their *trans* counterparts **264a-b** in a ratio of 2:3. In addition, exposing the *trans* γ-hydroxy enones **263a-b** to lithium hydroxide did not influence the ratio of isomers formed.

Although acetylation of the THP examples was found to enhance chromatographic separation of the *cis* and *trans* isomers, this was not the case for the THF's **268** and **269**. Fortunately, tetrahydrofuranols **264a-b** and **265a-b** were separable prior to their acetylation. Furanisation of tetrahydrofuranol **265b** was enhanced in the presence of silica and as a result it could not be isolated.

Exposure of the 1,2-dioxines **262a-b** to DABCO afforded the *cis* THF isomers **265a-b** as the major products while the 1,4-diketones **266a-b** were the minor products (**Scheme 5.2**). Similarly, furanisation of tetrahydrofuranol **265b** upon exposure to acetylation conditions

prevented isolation of the acetate **269b**. Yields for all these reactions are summarised in **Table 5.1**.

Table 5.1 Summary of yields for THF's **264-265** when 1,2-dioxines **262** or *trans* enones **263** are treated with base and/or their acetylation products **268-269**.

Starting Material	Base	Yield of **264** (%)[a]	Yield of **265** (%)[a]	Yield of **268** (%)[a]	Yield of **269** (%)[a]	Combined yield of **268 / 269** (%)[b]
262a	LiOH	-	-	-	-	46[c]
263a	LiOH	31	28	70	76	-
262a	DABCO	-	-	-	50[c]	-
262b	LiOH	29	24	67	-[d]	-

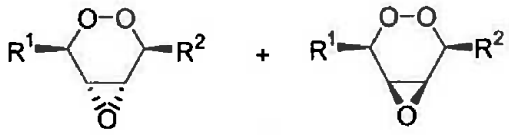
[a]Based on isolated yields after chromatography. [b]Obtained as an inseparable mixture of both acetates. [c]Isolated yield over two steps. [d]Furan **271b** was obtained in 64% yield from acetylation of **265b**.

As for the THP examples (**Section 4.5**), one would expect the C-O eclipsed rotamer to be preferred for the *cis* and *trans* γ-hydroxy enones that lead to THF formation. Consequently, we would expect the *cis* tetrahydrofurans to dominate in the absence of small highly coordinating cations and non-polar solvents. Indeed we observe in both cases *cis* THF formation dominating when 1,2-dioxines are treated with DABCO in chloroform. However, we also observe a slight dominance of the *cis* THF even in the presence of the highly coordinating cation of LiOH in THF. This contradicts the results obtained for THP formation. The difference in selectively observed for the THP and THF examples may be a consequence of the extent to which the lithium cation associates with the oxygen nucleophile in the transition states. Perhaps there is less lithium cation association in the THF transition states therefore leading to the GS conformational preferences being reflected to a greater extent in the product ratios. Furthermore, when starting from the *cis* γ-hydroxy enone it is possible that the transition state leading to the *cis* THF may be stabilized by hydrogen bonding between the γ-hydroxy group and the aromatic ketone. Nevertheless, the geometry of the starting enone does not influence the ratio of THF's. Other factors such as the planarity of the THF transition states compared to those of the THP are sure to influence the selectivity observed. Unfortunately, no examples of the effect of base and solvent on these types of cyclisations, in regards to THF formation, could be found.

5.2 THP's with an additional OH group

It was also envisaged that another series of novel THP's could be prepared if the tethered hydroxyl group was cyclized onto the 1,2-dioxine prior to cleavage of the peroxide bond (**Scheme 5.3**). Since intramolecular hydroxy epoxide openings are a common method for the construction of tetrahydropyrans (**Section 4.1**), the introduction of an epoxide across the double bond of the 1,2-dioxine **211** would be desirable for cyclisation of the tethered hydroxy portion. The epoxide functionality supplies an electrophilic site for nucleophilic oxygen addition of the tethered hydroxy moiety, which results in ring-opening of the epoxide.

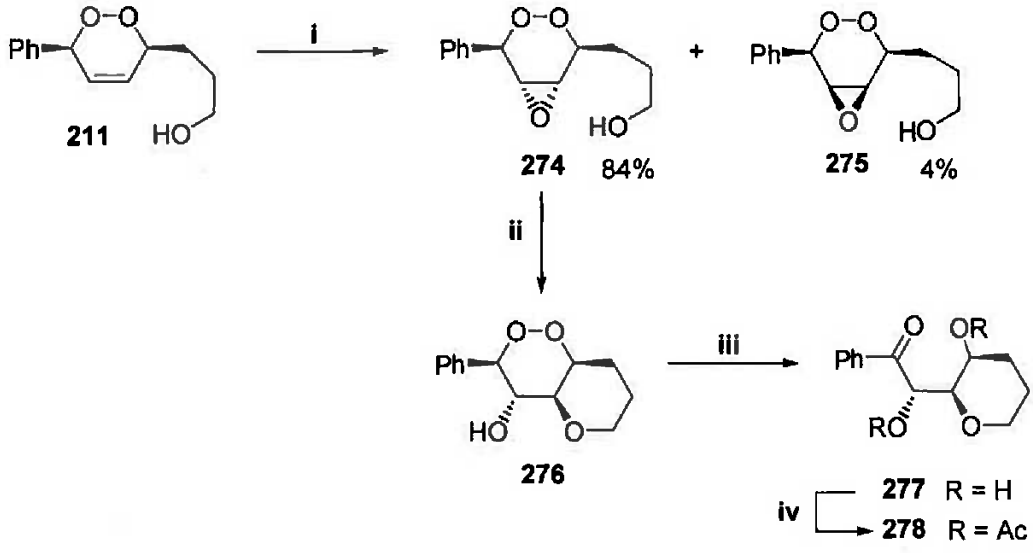
A wide range of epoxy 1,2-dioxines containing a combination of alkyl and aryl mono- and di-substitution have been prepared previously within the Taylor group.[238] The parent 1,2-dioxines readily undergo clean and efficient oxidation in the presence of *meta*-chloroperbenzoic acid (*m*-CPBA) at ambient temperature. For each 1,2-dioxine, two diastereomeric epoxy 1,2-dioxines are formed, one where the epoxide oxygen atom adds on the opposite face to the alkyl or aryl substitution **272** and the other where it adds on the same face **273**.



272 **273**

R^1, R^2 = combination of cyclohexyl, cyclopentyl, cyclobutyl, 1-adamantyl, CH_2-cyclohexyl, CH_2-OC(O)-1-adamantyl, *n*-propyl, *n*-heptyl, phenyl, methyl, hydrogen and *n*-propanol

Treatment of the 1,2-dioxine **211** with *m*-CPBA furnished two epoxy endoperoxides **274** and **275** in a ratio of 95:5. Compound **274** was subsequently cyclized by epoxy ring-opening in the presence of acid to afford the cyclic peroxide **276**. Not surprisingly, stereocontrol was observed in this cyclisation with the hydroxyl group generated from ring-opening of the epoxide being on the opposite face to the newly formed carbon-oxygen bond of the tetrahydropyran unit. Formation of the novel THP **277** was achieved by ring-opening of **276** upon treatment with triethylamine. Compound **277** was immediately acetylated to the diacetate **278** due to its instability (**Scheme 5.3**).



Scheme 5.3 (i) *m*-CPBA (3 equiv.), DCM, rt, 3 days, 88%. (ii) *p*-TSA (0.5 equiv.), DCM, rt, 16 hr, 47%. (iii) TEA, DCM, rt, 16 hr. (iv) Acetic anhydride, pyridine, 4-DMAP, rt, 16 hr, 69% (two steps).

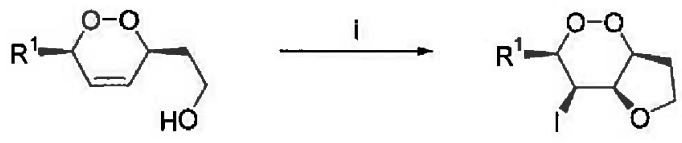
Overall this pathway resulted in formation of a novel THP possessing an additional hydroxy group in its side chain compared to those previously synthesised. This methodology is yet to be extended to other substrates but has the potential to form THP's of type **277**, possessing alternative aryl substitution. Aryl substitution is important to facilitate ring-opening of the 1,2-dioxine by providing an acidic proton *alpha* to the peroxide linkage. This methodology could also be used for the generation of a novel series of THF's possessing one extra hydroxyl group as compared to the series discussed in **Section 5.1**.

5.3 Iodo Cyclisations

Similarly to the work described in section 5.2, further procedures for the intramolecular cyclisations of the tethered hydroxy group of 1,2-dioxines prior to cleavage of the dioxygen linkage were investigated. Exploration into whether intramolecular cyclisation of the tethered hydroxyl group could occur directly onto the double bond of the 1,2-dioxine was undertaken.

Iodo cyclisations are one method, well documented in the literature, that involve intramolecular hydroxy addition onto an alkene along with simultaneous electrophilic iodide addition on the opposing end of the alkene. This method has been exploited to synthesis THF's,[239] THP's[240] and lactones.[241] These reactions occur in the presence of base and an electrophilic source of iodide, with sodium bicarbonate and iodine most commonly used. Greeves and Lee[240] found that better yields were obtained if iodine was utilised as the source of I^+ rather than *N*-iodosuccinimide or iodine monochloride.

Iodo cyclisations proceed in several solvent systems including acetonitrile,[240] dichloromethane[240,242] and biphasic systems consisting of water and chloroform[241] or dichloromethane.[239] However, reactions involving the 1,2-dioxines **262a** and **279** did not proceed in a biphasic solvent system. Solvation of the 1,2-dioxine **262a** with acetonitrile in the presence of sodium bicarbonate and iodine at ambient temperature afforded the iodo peroxide **280** in 38% yield (**Scheme 5.4**). The poor yield was a consequence of incomplete consumption of the starting material, which was recovered upon purification of the product. The iodo cyclisation of the 1,2-dioxine **279** proceeded in 71% yield to give **281.** The improved yield observed for **281** was a result of complete consumption of 1,2-dioxine **279** by providing additional energy to the reaction by heating the contents under reflux.

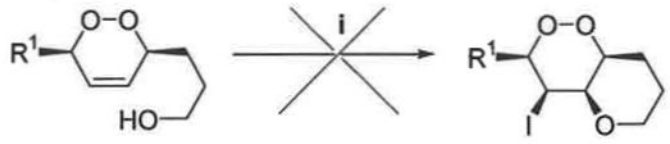


262 a R^1 = Ph
279 R^1 = Me

280 R^1 = Ph
281 R^1 = Me

Scheme 5.4 (i) MeCN, $NaHCO_3$ (1.25 equiv.), I_2 (1.25 equiv.), 38-71%.

To date, no tetrahydropyrans of type **282** have been synthesised via this methodology. The 1,2-dioxines **211** and **235c** were unreactive under the conditions employed for iodo cyclisation at ambient temperature (**Scheme 5.5**).



211 R^1 = Ph
235c R^1 = 2-Naphthyl

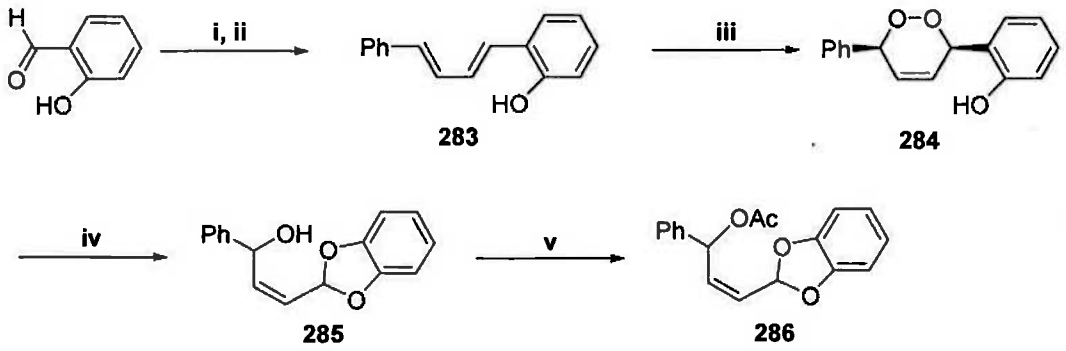
282 **a:** R^1 = Ph
b: R^1 = 2-Naphthyl

Scheme 5.5 (i) MeCN, $NaHCO_3$ (1.25 equiv.), I_2 (1.25 equiv.), rt.

Further studies are required to fully investigate whether formation of peroxides of type **282** are possible. This would not only involve performing these reactions at elevated temperatures but also exploring other sources of I^+ and other solvent systems. Furthermore, this methodology has the potential to be extended to include the generation of bromo and chloro derivatives.

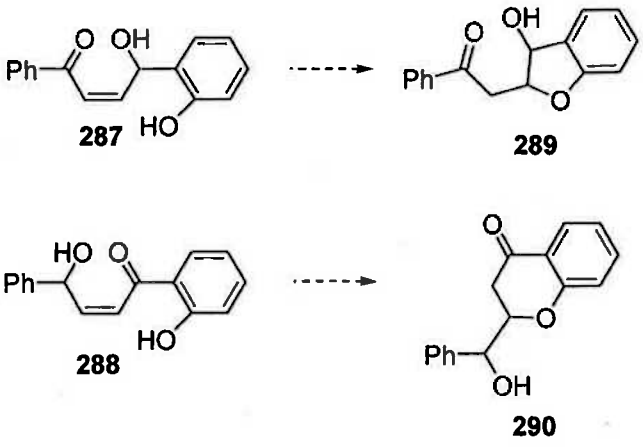
5.4 Formation of 1,3-benzodioxoles

The possible application of base-catalysed intramolecular 'oxa-Michael' cyclisations of *cis* γ-hydroxy enones to form bicyclic systems such as **289** and **290** was explored. To investigate this, 1,2-dioxine **284**, possessing a phenol ring, was synthesised by the pathway outlined in **Scheme 5.6**. The 1,2-dioxine **284** was prepared by photolysis of the corresponding 1,3-butadiene **283**, which was prepared by a Wittig reaction of salicyclic acid and the cinnamyl ylide salt **216**, by modification of a known method.[243]



Scheme 5.6 (i) KOBu^t (1 equiv.), diethyl ether, rt, 10 min. (ii) $[Ph_3P\text{-}CH\text{-}CH{=}CH\text{-}Ph]^+ Cl^-$ **144a** (1 equiv.), rt, 16 hr, 71% (2 steps). (iii) Rose Bengal *bis*(triethylammonium) salt, DCM, O_2, *hv*, 6 hr, 19%. (iv) LiOH (1 equiv.), THF, rt, 16 hr, 55%. (v) Acetic anhydride, pyridine, 4-DMAP, rt, 3 hr, 17%.

Treatment of the 1,2-dioxine **284** with lithium hydroxide afforded the 2-substituted 1,3-benzodioxole **285** in 55% yield rather than the anticipated bicyclic systems **289** or **290**, which were anticipated to form via the *cis* γ-hydroxy enones **287** and **288**, respectively, based on our previous findings (**Scheme 5.7**).

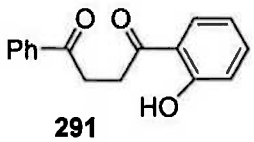


Scheme 5.7

Identification of the major product being the 1,3-benzodioxole **285** was determined through a combination of ^{1}H, ^{13}C, COSY, HMBC, HMQC and ROESY NMR experiments for this compound and the corresponding acetate **286**. The poor yield of 17% obtained for the acetate **286** was due to the decomposition of the precursor, which was enhanced under acetylation conditions. Mass spectroscopy confirmed that the product was an isomer of the starting dioxine with a molecular ion corresponding to $[C_{16}H_{14}O_3]^+$ observed at 254. As a result, furan formation during this reaction is invalidated as its formation results in an overall loss of water. Bicyclic systems containing THF or THP units, such as **289** or **290** along with the tricyclic systems that could form via their further cyclisation were discounted as eligible candidates for the product obtained. The reason being that the DEPT spectrum of the major product indicated that only CH's were present in the molecule. All possible bicyclic and tricyclic systems contain one CH_2 unit. The COSY spectrum indicated that all four non-aromatic CH's were joined in sequence, an observation that is consistent with the structure of the 1,3-benzodioxole **285**.

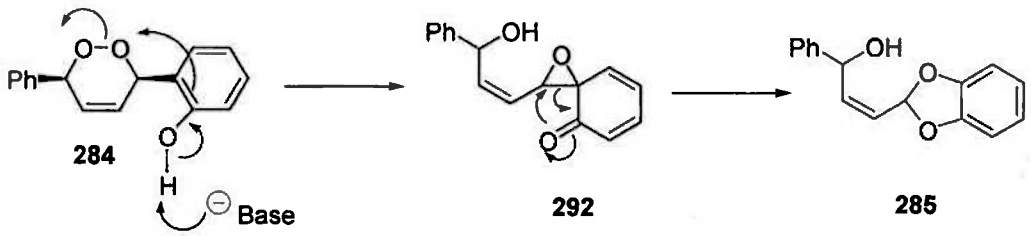
The ^{1}H and ^{13}C NMR spectra for the major product were also consistent with that expected for compound **285**. The broad singlet at δ2.38, integrating to one, in the ^{1}H NMR spectrum indicated that one hydroxy group was present. This observation was further supported by the ^{1}H and ^{13}C NMR spectra of the acetylated product **286**, showing signals corresponding to the presence of one acetate group. The ^{13}C NMR spectra of the major product and its acetate strongly correlated to that expected for **285** and **286**, respectively. In particular, these spectra indicated the presence of an acetal carbon in the region 105-106 ppm. A downfield shift of this magnitude for an sp^3 carbon is characteristic of an acetal carbon. The acetal carbon of 1,3-dioxolane resonates at 95 ppm in its ^{13}C NMR[244] while a 1,3-benzodioxole acetal carbon experiences a downfield shift due to it being deshielded by the phenyl group. Commonly, chemical shifts of 101-102 ppm are observed for the acetal carbon of 1,3-benzodioxoles that lack substitution at C_2.[245,246] The presence of the *Z* double bond in **285** was confirmed by the 11.4 Hz coupling constant between the vinylic protons.

Treatment of **284** with DABCO also furnished the 1,3-benzodioxole **285**, but as the minor product with the 1,4-diketone **291** now being the major product in a ratio of 3:1. When monitored by ^{1}H NMR, a precursor to the 1,3-benzodioxole **285** was observed. Isolation of this intermediate by acetylation was attempted, but the harsh basic conditions resulted in catalysis of this intermediate to the benzodioxole and its subsequent acetylation to afford **286**.



291

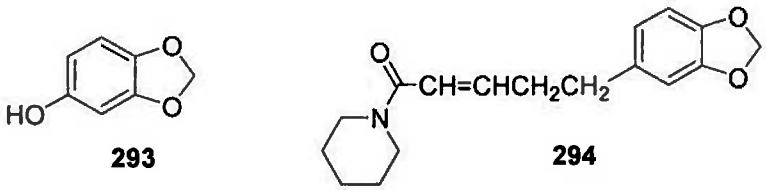
It is believed that the 1,3-benzodioxole **285** forms via cyclisation of the epoxy intermediate **292** generated by the mechanism outlined in **Scheme 5.8**. There is at least one reported study of 1,3-benzodioxole formation from spirodienones of similar type to **292**.[247]



284 **292** **285**

Scheme 5.8

The 1,3-benzodioxole unit is an important part of many biologically active natural products, such as sesamol **291**[248] and $\Delta^{\alpha\beta}$-dihydropiperine **292**.[249]

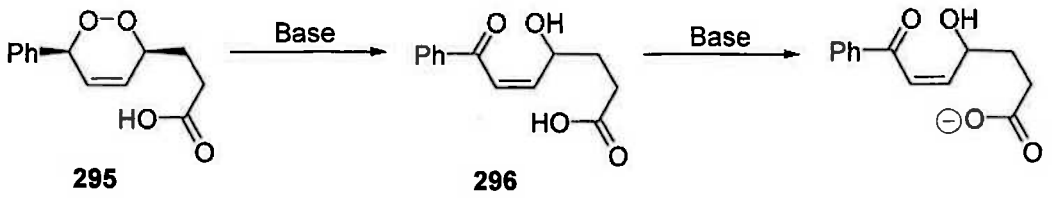


293 **294**

As these natural products, along with many others containing the 1,3-benzodioxole unit, lack substitution at C_2, there are very few reports of methods for the preparation of 2-substituted 1,3-benzodioxoles. The generation of 2-substituted 1,3-benzodioxoles from phenolic 1,2-dioxines represents a novel route to these compounds. The scope and mechanism of this reaction is under further investigation.

5.5 Formation of Lactones

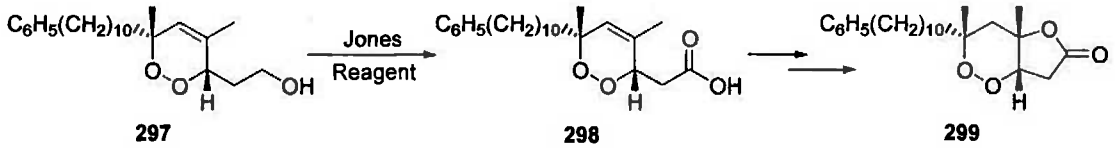
The methodology employed for THP and THF synthesis from 1,2-dioxines can be extended to the formation of lactones. It was anticipated that this could be achieved via base-catalysed intramolecular cyclisation of the carboxylate anion of the *cis* γ-hydroxy enone **296** generated from ring-opening of the 1,2-dioxine **295** (**Scheme 5.9**).



295 **296**

Scheme 5.9

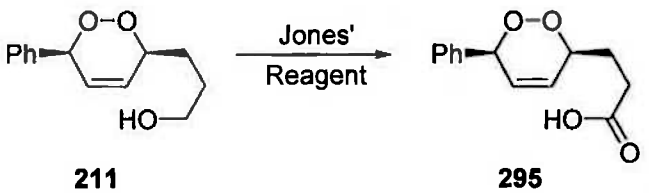
An initial attempt to prepare the carboxylic 1,2-dioxine **295** *in situ* by lithium hydroxide treatment of its methyl ester was unsuccessful and resulted in furanisation of the starting dioxine. The synthesis of 1,2-dioxines of type **295** appeared challenging until a publication by Jung and co-wokers,[241] In this publication, they reported the synthesis of the carboxylic acid containing 1,2-dioxine **298**, an intermediate in the total synthesis of natural 6-Epiplakortolide E **299**. The carboxylic acid **298** was simply prepared by oxidation of the alcohol **297** using Jones' reagent (**Scheme 5.10**).



297 **298** **299**

Scheme 5.10

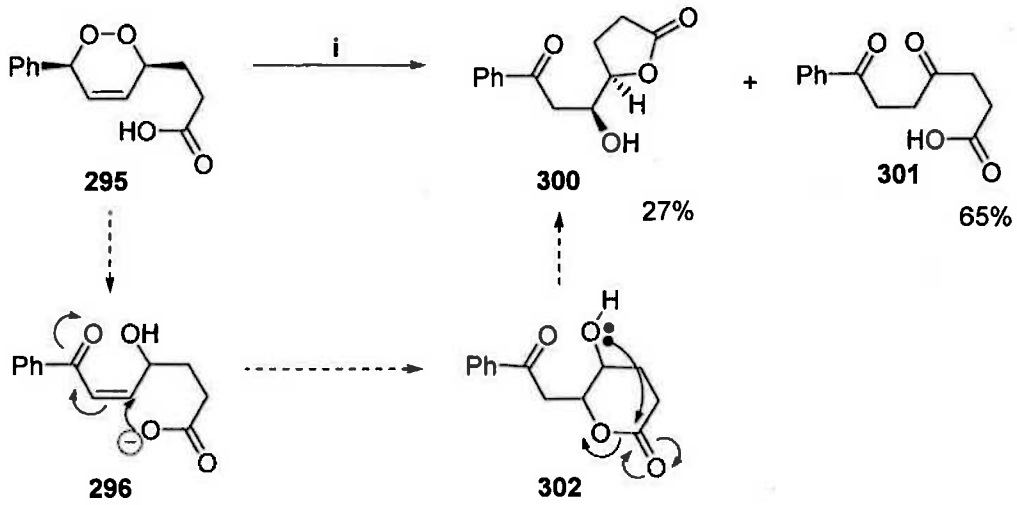
Using the method of Jung co-workers[241] the 1,2-dioxine **211** was converted to the corresponding acid **295** in a moderate yield of 55% (**Scheme 5.11**).



211 **295**

Scheme 5.11

Treatment of **295** with one equivalent of lithium hydroxide in THF resulted in the precipitation of its lithium salt rather than removal of the proton *alpha* to the endoperoxide linkage and hence ring-opening. This problem was overcome by using DABCO as base as it lacks a counterion required for salt formation. Treatment of **295** with two equivalents of DABCO in chloroform at 60°C gave the 5-membered lactone **300** in 27% (**Scheme 5.12**). As amine bases are known to favour diketone formation it was not surprising that the 1,4-diketone **301** was the major product under these conditions. The formation of the lactone **300**, during this reaction, was confirmed by X-ray crystallography (**Figure 5.1**). It was anticipated that the 6-membered lactone **302** would have formed in this reaction rather than the 5-membered lactone **300**, but it is likely that the latter forms by cyclisation and ring-opening of **302** (**Scheme 5.12**).



Scheme 5.12 (i) DABCO (2 equiv.), $CHCl_3$, 70°C oil bath, 16 hr.

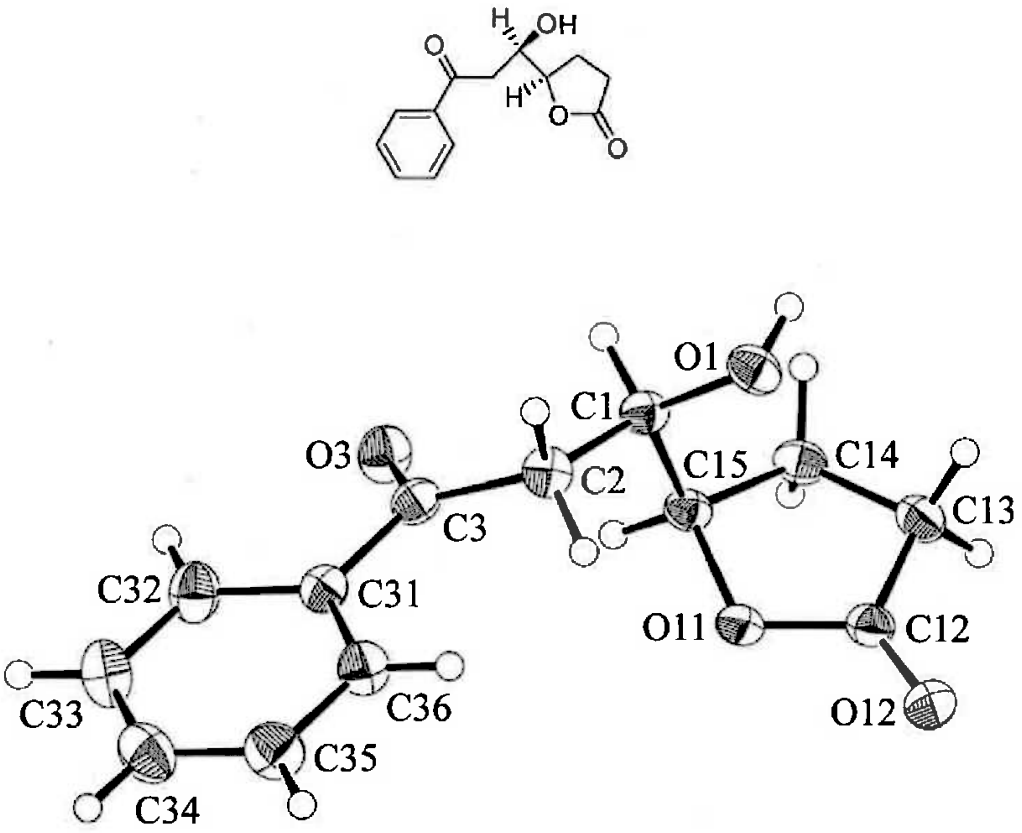


Figure 5.1 Crystal structure for the 5-membered lactone **300** showing the crystallographic numbering scheme employed.

X-ray crystallography of the 5-membered lactone **300** confirmed that hydrogen bonding existed between the hydrogen atom of the hydroxyl group of one molecule and the oxygen of the lactone carbonyl group of another (**Figure 5.2**).

The scope and mechanism of the base-catalysed lactone formation from a carboxylic acid containing 1,2-dioxine requires further elaboration. This includes extension of this methodology to other substrates, determination of the mechanism by which the reaction proceeds, as well as optimisation of the yield of the lactone **300** by exploring different bases and solvent systems. Potentially, the iodo cyclisations discussed in Section 5.3 could also be used on 1,2-dioxines of type **295** to generate a new series of lactones.

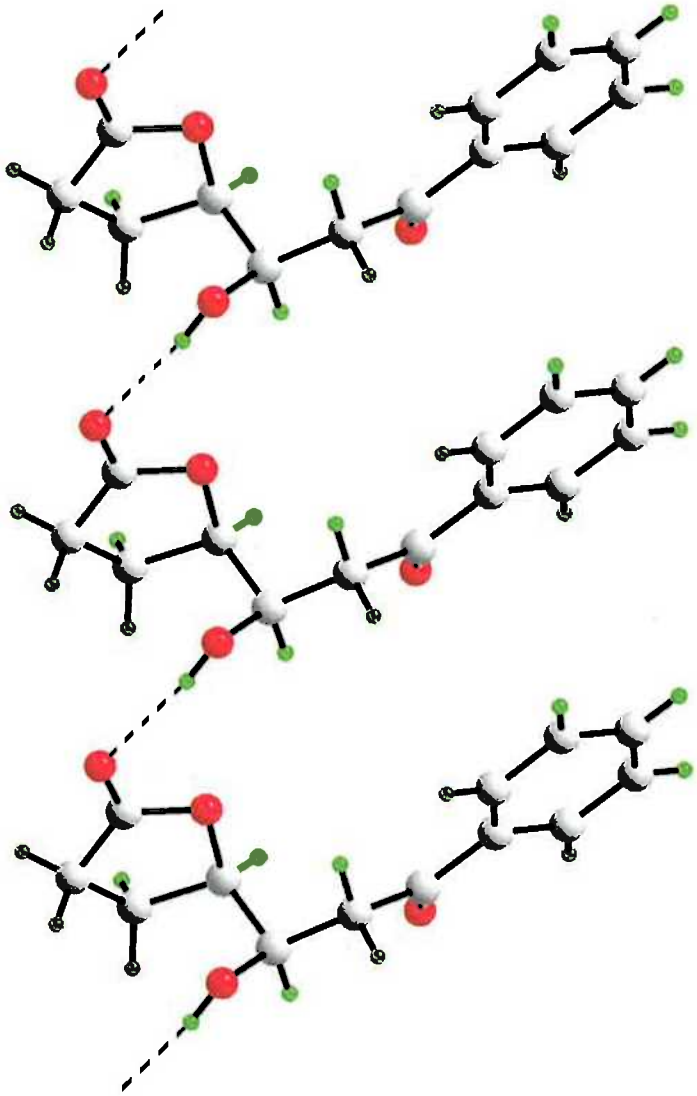
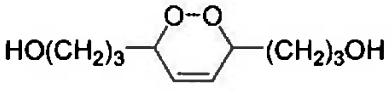


Figure 5.2 Hydrogen bonding between molecules of the lactone **300**.

5.6 Towards the Synthesis of Optically-enriched Tetrahydropyrans

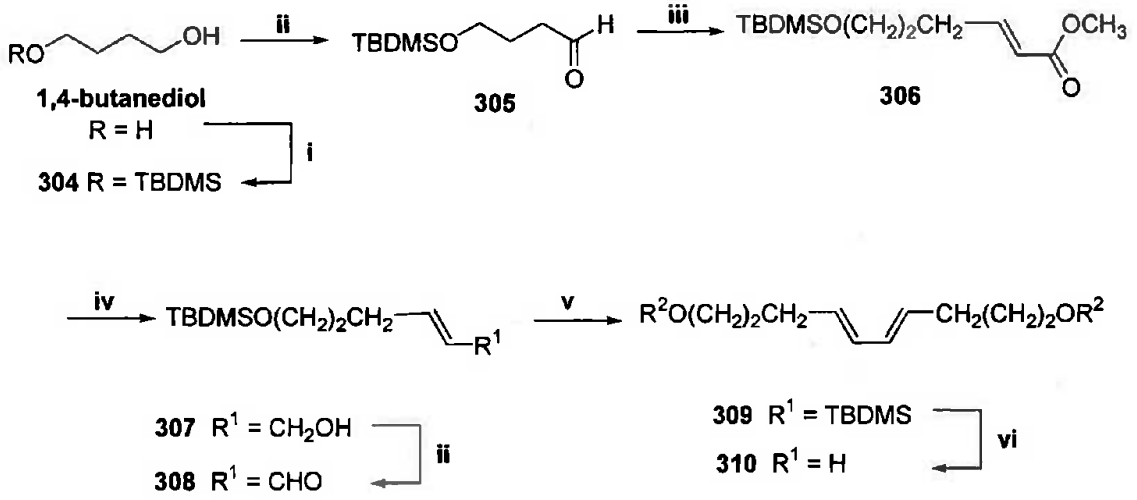
With a methodology for the synthesis of tetrahydropyrans from 1,2-dioxines established, we were interested in investigating whether this methodology could be utilised to generate optically-enriched THP's. As discussed in Chapter 1, optically-enriched cyclopropanes can be prepared from *meso* 1,2-dioxines by exploitation of chiral cobalt catalysts. Enantioselectivity is introduced in these reactions as a result of the generation of optically-enriched *cis* γ-hydroxy enone from asymmetric ring-opening of the parent 1,2-dioxine in the presence of a chiral cobalt catalyst.[160] This methodology has also been used to synthesise optically-enriched lactones[221] and *trans* 4-hydroxy-2,3-epoxyketones.[250,251] Therefore, it was logical to assume this methodology could be utilised to form optically-enriched THP's.

This method requires the use of symmetrical 1,2-dioxines so that only one *cis* γ-hydroxy enone is formed upon ring-opening. Therefore, symmetrical 1,2-dioxine **303** was targeted.



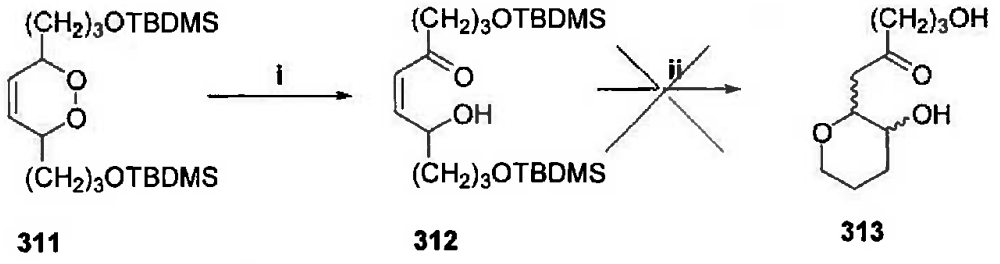
303

Scheme 5.13 outlines the synthetic strategy undertaken for the synthesis of novel 1,3-butadiene **310**. 1,4-Butanediol was mono-silylated in the presence of butyl lithium and TBDMSCl[252,253] and the remaining hydroxyl group oxidised under Swern conditions[252] to the aldehyde **305**. Treatment of **305** with (carbethoxymethylene)triphenyl-phosphorane[176] afforded the α,β-unsaturated methyl ester **306**, which was converted to the α,β-unsaturated aldehyde **308** by reduction with DIBAL-H[176] to the alcohol **307**, followed by reoxidation of **307** under Swern conditions.[171] A second Wittig reaction involving the phosphonium salt **229** and the aldehyde **308**, afforded the symmetrical di-TBDMS protected 1,3-butadiene **309**, which was desilylated upon treatment with tetrabutylammonium fluoride[166] to furnish the desired 1,3-butanediol **310**.



Scheme 5.13 (i) *n*-BuLi (1.1 equiv.), TBDMSCl (1 equiv.), DMF, rt, 16 hr, 60%. (ii) DMSO (4 equiv.), oxalyl chloride (2 equiv.), DCM, -78°C, 2hr, 65%. (iii) $Ph_3P{=}CHCO_2CH_3$, DCM, rt, 16 hr, 99%. (iv) DIBAL-H (2 equiv.), DCM, -78°C, 2 hr, 98%. (v) $[Ph_3P\text{-}(CH_2)_4OTBDMS]^+ I^-$ **229**, BuLi (1 equiv.), THF, -78°C (30 min) → rt (48 hr), 57%. (vi) TBAF (2.5 equiv.), THF, 0°C (5 min) → rt (1.5 hr), 87%.

The 1,2-dioxine **303** could not be formed from photo-oxidation of 1,3-butadiene **310** in the presence of Rose Bengal *bis*(triethylammonium) salt and oxygen. The reason for this is unknown but it appears that the 1,3-butadiene **310** may have formed a *bis*-tetrahydrofuran, a consequence of possible cyclisation of photolytic by-products. However, the di-TBDMS protected 1,2-dioxine **311** was prepared by photolysis of the 1,3-butadiene **309**. Although 1,2-dioxine **311** did ring-open in the presence of $Co(SALEN)_2$ to afford the *cis* γ-hydroxy enone **312**, no THP **313** was obtained by treatment of this enone with TBAF, which was expected to desilylate **312** and catalyse intramolecular ring-closure (**Scheme 5.14**). The enone **312** was consumed upon treatment with TBAF but the ^1H NMR for the product obtained does not correspond to that expected for **313**. At this stage the structure of the compound formed is unknown.



Scheme 5.14 (i) THF, $Co(SALEN)_2$ (7.5 mol %), rt, 6 hr. (ii) TBAF (2.5 equiv.), THF, rt, 16 hr.

The *cis* γ-hydroxy enone **312** can be captured by ylide to form cyclopropanes but its desilylation and cyclisation to afford the THP **313** is elusive at this stage. Further investigations are required in order to determine the by-product formed in the above reaction and the appropriate conditions required for desilylation and cyclisation of the enone **312** to afford **313**. If this is achieved then an appropriate chiral cobalt catalyst can be utilised for the preparation of optically-enriched THP's.

5.7 Summary and Conclusions

The methodology for the generation of THP's from 1,2-dioxines containing tethered hydroxy groups (**Chapter 4**) was extended to include the formation of the THF's **264** and **265**. Treatment of the parent 1,2-dioxines **262** with lithium hydroxide favoured formation of the *cis* isomers **265** over their *trans* counterparts **264** in a ratio of 3:2. Exposure of the same dioxines with DABCO afforded the *cis* THF isomers **265** as the major products while the 1,4-diketones **266** were minor products.

The novel THP **277** was prepared by intramolecular cyclisation of the tethered hydroxyl group onto the epoxy portion of 1,2-dioxine **274** prior to cleavage of the dioxygen bond. This methodology has the potential to give rise to a new series of THP's and THF's containing an additional hydroxyl group in their side chain relative to those prepared previously (**Chapter 4** and **5**, respectively). Similarly, iodo cyclisations of the 1,2-dioxines **262a** and **279** give rise to the novel peroxides **280** and **281**, respectively, which upon ring-opening can afford novel THF's possessing an iodine atom in its side chain rather than a hydroxyl group.

1,2-Dioxines containing tethered phenoxy groups and carboxylic acid groups can be manipulated to furnish 2-substituted 1,3-benzodioxoles, such as **285**, and lactones such as **300**, respectively. These preliminary findings require further investigations in order to determine the scope and mechanism of these reactions.

The synthesis of optically-enriched tetrahydropyrans from exploitation of 1,2-dioxine **311** and a chiral cobalt catalyst has been elusive at this stage. THP synthesis is yet to be established even with the use of a non-chiral cobalt catalyst such as $Co(SALEN)_2$. Ring opening of the 1,2-dioxine **311** to the enone **312** does occur in the presence of $Co(SALEN)_2$ but subsequent disilylation of **312** and cyclisation to afford the THP **313** is troublesome. Further investigations are therefore required to analyse whether optically-enriched THP's can be obtained by this method.

The work presented in this chapter highlights the utility of 1,2-dioxines for the preparation of a range of compounds including THF's, THP's, benzodioxoles and lactones.

Chapter 6 – Experimental

6.1 General experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution using a Varian Gemini-2000, Bruker ACP-300 or a Varian Innova-600 MHz spectrometer operating at 200, 300 and 600 MHz, respectively for ^{1}H and 50, 75 and 150 MHz, respectively for ^{13}C. ^{31}P NMR spectra were recorded in $CDCl_3$ solution using a Bruker ACP-300 spectrometer operating at 121 MHz for ^{31}P. ^{1}H NMR spectra are referenced to tetramethylsilane (TMS: δ0.0). ^{13}C NMR spectra are referenced to chloroform (δ 77.0). ^{31}P NMR spectra are referenced to phosphoric acid (δ0.0). All resonances are given in parts per million (ppm). Multiplicities are assigned as follows: br s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, quin: quintet, m: multiplet, and combinations thereof. All coupling constants are reported in Hz. Superscript *a* and *b* are assigned to ^{1}H NMR signals from a mixture to distinguish which of two isomers the signals belong to. In the case where both superscript *a* and *b* are assigned to the one signal (i.e. (m, XH)^{a,b}, where X designates the number of protons contributing to the signal) the proton signals from isomer a and isomer b are overlapping and each isomer contributes 0.5XH, unless otherwise noted. Non-first order ABX systems were analysed by the method of Gunther.[254]

Infrared spectra were recorded on an ATI Mattson Genesis Series FTIR spectrophotometer as either nujol mulls or in the neat form as denoted. Designation of split written in brackets after the IR frequency refers to the peak being split at its apex into two peaks of equal intensity. Melting points were taken on a *Reichert* Thermovar Kofler apparatus and are uncorrected. Electron Impact (EI) mass spectra were carried out using a VG ZAB 2HF mass spectrometer operating at 70eV. Accurate mass measurements were performed by the Organic Mass Spectrometry Facility, Central Science Laboratory, University of Tasmania, Tasmania, Australia or Monash University, Victoria, Australia. Microanalyses were performed by the Chemistry Department, University of Otago, Dunedin, New Zealand or the Chemical and Micro Analytical Services, Belmont, Victoria, Australia. X-ray crystallography was performed by Edward R. T. Tiekink at the National University of Singapore, Singapore, Malaysia.

Solvents were dried by appropriate methods wherever needed. Thin-layer chromatography (TLC) was performed using aluminium sheets coated with silica gel 60 F_{254} (40 x 80 mm) from Merck and visualized under 254 nm light, or developed in vanillin or permanganate dip. Flash chromatography was conducted using Merck silica gel 60 of particle size 0.040-0.063 mm. All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectroscopy.

Optical rotations were performed using a Polaar 21 optical activity automatic polarimeter with a sodium lamp. Concentration (c) is g/100 mL in the solvent indicated and the specific rotations ($[\alpha]_D$) are reported with the temperature used.

The following compounds were purchased from Aldrich Chemical Company, Inc. and used without further purification. *N,N'-bis*(salicylidene)ethylenediaminocobalt(II); *N,N'-bis*(salicylidene)ethylenediaminocobalt(II) hydrate; rose bengal, *bis*(triethylammonium) salt; (*S*)-4-benzyl-2-oxazolidinone; *o*-vanillin; lithium bromide.

1,2-dioxines were synthesised by the following procedure unless otherwise noted.

General procedure for 1,2-dioxine formation

To a solution of 1,3-butadiene in anhydrous dichloromethane (30 mL / g of 1,3-butadiene), in a Pyrex flask fitted with an external cooling jacket, was added Rose Bengal, *bis*(triethylammonium) salt (100 mg). The solution was cooled to 4°C by pumping ice water through the external cooling jacket and a stream of O_2 was passed through the solution. The reaction was then irradiated with 3 x 500W halogen lamps at a distance of 10 cm for 6 hours. After this time, the solvent was removed under reduced pressure and the resulting residue purified by flash chromatography.

6.2 Compounds discussed in Chapter 2

Synthesis of 1,2-dioxine 107

Methyltriphenylphosphonium Iodide

Under a N_2 atmosphere, iodomethane (42.45 g, 0.3 mol) was added dropwise to a solution of triphenylphosphine (78.5 g, 0.3 mol) in anhydrous toluene (400 mL) at 0°C. After the addition was complete, the solution was warmed to 20°C and stirred for 12 hours at this temperature. The precipitate was collected by vacuum filtration, washed with toluene (2 x 150 mL) and dried to give 111.9 g, 92% of methyltriphenylphosphonium iodide as a white powder.

1-[(1*E*)-1,3-Butadienyl]benzene (106)[155]

To a suspension of methyltriphenylphosphonium iodide (17.09 g, 42.3 mmol) in anhydrous diethyl ether (150 mL) under a N_2 atmosphere was added potassium *tert*-butoxide (6.0 g, 53 mmol). After stirring at 0°C for 30 minutes, a solution of *trans*-cinnamaldehyde (5.08 g, 38.4 mmol) in anhydrous diethyl ether (50 mL) was added dropwise at 0°C. The solution was warmed to 20°C and stirred for 16 hours, protected from light, at this temperature. The solution was filtered through 1-2 cm of silica and the silica washed with hexane (100 mL). The combined filtrates were concentrated under reduced pressure and the residue purified by flash chromatography to give 3.35 g, 67% of 1,3-butadiene **106** as a colourless liquid consisting of two isomers; R_f 0.54 (100% hexanes); ^{1}H NMR (200 MHz) δ 5.17 (dd, J = 11.0, 1.2 Hz, 1H), 5.33 (dd, J = 15.6, 1.2 Hz, 1H), 6.54 (m, 2H), 6.79 (m, 1H), 7.3 (m, 5H); ^{13}C NMR (50 MHz) δ 117.6, 126.4, 127.6, 128.6, 129.6, 132.9, 137.2.

3-Phenyl-3,6-dihydro-1,2-dioxine (107)[255]

Prepared by photolysis of 1,3-butadienes **106** by the general procedure for 1,2-dioxine synthesis. Yield: 1.8 g, 52%: Colourless liquid. R_f 0.49 (1:19 ethyl acetate:hexanes). Unreacted diene was also recovered (1.31 g, 47%).

Ethyl 2-(2-benzoylcyclopropyl)propanoate (108)

To a solution of 1,2-dioxine **107** (0.9 g, 5.5 mmol) in dichloromethane (30 mL) under N_2 was added (carbethoxyethylidene)triphenylphosphorane (3.0 g, 8.3 mmol). The solution was stirred at 20°C for 14 days. The solvent was removed *in vacuo* and the residue purified by flash chromatography (3:10 ethyl acetate:hexanes) to give 0.41 g, 30% of cyclopropane **108** as a pale yellow oil, consisting of a mixture of three isomers. Further attempts to

purify the isomeric cyclopropanes by flash chromatography (1:19, diethyl ether:benzene) only resulted in partial purification of the most non-polar isomer. R_f 0.51, 0.53 and 0.57 (1:19 diethyl ether:benzene).

Synthesis and treatment of (*E*)-4-hydroxy-1-phenyl-2-buten-1-one (111a)[156] with (Carbethoxyethylidene)triphenylphosphorane

(Benzoylmethylene)triphenylphosphorane (1.27 g, 3.5 mmol) was added to a solution of glycoaldehyde dimer (0.20 g, 1.7 mmol) in dichloromethane (13 mL). The mixture was heated under reflux for 4 hours, after which time the *trans* enone **111a** had formed and was reacted immediately without isolation. (Carbethoxyethylidene)triphenylphosphorane (1.80 g, 5 mmol) was added to the reaction vessel and the solution heated by irradiation with light from 2 sun lamps (300W) at a distance of 10 cm and in the presence of benzophenone (10 mol %) for 30 hours. The solvent was removed *in vacuo* and ^{1}H NMR analysis of the residue indicated a complex mixture of decomposition products had formed.

Synthesis and treatment of (*E*)-5-hydroxy-3-penten-2-one (111b)[156] with (Carbethoxyethylidene)triphenylphosphorane

1-Triphenylphosphoranylidene-2-propanone (1.12 g, 3.5 mmol) was added to a solution of glycoaldehyde dimer (0.20 g, 1.7 mmol) in dichloromethane (13 mL). The mixture was heated under reflux for 4 hours, after which time the *trans* enone **111b** had formed and was reacted immediately without isolation. (Carbethoxyethylidene)-triphenylphosphorane (1.81 g, 5 mmol) was added to the reaction vessel and the solution heated by irradiation with light from 2 sun lamps (300W) at a distance of 10 cm and in the presence of benzophenone (10 mol %) for 72 hours. The solvent was removed in *vacuo* and ^{1}H NMR analysis of the residue indicated a complex mixture of decomposition products had formed.

Synthesis of 1,2-dioxine 117

Benzyltriphenylphosphonium bromide

Triphenylphosphine (40.25 g, 153 mmol) was added to a solution of benzyl bromide (25 g, 146 mmol) in anhydrous toluene (215 mL) under N_2. The solution was heated under reflux for 48 hours and the resulting white precipitate collected by vacuum filtration. The salt was washed with toluene (100 mL), hexane (100 mL) and dried to give 50.2 g, 79% of benzyltriphenylphosphonium bromide as a white powder; m.p. 292–298 °C (lit.[256] 295-298°C).

1-[(1*E*, 3*E*)-1,3-Pentadienyl]benzene (116)[155]

Potassium *tert*-butoxide (6.0 g, 53 mmol) was added to a suspension of benzyltriphenylphosphonium bromide (20.40 g, 47 mmol) in anhydrous diethyl ether (150 mL) under N_2. After stirring at 20°C for 15 minutes, the mixture was cooled to 0°C and a solution of crotonaldehyde (3.01 g, 43 mmol) in anhydrous diethyl ether (50 mL) added dropwise. The solution was warmed to 20°C and stirred for 16 hours, protected from light, at this temperature. The solution was filtered through 1-2 cm of silica and the silica washed with hexanes (100 mL). The combined filtrates were taken to dryness and the residue purified by flash chromatography (100% hexanes) to give 5.57 g, 90% of 1,3-butadienes **116** as a colourless liquid consisting of two isomers; R_f 0.49 (1:19 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 1.78 (m, 3H), 5.85 (m, 1H), 6.18–6.81 (m, 3H), 7.15–7.38 (m, 5H).

(±) (3*R*, 6*R*)-3-Methyl-6-phenyl-3,6-dihydro-1,2-dioxine (117)[255]

Prepared by photolysis of 1,3-butadienes **116** by the general procedure for 1,2-dioxine synthesis. Yield: 1.80 g, 42%; Pale yellow liquid; R_f 0.50 (1:9 ethyl acetate:hexane); ^{1}H NMR: δ 1.35 (d, J = 10.2 Hz, 3H), 4.76 (s, 1H), 5.47 (s, 1H), 6.06 (s, 2H), 7.34-7.41 (m, 5H). Unreacted diene was also recovered (1.41 g, 40%).

Synthesis of cyclopropane 119 and its attempted methylation

(*tert*-Butoxycarbonylmethylene)triphenylphosphorane (118)

To a solution of *tert*-butylchloroacetate (28.85 g, 192 mmol) in anhydrous toluene (250 mL) was added triphenylphosphine (52.75 g, 201 mmol). The resulting solution was heated under reflux for 16 hours. The precipitate formed was collected by suction filtration, washed with toluene (100 mL) and then hexane (100 mL). Once dried, the salt was dissolved in the minimal amount of 1:1, MeOH:H_2O and 1M NaOH added in small portions (5-10 mL) until no further precipitation occurred. The precipitate was collected by filtration, washed with water and dried to give 69.3 g, 96% of (*tert*-butoxycarbonylmethylene)triphenylphosphorane as a pale yellow powder; m.p. 151-154°C (lit.[257] 152-155°C); ^{1}H NMR (300 MHz) δ 1.22 (br s, 9H), 2.68 (br s, 1H), 7.41–7.67 (m, 15H).[256]

(±) *tert*-Butyl(1*S*,2*R*,3*R*)-2-methyl-3-(2-oxo-2-phenylethyl)cyclopropane-1-carboxylate (119)[159]

To a solution of 1,2-dioxine **117** (2.11 g, 12 mmol) in dichloromethane (210 mL) was added lithium bromide (1.27 g, 14.6 mmol) and (*tert*-butoxycarbonylmethylene)-triphenylphosphorane (6.38 g, 16.9 mmol). The mixture was stirred at ambient temperature for 3 days. The solvent was removed *in vacuo* and the residue purified by flash chromatography to give 2.65 g, 80% of cyclopropane **119** as a colourless oil; R_f 0.48 (1:4 ethyl acetate:hexane); Crystallisation from heptane gave a white solid, m.p. 47-49°C; ^{1}H NMR (600 MHz) δ 1.14–1.18 (m, 1H), 1.23, (d, J = 6.0 Hz, 3H), 1.45 (s, 9H), 1.50 (dd, J = 9.0, 5.4 Hz, 1H), 1.60–1.64 (m, 1H), 2.75 (dd, J = 16.6, 7.8 Hz, 1H), 3.16 (dd, J = 16.2, 6.0 Hz, 1H), 7.46 (tt, J = 9.0, 1.2 Hz, 2H), 7.56 (tt, J = 7.2, 1.2 Hz, 1H), 7.92 (dt, J = 7.8, 1.8 Hz, 2H). ^{13}C NMR (75 MHz) δ 11.7, 22.7, 22.9, 26.7, 28.3, 42.2, 80.2, 128.1, 128.6, 133.0, 136.8, 171.2, 198.6.

***tert*-Butyl 2-hydroxy-5-methyl-2-phenyl-3-cyclopentene-1-carboxylate (123)** (where R^1 = Ph, R^2 = Me, R^3 = Bu^t)[164]

To a 0°C solution of anhydrous diisopropylamine (101 mg, 1 mmol) and THF (0.8 mL) under N_2 was added *n*-BuLi (2.5 M solution in hexanes, 0.31 mL, 0.75 mmol). After stirring for 10 minutes at 0°C the solution was cooled to -78°C and a solution of the cyclopropane **119** (100 mg, 0.36 mmol) in anhydrous THF (0.3 mL) added to the reaction flask. The solution was stirred for 30 minutes at -78°C prior to the addition of iodomethane (0.14 mL, 2.16 mmol). The solution was allowed to warm to 20°C and then partitioned between aqueous ammonium chloride (saturated, 10 mL) and diethyl ether (20 mL). The aqueous phase was separated and washed with diethyl ether (2 x 20mL). The combined organic extracts were washed with water (30 mL), dried (Na_2SO_4) and concentrated to give a pale yellow oil (84 mg). The residue was purified by flash chromatography (1:4 ethyl acetate:hexane) to give 45 mg, 45% of cyclopentenol **123** as a colourless oil. R_f 0.25 (100% dichloromethane); ^{1}H NMR (200 MHz) δ 1.20 (d, J = 7.2 Hz, 3H), 1.42 (s, 9H), 2.65 (d, J = 7.2 Hz, 1H), 3.30-3.36 (m, 1H), 3.74 (br s, 1H), 5.75 (dd, J = 5.6, 2.4 Hz, 1H), 5.98 (dd, J = 5.6, 2.0 Hz, 1H), 7.26-7.45 (m, 5H). (Nb. Lit.[164] has incorrectly quoted signal at 2.41 instead of 1.41 and signal at 2.65 as integrating to 3H instead of 1H).

***tert*-Butyl (*E*)-3,5-dimethyl-6-oxo-6-phenyl-4-hexenoate (131)**

The cyclopropane **119** (100mg, 0.36 mmol) was added to a –78°C solution of potassium *bis*(trimethylsilyl) amide (0.5 M solution in toluene, 1.09 mL, 0.55 mmol) in anhydrous

THF (2 mL) under N_2. After stirring for 30 minutes at this temperature, iodomethane (0.14 mL, 2.2 mmol) was added dropwise to the solution. The solution was warmed to 20°C and stirred for 16 hours at this temperature. The solution was partitioned between aqueous ammonium chloride (sat., 15 mL) and hexanes (15 mL). The organic phase was separated, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (1:19 ethyl acetate:hexanes) to give 40 mg, 38% of compound **131** as a colourless oil; ^{1}H NMR (600 MHz) δ 1.07 (d, J = 6.3 Hz, 3H), 1.44 (s, 9H), 2.02 (s, 3H), 2.22 (dd, J = 15.0, 8.4 Hz, 1H), 2.32 (dd, J = 14.4, 6.0 Hz, 1H), 3.10-3.17 (m, 1H), 6.05-6.08 (m, 1H), 7.40-7.43 (m, 2H), 7.46-7.52 (m, 1H), 7.64-7.66 (m, 2H); ^{13}C NMR (150 MHz) δ 12.6, 19.7, 28.0, 31.0, 42.5, 80.6, 128.0, 129.5, 131.5, 138.4, 149.2, 171.2, 199.0.

(±) (1*S*,2*R*,3*R*)-2-Methyl-3-(2-oxo-2-phenylethyl)cyclopropane-1-carboxylic acid (132)

Trifluoroacetic acid (15 mL) was added to a solution of the cyclopropyl ester **119** (3.0 g, 10.9 mmol) in dichloromethane (15 mL). The solution was stirred at 20°C for 20 hours after which time TLC analysis indicated that the ester had been fully consumed. The solution was taken to dryness and the residue taken up into dichloromethane (120 mL) and washed with aqueous sodium carbonate (5%, 2 x 100 mL). The combined aqueous layers were acidified to pH 1 using aqueous hydrogen chloride (10%). The resulting precipitate was dissolved in dichloromethane (120 mL) and separated from the aqueous layer. The aqueous layer was further extracted with dichloromethane (120 mL) and the combined organic layers washed with water (100 mL), dried (Na_2SO_4), filtered and concentrated to give the crude acid **132** as a pale peach coloured powder. Hot filtration in ethanol and in the presence of charcoal, followed by concentration of the filtrate *in vacuo* gave 1.82 g, 77% of the cyclopropyl acid **132** as a white solid; m.p. 136–140 °C; IR (nujol) 2400-2720, 1684 cm^{-1}; ^{1}H NMR (600 MHz) δ 1.28-1.34 (m, 4H), 1.56-1.61 (m, 1H), 1.73-1.77 (m, 1H), 2.88 (dd, J = 17.4, 7.2 Hz, 1H), 3.13 (dd, J = 17.4, 6.6 Hz, 1H), 7.43-7.48 (m, 2H), 7.55-7.59 (m, 1H), 7.91-7.93 (m, 2H), 9.70-11.40 (br s, 1H); ^{13}C NMR (75 MHz) δ 11.8, 24.3, 24.4, 25.2, 41.9, 128.0, 128.6, 133.2, 136.5, 178.6, 198.2; MS (EI) *m/z* (%): 219 ([M+H]$^+$, 19), 201 (100), 173 (3), 156 (6), 155 (2), 105 (23), 77 (3).

(±) 2-[(1*R*,2*S*)-2-Methylcyclopropyl]-1-phenyl-1-ethanone (134)

To a 0°C solution of the cyclopropyl acid **132** (0.80 g, 3.7 mmol) in dichloromethane (60 mL) under N_2 was added DCC (0.76 g, 3.7 mmol) and 2-mercaptopyridine *N*-oxide (0.47 g, 3.7 mmol). The solution was stirred for 3 hours protected from light. The precipitated DCU was removed by filtration and washed with dichloromethane (10 mL). The filtrate

was taken to dryness and the residue, consisting of the crude 'Barton ester' **133**, was immediately taken up into anhydrous de-gassed benzene and irradiated with one sun lamp (300 W) in the presence of *tert*-butyl thiol (0.83 mL, 7.4 mmol) for 2 hours. The solution was taken to dryness and the residue purified by flash chromatography to give 0.42 g, 65% of the cyclopropane **134** as a colourless oil; R_f 0.26 (3:97 ethyl acetate:hexanes); IR (neat) 3064, 2997, 2952, 2869, 1689, 1598, 1580 cm^{-1}; ^1H NMR (300 MHz) δ 0.31-0.36 (m, 2H), 0.62-0.64 (m, 1H), 0.79-0.90 (m, 1H), 1.06 (d, J = 6.0 Hz, 3H), 2.84 (dd, J = 16.5, 6.6 Hz, 1H), 2.91 (dd, J = 10.5, 6.6 Hz, 1H), 7.41-7.47 (m, 2H), 7.51-7.56 (m, 1H), 7.92-7.96 (m, 2H); ^{13}C NMR (75 MHz) δ 12.8, 12.9, 15.0, 18.6, 43.3, 128.0, 128.4, 132.7, 136.9, 199.8; MS (EI) *m/z* (%): 174 (M^+, 8), 159 (2), 145 (2), 133 (1), 121 (1), 120 (12), 105 (100), 77 (50), 51 (15), 41 (13); HRMS Calcd for [$C_{12}H_{14}O$ + Na] 197.0942, found 197.0933.

(±) (2*S*)-2-[(1*S*,2*S*)-2-Methylcyclopropyl]-1-phenylpropan-1-one (135)

n-BuLi (2.05 M in hexane, 0.14 mL, 0.29 mmol) was added to a 0°C solution of anhydrous diisopropylamine (0.11 mL, 0.81 mmol) and THF (0.2 mL) under N_2. After stirring for 10 minutes at 0°C, a solution of the cyclopropane **134** (50 mg, 0.29 mmol) in anhydrous THF (2 mL) was added. The solution was stirred for a further 30 minutes, maintaining the temperature at 0°C, before the addition of MeI (0.054 mL, 0.86 mmol). The solution was warmed to ambient temperature and partitioned between sat. aqueous ammonium chloride (5 mL) and diethyl ether (10 mL). The organic extract was separated, washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography to give 43 mg, 80% of **135** as a 1:1 mixture of two diastereomers. Colourless oil; R_f 0.30 (3:97 ethyl acetate:hexanes); ^1H NMR (300 MHz) δ 0.20-0.37 (m, 2H), 0.50-0.66 (m, 1H), 0.70-0.80 (m, 1H), 0.92 and 1.05 (both d, J = 5.7 Hz, 3H), 1.24 and 1.28 (both d, J = 6.9 Hz, 3H), 2.79-2.93 (m, 1H), 7.43-7.49 (m, 2H), 7.53-7.55 (m, 1H), 7.89-7.92 (m, 2H); ^{13}C NMR (75 MHz) δ 11.8, 11.9, 12.7, 12.8, 16.8, 17.2, 18.5, 18.9, 23.2, 23.3, 44.78, 44.81, 128.2, 128.3, 128.5, 132.68, 132.74, 137.1, 137.2, 204.1, 204.3; MS (EI) *m/z* (%): 188 (M^+, 11), 173 (4), 159 (3), 145 (1), 134 (24), 120 (3), 115 (1), 105 (100), 83 (21), 77 (30), 67 (2), 55 (31), 41 (8); HRMS Calcd for [$C_{13}H_{16}O$ + Na] 211.1099, found 211.1093.

Steroidal Compounds

Methyl (4*S*)-4-[(3*S*, 5*S*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-3,12-dihydroxy-10,13-dimethyl-perhydrocyclopenta[*a*]phenanthren-17-yl] pentanoate (138)[258,259]

A solution of deoxycholic acid (5 g, 0.13 mol) in methanol (200 mL) was heated under reflux in the presence of Dowex-H^+ (0.5 g) for 16 hours. The cooled solution was filtered and the mother liquor taken to dryness *in vacuo*. The residue was taken up into diethyl ether (40 mL) and washed with aqueous sodium hydrogen carbonate solution (5%, 2 x 40mL) followed by water (40 mL). The organic phase was dried (Na_2SO_4), filtered and the solvent evaporated *in vacuo* to give 4.88 g, 94% of the methyl ester **138** as white crystals; m.p. 62-64°C (lit.[258] m.p. 75-86°C); R_f 0.59 (100% ethyl acetate); ^{1}H NMR (300 MHz) δ 0.68 (s, 3H), 0.91 (s, 3H), 0.97 (d, J = 6.2 Hz, 3H), 1.0-2.0 (m, 26H), 2.30 (m, 2H), 3.61 (m, 1H), 3.67 (s, 3H), 3.98 (br s, 1H); ^{13}C NMR (75 MHz) δ 12.7, 17.3, 23.2, 23.6, 26.1, 27.1, 27.4, 28.7, 30.5, 30.9, 31.1, 33.7, 34.1, 35.1, 35.2, 36.1, 36.5, 42.1, 46.5, 47.3, 48.3, 51.5, 71.8, 73.1, 174.7.[258,259]

Methyl (4*S*)-4-[(3*S*, 5*S*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-3-{[1-(*tert*-butyl)-1,1-dimethyl-silyl]oxy} – 12 – hydroxy - 10,13 – dimethylperhydrocyclopenta [*a*] phenanthren-17-yl] pentanoate (140)

To a solution of **138** (4 g, 9.8 mmol) in anhydrous DMF (10 mL) was added TBDMSCl (3.56 g, 24 mmol) and imidazole (3.34 g, 49 mmol). The solution was stirred at 20°C for 16 hours under a nitrogen atmosphere. The white solid formed was dissolved in hexane (50 mL) and the resulting solution washed with aqueous sodium hydrogen carbonate solution (5%, 50 mL) followed by water (50 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The residue was recrystallised from hexane to give 3.53 g, 69% of the mono-protected steroid **140** as white needles; m.p. 108-109.5°C; R_f 0.56 (1:4 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 0.05 (s, 6H), 0.67 (s, 3H), 0.88 (s, 9H), 0.89 (s, 3H), 0.97 (d, J = 6.0 Hz, 3H), 1.0-1.9 (m, 24H), 2.23 (m, 1H), 2.39 (m, 1H), 3.57 (m, 1H), 3.66 (s, 3H), 3.96 (br s, 1H); ^{13}C NMR (50 MHz) δ -4.7, 12.7, (14.0), 17.2, 18.2, (22.6), 23.2, 23.6, 25.9, 26.1, 27.2, 27.4, 28.7, 30.9, 31.0, (31.5), 33.6, 34.1, 35.0, 35.4, 36.1, 36.8, 42.3, 46.5, 47.2, 48.2, 51.3, 72.7, 73.01, 174.6; MS (EI) *m/z* (%): 549 ($[M+CO]^+$, 8), 521 (4), 463 (2), 446 (11), 404 (4), 371 (48), 321 (1), 277 (2), 229 (3), 215 (7), 161 (8), 121 (14), 75 (100), 43 (64). The reaction was repeated at both 40 and 70°C but

no double-protected steroid **139** was obtained. The 3' mono-protected steroid has been reported in the literature[260] but no data was available on this compound.

(4*S*)-4-[(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-3,12-Di(acetyloxy)-10,13-dimethyl-perhydrocyclopenta[a]phenanthren-17-ly]pentanoic acid (141)[261-264]

To a suspension of deoxycholic acid (10 g, 25 mmol) in acetic anhydride (20 mL) and pyridine (30 mL) at 0°C was added 4-DMAP (1.25 g, 10 mmol). The reaction mixture was warmed to 20°C and stirred for 3.5 hours at this temperature. The solution was concentrated *in vacuo* and the residue placed in diethyl ether (45 mL) and washed with aqueous hydrogen chloride (0.15 M, 45 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 11.73 g, 97% of the diacetate **141** as pale yellow fluffy crystals; m.p. 79-82°C (lit.[261] m.p. 84-85°C); R_f 0.65 (100% ethyl acetate); This compound was unable to be recrystallised; IR (nujol) 3125-3420, 1738, 1732, 1706 cm-^{1}; ^{1}H NMR (200 MHz) δ 0.73 (s, 3H), 0.82 (d, J = 6.0 Hz, 3H), 0.91 (s, 3H), 1.00-2.00 (m, 25H), 2.04 (s, 3H), 2.11 (s, 3H), 2.30 (m, 2H), 4.71 (m, 1H), 5.09 (br s, 1H); ^{13}C NMR (50 MHz) δ 12.2, 17.3, 21.1, 21.2, 22.9, 23.3, 25.5, 25.7, 26.4, 26.7, 27.1, 30.5, 30.8, 32.1, 33.9, 34.2, 34.5, 35.5, 34.6, 41.7, 44.9, 47.4, 49.3, 74.1, 75.8, 170.4, 170.5, 179.4.[261-264]

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-17-[(1*S*)-4-hydroxy-1-methyl-butyl]-10,13-dimethylperhydrocyclopenta[*a*]phenanthren-3-yl acetate (142)[265]

A solution of BH_3.THF (9.23 mL, 1 M, 9.23 mmol) was added dropwise over 10 minutes to a solution of **141** (4.0 g, 8.39 mmol) in anhydrous THF (160 mL). After stirring for 16 hours at 20°C the reaction was quenched with aqueous hydrogen chloride (0.5 M, 40 mL). The resulting solution was extracted with diethyl ether (3 x 100 mL) and the combined organic extracts washed with aqueous hydrogen chloride (0.15 M, 1 x 150 mL), water (1 x 100 mL), aqueous sodium carbonate solution (10%, 3 x 150 mL), water (1 x 150 mL) and finally brine (1 x 150 mL). The organic layer was dried (Na_2SO_4), filtered and taken to dryness to give 3.35 g, 86% of the alcohol **142** as white fluffy crystals; m.p. 68-70°C; R_f 0.56 (3:2 ethyl acetate:hexanes); IR (nujol) 3140-3580, 1737, 1728 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.73 (s, 3H), 0.82 (d, J = 6.4 Hz, 3H), 0.91 (s, 3H), 0.95-2.00 (m, 26H), 2.04 (s, 3H), 2.10 (s, 3H), 3.62 (m, 2H), 4.70 (m, 1H), 5.09 (br s, 1H); ^{13}C NMR (50 MHz) δ 12.4, 17.9, 21.3, 21.4, 23.0, 23.4, 25.6, 25.9, 26.6, 26.9, 27.4, 29.3, 31.7, 32.3, 34.0, 34.4, 34.7, 34.9, 35.7, 41.8, 45.0, 47.8, 49.4, 63.4, 74.2, 76.0, 170.4, 170.52; MS (EI) *m/z* (%): 447 ([M-CH_3]$^+$, 30), 403 (100), 344 (34).[265]

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-1-methyl-4-oxobutyl]perhydrocyclopenta[*a*]phenanthrene-3-yl acetate (143)

Method 1: PCC Oxidation

To a solution of **142** (3.35 g, 7.24 mmol) in anhydrous dichloromethane (15 mL) was added PCC (3.5 g, 16.2 mmol, 2.24 equiv.). After stirring at 20°C for 2 hours the insoluble portion was removed by filtration over florisil. The florisil was washed with dichloromethane (100 mL) followed by 40% ethyl acetate in hexanes (200 mL). The combined filtrates were concentrated to furnish 2.6 g, 78% of the desired aldehyde **143** as white sticky crystals; m.p. 62-65°C; It was used without further purification; R_f 0.50 (3:7 ethyl acetate:hexanes); ^{1}H NMR (200 MHz) δ 0.73 (s, 3H), 0.81 (d, J = 6.2 Hz, 3H), 0.91 (s, 3H), 0.95-2.00 (m, 24H), 2.04 (s, 3H), 2.11 (s, 3H), 2.40 (m, 2H), 4.70 (m, 1H), 5.08 (br s, 1H), 9.77 (s, 1H); ^{13}C NMR (50 MHz) δ 12.3, 17.6, 21.3, 21.3, 23.0, 23.3, 25.6, 25.8, 26.5, 26.8, 27.3, 27.7, 32.2, 34.0, 34.3, 34.6, 35.6, 40.8, 41.8, 43.0, 45.0, 47.6, 49.4, 74.1, 75.8, 170.3, 170.4, 202.7.[265,266]

Method 2: Swern oxidation

Dimethylsulfoxide (0.52 mL, 7.35 mmol) was added to a -78°C solution of oxalyl chloride (0.32 mL, 3.67 mmol) and dichloromethane (12 mL) under a nitrogen atmosphere. After 10 minutes of stirring, a solution of **142** (0.85 g, 1.84 mmol) in dichloromethane (8 mL) was added and the mixture stirred for a further 15 minutes at -78°C. Triethylamine (2.05 mL) was added to the reaction mixture and after 5 minutes the solution was warmed to 20°C. The reaction mixture was diluted with water (30 mL) and the aqueous layer separated and extracted with dichloromethane (30 mL). The combined organic extracts were washed with water until the washings were neutral, dried (Na_2SO_4), filtered and concentrated to give the crude product as a yellow oil. Purification by flash chromatography gave 0.66 g, 78% of the desired aldehyde **143** as white fluffy crystals; m.p. 62-65°C; The crude aldehyde was used without further purification. The ^{1}H and ^{13}C NMR data was identical to that given above for the same compound.

Synthesis of sterol dienes 146a-c from steroid aldehyde 143

General procedure

Potassium *tert*-butoxide (1.4-1.5 equiv.) was added to a 0°C solution of the desired phosphonium salt (1.2-1.3 equiv.) in anhydrous THF (~10 mL / g of ylide) under nitrogen. After 10 minutes of stirring, a solution of the desired aldehyde (1 equiv.) in THF (10 mL /

g) was added dropwise. The resulting solution was stirred for 16 hours protected from light. The solvent was removed *in vacuo* and the residue taken up into dichloromethane. The organic phase was washed with water, dried (Na_2SO_4), filtered, and taken to dryness to give the crude 1,3-butadiene. Purification by flash chromatography (1:9 ethyl acetate:hexane to 1:4 ethyl acetate:hexanes) gave the desired pure 1,3-butadiene.

Cinnamyltriphenylphosphonium chloride (144a)

To a solution of cinnamyl chloride (60.0 g, 393 mmol) in anhydrous toluene (540 mL) was added triphenylphosphine (108.3 g, 413 mmol). The solution was heated under reflux for 20 hours under an inert atmosphere (N_2). The precipitate was collected, washed with toluene (200 mL), hexanes (2 x 300 mL) and diethyl ether (400 mL) and dried to give 122.7 g, 74% of cinnamyl phosphonium salt **144a** as a pale yellow powder; m.p. 225–226.5 °C (lit.[267] 225–226 °C).

Crotyltriphenylphosphonium bromide (144b)

Crotyl bromide (20.25 g, 150 mmol) and triphenylphosphine (39.34 g, 150 mmol) were dissolved in anhydrous toluene (150 mL) and the reaction mixture stirred at ambient temperature for 5 days under N_2. The precipitated salt was collected by suction filtration, washed with toluene (100 mL) followed by diethyl ether (100 mL) and dried *in vacuo* to afford 42.4 g, 71% of **144b** as a white powder; m.p. 224-228°C.

Allyltriphenylphosphonium chloride (144c)

A solution of allyl chloride (5.0 g, 65 mmol) and triphenylphosphine (21.42 g, 82 mmol) in anhydrous toluene (150 mL) was heated under reflux for 16 hours under a N_2 atmosphere. The precipitated salt was collected by suction filtration, washed with toluene (100 mL) followed by hexanes (100 mL) and dried *in vacuo* to afford 10.4 g, 47% of **144c** as a pale brownish powder; m.p. 226-230°C (lit.[268] 229-232°C).

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-(4*Z*,6*E*)-1-methyl-7-phenyl-4,6-heptadienyl] perhydrocyclopenta[*a*]phenanthrene–3-yl acetate and

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-(4*E*,6*E*)-1-methyl-7-phenyl-4,6-heptadienyl] perhydrocyclopenta [*a*] phenanthrene–3-yl acetate (146a)

To the cinnamyl phosphonium salt **144a** (1.35 g, 3.26 mmol) and potassium *tert*-butoxide (0.44 g, 3.91 mmol) in THF (25 mL) was added aldehyde **143** (1.2 g, 2.61 mmol) in THF

(10 mL). 1,3-butadienes **146a** were obtained as white crystals (0.9 g, 62%) consisting of a 2:3 mixture of 4*Z*,6*E*^{a}:4*E*,6*E*^{b} isomers; m.p. 57-60°C; R_f 0.50 (1:4, ethyl acetate:hexanes); ^{1}H NMR (600 MHz): δ 0.73 (s, 6H)^{a,b}, 0.83 (d, J = 6.6 Hz, 3H)^b, 0.88 (d, J = 6.6 Hz, 3H)^a, 0.91 (s, 6H)^{a,b}, 0.99-1.04 (m, 2H)^{a,b}, 1.06-1.14 (m, 6H)^{a,b}, 1.16-1.30 (m, 6H)^{a,b}, 1.37-1.73 (m, 28H)^{a,b}, 1.79-1.89 (m, 6H)^{a,b}, 2.00-2.32 (m, 4H)^{a,b}, 2.03 (s, 6H)^{a,b}, 2.11 (s, 6H)^{a,b}, 4.68-4.73 (m, 2H)^{a,b}, 5.09-5.12 (m, 2H)^{a,b}, 5.50 (dt, J = 10.8, 7.2 Hz, 1H)^a, 5.80 (dt, J = 15.0, 7.2 Hz, 1H)^b, 6.13 (dd, J = 10.2, 10.2 Hz, 1H)^a, 6.20 (dd, J = 15.0, 10.2 Hz, 1H)^b, 6.43 (d, J = 15.6 Hz, 1H)^b, 6.52 (d, J = 15.6 Hz, 1H)^a, 6.74 (dd, J = 15.6, 10.2 Hz, 1H)^b, 7.04 (dd, J = 15.6, 10.2 Hz, 1H)^a, 7.18-7.23 (m, 2H)^{a,b}, 7.28-7.33 (m, 4H)^{a,b}, 7.36-7.41 (m, 4H)^{a,b}; ^{13}C NMR (75 MHz) δ 12.3, 17.66, 17.73, 21.2, 21.3, 23.0, 23.4, 24.6, 25.5, 25.8, 26.5, 26.8, 27.4, 29.4, 32.2, 33.9, 34.3, 34.6, 34.7, 34.8, 35.4, 35.6, 35.7, 41.7, 44.9, 47.5, 47.7, 49.4, 74.1, 75.9, 124.2, 126.0, 126.2, 127.0, 127.2, 128.4, 128.5, 129.3, 129.9, 130.3, 131.9, 133.3, 136.0, 137.5, 137.6, 170.36, 170.44; MS (EI) *m/z* (%): 561 (M^+, 9), 560 (20), 500 (19), 446 (18), 425 (4), 368 (4), 315 (5), 284 (8), 255 (13), 184 (8), 156 (93), 91 (37), 55 (51), 43 (100); HRMS Calcd for $C_{37}H_{52}O_4$ 560.3865, found 560.3872.

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-(4*Z*,6*E*)-1-methyl-4,6-octadienyl]perhydrocyclopenta[*a*]phenanthren-3-yl acetate

and

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-(4*E*,6*E*)-1-methyl-4,6-octadienyl]perhydrocyclopenta[*a*]phenanthren-3-yl acetate (146b)

To the crotyl phosphonium salt **144b** (0.90 g, 2.28 mmol) and potassium *tert*-butoxide (0.31 g, 2.74 mmol) in THF (25 mL) was added aldehyde **143** (0.84 g, 1.82 mmol) in THF (10 mL). 1,3-butadienes **146b** were obtained as sticky pale yellow crystals (0.54 g, 59%) consisting of a 2:3 mixture of 4*Z*,6*E*^{a}:4*E*,6*E*^{b} isomers; R_f 0.56 (1:4 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 0.72 (s, 3H)^b, 0.73 (s, 3H)^a, 0.81 (d, J = 6.3 Hz, 3H)^b, 0.84 (d, J = 6.6 Hz, 3H)^a, 0.91 (s, 6H)^{a,b}, 0.95-1.91 (m, 54H)^{a,b}, 1.95-2.31 (m, 4H)^{a,b}, 2.03 (s, 6H)^{a,b}, 2.09 (s, 3H)^b, 2.10 (s, 3H)^a, 4.66-4.74 (m, 2H)^{a,b}, 5.08-5.10 (m, 2H)^{a,b}, 5.25 (dt, J = 10.8, 7.5 Hz, 1H)^a, 5.46-5.62 (m, 2H)^b, 5.61-5.72 (m, 1H)^a, 5.92 (dd, J = 10.8, 10.8 Hz, 1H)^a, 5.92-6.06 (m, 2H)^b, 6.25-6.39 (m, 1H)^a;

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-(4*Z*,6*E*)-1-methyl-4,6-heptadienyl]perhydrocyclopenta[*a*]phenanthren-3-yl acetate

and

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-(4*E*,6*E*)-1-methyl-4,6-heptadienyl]perhydrocyclopenta[*a*]phenanthren-3-yl acetate (146c)

To the allyl phosphonium salt **144c** (1.01 g, 2.98 mmol) and potassium *tert*-butoxide (0.40 g, 3.58 mmol) in THF (25 mL) was added aldehyde **143** (1.1 g, 2.39 mmol) in THF (10 mL). 1,3-butadienes **146c** were obtained as white sticky crystals (0.433 g, 37%) consisting of a 9:11 mixture of $4Z,6E^a$:$4E,6E^b$ isomers; R_f 0.58 (1:4 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 0.72 (s, 6H)^{a,b}, 0.82 (d, J = 6.6 Hz, 3H)^b, 0.84 (d, J = 6.6 Hz, 3H)^a, 0.91 (s, 6H)^{a,b}, 0.95-2.30 (m, 52H)^{a,b}, 2.03 (s, 6H)^{a,b}, 2.10 (s, 6H)^{a,b}, 4.64-4.76 (m, 2H)^{a,b}, 4.93-5.20 (m, 6H)^{a,b}, 5.42 (dt, J = 10.2, 7.8 Hz 1H)^a, 5.68 (dt, J = 15.0, 7.2 Hz, 1H)^b, 5.94-5.08 (m, 2H)^{a,b}, 6.30 (dt, J = 17.1, 10.2 Hz, 1H)^b, 6.63 (m, 1H)^a.

Synthesis of steroidal phosphonium salt 148

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-17-[(1*S*)-4-iodo-1-methylbutyl]-10,13-dimethylperhydrocyclopenta[*a*]phenanthren-3-yl acetate (147)

To a 0°C solution of **142** (2.12 g, 4.58 mmol) in dichloromethane (25 mL) was added triphenylphosphine (1.5 g, 5.73 mmol) and imidazole (0.39 g, 5.73 mmol) followed by iodine (1.45 g, 5.73 mmol, 1.25 equiv.) in small portions. The solution was warmed to 20°C and stirred at that temperature for 16 hours. The reaction was quenched by aqueous sodium thiosulphate (5%, 30 mL). The organic layer was separated, washed with water (30 mL), dried (Na_2SO_4), filtered and taken to dryness. The residue was placed in diethyl ether and the insoluble portion (TPPO, 0.53 g) removed by filtration. The diethyl ether extract was concentrated *in vacuo* and the residue purified by flash chromatography to give 1.5 g, 58% of the iodo compound **147** as white sticky crystals; m.p. 27-30°C; R_f 0.43 (1:4, ethyl acetate:hexanes); IR (nujol) 3445, 1739, 1715 cm^{-1}; ^{1}H NMR (600 MHz) δ 0.73 (s, 3H), 0.81 (d, J = 6.6 Hz, 3H), 0.91 (s, 3H), 0.99-1.04 (m, 1H), 1.08-1.15 (m, 3H), 1.20-1.30 (m, 3H), 1.36-1.40 (m, 1H), 1.42-1.49 (m, 5H), 1.54-1.72 (m, 9H), 1.78-1.90 (m, 4H), 2.03 (s, 3H), 2.10 (s, 3H), 3.13 (ddd, J = 9.6, 7.2, 7.2 Hz, 1H), 3.19 (ddd, J = 9.6, 7.2, 7.2 Hz, 1H),, 4.67-4.73 (m, 1H), 5.07-5.08 (m, 1H); ^{13}C NMR (50 MHz) δ 7.6, 12.4, 17.9, 21.3, 21.4, 23.0, 23.4, 25.57, 25.8, 26.6, 26.8, 27.4, 30.2, 32.2, 34.0, 34.3, 34.4, 34.7, 35.6, 36.6, 41.8, 45.0, 47.6, 49.4, 74.1, 75.8, 170.3, 170.4. MS (EI) *m/z* (%): 531 ([M-C_2H_2O]$^+$, 4), 495 (4),

480 (100), 417 (4), 376 (2), 356 914), 324 (8), 277 (25), 244 (5), 209 (3), 159 (3), 147 (4), 91 (4), 43 (27); Anal. Calcd for $C_{28}H_{45}O_4I$: C, 58.74; H, 7.92; Found C, 58.76; H, 7.99.

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-1-methyl-4-(1,1,1-triphenylphosphonio-iodosalt)butyl] perhydrocyclopenta [*a*] phenanthren-3-yl acetate (148)

The iodo sterol **147** (3.48 g, 6.08 mmol) and triphenylphosphine (6.38 g, 1.17 mmol) were melted together by heating to 130°C for 1.5 hours with stirring. Diethyl ether (5 x 40 mL) was added to the cooled flask and decanted from the salt once it had been finely broken up. The white powder was placed in fresh diethyl ether (50 mL) and stirred overnight. The solution was filtered to give 4.11 g, 81% of pure steroidal phosphonium salt **148** as a fine white powder; m.p. 134-136°C; ^{1}H NMR (300 MHz) δ 0.65 (d, J = 5.4 Hz, 3H), 0.68 (s, 3H), 0.89 (s, 3H), 0.94-1.94 (m, 26H), 2.03 (s, 3H), 2.07 (s, 3H), 0.71 (m, 2H), 4.69 (m, 1H), 5.03 (br s, 1H), 7.77 (m, 15H); ^{13}C NMR (75 MHz) δ 12.3, 15.0, 17.4, 19.6, 19.7, 21.2, 22.6, 22.8, 23.1, 23.6, 25.4, 25.5, 26.3, 26.6, 27.2, 32.0, 33.7, 34.1, 34.5, 34.7, 35.4, 36.2, 36.5, 41.6, 47.7, 49.0, 65.5, 73.9, 75.6, 117.0, 188.7, 130.2, 130.5, 133.3, 133.5, 134.9, 134.9, 170.2, 170.3; ^{31}P NMR (121 MHz): δ 24.4.

Synthesis of Steroidal 1,3-butadienes 146a-b using the steroidal phosphonium salt 148

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-(4*Z*,6*E*)-1-methyl - 7 -phenyl - 4,6 - heptadienyl] perhydrocyclopenta [*a*] phenanthrene–3-yl acetate

and

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-(4*E*,6*E*)-1-methyl - 7 -phenyl - 4,6 - heptadienyl] perhydrocyclopenta [*a*] phenanthrene–3-yl acetate (146a)

The steroid phosphonium salt **148** (2.5 g, 3 mmol) and potassium *tert*-butoxide (0.4 g, 3.6 mmol) were stirred at room temperature for 15 minutes in anhydrous THF (30 mL) and under N_2. The solution was cooled to 0°C and a solution of *trans*-cinnamaldehyde (0.32 g, 2.4 mmol) in anhydrous THF (10 mL) added dropwise. The solution was warmed to 20°C and stirred for 3 days at this temperature. The solution was concentrated and the residue purified by flash chromatography (1:4 ethyl acetate:hexanes). 1,3-Butadienes **146a** were obtained as a 17:3 mixture of 4*Z*,6*E*^{a}:4*E*,6*E*^{b} isomers (0.534 g, 40%); The ^{1}H NMR was consistent with that previously quoted. 4*Z*,6*E* isomer: ^{13}C NMR (75 MHz) δ 12.4, 17.8,

21.37, 21.43, 23.1, 23.5, 24.7, 25.6, 25.9, 26.6, 26.9, 27.5, 32.3, 34.0, 34.4, 34.7, 34.9, 35.7, 35.8, 41.8, 45.0, 47.8, 49.5, 74.2, 76.0, 124.3, 126.3, 127.3, 128.6, 132.0, 133.4, 137.6, 170.5, 170.6.

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-(4*Z*,6*E*)-1-methyl-4,6-octadienyl]perhydrocyclopenta[*a*]phenanthren-3-yl acetate
and
(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-[(1*S*)-(4*E*,6*E*)-1-methyl-4,6-octadienyl]perhydrocyclopenta[*a*]phenanthren-3-yl acetate (146b)

The steroid phosphonium salt **148** (1.0 g, 1.2 mmol) and potassium *tert*-butoxide (0.16 g, 1.44 mmol) were stirred at room temperature for 15 minutes in anhydrous THF (15 mL) and under N_2. The mixture was cooled to 0°C and a solution of crotonaldehyde (0.067 g, 0.96 mmol) in anhydrous THF (5 mL) added dropwise. The solution was warmed to 20°C and stirred for 3 days at this temperature. The solution was concentrated and the residue purified by flash chromatography (1:4 ethyl acetate:hexanes). 1,3-Butadienes **146b** were obtained as a 97:3 mixture of $4Z,6E^a$:$4E,6E^b$ isomers (0.153 g, 32%); Data for 4*Z*,6*E* isomer: ^{1}H NMR (300 MHz) δ 0.73 (s, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.91 (s, 3H), 0.95-1.95 (m, 26H), 2.00-2.25 (m, 2H), 2.03 (s, 3H), 2.11 (s, 3H), 4.65-4.76 (m, 1H), 5.09-5.11 (m, 1H), 5.25 (dt, J = 10.8, 7.5 Hz, 1H), 5.61-5.73 (m, 1H), 5.92 (dd, J = 10.8, 10.8 Hz, 1H), 6.25-6.39 (m, 1H); ^{13}C NMR (75 MHz) δ 12.4, 17.8, 18.2, 21.3, 21.4, 23.0, 23.5, 24.3, 25.6, 25.9, 26.6, 26.9, 27.4, 32.3, 34.0, 34.4, 34.7, 34.8, 35.7, 35.8, 41.8, 45.0, 47.8, 49.5, 74.2, 76.0, 126.9, 128.3, 129.0, 129.9, 170.4, 170.5.

(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-12-(Acetyloxy)-10,13-dimethyl-17-(1*S*)-1-methyl- 3 -[(±)-(3*R*,6*S*)-6-phenyl-3,6-dihydro-1,2-dioxin-3-yl]propylperhydrocyclopenta[*a*]phenanthren-3-yl acetate (149) and (150)

A solution of 1,3-butadienes **146a** (51 mg, 0.091 mmol) in $CDCl_3$ (1 mL) was irradiated in an NMR tube (2 mL) (placed inside a condenser) in the presence of Rose Bengal *bis*(triethylammonium) salt (5 mg) and oxygen with a 500 W tungsten halogen lamp for 3 hours. The solvent was removed *in vacuo* and the residue purified by flash chromatography to give 36.4 mg, 67% of a 1:1 mixture of diastereomeric 1,2-dioxines **149**^{a} and **150**^{b} as a pale yellow oil; R_f 0.37 (1:4 ethyl acetate:hexanes); ^{1}H NMR (600 MHz) δ 0.72 (s, 6H)^{a,b}, 0.81 (d, J = 6.6 Hz, 3H)^c, 0.82 (d, J = 6.6 Hz, 3H)^c, 0.99-1.88 (m, 52H)^{a,b}, 2.03 (s, 6H)^{a,b}, 2.09 (s, 3H)^c, 2.10 (s, 3H)^c, 4.49-4.54 (m, 2H)^{a,b}, 4.67-4.73 (m, 2H)^{a,b}, 5.08-5.09 (m, 2H)^{a,b}, 5.50-5.51 (m, 2H)^{a,b}, 6.04-6.12 (m, 4H)^{a,b}, 7.34-7.39 (m, 10H)^{a,b} (^{c} Signal comes

from only one diastereomer but could not be assigned); ^{13}C NMR (150 MHz) δ 12.4, 17.7, 17.8, 21.38, 21.44, 23.1, 23.4, 25.6, 25.8, 26.6, 26.9, 27.4, 29.7, 29.8, 31.2, 31.5, 32.3, 34.0, 34.4, 34.7, 34.8, 35.1, 35.7, 41.8, 45.0, 47.8, 47.9, 49.42, 49.44, 74.2, 75.9, 76.0, 78.5, 79.0, 80.18, 80.20, 126.36, 126.44, 128.48, 128.49, 128.54, 128.58, 128.66, 128.71, 128.74, 128.8, 137.65, 137.72, 170.47, 170.48, 170.55, 170.56; MS (EI) *m/z* (%): 574 ([M-H_2O]$^+$, 78), 560 (1), 514 (5), 454 (3), 416 (3), 356 (9), 315 (3), 283 (1), 255 (14), 197 (6), 170 (42), 105 (60), 84 (100), 43 (48); HRMS unable to be Calcd for $C_{37}H_{52}O_6$ since no M^+ was observable.

Benzyl 2-(2–benzoyl–3-(3*S*)–3-[(3*S*, 5*R*, 10*R*, 12*R*, 13*S*, 14*R*, 17*S*)-3,12-di(acetyloxy)-10,13-dimethylperhydrocyclopenta[*a*]phenanthren-17-yl]butylcyclopropyl)acetate (151)

A solution containing the diastereomeric 1,2-dioxines **149** and **150** (130 mg, 0.22 mmol) and benzyl ester ylide (100 mg, 0.24mmol) in $CDCl_3$ (4 mL) was heated at 65°C. The solution was monitored for consumption of the 1,2-dioxines by ^{1}H NMR analysis. After 14 days the solvent was removed *in vacuo* and the residue purified by flash chromatography to give 60 mg, 38% of cyclopropyl steroid **151** as white fluffy crystals consisting of two diastereomers[a,b]; R_f 0.57 (3:7 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 0.64 (s, 3H)[c], 0.68 (s, 3H)[c], 0.78 (d, J = 6.3 Hz, 3H)[c], 0.79 (d, J = 6.3 Hz, 3H)[c], 0.90 (s, 6H)[a,b], 0.94-1.90 (m, 56H)[a,b], 2.03 (s, 3H)[c], 2.04 (s, 3H)[c], 2.09 (s, 6H)[a,b], 2.27 (dd, J = 4.2, 4.2 Hz, 1H)[c], 2.30 (dd, J = 4.5, 4.5 Hz, 1H)[c], 2.47 (dd, J = 15.9, 8.1 Hz, 1H)[c], 2.48 (dd, J = 15.9, 8.1 Hz, 1H)[c], 2.64 (dd, J = 15.9, 6.9 Hz, 1H)[c], 2.65 (dd, J = 15.9, 6.6 Hz, 1H)[c], 4.64-4.76 (m, 2H)[a,b], 5.08-5.09 (m, 2H)[a,b], 5.11 (s, 4H)[a,b], 7.28-7.30 (m, 10H)[a,b], 7.41-7.48 (m, 4H)[a,b], 7.52-7.58 (m, 2H)[a,b], 7.92-7.96 (m, 4H)[a,b] ([c] Signal comes from only one diastereomer but could not be assigned); ^{13}C NMR (75 MHz) δ 12.3, 12.4, 17.8, 17.9, 21.3, 21.4, 23.0, 23.4, 24.6, 25.6, 25.9, 26.2, 26.6, 26.9, 27.5, 30.9, 31.5, 31.7, 32.3, 33.1, 34.0, 34.4, 34.7, 34.9, 35.4, 35.7, 41.8, 45.0, 47.7, 47.8, 49.4, 66.5, 74.2, 75.9, 128.0, 128.1, 128.2, 128.5, 128.5, 128.6, 132.6, 133.1, 135.7, 137.9, 170.4, 170.5, 171.9, 199.0; MS (EI) *m/z* (%): 665 ([M-CO_2CH_3]$^+$, 5), 604 (1), 574 (4), 513 (7), 478 (13), 388 (5), 105 (27), 91 (100), 43 (44); HRMS unable to be Calcd for $C_{46}H_{60}O_7$ since no M^+ was observable.

Investigations into the ring-opening of steroid 1,2-dioxines 149 and 150 using Co(SALEN)$_2$

To a solution consisting of a 1:1 mixture of 1,2-dioxines **149** and **150** (75 mg, 0.13 mmol) in $CDCl_3$ (1 mL) was added Co(SALEN)$_2$ (0.82 mg, 2 mol%). A carbon spectrum was

taken at 30 minute intervals over 6 hours. The relative consumption of the two diastereomers was determined by comparing the integrations of signals at 78.5 and 78.9 ppm. The two diastereomers were consumed at similar rates.

Attempts to kinetically resolve steroid 1,2-dioxines 149 and 150 using a chiral cobalt catalyst

To a solution consisting of a 1:1 mixture of 1,2-dioxines **149** and **150** (48 mg, 8.1 x 10^{-2} mmol) in $CDCl_3$ (1 mL) was added *S,S* bornyl catalyst[161] (1.4 mg, 2 mol%). After stirring at ambient temperature for 2 days no reaction had taken place so additional catalyst was added (1.0 mg, 1.4 mol %) and the reaction vessel heated in a 50°C oil bath. A carbon spectrum taken 24 hours later indicated that the two diastereomers were consumed at similar rates by comparison of the integrations of the signals at 78.5 and 78.9 ppm.

6.3 Compounds discussed in Chapter 3

Octyltriphenylphosphine iodide (155)

A solution of 1-iodooctane (40.0 g = 30.08 mL, 167 mmol) and triphenylphosphine (45.88 g, 175 mmol) in acetonitrile (260 mL) was heated under reflux for 16 hours under a N_2 atmosphere. Acetonitrile was removed under reduced pressure and the resulting thick colourless oil placed in diethyl ether (200 mL) for 16 hours. The diethyl ether was decanted and fresh diethyl ether was added to the thick oil for an additional 16 hours. Once again the diethyl ether was decanted and the salt was dried under reduced pressure to afford 75.2 g, 90% of octyltriphenylphosphine iodide as a colourless oil. On standing for 10-14 days octyltriphenylphosphine iodide recrystallised out of the oil to give a white solid.

(1*E*,3*Z*) and (1*E*,3*E*)-1-Phenyl-1,3-undecadiene (156)[269]

To a solution of octyltriphenylphosphonium iodide **155** (23.93 g, 52.5 mmol) in anhydrous THF (280 mL) at ambient temperature and under a nitrogen atmosphere was added potassium *tert*-butoxide (6.88 g, 61.3 mmol). After stirring for 15 minutes the orange solution was cooled to 0°C and a solution of *trans*-cinnamaldehyde (5.79 g, 43.8 mmol) in anhydrous THF (50 mL) was added dropwise. The solution was allowed to warm to 20°C, stirred for 16 hours at this temperature, diluted with hexanes (300 mL) and filtered over silica. The silica was washed with 1:19 ethyl acetate:hexanes (300 mL). The combined filtrates were concentrated *in vacuo* and the residue purified by column chromatography to yield 6.68g, 67% of 1,3-butadienes **156**, in a ratio of 20:1, $1E,3Z^a$: $1E,3E^b$ as a colourless oil; R_f 0.55 (100% hexanes); IR (neat) 2926, 2854, 1681 (weak), 1644 (weak), 1596 (weak), 1494 (weak), 1466, 1448 cm^{-1}; ^1H NMR (300 MHz) δ 0.86-0.93 (m, 6H)^{a,b}, 1.28-1.48 (m, 20H)^{a,b}, 2.09-2.18 (m, 2H)^b, 2.24-2.32 (m, 2H)^a, 5.53 (dt, J = 10.5, 7.8 Hz, 1H)^a, 5.82 (dt, J = 15.0, 7.8 Hz, 1H)^b, 6.10-6.19 (m, 1H)^a, 6.16-6.24 (m, 1H)^b, 6.30 (d, J = 15.6 Hz, 1H)^b, 6.52 (d, J = 15.6 Hz, 1H)^a, 6.75 (dd, J = 15.6, 10.5 Hz, 1H)^b, 7.06 (ddd, J = 15.6, 11.1, 1.2 Hz, 1H)^a, 7.17-7.23 (m, 2H)^{a,b}, 7.28-7.33 (m, 4H)^{a,b}, 7.39-7.43 (m, 4H)^{a,b}; MS (EI) *m/z* (%): 228 (M^+, 52), 143 (67), 129 (100); HRMS Calcd for $C_{17}H_{24}$ 228.1878, found 228.1875.

3-Heptyl-6-phenyl-3,6-dihydro-1,2-dioxine (157)

Prepared by photolysis of 1,3-butadienes **156** by the general procedure for 1,2-dioxine synthesis. Yield 2.21 g, 59%; Colourless oil; R_f 0.38 (1:19 ethyl acetate:hexanes); IR (neat)

1683, 1494, 1455 cm^{-1}; ^1H NMR (200 MHz) δ 0.84-0.91 (m, 3H), 1.20-1.40 (m, 9H), 1.40-1.80 (m, 3H), 4.53-4.58 (m, 1H), 5.49-5.52 (m, 1H), 6.02-6.16 (m, 2H), 7.33-7.42 (m, 5H); ^{13}C NMR (50 MHz) δ 14.0, 22.6, 25.5, 29.2, 29.5, 31.8, 33.1, 78.5, 80.2, 126.3, 128.5, 128.6, 128.7, 128.9, 137.8; MS (EI) *m/z* (%): 260.3 (M^+, 10), 228.2 (100), 143.2 (46), 129.1 (95), 105.1 (40); HRMS Calcd for $C_{17}H_{24}O_2$ 260.1776, found 260.1765; Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29; Found C, 78.12; H, 9.34.

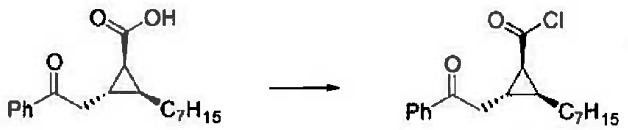
(±) *tert*-Butyl (1*R*,2*R*,3*R*)-2-heptyl-3-(2-oxo-2-phenylethyl)cyclopropane-1-carboxylate (158)

To a solution of 1,2-dioxine **157** (4.33 g, 16.6 mmol) in anhydrous dichloromethane (250 mL) was added LiBr (1.59 g, 18.3 mmol) and (*tert*-butoxycarbonylmethylene)-triphenylphosphorane **118** (8.76 g, 23.3 mmol). After stirring vigorously for 5 days at 20°C the reaction mixture was taken to dryness and the residue purified by flash chromatography to yield 3.07 g, 52% of cyclopropane **158** as a pale yellow oil; R_f 0.36 (1:9 ethyl acetate:hexanes); IR (neat) 1718, 1690, 1598, 1581 cm^{-1}; ^1H NMR (600 MHz) δ 0.87 (t, J = 7.8 Hz, 3H), 1.11 (dddd, J = 9.6, 6.6, 6.6, 6.6 Hz, 1H), 1.20-1.35 (m, 10H), 1.45 (s, 9H), 1.47-1.53 (m, 1H), 1.51 (dd, J = 9.6, 4.8 Hz, 1H), 1.59-1.64 (m, 1H), 1.65 (dddd, J = 4.8, 5.4, 6.6, 7.8 Hz, 1H), 2.72 (dd, J = 16.2, 7.8 Hz, 1H), 3.18 (dd, J = 16.2, 5.4 Hz, 1H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 7.91-7.93 (m, 2H); ^{13}C NMR (150 MHz) δ 14.1, 22.3, 22.6, 26.3, 26.7, 28.2, 29.1, 29.26, 29.32, 29.5, 31.8, 42.2, 80.2, 128.1, 128.6, 133.1, 136.7, 171.3, 198.7; MS (EI) *m/z* (%): 359 (M^+, 4), 285 (9), 243 (4), 120 (26), 105 (100); Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; Found C, 77.16; H, 9.40.

(±)-(1*R*,2*R*,3*R*)-2-Heptyl-3-(2-oxo-2-phenylethyl)cyclopropane-1-carboxylic acid (160)

Trifluoroacetic acid (3.5 mL) was added to a solution of ester **158** (0.91 g, 2.5 mmol) in dichloromethane (3.5 mL). The solution was stirred at 20°C for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue taken up into dichloromethane (40 mL). The organic phase was extracted with aqueous Na_2CO_3 (5%, 2 x 30 mL) and the combined aqueous phases acidified to pH 1 with conc. HCl. The precipitate was dissolved in dichloromethane and the organic phase separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 0.72 g, 92% of acid **160** as an off-white solid; The acid was recrystallised from heptane / dichloromethane to afford 0.55 g, 70% of pure **160** as white crystals; m.p. 85–86 °C; IR (neat) 2482-2739, 1787 (weak), 1681, 1597, 1580 cm^{-1}; ^1H NMR (600 MHz) δ 0.87 (t, J = 6.6 Hz, 3H), 1.18-1.42 (m, 12H), 1.54-1.66 (m, 3H), 1.74-1.83 (m, 1H), 2.85 (dd, J = 16.8, 7.2 Hz, 1H), 3.15 (dd, J = 16.8, 6.0 Hz, 1H), 7.43-7.49

(m, 2H), 7.54-7.60 (m, 1H), 7.91-7.94 (m, 2H), 9.60-10.90 (br s, 1H); ^{13}C NMR (75 MHz) δ 14.1, 22.6, 23.8, 24.9, 26.6, 29.16, 29.21, 29.23, 30.3, 31.8, 42.1, 128.1, 128.7, 133.2, 136.6, 178.6, 198.3; MS (EI) *m/z* (%): 302 (M^+, 16), 105 (100), 45 (92); Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67; Found C, 75.36; H, 8.76.



160 S1

Acid chloride S1

To a solution of cyclopropyl acid **160** (300 mg, 0.99 mmol) and DMF (1 drop) in anhydrous dichloromethane (15 mL) at 0°C under a nitrogen atmosphere was added oxalyl chloride (0.26 ml, 2.98 mmol) as a solution in anhydrous dichloromethane (15 mL). The solution was then stirred for 2 hours at 0°C then allowed to attain ambient temperature and stirred for a further 2 hours. The volatiles were then removed *in vacuo* to give crude acid chloride, which was used without further purification.

(4*S*)-4-Benzyl-3-[(1*S*,2*S*,3*S*)-2-heptyl-3-(2-oxo-2-phenylethyl)cyclopropyl]carbonyl-1,3-oxazolan-2-one and (4*S*)-4-Benzyl-3-[(1*R*,2*R*,3*R*)-2-heptyl-3-(2-oxo-2-phenylethyl)cyclopropyl]carbonyl-1,3-oxazolan-2-one (161) and (162)

To a solution of (*S*)-(-)-4-benzyl-2-oxazolidinone (176 mg, 0.99 mmol) in anhydrous THF (5 ml) at –78°C under a nitrogen atmosphere was added *n*-BuLi (0.9 ml, 1.12 M) and the solution stirred for 0.5 hours. After this time the solution of acid chloride **S1** (synthesised from 300 mg, 0.99 mmol of acid **160**) in anhydrous THF (15 mL) was added dropwise and the solution stirred at –78°C for 4 hours. The reaction mixture was warmed to ambient temperature, quenched with saturated NH_4Cl, diluted with water and extracted with dichloromethane. The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude oxazolidinones. Oxazolidinones **161** and **162** were purified by column chromatography. First eluted oxazolidinone: Yield: 153 mg, 33%; Colourless oil; R_f 0.49 (3:7 ethyl acetate:hexanes); IR (neat) 2926, 2856, 1778, 1770, 1694, 1681 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.86 (t, J = 7.2 Hz, 3H), 1.18-1.67 (m, 13H), 1.99-2.07 (m, 1H), 2.30 (dd, J = 13.5, 9.3 Hz, 1H), 2.97 (dd, J = 16.8, 6.9 Hz, 1H), 3.07 (dd, J = 8.7, 5.1 Hz, 1H), 3.19 (dd, J = 16.8, 6.3 Hz, 1H), 3.31 (dd, J = 13.5, 3.3 Hz, 1H), 4.14-4.21 (m, 2H), 4.68-4.76 (m, 1H), 7.22-7.36 (m, 5H), 7.45-7.50 (m, 2H), 7.54-7.60 (m, 1H), 7.93-7.97 (m, 2H); ^{13}C NMR (75 MHz) δ 14.0, 22.6, 23.8, 25.6, 26.5, 29.2, 29.3, 31.7, 31.8, 37.9, 42.1, 55.3, 65.8,

127.2, 128.0, 128.6, 128.9, 129.5, 133.1, 135.3, 136.7, 153.8, 171.0, 198.3; MS (EI) *m/z* (%): 461.5 (M^+, 9), 356.5 (16), 342.5 (35), 284.3 (25), 256.3 (7), 243.3 (44), 105.0 (100); HRMS Calcd for $C_{29}H_{35}NO_4$ 461.2566, found 461.2558. Second eluted oxazolidinone: Yield: 110 mg, 24%; White solid; m.p. 94-96°C; R_f 0.34 (3:7 ethyl acetate:hexanes); IR (neat) 3090, 3026, 2920, 2889, 1789, 1757, 1682, 1596 (weak), 1580 (weak) cm^{-1}; ^1H NMR (300 MHz) δ 0.85 (t, J = 7.2 Hz, 3H), 1.23-1.73 (m, 13H), 1.99-2.07 (m, 1H), 2.67 (dd, J = 13.2, 9.9 Hz, 1H), 3.00 (dd, J = 16.8, 7.2 Hz, 1H), 3.01 (dd, J = 9.0, 4.8 Hz, 1H), 3.10 (dd, J = 16.8, 6.6 Hz, 1H), 3.33 (dd, J = 13.2, 3.3 Hz, 1H), 4.12-4.21 (m, 2H), 4.64-4.72 (m, 1H), 7.21-7.37 (m, 5H), 7.43-7.50 (m, 2H), 7.54-7.60 (m, 1H), 7.91-7.95 (m, 2H); ^{13}C NMR (75 MHz) δ 14.0, 22.6, 23.4, 25.7, 26.4, 29.26, 29.28, 29.5, 31.76, 31.79, 38.1, 42.0, 55.8, 66.0, 127.2, 128.0, 128.6, 128.9, 129.4, 133.1, 135.5, 136.7, 153.8, 170.8, 198.4; MS (EI) *m/z* (%): 461.6 (M^+, 6), 342.5 (23), 284.4 (18), 243.3 (30), 178.2 (9), 117.2 (6), 105.1 (100); Anal. Calcd for $C_{19}H_{35}NO_4$: C, 75.46; H, 7.64; N, 3.03; Found C, 75.51; H, 7.94; N, 3.07.

(±) 2-[(1*R*,2*S*)-2-Heptylcyclopropyl]-1-phenyl-1-ethanone (164)

Method 1: Tributyltin hydride as the reducing agent.

To a solution of cyclopropane acid **160** (1.02 g, 3.37 mmol) in anhydrous dichloromethane (44 mL) at 0°C under a nitrogen atmosphere and protected from light was added 2-mercaptopyridine *N*-oxide (0.43 g, 3.37 mmol) followed by DCC (0.77 g, 3.71 mmol). The reaction mixture was then stirred for 3 hours under the stated conditions. After this time the precipitate was filtered off and washed with cold dichloromethane (2 x 5 mL). The volatiles were removed *in vacuo* and the crude 'Barton ester' **163** reconstituted with anhydrous benzene (40 mL). Upon addition of excess tributyltin hydride (2.94 g, 10.1 mmol), the solution was irradiated with 1 sun lamp under a nitrogen atmosphere for 3 hours. The volatiles were then removed *in vacuo* and the residue reconstituted in diethyl ether (100 mL). The organic phase was washed with dilute HCl (10%, 75 mL), $NaHCO_3$ (5%, 100 mL) and then dried (Na_2SO_4), filtered and taken to dryness *in vacuo*. The residue was vigorously stirred overnight in a two-phase system consisting of saturated solutions of I_2 in dichloromethane (50 mL) and KF in water (50 mL), respectively. Sodium thiosulfate (2M) was added to the solution until the iodine colour disappeared. The solution was filtered to remove the white precipitate and the organic layer separated, washed with water (75 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by

flash chromatography (1:19 ethyl acetate:hexanes) to yield 0.299g, 34% of cyclopropane **164** as a colourless oil. Analytical data identical to that given below.

Method 2: *tert*-Butylthiol as the reducing agent.

The crude 'Barton ester' **163** was prepared using the same procedure given above using cyclopropane acid **160** (131 mg, 0.43 mmol) in anhydrous dichloromethane (10 mL), 2-mercaptopyridine *N*-oxide (55.1 mg, 0.43 mmol) and DCC (89.4 mg, 0.43 mmol). The crude 'Barton ester' **163** was reconstituted with anhydrous benzene (15 mL). The solution was then degassed and *tert*-butylthiol (0.1 mL, 0.86 mmol) added; irradiation of the solution was performed with 1 sun lamp under a nitrogen atmosphere for 2 hours. The volatiles were then removed *in vacuo* and the crude oil purified by column chromatography to yield 73 mg, 65% of cyclopropane **164** as a colourless oil; R_f 0.38 (1:9 ethyl acetate:hexanes); IR (neat) 2925, 2854, 1693, 1682, 1599 (weak), 1583 (weak) cm^{-1}; ^1H NMR (300 MHz) δ 0.31-0.39 (m, 2H), 0.52-0.62 (m, 1H), 0.88 (t, J = 6.6 Hz, 3H), 1.18-1.38 (m, 13H), 2.88 (d, J = 6.6 Hz, 2H), 7.43-7.49 (m, 2H), 7.53-7.59 (m, 1H), 7.93-7.96 (m, 2H); ^{13}C NMR (75 MHz) δ 11.9, 14.1, 14.2, 18.9, 22.7, 29.3, 29.37, 29.41, 31.9, 34.0, 43.5, 128.2, 128.5, 132.8, 137.1, 200.1; MS (EI) *m/z* (%): 243 (M^+, 18), 201 (3), 159 (8), 145 (38), 120 (56), 105 (100), 77 (26); HRMS Calcd for $C_{18}H_{26}O$ 258.1984, found 258.1984.

(±) Phenyl 2-[(1*R*,2*S*)-2-heptylcyclopropyl]acetate (168) and (±) [(1*R*,2*S*)-2-heptylcyclopropyl]methyl benzoate (169)

To a solution of cyclopropane **164** (117 mg, 0.45 mmol) in dichloromethane (2 mL) was added 70% *m*-CPBA (167 mg, 0.97 mmol) and the mixture was stirred for 2 days. Dichloromethane (10 mL) was then added and the solution extracted with saturated $Na_2S_2O_3$ followed by saturated $NaHCO_3$. The organic layers were combined, dried ($MgSO_4$), filtered and the volatiles removed *in vacuo* to yield 99 mg, 80% of a mixture of cyclopropyl esters **168** and **169** as a colourless oil. R_f 0.71 (for compound **169**), 0.65 (for compound **168**) (1:9 ethyl acetate:hexanes). Ratio of compounds **168** and **169** were determined to be 15:85 by ^1H NMR.

Synthesis of p-Methoxy Phenyl and o-Methoxy Phenyl derivatives

Ethyl (*E*)-3-(4-methoxyphenyl)-2-propenoate (173)[270]

Procedure as for the preparation of α,β-unsaturated esters **226b-c**. Yield: 8.13 g, 100%; White solid; R_f 0.60 (1:4 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ1.33 (t, J = 7.2 Hz, 3H), 3.83 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 6.31 (d, J = 15.9 Hz, 1H), 6.90 (d, J = 6.9 Hz, 2H), 7.47 (d, J = 6.9 Hz, 2H),7.64 (d, J = 15.9 Hz, 1H).

(*E*)-3-(4-Methoxyphenyl)-2-propen-1-ol (174)[176]

To a 0°C suspension of $LiAlH_4$ powder (4.04 g, 106.5 mmol) in diethyl ether (100 mL) was added a solution of $AlCl_3$ (4.57 g, 34.3 mmol) in diethyl ether (100 mL) (nb. CAUTION – add $AlCl_3$ slowly to diethyl ether as the additional is extremely exothermic). The mixture was warmed to ambient temperature and stirred for 30 minutes at this temperature before being re-chilled to 0°C. A solution of ester **173** in diethyl ether was added to the reaction vessel. The reaction mixture was warmed to ambient temperature and stirred for 1 hour. The solution was neutralised with aqueous NaOH (1M), acidified with aqueous HCl (10%) and extracted with diethyl ether. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 6.06 g, 94% of alcohol **174** as a white solid. m.p. 74–79 °C (lit.[176] 78–80 °C); R_f 0.50 (2:3 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ3.80 (s, 3H), 4.28 (d, J = 5.7 Hz, 2H), 4.60 (br s, 1H), 6.22 (dt, J = 15.3, 5.7 Hz, 1H), 6.54 (d, J = 15.3 Hz, 1H), 6.83-6.91 (m, 2H), 7.26-7.34 (m, 2H).

(*E*)-3-(4-Methoxyphenyl)-2-propenal (170a)[271]

Procedure as for the preparation of α,β-unsaturated aldehydes **228b-c** (PDC oxidation) or aldehydes **234a-b** (Swern oxidation). Yield: 3.80 g, 63%; Pale yellow oil; ^{1}H NMR (300 MHz) δ3.86 (s, 3H), 6.61 (dd, J = 15.9, 7.8 Hz, 1H), 6.95, (d, J = 7.8 Hz, 2H), 7.43 (d, J = 15.9 Hz, 1H), 7.53 (d, J = 7.8 Hz, 2H), 9.65 (d, J = 7.8 Hz, 1H).

(1*E*,3*E*) and (1*E*,3*Z*)-1-(4-Methoxyphenyl)-1,3-undecadiene (171a)

Procedure as for 1,3-butadienes **156**. Octyltriphenylphosphonium iodide (29.2 g, 58.1 mmol) in anhydrous THF (300 mL); Potassium *tert*-butoxide (6.53 g, 58.2 mmol); 4-methoxycinnamaldehyde (6.51 g, 40.1 mmol) in anhydrous THF (65 mL); Yield 7.99 g, 77% of 1,3-butadienes **171a**, in a ratio of 95:5, 1*E*,3*E* : 1*E*,3*Z*; Colourless oil; R_f 0.39 (1:99 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 0.85-0.90 (m, 3H), 1.26-1.44 (m, 10H), 2.23-2.32 (m, 2H), 3.80 (s, 3H), 5.49 (ddd, J = 10.8, 6.0, 6.0 Hz, 1H), 6.13 (dd, J = 10.8,

10.8 Hz, 1H), 6.47 (d, J = 15.3 Hz, 1H), 6.82-6.89 (m, 2H), 6.93 (ddd, J = 15.3, 10.8, 0.9 Hz, 1H), 7.32-7.36 (m, 2H).

(1*E*, 3*Z*) and (1*E*,3*E*)-1-(2-Methoxyphenyl)-1,3-undecadiene (171b)

Procedure as for 1,3-butadienes **156**. Octyltriphenylphosphonium iodide (27.26 g, 54.3 mmol) in anhydrous diethyl ether (250 mL); Potassium *tert*-butoxide (6.64 g, 59.2 mmol); 2-methoxycinnamaldehyde (8.0 g, 49.3 mmol) in anhydrous THF (80 mL); Yield 11.45 g, 90%; 1,3-Butadienes **171b** obtained in a ratio of 85:15, 1*E*,3*E* : 1*E*,3*Z*; Colourless oil; R_f 0.66 (1: 9 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 0.91-0.96 (m, 3H), 1.30-1.52 (m, 10H), 2.33 (q, J = 6.6 Hz, 2H), 3.91 (s, 3H), 5.56 (dt, J = 10.8, 7.8 Hz, 1H), 6.24 (dd, J = 10.8, 10.8 Hz, 1H), 6.89-6.94 (m, 2H), 6.95-7.01 (m, 1H), 7.14 (dd, J = 15.6, 10.8 Hz, 1H), 7.25 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H), 7.55 (dd, J = 7.8, 1.8 Hz, 1H).

4-(6-Heptyl-3,6-dihydro-1,2-dioxin-3-yl)phenyl methyl ether (172a)

A solution of 1,3-butadienes **171a** (13.5 g, 52.2 mmol) in anhydrous dichloromethane (300 mL) was photolysed with 3 x 500W halogen lamps in the presence of Rose Bengal *bis*(triethylammonium) salt (200 mg) with oxygen bubbled through the solution for 6 hours. The reaction was performed in a Pyrex flask fitted with an external cooling jacket. Additional rose bengal *bis*(triethylammonium) salt (50 mg) was added after 4 hours. The solution was concentrated and the resulting residue purified by column chromatography to yield 5.65 g, 37% of 1,2-dioxine **172a** as a colourless oil; R_f 0.31 (1:19 ethyl acetate:hexanes); IR (neat) 1725, 1689, 1681, 1612, 1586, 1513, 1465 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.87 (t, J = 6.6 Hz, 3H), 1.22-1.54 (m, 10H), 1.56-1.65 (m, 1H), 1.73-1.80 (m, 1H), 3.80 (s, 3H), 4.49-4.56 (m, 1H), 5.45-5.48 (m, 1H), 6.00-6.13 (m, 2H), 6.86-6.91 (m, 2H), 7.28-7.33 (m, 2H); ^{13}C NMR (75 MHz) δ 14.0, 22.6, 25.5, 29.1, 29.5, 31.7, 33.1, 55.2, 78.4, 79.8, 113.8, 126.5, 128.8, 129.7, 130.1, 160.0; MS (EI) *m/z* (%): 290 (M^+, 16), 272 (53), 258 (100), 187 (9), 173 (24), 134 (22); HRMS Calcd for [$C_{18}H_{26}O_3$+Na] 313.1780, found 313.1776.

3-Heptyl-6-(2-methoxyphenyl)-3,6-dihydro-1,2-dioxine (172b)

Prepared by photolysis of 1,3-butadienes **171b** by the general procedure for 1,2-dioxine synthesis. Yield: 5.98 g, 39%; Colourless oil; R_f 0.39 (1:19 ethyl acetate:hexanes); IR (neat) 2927, 2856, 1603, 1589 cm^{-1}; ^{1}H NMR (300 MHz) δ0.87 (t, J = 7.2 Hz, 3H), 1.22-1.34 (m, 8H), 1.34-1.78 (m, 4H), 3.84 (s, 3H), 4.57-4.63 (m, 1H), 5.94-5.97 (m, 1H), 6.01-6.10 (m, 2H), 6.89 (dd, J = 8.7, 0.9 Hz, 1H), 6.94 (ddd, J = 7.5, 7.5, 0.9 Hz, 1H), 7.30

(ddd, J = 8.7, 7.5, 0.9 Hz, 1H), 7.39 (dd, J = 7.5, 1.8 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.0, 22.6, 25.4, 29.1, 29.5, 31.8, 32.9, 55.5, 74.1, 78.3, 110.6, 120.3, 126.2, 126.4, 128.6, 129.2, 129.7, 157.3; MS (EI) *m/z* (%): 290 (M^+, 25), 272(31), 258(91), 187(79), 173(37), 159(40), 135(100), 121(67), 105(16), 77(61), 60(67), 43(62); HRMS (EI) calcd for [$C_{18}H_{26}O_3$ + Na] 313.1780, found 313.1772.

(±) *tert*-Butyl [(1*S*,2*R*,3*R*)-2-heptyl-3-[2-(4-methoxyphenyl)-2-oxoethyl]cyclopropane-1-carboxylate (175a) and (±) *tert*-Butyl [(1*R*,2*S*,3*S*)-2-heptyl-3-(4-methoxybenzoyl)]cyclopropyl]acetate (176a)

Procedure as for cyclopropyl ester **158** synthesis. Reaction was complete after 15 days stirring at ambient temperature. Purification by flash chromatography gave cyclopropanes **175a** and **176a**. Cyclopropane **175a**: Yield: 4.83 g, 55%; Colourless oil; R_f 0.43 (3:17 ethyl acetate:hexanes); IR (neat) 1722, 1715, 1682, 1602, 1576, 1511 cm^{-1}; ^{1}H NMR (600 MHz) δ 0.86 (t, J = 6.6 Hz, 3H), 1.09-1.14 (m, 1H), 1.23-1.34 (m, 10H), 1.46-1.52 (m, 1H), 1.44 (s, 9H), 1.50 (dd, J = 9.0, 4.8 Hz, 1H), 1.53-1.67 (m, 2H), 2.65 (dd, J = 16.2, 8.4 Hz, 1H), 3.14 (dd, J = 16.2, 6.0 Hz, 1H), 3.87 (s, 3H), 6.93 (dd, J = 6.9, 2.1 Hz, 2H), 7.91 (dd, J = 6.9, 2.1 Hz, 2H); ^{13}C NMR (75 MHz) δ 14.0, 22.58, 22.61, 26.3, 26.7, 28.2, 29.1, 29.27, 29.32, 29.5, 31.8, 41.9, 55.4, 80.1, 113.8, 129.8, 130.4, 163.5, 171.4, 197.2; MS (EI) *m/z* (%): 388 (M^+, 40), 332 (33), 330 (36), 314 (100), 272 (38), 186 (7), 149 (7), 134 (55), 56 (29), 41 (18); HRMS Calcd for $C_{24}H_{36}O_4Na$ 411.2511, found 411.2513. Cyclopropane **176a**: Yield: 1.76 g, 20%; Colourless oil; R_f 0.36 (3:17 ethyl acetate:hexanes); IR (neat) 1714, 1614, 1515, 1365, 1247 cm^{-1}; ^{1}H NMR (600 MHz) δ 0.86 (t, J = 7.2 Hz, 3H), 1.17 (s, 9H), 1.21-1.31 (m, 7H), 1.57-1.62 (m, 3H), 1.76 (dd, J = 9.0, 4.8 Hz, 1H), 2.19-2.24 (m, 1H), 2.28-2.30 (m, 1H), 2.33 (dd, J = 16.8, 8.4 Hz, 1H), 2.42-2.50 (m, 2H), 2.75 (dd, J = 16.8, 5.4 Hz, 1H), 3.77 (s, 3H), 6.79-6.81 (m, 2H), 7.23-7.25 (m, 2H); ^{13}C NMR (75 MHz) δ 14.0, 19.8, 22.6, 23.7, 27.8, 28.8, 29.1, 29.2, 31.6, 31.7, 42.6, 45.9, 55.3, 80.3, 113.4, 128.4, 130.5, 158.4, 169.6, 209.5; MS (EI) *m/z* (%): 388 (M^+, 13), 332 (18), 205 (43), 190 (39), 127 (19), 67 (100); HRMS Calcd for [$C_{24}H_{36}O_4$+Na] 411.2511, found 411.2514.

(±) *tert*-Butyl (1*R*,2*R*,3*R*)-2-heptyl-3-[2-(2-methoxyphenyl)-2-oxoethyl]cyclopropane-1-carboxylate (175b) and (±) *tert*-Butyl [(1*R*,2*S*,3*S*)-2-heptyl-3-(2-methoxybenzoyl)]cyclopropyl]acetate (176b)

Procedure as for cyclopropyl ester **158** synthesis. Reaction was complete after 12 days stirring at ambient temperature. Purification by flash chromatography gave cyclopropanes **175b** and **176b**. Cyclopropane **175b**: Yield: 3.15 g, 50%; Colourless oil; R_f 0.50 (3:17

ethyl acetate:hexanes); IR (neat) 2926, 2856, 1716, 1681, 1599, 1583 cm^{-1}; ^1H NMR (600 MHz) δ 0.87 (t, J = 7.2 Hz, 3H), 1.04-1.09 (m, 1H), 1.20-1.32 (m, 10H), 1.34-1.48 (m, 3H), 1.43 (s, 9H), 1.55-1.62 (m, 1H), 2.76 (dd, J = 16.2, 7.8 Hz, 1H), 3.12 (dd, J = 16.2, 6.0 Hz, 1H), 3.88 (s, 3H), 6.94-6.95 (m, 1H), 6.98-7.01 (m, 1H), 7.43-7.45 (m, 1H), 7.65-7.66 (m, 1H); ^{13}C NMR (75 MHz) δ 14.0, 22.5, 22.6, 26.0, 26.7, 28.1, 29.0, 29.2, 29.3, 29.4, 31.8, 47.2, 55.3, 79.9, 111.3, 120.6, 128.2, 130.2, 133.3, 158.3, 171.5, 201.2; MS (EI) *m/z* (%): 388 (M^+, 6), 359(1), 331(16), 287(2), 273(18), 247(2), 219(2), 175(2), 150(5), 135(100), 92(4), 57(15), 42(9); HRMS (EI) calcd for [$C_{24}H_{36}O_4$ + Na] 411.2511, found 411.2504. Cyclopropane **176b**: Yield: 1.40 g, 22%; Colourless oil; R_f 0.39 (3:17 ethyl acetate:hexanes); IR (neat) 2929, 1718, 1708, 1603, 1585 cm^{-1}; ^1H NMR (300 MHz) δ0.87 (t, J = 6.6 Hz, 3H), 1.11 (s, 9H), 1.23-1.32 (m, 8H), 1.54-1.64 (m, 2H), 1.82 (dd, J = 8.7, 5.1 Hz, 1H), 2.15-2.27 (m, 2H), 2.36 (dd, J = 16.8, 8.1 Hz, 1H), 2.47 (t, J = 7.2 Hz, 2H), 2.77 (dd, J = 16.8, 5.1 Hz, 1H), 3.79 (s, 3H), 6.78 (dd, J = 7.8, 0.9 Hz, 1H), 6.90 (ddd, J = 7.8, 7.8, 0.9 Hz, 1H), 7.16-7.22 (m, 1H), 7.37 (dd, J = 7.5, 0.9 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.0, 19.9, 22.5, 23.6, 27.6, 28.2, 29.0, 29.1, 31.6, 42.6, 46.0, 55.1, 79.7, 109.4, 120.0, 125.0, 127.8, 130.6, 158.5, 169.9, 209.6; MS (EI) *m/z* (%): 388 (M^+, 9), 342(2), 315(12), 287(3), 273(1), 247(1), 205(11), 190(80), 160(41), 127(49), 91(14), 57(100), 42(54); Anal. Calcd for $C_{20}H_{28}O_4$: C, 74.19; H, 9.34: found C, 74.35; H, 9.29.

(±)-(1*S*,2*R*,3*R*)-2-Heptyl-3-[2-(4-methoxyphenyl)-2-oxoethyl]cyclopropane-1-carboxylic acid (177a)

99% Formic acid (2 mL) was added to cyclopropyl ester **175a** (400 mg, 1.03 mmol) and the solution stirred for 3 hours. The formic acid was then removed *in vacuo*, the resulting crude acid **177a** was dissolved in ethyl acetate and washed with 6% $NaHCO_3$ solution. The organics were then dried ($MgSO_4$), filtered and the volatiles removed *in vacuo* to yield 304 mg, 89% of cyclopropyl acid **177a** as a colourless crystalline solid; m.p. 116-117°C; R_f 0.60 (1:3 ether:dichloromethane); IR (neat) 2601, 1688, 1682, 1668, 1602, 1574, 1171, 1027, 925 cm^{-1}; ^1H NMR (600 MHz) δ 0.87 (t, J = 6.6 Hz, 3H), 1.21-1.29 (m, 12H), 1.54-1.67 (m, 3H), 1.75-1.79 (m, 1H), 2.79 (dd, J = 16.2, 7.2 Hz, 1H), 3.09 (dd, J = 16.2, 6.6 Hz, 1H), 3.87 (s, 3H), 6.93 (dd, J = 7.2, 2.4 Hz, 2H), 7.90 (dd, J = 7.2, 2.4 Hz, 2H); ^{13}C NMR (75 MHz) δ 14.1, 22.6, 24.1, 24.9, 26.6, 29.17, 29.22, 29.3, 30.4, 31.8, 41.8, 55.5, 113.8, 129.7, 130.4, 163.6, 178.3, 196.8; MS (EI) *m/z* (%): 332 (M^+, 16), 315 (65), 273 (45), 247 (4), 219 (21), 187 (11), 150 (31), 135 (100), 121 (12), 92 (19), 77 (24), 55 (17), 41 (41); HRMS Calcd for $C_{20}H_{28}O_4Na$ 355.1885, found 355.1879.

(±)-(1*R*,2*R*,3*R*)-2-Heptyl-3-[2-(2-methoxyphenyl)-2-oxoethyl]cyclopropane-1-carboxylic acid (177b)

Procedure as for cyclopropyl acid **177a** synthesis. Yield: 2.36 g, 97%; Colourless oil; IR (neat) 2927, 2866, 2392-2773, 1727, 1694, 1681, 1598 cm^{-1}; ^1H NMR (600 MHz) δ 0.87 (t, J = 6.6 Hz, 3H), 1.19-1.38 (m, 12H), 1.53 (dd, J = 9.0, 4.8 Hz, 1H), 1.58 (dddd, J = 11.4, 9.0, 6.0, 6.0 Hz, 1H), 1.74 (dddd, J = 11.4, 7.2, 6.0, 4.8 Hz, 1H), 2.86 (dd, J = 16.8, 7.2 Hz, 1H), 3.12 (dd, J = 16.8, 6.0 Hz, 1H), 3.89 (s, 3H), 6.95 (d, J = 8.4 Hz, 1H), 6.98-7.01 (m, 1H), 7.44-7.47 (m, 1H), 7.68 (dd, J = 7.8, 1.8 Hz, 1H), 9.90 (br s, 1H); ^{13}C NMR (150 MHz) δ 14.0, 22.6, 24.2, 24.8, 26.6, 29.15, 29.21, 29.22, 30.3, 31.8, 47.1, 55.4, 111.4, 120.7, 127.9, 130.3, 133.5, 158.4, 178.9, 200.6; MS (EI) *m/z* (%): 332.6 (M^+, 2), 315.7(0.5), 286.7(0.5), 273.5(10), 247.6(1), 219.5(5), 205.6(0.5), 178.3(10), 173.3(5), 135.3(100), 118.3(5), 92.2(11), 77.2(29), 43.7(16), 41.7(31); HRMS (EI) calcd for [$C_{20}H_{28}O_4$ + Na] 355.1885, found 355.1887.

(±) 2-[(1*R*,2*S*)-2-Heptylcyclopropyl]-1-(4-methoxyphenyl)-1-ethanone (179a)

Procedure as for cyclopropane **164** synthesis. Yield 287 mg, 86%; Colourless oil; R_f 0.50 (3:1 dichloromethane:hexanes); IR (neat) 1681, 1602, 1577, 1510, 1259, 1170, 1033 cm^{-1}; ^1H NMR (300 MHz) δ 0.31-0.36 (m, 2H), 0.51-0.62 (m, 1H), 0.87 (t, J = 6.6 Hz, 3H), 1.19-1.39 (m, 13H), 2.82 (d, J = 6.9 Hz, 2H), 3.86 (s, 3H), 6.93 (dd, J = 6.9, 2.1 Hz, 2H), 7.93 (dd, J = 6.9, 2.1 Hz, 2H); ^{13}C NMR (75 MHz) δ 11.9, 14.1, 14.5, 18.9, 22.6, 29.3, 29.36, 29.39, 31.8, 34.0, 43.1, 55.4, 113.7, 130.2, 130.4, 163.3, 198.6; MS (EI) *m/z* (%): 288 (M^+, 51), 273 (79), 175 (12), 135 (65), 92 (12), 77 (11), 64 (11), 55 (13), 41 (100); HRMS Calcd for [$C_{19}H_{28}O_2$ + Na] 311.1987, found 311.1984.

(±) 2-[(1*R*,2*S*)-2-Heptylcyclopropyl]-1-(2-methoxyphenyl)-1-ethanone (179b)

Procedure as for cyclopropane **164** synthesis. Yield: 1.42 g, 76%; Colourless oil; R_f 0.44 (3:7 ethyl acetate:hexanes); IR (neat) 2924, 2852, 1678, 1599 cm^{-1}; ^1H NMR (300 MHz) δ 0.27 (ddd, J = 7.2, 4.8, 4.8 Hz, 1H), 0.29 (ddd, J = 7.2, 4.8, 4.8 Hz, 1H), 0.48-0.53 (m, 1H), 0.80-0.85 (m, 1H), 0.88 (t, J = 6.6 Hz, 3H), 1.14-1.23 (m, 2H), 1.23-1.25 (m, 8H), 1.25-1.34 (m, 2H), 2.87 (d, J = 6.6 Hz, 2H), 3.88 (s, 3H), 6.94 (dd, J = 8.4, 0.6 Hz, 1H), 6.98-7.01 (m, 1H), 7.42-7.64 (m, 1H), 7.65-7.66 (m, 1H); ^{13}C NMR (75 MHz) δ 11.6,14.0, 14.1, 18.5, 22.6, 29.28, 29.34, 29.4, 31.8, 34.0, 48.5, 55.3, 111.3, 120.6, 128.7, 130.1, 133.0, 158.2, 202.8; MS (EI) *m/z* (%): 288 (M^+, 31), 273(100), 259(5), 231(11), 217(1),

203(29), 189(19), 175(17), 150(3), 135(100), 121(2), 105(1), 77(15), 69(2), 55(9); HRMS (EI) calcd for [$C_{19}H_{28}O_2$ + Na] 311.1987, found 311.1985.

(±) 4-Methoxyphenyl 2-[(1*R*,2*S*)-2-heptylcyclopropyl]acetate (180a)

Procedure as for cyclopropane **168** and **169** synthesis. Yield 947 mg, 91% of cyclopropyl ester **180a** as a colourless oil; R_f 0.60 (7:3 dichloromethane:hexanes); IR (neat) 1760, 1608, 1598, 1506, 1249, 1196, 1036 cm^{-1}; ^1H NMR (300 MHz) δ 0.39-0.47 (m, 2H), 0.63-0.74 (m, 1H), 0.92 (t, J = 6.9 Hz, 3H), 1.23-1.50 (m, 13H), 2.43 (dd, J = 15.3, 7.5 Hz, 1H), 2.53 (dd, J = 15.3, 6.6 Hz, 1H), 3.84 (s, 3H), 6.93 (dd, J = 6.6, 2.4 Hz, 2H), 7.05 (dd, J = 6.6, 2.4 Hz, 2H); ^{13}C NMR (75 MHz) δ 11.7, 14.1, 14.3, 18.8, 22.7, 29.3, 29.4, (masked carbon), 31.9, 33.9, 39.1, 55.6, 114.4, 122.3, 144.4, 157.2, 172.0; MS (EI) *m/z* (%): 304 (M^+, 51), 273 (7), 203 (7), 175 (31), 163 (5), 135 (17), 124 (100), 109 (9), 82 (10), 55 (14), 41 (15); HRMS Calcd for $C_{19}H_{28}O_3Na$ 327.1936, found 327.1936.

(±) 2-Methoxyphenyl 2-[(1*R*,2*S*)-2-heptylcyclopropyl]acetate (180b) and (±) [(1*R*,2*S*)-2-heptylcyclopropyl]methyl 2-methoxybenzoate (181b)

Procedure as for cyclopropane **168** and **169** synthesis. Cyclopropane **180b**: Yield: 1.04 g, 77%; Colourless oil; R_f 0.43 (3:17 ethyl acetate:hexanes); IR (neat) 2925, 2854, 1767, 1607, 1503 cm^{-1}; ^1H NMR (300 MHz) I 0.38 (ddd, J = 8.4, 5.4, 5.4 Hz, 1H), 0.42 (ddd, J = 8.4, 4.8, 4.8 Hz, 1H), 0.65 (ddddd, J = 9.0, 7.2, 6.6, 5.4, 4.8 Hz, 1H), 0.88 (t, J = 6.6 Hz, 3H), 0.86-0.94 (m, 1H), 1.22-1.32 (m, 10H), 1.38-1.43 (m, 2H), 2.46 (dd, J = 15.6, 7.2 Hz, 1H), 2.51 (dd, J = 15.6, 6.6 Hz, 1H), 3.82 (s, 3H) 6.92-6.97 (m, 2H), 7.03 (dd, J = 7.8, 0.9 Hz, 1H), 7.17-7.25 (m, 1H); ^{13}C NMR (75 MHz) I 11.6, 14.1, 14.2, 18.8, 22.7, 29.3, 29.4, 29.5, 31.9, 33.9, 38.7, 55.8, 112.4, 120.7, 122.8, 126.7, 139.9, 151.1, 171.3; MS (EI) *m/z* (%): 304 (M^+, 26), 281(3), 256(2), 239(2), 197(2), 180(28), 173(6), 137(13), 124(100), 95(6), 82(22), 55(10), 41(13); HRMS (EI) calcd for [$C_{19}H_{28}O_3$ + Na] 327.1936, found 327.1932. Cyclopropane **181b**: Yield: 72 mg, 5%; Colourless oil; R_f 0.27 (3:17 ethyl acetate:hexanes); IR (neat) 2925, 2854, 1728, 1601, 1583 cm^{-1}; ^1H NMR (600 MHz) δ0.38 (ddd, J = 8.4, 4.8, 4.8 Hz, 1H), 0.50 (ddd, J = 8.4, 4.8, 4.8 Hz, 1H), 0.72-0.78 (m, 1H), 0.87 (t, J = 7.2 Hz, 3H), 0.98 (ddddd, J = 8.4, 7.2, 7.2, 4.8, 4.8 Hz, 1H), 1.14-1.22 (m, 2H), 1.21-1.35 (m, 8H), 1.35-1.41 (m, 2H), 3.90 (s, 3H), 4.09 (dd, J = 11.4, 7.2 Hz, 1H), 4.19 (dd, J = 11.4, 7.2 Hz, 1H), 6.97-7.00 (m, 2H), 7.47 (ddd, J = 8.4, 7.2, 1.8 Hz, 1H), 7.82 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR (75 MHz) δ10.4, 14.1, 17.3, 17.7, 22.7, 29.32, 29.34, 29.5, 31.8, 33.6, 55.9, 69.1, 111.9, 120.0, 120.5, 131.5, 133.3, 159.1, 166.3; MS (EI) *m/z* (%): 304 (M^+, 4), 262 (7), 261 (2), 219 (13), 206 (1), 183 (4), 153 (4), 135 (100), 123 (5),

97 (8), 69 (9), 57 (9), 43 (4); HRMS (EI) calcd for [$C_{19}H_{28}O_3$ + Na] 327.1936, found 327.1930.

(±) Methyl 2-[(1*S*,2*R*)-2-heptylcyclopropyl]acetate (182)

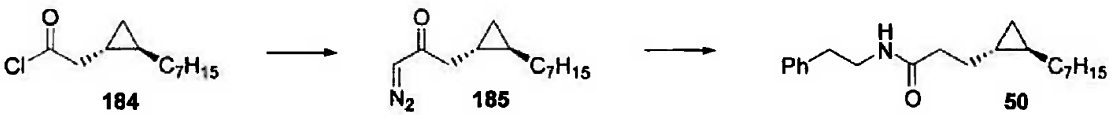
To a solution of cyclopropyl ester **180a** or **180b** (1.031 g, 3.39 mmol) in anhydrous methanol (20 mL) was added concentrated H_2SO_4 (1 drop) and the solution refluxed for 16 hours under a nitrogen atmosphere. $NaHCO_3$ (50 mg, 0.6 mmol) was then added and the volatiles removed *in vacuo* until approximately 5 mL remained, dichloromethane (20 mL) was then added and the solution extracted with saturated $NaHCO_3$, dried ($MgSO_4$), filtered and the volatiles removed *in vacuo*. Column chromatography of the crude residue gave 670 mg, 93% of cyclopropyl ester **182** as a colourless oil; R_f 0.63 (7:3 dihloromethane:hexanes); IR (neat) 1746, 1436, 1256, 1171, 1020 cm^{-1}; ^1H NMR (300 MHz) δ 0.28-0.32 (m, 2H), 0.50-0.55 (m, 1H), 0.74-0.79 (m, 1H), 0.88 (t, J = 6.6 Hz, 3H), 1.16-1.23 (m, 1H), 1.23-1.31 (m 9H), 1.34-1.39 (m, 2H), 2.21 (dd, J = 15.6, 7.2 Hz, 1H), 2.23 (dd, J = 15.6, 7.2 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (75 MHz) δ 11.6, 14.1, 14.2, 18.6, 22.7, 29.3, 29.4, (masked carbon), 31.9, 33.9, 38.9, 51.5, 173.8; MS (EI) *m/z* (%): 213 ($[M+H]^+$, 13), 197 (7), 183 (8), 180 (66), 169 (14), 152 (3), 138 (50), 128 (13), 110 (16), 101 (61), 83 (57), 74 (94), 59 (85), 55 (87), 41 (100); HRMS (EI) calcd for $C_{13}H_{24}O_2$ 212.1776, found 212.1771.

(±) 2-[(1*R*,2*S*)-2-Heptylcyclopropyl]acetic acid (183)

To a solution of cyclopropyl ester **182** (1.209 g, 5.69 mmol) in water and methanol (15 mL, 1:4 v/v) was added aqueous KOH (4 mL, 2M) and the solution stirred for 6 hours. After this time water (10 mL) was added and the solution was acidified (conc. HCl) to pH 1. Following acidification the solution was extracted with ether, the organics were dried ($MgSO_4$), filtered and the volatiles removed *in vacuo* to yield 1.05, 93% of cyclopropyl acid **183** as a colourless oil; R_f 0.40 (1:9 ether:dichloromethane); IR (neat) 2673, 1714, 1416, 1304, 1223, 940 cm^{-1}; ^1H NMR (600 MHz) δ 0.31-0.35 (m, 2H), 0.53-0.58 (m, 1H), 0.75-0.80 (m, 1H), 0.88 (t, J = 7.2 Hz, 3H), 1.21-1.31 (m, 11H), 1.35-1.40 (m, 2H), 2.25 (dd, J = 16.2, 6.7 Hz, 1H), 2.27 (dd, J = 16.2, 7.7 Hz, 1H); ^{13}C NMR (75 MHz) δ 11.6, 14.0, 14.1, 18.7, 22.7, 29.32, 29.35, 29.4, 31.9, 33.8, 38.8, 179.2; MS (EI) *m/z* (%): 199 ($[M+H]^+$, 100), 181 (64), 163 (20), 151 (6), 138 (63), 123 (17), 112 (34), 97 (63), 83 (98), 82 (53), 69 (45), 55 (36), 41 (53); HRMS Calcd for [$C_{12}H_{22}O_2$ - H] 197.1542, found 197.1540.

(±) 2-[(1*S*,2*R*)-2-Heptylcyclopropyl]ethanoyl chloride (184)

Procedure as for acid chloride **S1** synthesis. Crude acid chloride **184** was used without further purification. ^{1}H NMR (300 MHz) δ 0.37-0.45 (m, 2H), 0.59-0.65 (m, 1H), 0.82-0.91 (m, 4H), 1.21-1.38 (m, 12H), 2.75 (dd, J = 16.8, 7.1 Hz, 1H), 2.80 (dd, J = 16.8, 6.8 Hz, 1H).



(±) Grenadamide (50)

A solution of acid chloride **184** (synthesised from 250 mg, 1.26 mmol of acid **183**) in anhydrous ether (8 ml) was added to a stirred solution of diazomethane[1] (~80 mg, 1.9 mmol) in ether (~60 ml) and triethylamine (0.2 ml, 1.43 mmol) at 0°C. The mixture was stirred of 0.5 hours after which time half the volume of ether was evaporated under a stream of nitrogen. The precipitated $N(Et)_3$.HCl was then filtered off and washed with cold ether. The volatiles were removed *in vacuo* to give crude diazoketone **185**. R_f 0.67 (1:9 ether:dichloromethane). Diazoketone **185** was reconstituted in anhydrous, degassed THF (4 ml) and cooled to –20°C, to this solution was added phenethylamine (0.63 ml, 5.04 mmol). The reaction was then protected from light and a solution of silver benzoate (317 mg, 1.39 mmol) in triethylamine (5.4 mL) was added. On complete addition of the silver benzoate solution the mixture was allowed to attain ambient temperature and was stirred for 16 hours. The volatiles were removed *in vacuo* and the residue purified by column chromatography to yield 329 mg, 83% of racemic grenadamide **50** as a colourless solid; m.p. 54-56°C; R_f 0.66 (1:1 ethyl acetate:hexanes); IR (nujol) 3312, 1636, 1549, 1194, 1024, 747 cm^{-1}; ^{1}H NMR (300 MHz) δ0.12-0.21 (m, 2H), 0.32-0.47 (m, 2H), 0.88 (t, J = 6.9 Hz, 3H), 1.05-1.24 (m, 2H), 1.20-1.38 (m, 10H), 1.44-1.57 (m, 2H), 2.21 (t, J = 7.5 Hz, 2H), 2.82 (t, J = 6.9 Hz, 2H), 3.52 (q, J = 6.3 Hz, 2H), 5.78 (br s, 1H), 7.18-7.33 (m, 5H); ^{13}C NMR (75 MHz) δ11.7, 14.1, 18.1, 18.8, 22.6, 29.3, 29.4, 29.6, 30.4, 31.8, 34.1, 35.6, 36.7, 40.5, 126.4, 128.6, 128.7, 138.8, 173.2; MS (EI) *m/z* (%): 315 (M^+, 16), 286 (8), 267 (6), 244 (8), 230 (18), 217 (8), 182 (20), 163 (33), 132 (12), 115 (20), 140 (100), 72 (71), 55 (87), 43 (73); Anal. Calcd for $C_{21}H_{33}NO$: C, 79.95; H, 10.54: found C, 80.14; H, 10.72.

(4*S*)-4-Benzyl-3-2-[(1*S*,2*R*)-2-heptylcyclopropyl]acetyl-1,3-oxazolan-2-one (186) and (4*S*)-4-Benzyl-3-2-[(1*R*,2*S*)-2-heptylcyclopropyl]acetyl-1,3-oxazolan-2-one (187)

Procedure as for the synthesis of oxazolidinones **161** and **162**. Oxazolidinones **186** and **187** were purified by column chromatography to give a combined yield of 789 mg, 59%. The oxazolidinones were resolved by successive column chromatography. First eluted oxazolidinone **186**: m.p. 45-46°C; R_f 0.44 (1:4 ethyl acetate:hexanes); IR (nujol) 1790, 1691, 1225, 1151, 758 cm^{-1}; ^1H NMR (300 MHz) δ 0.33-0.41 (m, 2H), 0.54-0.65 (m, 1H), 0.87 (t, J = 6.9 Hz, 3H), 1.18-1.44 (m, 13H), 2.78 (dd, J = 13.2, 9.6 Hz, 1H), 2.81 (dd, J = 17.1, 7.2 Hz, 1H), 2.92 (dd, J = 17.1, 6.9 Hz, 1H), 3.33 (dd, J = 13.2, 3.0 Hz, 1H), 4.16 (dd, J = 9.0, 3.6 Hz, 1H), 4.20 (dd, J = 9.0, 7.2 Hz, 1H), 4.69 (dddd, J = 9.6, 7.2, 3.6, 3.6 Hz, 1H), 7.20-7.37 (m, 5H); ^{13}C NMR (75 MHz) δ 11.6, 13.7, 14.1, 18.5, 22.7, 29.3, 29.4, (masked carbon), 29.5, 31.9, 34.0, 38.0, 40.3, 55.2, 66.2, 127.3, 128.9, 129.4, 135.3, 153.5, 173.0; MS (EI) *m/z* (%): 357 (M^+, 37), 342 (5), 272 (7), 244 (19), 219 (9), 178 (43), 152 (6), 134 (20), 117 (48), 91 (83), 55 (69), 41 (100); Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74: found C, 74.04; H, 8.67. Second eluted oxazolidinone **187**: m.p. 46-48°C; R_f 0.38 (1:4 ethyl acetate:hexanes); IR (nujol) 1786, 1696, 1222, 1118, 998 cm^{-1}; ^1H NMR (300 MHz) δ 0.33-0.39 (m, 2H), 0.56-0.66 (m, 1H), 0.87 (t, J = 6.6 Hz, 3H), 1.22-1.44 (m, 13H), 2.76 (dd, J = 17.1, 7.2 Hz, 1H), 2.78 (dd, J = 13.5, 9.6 Hz, 1H), 2.98 (dd, J = 17.1, 6.6 Hz, 1H), 3.32 (dd, J = 13.5, 3.3 Hz, 1H), 4.16 (dd, J = 9.0, 3.6 Hz, 1H), 4.20 (dd, J = 9.0, 7.2 Hz, 1H), 4.69 (dddd, J = 9.6, 6.9, 3.6, 3.6 Hz, 1H), 7.20-7.37 (m, 5H); ^{13}C NMR (75 MHz) δ 11.5, 13.7, 14.1, 18.7, 22.7, 29.3, 29.4, (masked carbon), 31.9, 33.9, 38.0, 40.2, 55.2, 66.2, 127.3, 128.9, 129.4, 135.3, 153.5, 173.0; MS (EI) *m/z* (%): 357 (M^+, 23), 342 (3), 272 (8), 244 (19), 219 (11), 181 (40), 134 (20), 117 (39), 91 (80), 55 (58), 41 (100); HRMS (EI) calcd for [$C_{22}H_{31}NO_3$ + Na] 380.2202, found 380.2199.

(-) 2-[(1*S*,2*R*)-2-Heptylcyclopropyl]acetic acid (-)-(183)

To a solution of oxazolidinone **186** (516 mg, 1.44 mmol) in THF and water (10 mL, 3:1 v/v) at 0°C was added 30% hydrogen peroxide (1.31 ml, 11.6 mmol) and LiOH (138 mg, 5.76 mmol), the solution was then stirred for 0.5 hours. After this time the reaction was quenched with 1.5M Na_2SO_3 and extracted with dichloromethane, the addition of brine was necessary to break up the emulsions formed. The aqueous layer was then acidified (conc. HCl) to pH 1 and extracted with dichloromethane, the organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 254 mg, 89% of cyclopropyl acid (-)-**183** as a colourless oil. $[\alpha_D]^{20.5}$ –14.0° ($CHCl_3$, c = 0.01).

(+) 2-[(1*R*,2*S*)-2-Heptylcyclopropyl]acetic acid (+)-(183)

Procedure as for acid **(-)-183** synthesis but using oxazolidinone **187**. Yield 275 mg, 86%. $[\alpha_D]^{20.5}$ +14.0° ($CHCl_3$, c = 0.01).

(-)-(*R*,*R*) Grenadamide

Procedure as for (±)-grenadamide synthesis. Yield 296 mg, 80% $[\alpha_D]^{20.5}$–12.0° ($CHCl_3$, c = 0.005).

(+)-(*S*,*S*) Grenadamide

Procedure as for (±)-grenadamide synthesis. Yield 308 mg, 83% $[\alpha_D]^{20.5}$ +12.0° ($CHCl_3$, c = 0.005).

6.4 Compounds discussed in Chapter 4

Formation of 1,3-butadiene 216 from 4-hydroxybutanal

Tetrahydro-2-furanol (214a) / 4-Hydroxybutanal (214b)[222]

2,3-Dihydrofuran (3.17 g, 45.2 mmol) was added dropwise to a cooled solution (0°C) of concentrated hydrochloric acid (32%, 1 mL) and water (10 mL) over two minutes. After stirring for 30 minutes at 0°C the solution was neutralised to pH 8 with sodium hydroxide (20% aq.). The aqueous solution was saturated with NaCl and extracted twice with CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), filtered and concentrated to give 2.70 g, 68% of **214a-b** as a colourless oil. The product was used without further purification.

(4*Z*,6*E*) and (4*E*,6*E*)-7-Phenyl-4,6-heptadien-1-ol (216)

Method 1: To a suspension of cinnamyl phosphonium salt **144a** (34.2 g, 82.4 mmol) in dry THF (275 mL) at ambient temperature and under a nitrogen atmosphere was added potassium *tert*-butoxide (9.25 g, 82.4 mmol). After stirring for 15 minutes the red solution was cooled to 0°C and a solution of **214a-b** (9.03 g, 102.5 mmol) in dry THF (75 mL) was added dropwise. The solution was stirred for 16 hours at ambient temperature, then diluted with hexanes (350 mL) and filtered over silica (3 cm). The silica was washed with 2:3 ethyl acetate:hexanes (3 x 250 mL). The combined filtrates were concentrated and the resulting residue purified by flash chromatography (1:4 ethyl acetate:hexanes followed by 2:3 ethyl acetate:hexanes) to furnish 9.96 g, 64% of 1,3-butadienes **216** as a colourless oil consisting of a 2:3 mixture of 4*Z*,6*E*[a] and 4*E*,6*E*[b] isomers. A small amount of each isomer was isolated. **(4*Z*,6*E*)-7-phenyl-4,6-heptadien-1-ol** R_f 0.43 (2:3 ethyl acetate:hexanes); ^{1}H NMR (600 MHz) δ 1.71 (quin, J = 6.6 Hz, 2H), 2.11 (br s, 1H), 2.39 (dq, J = 6.6, 1.2 Hz, 2H), 3.69 (t, J = 6.6 Hz, 2H), 5.53 (dt, J = 10.2, 6.6 Hz, 1H), 6.19 (ddd, J = 11.4, 10.2, 1.2, Hz, 1H), 6.54 (d, J = 15.6 Hz, 1H), 7.08 (ddd, J = 15.6, 11.4, 1.2 Hz, 1H), 7.19-7.22 (m, 1H), 7.28-7.31 (m, 2H), 7.39-7.41 (m, 2H); ^{13}C NMR (75 MHz) δ 29.0, 32.0, 62.2, 126.1, 127.1, 128.5, 129.1, 130.3, 131.0, 134.6, 137.5; **(4*E*,6*E*)-7-phenyl-4,6-heptadien-1-ol** R_f 0.36 (2:3 ethyl acetate:hexanes); ^{1}H NMR (600 MHz) δ 1.68 (quin, J = 6.6 Hz, 2H), 2.20-2.24 (m, 3H), 3.63 (t, J = 6.6 Hz, 2H), 5.81 (dt, J = 15.0, 7.2 Hz, 1H), 6.22 (ddd, J = 15.0, 10.2, 0.6 Hz, 1H), 6.43 (d, J = 15.6 Hz, 1H), 6.73 (dd, J = 15.6, 10.2 Hz, 1H), 7.16-7.19 (m, 1H), 7.26-7.29 (m, 2H), 7.34-7.36 (m, 2H); ^{13}C NMR (75 MHz) δ 29.0, 32.1, 62.0, 126.0, 127.0, 128.4, 129.1, 130.2, 130.9, 134.6, 137.4; **Analysis of mixture** IR (neat) 3130-3600, 1668, 1625 (weak), 1596, 1569 (weak) cm^{-1}; MS (EI) *m/z* (%): 188 (M^+, 64),

170 (6), 169 (8), 155 (34), 141 (48), 128 (100), 115 (61), 104 (27), 91 (86), 77 (34); HRMS (EI) Calcd for $C_{13}H_{16}O$ 188.1201, found 188.1206.

Formation of 1,3-butadiene 216 from trans-cinnamaldehyde

(3-Hydroxybutyl)(triphenyl)phosphonium chloride

4-Chloro-butan-1-ol (20.0 g = 18.4 mL, 184 mmol) and triphenylphosphine (48.32 g, 184 mmol) were heated neat at 160°C (oil bath temperature) for 16 hours. Diethyl ether (100 mL) was added to the cooled flask and the white solid broken up into a fine powder. The diethyl ether was decanted from the solid and fresh diethyl ether added and the precipitate stirred for 16 hours. The salt was collected by suction filtration and dried to afford 29.0 g, 42% of (3-hydroxybutyl)(triphenyl)phosphonium chloride as a white powder.

(4*Z*,6*E*) and (4*E*,6*E*)-7-Phenyl-4,6-heptadien-1-ol (216)

Method 2: To a suspension of (3-hydroxybutyl)(triphenyl)phosphonium chloride (15.1 g, 40.7 mmol) in anhydrous THF (150 mL) at -10°C was added a 1.9 M solution of *n*-BuLi (19.9 mL, 37.8 mmol). After stirring for 10 minutes at –10°C, stirring was ceased to allow the precipitate to settle. The solution was then canulated into a solution of *trans*-cinnamaldehyde (5.09 g, 38.5 mmol) in anhydrous THF (50 mL). The solution was allowed to warm to ambient temperature and stirred for 16 hours at this temperature. Work up was identical to that previously given for 1,3-butadienes **216**. Yield: 1.16 g, 16%.

3-(6-Phenyl-3,6-dihydro-1,2-dioxin-3-yl)-1-propanol (211)

Prepared by photolysis of 1,3-Butadienes **216** by the general procedure for 1,2-dioxine synthesis. Yield: 1.76 g, 43%; Colourless oil; R_f 0.27 (2:3 ethyl acetate:hexanes); IR (neat) 3180-3600, 1599 (weak) cm^{-1}; ^1H NMR (300 MHz) δ 1.66-1.89 (m, 5H), 3.67 (t, J = 6.0 Hz, 2H), 4.56-4.61 (m, 1H), 5.53-5.55 (m, 1H), 6.05-6.15 (m, 2H), 7.33-7.40 (m, 5H); ^{13}C NMR (75 MHz) δ 28.8, 29.5, 60.4, 78.3, 80.3, 126.7, 128.5, 128.8, 137.4; MS (EI) *m/z* (%): 220 (M^+, 5), 188 (100), 170 (6), 155 (14). HRMS Calcd for $C_{13}H_{16}O_3$ 220.10994, found 220.10920.

Preparation of THP's 217 and 218 and 1,4-diketone 219 from 1,2-dioxine 211

To a 0.1 M solution of 1,2-dioxine **211** or *trans* enone **220** in THF or $CHCl_3$ was added LiOH (1 equiv.) or DABCO (0.4 equiv.), respectively. After stirring for 16 hours at ambient temperature the reaction mixture was taken to dryness and the residue purified by flash chromatography. Combined yield of **217** and **218** from LiOH treatment of 1,2-

dioxine **211** (82%) or *trans* enone **220** (75%). Combined yield of **218** and **219** from DABCO treatment of 1,2-dioxine **211** (82%).

(±) 2-[(2*S*,3*R*)-3-Hydroxytetrahydro-2*H*-2-pyranyl]-1-phenyl-1-ethanone (217)

White needles; m.p. 94-96°C; R_f 0.48 (3:2 ethyl acetate:hexanes); IR (nujol) 3503, 1669, 1594, 1579 cm^{-1}; ^1H NMR (600 MHz) δ 1.46 (dddd, J = 12.0, 12.0, 12.0, 5.4 Hz, 1H), 1.66-1.74 (m, 2H), 2.14-2.19 (m, 1H), 2.32 (d, J = 6.0 Hz, 1H), 3.24 (dd, J = 16.2, 7.2 Hz, 1H), 3.37 (ddd, J = 11.4, 11.4, 3.6 Hz, 1H), 3.41 (dd, J = 16.2, 4.2 Hz, 1H), 3.40-3.44 (m, 1H), 3.70 (ddd, J = 9.0, 7.2, 4.2 Hz, 1H), 3.85-3.88 (m, 1H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 7.97-8.00 (m, 2H); ^{13}C NMR (150 MHz) δ 25.6, 33.2, 42.3, 67.8, 70.7, 78.9, 128.4, 128.5, 133.2, 137.2, 199.6; MS (EI) *m/z* (%): 221(M^+, 82), 203 (100). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32 : found C, 70.92; H, 7.39.

Details of crystal structure determination of 217.

Crystal data for $C_{13}H_{16}O_3$: M = 220.3, T = 223(2) K, orthorhombic, $P2_12_12_1$, a = 5.7086(3), b = 13.0589(7), c = 15.2878(8) Å, V = 1139.68(10) $Å^3$, Z = 4, D_x = 1.284, $F(000)$ = 472, μ = 0.090 mm^{-1}, no. of unique data (Bruker AXS SMART CCD using Mo Kα radiation so that θ_{max} = 30.0°) = 3280, no. of parameters = 145, R (all data) = 0.073, wR (all data) = 0.179, ρ = 0.51 e $Å^{-3}$. The structure was solved by direct-methods (SIR92) and refined (anisotropic displacement parameters, H atoms in the riding model approximation and a weighting scheme $w = 1/[\sigma^2(F_o^2) + 0.0933P^2 + 0.3462P]$ where $P = (F_o^2 + 2F_c^2)/3$) with SHELXL-97 on F^2 using all reflections. The absolute configuration was not determined unambiguously.

(±) 2-[(2*S*,3*S*)-3-Hydroxytetrahydro-2*H*-2-pyranyl]-1-phenyl-1-ethanone (218)

Colourless oil; R_f 0.25 (3:2 ethyl acetate:hexanes); IR (neat) 3200-3600, 1683, 1597, 1580 cm^{-1}; ^1H NMR (600 MHz) δ 1.42-1.46 (m, 1H), 1.76-1.82 (m, 1H), 1.88-1.94 (m, 1H), 1.96-2.00 (m, 1H), 2.19 (d, J = 9.0 Hz, 1H), 3.19 (dd, J = 16.8, 6.6 Hz, 1H), 3.32 (dd, J = 16.8, 6.6 Hz, 1H) 3.55 (ddd, J =12.6, 12.0, 3.0 Hz, 1H), 3.75-3.79 (m, 1H), 3.94-3.98 (m, 1H), 4.07 (ddd, J = 6.6, 6.6, 1.2 Hz, 1H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 7.97-7.99 (m, 2H); ^{13}C NMR (150 MHz) δ 19.9, 30.4, 40.7, 66.6, 68.6, 76.3, 128.2, 128.5, 133.2, 137.1, 198.2; MS (EI) *m/z* (%): 221 ($[M+H]^+$, 8), 202 (27), 105 (100). No microanalysis was obtained as compound **218** was unstable and decomposed to furan **221**. The corresponding acetate **223** was fully characterised.

7-Hydroxy-1-phenyl-1,4-heptanedione (219)

Colourless oil; R_f 0.42 (3:2 ethyl acetate:hexanes); IR (neat) 3200-3600, 1712, 1683, 1597, 1581 cm^{-1}; ^1H NMR (300 MHz) δ 1.83-2.04 (m, 2H), 2.70 (t, J = 6.6 Hz, 2H), 2.88 (t, J = 6.3 Hz, 2H), 3.31 (t, J = 6.3 Hz, 2H), 3.66 (t, J = 6.3 Hz, 2H), 4.92 (br s, 1H), 7.42-7.49 (m, 2H), 7.53-7.60 (m, 1H), 7.95-8.00 (m, 2H). ^{13}C NMR (75 MHz) δ 26.6, 32.5, 36.3, 39.5, 62.1, 128.0, 128.6, 133.2, 136.6, 198.7, 210.0; The diketone was unstable and was therefore fully characterised as its corresponding acetate **224**.

(*E*)-4,7-Dihydroxy-1-phenyl-2-hepten-1-one (220)

To a solution of 1,2-dioxine **211** (160 mg, 0.73 mmol) in acetone (7 mL) was added triphenylphosphine (95.3 mg, 0.36 mmol) and triethylamine (16 drops). The solution was stirred for 2 hours and monitored by TLC until all 1,2-dioxine was consumed. Once complete the volatiles were removed *in vacuo* and the residue purified by flash chromatography (100% ethyl acetate) to give 134 mg 84% of *trans* enone **220** as a colourless oil; R_f 0.11 (3:2 ethyl acetate:hexanes); The *trans* enone **220** was used immediately due to its instability.

3-(5-Phenyl-2-furyl)-1-propanol (221)[272]

Colourless oil; IR (neat) 3200-3500, 2945, 2948, 1610, 1595, 1578, 1548, 1487 cm^{-1}; ^1H NMR (300 MHz) δ 1.60 (br s, 1H), 1.91-2.04 (m, 2H), 2.79 (t, J = 7.8 Hz, 2H), 3.73 (t, J = 6.3 Hz, 2H), 6.09 (dt, J = 3.3, 0.9 Hz, 1H), 6.54 (d, J = 3.3 Hz, 1H), 7.18-7.24 (m, 1H), 7.32-7.38 (m, 2H), 7.60-7.64 (m, 2H); ^{13}C NMR (75 MHz) δ 24.5, 31.0, 62.1, 105.6, 107.3, 123.3, 126.8, 128.6, 131.0, 152.4, 155.3.

Preparation of acetates 222-224

To a 0.1 M solution of 1,2-dioxine **211** or *trans* enone **220** in THF or $CHCl_3$ was added LiOH (1 equiv.) or DABCO (0.4 equiv.), respectively. After stirring for 16 hours at ambient temperature the reaction mixture was filtered through a 1 cm pad of silica in a 1 mL glass pipette. The silica was washed with 3:2 ethyl acetate:hexanes (5 mL) and the combined eluting solvents concentrated in *vacuo*. Pyridine (15 equiv.), acetic anhydride (9 equiv.) and DMAP (0.2 equiv) were then added to the combined pyrans and/or diketone and the solution stirred overnight. Dichloromethane was then added and the solution extracted with water and the organic layer dried ($MgSO_4$), filtered and the volatiles removed *in vacuo*. The crude pyrans were purified by column chromatography. Combined yield of **222** and **223** from LiOH treatment of 1,2-dioxine **211** was 64% (two steps).

Combined yield of **223** and **224** from DABCO treatment of 1,2-dioxine **211** was 69% (two steps). Reactions of *trans* enone **220** gave similar yields.

(±) (2*S*,3*R*)- 2-(2-Oxo-2-phenylethyl)tetrahydro-2*H*-3-pyranyl acetate (222)

Colourless oil; R_f 0.25 (1:3 ethyl acetate:hexanes); IR (neat) 1732, 1683, 1598, 1581 cm^{-1}; ^1H NMR (600 MHz) δ 1.52 (dddd, J = 12.6, 10.8, 10.8, 4.2 Hz, 1H), 1.67-1.71 (m, 1H), 1.73-1.81 (m, 1H), 1.96 (s, 3H), 2.17-2.24 (m, 1H), 3.03 (dd, J = 16.2, 3.6 Hz, 1H), 3.19 (dd, J = 16.2, 8.4 Hz, 1H), 3.42 (ddd, J = 12.0, 12.0, 2.4 Hz, 1H), 3.86-3.90 (m, 1H), 3.99 (ddd, J = 9.6, 8.4, 3.6 Hz, 1H), 4.64 (ddd, J = 10.8, 9.6, 4.8 Hz, 1H), 7.44-7.48 (m, 2H), 7.54-7.57 (m, 1H), 7.95-7.97, (m, 2H); ^{13}C NMR (150 MHz) δ21.1, 25.2, 29.4, 41.5, 67.8, 72.0, 76.3, 128.3, 128.6, 133.1, 137.2, 170.3, 197.8; MS (EI) *m/z* (%): 263 ($[M+H]^+$, 27), 202 (12), 174 (1), 105 (100), 77 (27), 71 (11), 43 (46); Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92; Found C, 68.04; H, 6.71.

(±) (2*S*,3*S*)- 2-(2-Oxo-2-phenylethyl)tetrahydro-2*H*-3-pyranyl acetate (223)

Colourless oil; R_f 0.38 (1:3 ethyl acetate:hexanes); IR (neat) 1732, 1682, 1598, 1581 cm^{-1}; ^1H NMR (600 MHz) δ 1.42-1.46 (m, 1H), 1.78-1.84 (m, 1H), 1.87-1.95 (m, 1H), 2.02-2.09 (m, 1H), 2.13 (s, 3H), 2.97 (dd, J = 16.8, 5.4 Hz, 1H), 3.29 (dd, J = 16.8, 7.2 Hz, 1H), 3.57 (ddd, J = 12.6, 11.4, 2.4 Hz, 1H), 3.99-4.02 (m, 1H), 4.19 (ddd, J = 7.2, 5.4, 1.8 Hz, 1H), 4.96-4.98 (m, 1H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 7.93-7.95 (m, 2H); ^{13}C NMR (150 MHz) δ 20.5, 21.1, 27.8, 40.6, 68.2, 69.2, 74.4, 128.1, 128.5, 133.2, 137.0, 170.6, 197.3; MS (EI) *m/z* 263 ($[M+H]^+$, 71), 202 (52), 174 (5), 105 (71), 77 (51), 71 (34), 43 (100). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H:6.92: found C, 68.43; H, 7.02.

4,7-Dioxo-7-phenylheptyl acetate (224)

Colourless oil; R_f 0.25 (3:7 ethyl acetate:hexanes); IR (neat) 1738, 1715, 1684, 1597, 1582 cm^{-1}; ^1H NMR (300 MHz) δ1.91-2.00 (m, 2H), 2.05 (s, 3H), 2.64 (t, J = 7.2 Hz, 2H), 2.86 (t, J = 6.3 Hz, 2H), 3.30 (t, J = 6.3 Hz, 2H), 4.09 (t, J = 6.3 Hz, 2H), 7.43-7.49 (m, 2H), 7.53-7.59 (m, 1H), 7.96-8.00 (m, 2H); ^{13}C NMR (75 MHz) δ20.8, 22.7, 32.3, 36.1, 39.0, 63.5, 127.9, 128.5, 133.0, 136.6, 170.9, 198.4, 208.2; MS (EI) *m/z* (%): 262 (M^+, 18), 234 (1), 219 (3), 202 (5), 176 (27), 161 (49), 133 (15), 105 (100); Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92; Found C, 68.25; H, 6.89.

General procedure for formation of α,β-unsaturated esters 226[176]

Methyl (triphenylphosphoranylidene)acetate or ethyl (triphenylphosphoranylidene)-acetate (1.05 equiv) was added to a solution of aldehyde **225** (1 equiv.) in anhydrous dichloromethane (10 mL / g) under an inert atmosphere (N_2). The solution was stirred for 16 hours at 22°C. Solvent was removed and the resulting solid purified by flash chromatography to give the desired α,β-unsaturated ester.

Ethyl (*E*)-3-(4-bromophenyl)-2-propenoate (226b)[273]

Yield: 10.68 g, 100%; Colourless oil; ^{1}H NMR (300 MHz) δ1.27 (t, J = 6.9 Hz, 3H), 4.22 (q, J = 6.9 Hz, 2H), 6.32 (d, J = 15.9 Hz, 1H), 7.33-7.35 (m, 4H), 7.59, (d, J = 15.9 Hz, 1H).[273]

Methyl (*E*)-3-(2-naphthyl)-2-propenoate (226c)[176]

Yield: 6.80 g, 99%; White solid; m.p. 90–93 °C (lit.[274] 89–91°C); R_f 0.77 (2:3 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ3.83 (s, 3H), 6.55 (d, J = 15.9 Hz, 1H), 7.48-7.54 (m, 2H), 7.66 (dd, J = 8.4, 1.8 Hz, 1H), 7.82-7.89 (m, 4H), 7.92 (br s, 1H).[176]

General procedure for formation of α,β-unsaturated alcohols 227[176]

To a cooled solution (-78°C) of α,β-unsaturated ester **226** (1 equiv.) in dry dichloromethane under N_2 was added dropwise a 1.5 M solution of DIBAL in toluene (2.1 equiv.) over 30-60 minutes. The reaction was quenched after stirring for 90 minutes at -78°C by the slow addition of 10% aqueous NaOH solution at this temperature. The solution was warmed to 22°C and the organic phase separated. The aqueous phase was further extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered and concentrated to give the desired alcohol.

(*E*)-3-(4-Bromophenyl)-2-propen-1-ol (227b) [275]

Yield: 8.23 g, 98%; White solid; m.p. 54–57 °C (lit.[275] 56–59 °C); ^{1}H NMR (300 MHz) δ 2.40 (br s, 1H), 4.16 (d, J = 5.7 Hz, 2H), 6.13 (dt, J = 15.3, 5.7 Hz, 1H), 6.42, (d, J = 15.3 Hz, 1H), 7.03, (d, J = 6.9 Hz, 2H), 7.24 (d, J = 6.9 Hz, 2H).

(*E*)-3-(2-Naphthyl)-2-propen-1-ol (227c)[176]

Yield: 5.26 g, 97%; White platelets; m.p. 109–112 °C (lit.[276] 112-114°C); R_f 0.38 (2:3 ethyl acetate:hexanes); ^{1}H NMR (200 MHz) δ1.59 (br s, 1H), 4.38 (t, J = 5.6 Hz, 2H), 6.49 (dt, J = 16.0, 5.6 Hz, 1H), 6.79 (d, J = 16.0 Hz, 1H), 7.42-7.50 (m, 2H), 7.60 (dd, J = 8.6, 1.8 Hz, 1H), 7.73-7.83 (m, 4H).[176]

General procedure for formation of α,β-unsaturated aldehydes 228[178]

To a solution of α,β-unsaturated alcohol **227** (1 equiv.) in dry dichloromethane was added PDC (1.5 equiv.). After stirring for 24 hours at 22°C, the solution was diluted by half with diethyl ether and hexane (1:1) and filtered through silica (5 cm). The silica was washed with 2:3 ethyl acetate:hexanes until all aldehyde had been removed from the silica.. The combined filtrate was concentrated to give the desired aldehyde. The aldehyde was used without further purification.

(*E*)-3-(4-Bromophenyl)-2-propenal (228b)[277]

Yield: 6.64 g, 82%; White solid; m.p. 77–80 °C (lit.[277] 80 °C); ^{1}H NMR (300 MHz) δ 6.71 (dd, J = 16.2, 7.5 Hz, 1H), 7.40-7.46 (m, 3H), 7.55-7.59 (m, 2H), 9.71 (d, J = 7.5 Hz, 1H).

(*E*)-3-(2-Naphthyl)-2-propenal (228c)[271]

Yield: 2.36 g, 92%; Pale yellow plates; m.p. 122–125 °C (lit.[271] 126–127 °C); R_f 0.42 (1:4 ethyl acetate:hexanes). ^{1}H NMR (300 MHz) δ 6.80 (dd, J = 15.6, 7.8 Hz, 1H), 7.51-7.57 (m, 2H), 7.64 (dd, J = 8.7, 1.8 Hz, 1H), 7.81-7.88 (m, 4H), 7.94 (br s, 1H) 9.75 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz) δ 123.5, 126.9, 127.7, 127.8, 128.6, 128.7, 128.9, 130.6, 131.5, 133.1, 134.6, 152.6, 193.5.

General procedure for formation of protected 1,3-butadienes 230

To a cooled suspension (-10 to -15°C) of phosphonium salt **229** (1.05 equiv.) in anhydrous THF (10 mL / g of ylide salt) was added dropwise and with stirring a solution of *n*-BuLi in hexanes (1.05 equiv.). After stirring for 30 minutes a solution of aldehyde **170a** or **228a-b** (1 equiv.) in anhydrous THF (10 mL / g of aldehyde) was added at -10°C. After stirring for 16 hours at 22°C, protected from light, the solution was diluted by half with hexanes and filtered through silica (3 cm). The silica was washed with 2:3 ethyl acetate:hexanes until all diene had been removed and the combined filtrates taken to dryness. The residue obtained was further purified by flash chromatography to give a mixture of *Z,E* and *E,E* dienes.

4-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}butyl)(triphenyl)phosphonium iodide (229)

1-[(*tert*-butyldimethylsilyl)oxy]-4-iodobutane[231] (20.4 g, 64.9 mmol) and triphenylphosphine (22.13 g, 84.4 mmol) were melted together at 90°C (oil bath temp) for 3 hours. Diethyl ether (100 mL) was added to the cooled solution. The white precipitate was broken up into a fine powder and stirred for 2 hours prior to collection by vacuum

filtration. The powder was washed with diethyl ether (3 x 100 mL) and dried *in vacuo* to give 31.42 g, 84% of phosphonium salt **229** as a white powder. Decomposed below m.p.

***tert*-Butyl{[(4*Z*,6*E*)-7-(4-methoxyphenyl)-4.6-hepta-dienyl]oxy} dimethylsilane and *tert*-Butyl{[(4*E*,6*E*)-7-(4-methoxyphenyl)-4.6-hepta-dienyl]oxy} dimethylsilane (230a)**
Yield: 2.78 g, 79%; White solid; R_f 0.69 (1:19 ethyl acetate:hexanes); The protected diene was fully characterised as its corresponding hydroxy derivative.

{[4*Z*,6*E*-7-(4-Bromophenyl)-4,6-heptadienyl]oxy}(*tert*-butyl)dimethylsilane and {[4*Z*,6*E*-7-(4-Bromophenyl)-4,6-heptadienyl]oxy}(*tert*-butyl)dimethylsilane (230b)
Yield: 6.96 g, 86%; Colourless oil; R_f 0.65 (1:19 ethyl acetate:hexanes); The protected diene was fully characterised as its corresponding hydroxy derivative.

{[4*Z*,6*E*-7-(2-Naphthyl)-4,6-heptadienyl]oxy}(*tert*-butyl)dimethylsilane and {[4*E*,6*E*-7-(2-Naphthyl)-4,6-heptadienyl]oxy}(*tert*-butyl)dimethylsilane (230c)
Yield: 2.11 g, 70%; Yellow powder; Obtained as a 47:53 mixture of 4*Z*,6*E* : 4*E*,6*E* isomers; R_f 0.42 (1:4 ethyl acetate:hexanes); The protected diene was fully characterised as its corresponding hydroxy derivative.

General procedure for TBDMS cleavage to afford 1,3-butadienes 231[166]
To a solution of protected 1,3-butadiene **230a-c** (1 equiv.) in dry THF (10 mL / g of diene) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (1.5 equiv.). The solution was stirred for at 22°C protected from light until TLC analysis (1:9 ethyl acetate:hexanes) indicated that all protected diene had been cleaved (4-16 hours). The solution was concentrated and the resulting residue purified by flash chromatography to give a mixture of 4*Z*,6*E* and 4*E*,6*E*-hydroxy dienes.

(4*Z*,6*E*) and (4*E*,6*E*)-7-(4-Methoxyphenyl)-4,6-heptadien-1-ol (231a)
Yield: 1.78 g, 98%; Colourless oil; Obtained as a 2:3 mixture of 4*Z*,6*E* : 4*E*,6*E* isomers; A small amount of each isomer was isolated; **(4*Z*,6*E*)-7-(4-Methoxyphenyl)-4,6-heptadien-1-ol:** R_f 0.41 (7:13 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 1.65-1.74 (m, 3H), 2.33-2.42 (m, 2H), 3.69 (t, J = 6.6 Hz, 2H), 3.80 (s, 3H), 5.47 (dt, J = 10.8, 7.8 Hz, 1H), 6.13-6.20 (m, 1H), 6.48 (d, J = 15.6 Hz, 1H), 6.82-6.87 (m, 2H), 6.95 (ddd, J = 15.6, 10.8, 1.2 Hz, 1H), 7.32-7.37 (m, 2H); ^{13}C NMR (300 MHz) δ 24.2, 32.4, 55.2, 62.2, 114.0, 122.6, 127.5, 129.5, 130.3, 130.8, 131.9, 159.1; **(4*E*,6*E*)-7-(4-Methoxyphenyl)-4,6-heptadien-1-ol:** R_f 0.39 (7:13 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 1.57 (br s, OH), 1.57-1.67

(m, 2H), 2.16-2.27 (m, 2H), 3.67 (t, J = 6.6 Hz, 2H), 3.79 (s, 3H), 5.77 (dt, J = 15.3, 7.8 Hz, 1H), 6.17-6.26 (m, 1H), 6.40 (d, J = 15.6 Hz, 1H), 6.95 (dd, J = 15.6, 10.5 Hz, 1H) 6.81-6.89 (m, 2H), 7.28-7.37 (m, 2H); ^{13}C NMR (75 MHz) δ24.2, 32.3, 55.3, 62.4, 114.0, 127.2, 127.3, 130.0, 130.4, 131.2, 133.4, 159.0; **Analysis of mixture:** IR (neat) 3100-3500, 1602, 1511 cm^{-1}; MS (EI) *m/z* (%): 234 ([M + H_2O]$^+$, 16), 218 (M$^+$, 100), 187 (6), 173 (30), 163 (28), 147 (35), 121 (41), 108 (10), 91 (18), 71 (23), 43 (12); HRMS (EI) calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1302.

(4*Z*,6*E*) and (4*E*,6*E*)-7-(4-Bromophenyl)-4,6-heptadien-1-ol (231b)

Yield : 2.46 g, 50%; Pale yellow solid; m.p. 90 °C; Obtained as a 2:3 mixture of 4*Z*,6*E* : 4*E*,6*E* isomers; A small amount of each isomer was isolated; **(4*Z*,6*E*)-7-(4-Bromophenyl)-4,6-heptadien-1-ol:** R_f 0.71 (1:1 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 1.64-1.74 (m, 2H), 1.98 (br s, 1H), 2.33-2.41 (m, 2H), 3.65 (t, J = 6.6 Hz, 2H), 5.55 (dt, J = 10.5, 7.5 Hz, 1H), 6.12-6.24 (m, 1H), 6.44 (d, J = 15.9 Hz, 1H), 7.05 (ddd, J = 15.9, 11.1, 1.2 Hz, 1H), 7.18-7.27 (m, 2H), 7.37-7.43 (m, 2H); ^{13}C NMR (75 MHz) δ24.3, 32.3, 62.1, 121.0, 124.8, 127.8, 129.1, 131.0, 131.6, 132.7, 136.42; MS (EI) *m/z* 268 ([M + H]$^+$, 54), 266 (55), 221 (20), 197 (4), 182 (14), 169 (68), 142 (100), 128 (60), 91 (20), 84 (28), 51 (14), 39 (23); **(4*E*,6*E*)-7-(4-Bromophenyl)-4,6-heptadien-1-ol:** R_f 0.61 (1:1 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 1.50 (br s, 1H), 1.66-1.75 (m, 2H), 2.21-2.28 (m, 2H), 3.68 (t, J = 6.6 Hz, 2H), 5.85 (dt, J = 15.0, 7.8 Hz, 1H), 6.18-6.26 (m, 1H), 6.37 (d, J = 15.6 Hz, 1H), 6.73 (dd, J = 15.6, 7.5 Hz, 1H), 7.20-7.25 (m, 2H), 7.39-7.43 (m, 2H); ^{13}C NMR (300 MHz) (4*E*,6*E*) δ 29.1, 32.1, 62.3, 120.8, 127.6, 129.1, 129.9, 130.8, 131.6, 135.5, 136.5; MS (EI) *m/z* (%): 268 ([M + H]$^+$, 100), 266 (100), 221 (17), 182 (11), 169 (51), 142 (74), 128 (46), 91 (19), 84 (33), 51 (12), 39 (21). **Analysis of mixture:** IR (nujol) 3200-3500, 1641 (weak), 1583 (weak), 1487 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{15}OBr$ 266.0307, found 266.0309.

(4*Z*,6*E*)-7-(2-Naphthyl)-4,6-heptadien-1-ol and (4*E*,6*E*)-7-(2-Naphthyl)-4,6-heptadien-1-ol (231c)

Yield: 1.22 g, 88%; Pale yellow crystals; Obtained as a 37:63 mixture of 4*Z*,6*E*^{a} : 4*E*,6*E*^{b} isomers; R_f 0.68^a and 0.61^b (3:2 ethyl acetate:hexanes); IR (nujol) 3100-3550, 1621 (weak), 1590 (weak), 1506 (weak) cm^{-1}; ^{1}H NMR (600 MHz) δ 1.34 (br s, 2H)^{a,b}, 1.70-1.77 (m, 4H)^{a,b}, 2.27 (dq, J = 7.8, 1.8 Hz, 2H)^b, 2.44 (dq, J = 7.8, 1.8 Hz, 2H)^a, 3.70 (t, J = 6.6 Hz, 2H)^b, 3.72 (t, J = 6.6 Hz, 2H)^a, 5.57 (dt, J = 10.8, 7.8 Hz, 1H)^a, 5.88 (dt, J = 15.6,

7.8 Hz, 1H)[b], 6.23-6.32 (m, 2H)[a,b], 6.61 (d, *J*=15.6Hz, 1H)[b], 6.70 (d, *J*=15.6Hz, 1H)[a], 6.87 (dd, *J* = 15.6, 10.2 Hz, 1H)[b], 7.20 (ddd, *J* = 15.6, 11.4, 1.8 Hz, 1H)[a], 7.39-7.46 (m, 4H)[a,b], 7.59-7.66 (m, 2H)[a,b], 7.70-7.80 (m, 8H)[a,b]; ^{13}C NMR (150 MHz) δ 24.3, 29.1, 32.1, 32.4, 62.1, 62.2, 123.4, 123.5, 124.5, 125.6, 125.7, 125.9, 126.1, 126.2, 127.6, 127.8, 127.9, 128.1, 128.1, 129.4, 129.5, 130.4, 131.1, 132.2, 132.5, 132.8, 132.9, 133.6, 134.9, 135.0; MS (EI) *m/z* (%): 238.3 (M^+, 94), 219.2 (11), 191.2 (43), 179.2 (100). HMRS Calcd for $C_{17}H_{18}O$ 238.1358, found 238.1356.

General procedure for grignard addition to γ-butyrolactone[232]

To a solution of γ-butyrolactone (1 equiv.) in dry diethyl ether (10 mL / g) was added dropwise and in excess a solution of grignard reagent (Methyl or Phenyl magnesium bromide, 3 equiv.) at 22°C and under an inert atmosphere (N_2). After the addition of grignard reagent was complete the solution was stirred for a further 6 hours at 22°C. The reaction was quenched by the slow addition of saturated aqueous NH_4Cl. The solution was taken to dryness and the residue obtained extracted several times with dichloromethane. The organic phases were combined, dried ($MgSO_4$), filtered and concentrated to give the crude diol. The diol was used without further purification.

4-Methyl-1,4-pentanediol[232]

Yield: 3.67 g, 67%; Pale yellow oil; ^{1}H NMR (200 MHz) δ 1.24 (s, 6H), 1.50-1.72 (m, 4H), 3.19 (br s, 2H), 3.64 (t, *J* = 6.0 Hz, 2H).

1,1-Diphenyl-1,4-butanediol

Yield: 6.23 g, 71%; Pale white crystals; Recrystallised from dichloromethane/hexane; m.p. 102–105 °C; ^{1}H NMR (300 MHz) δ 1.53-1.62 (m, 2H), 1.96 (br s, 1H), 2.42 (t, *J* = 7.2 Hz, 2H), 3.23 (br s, 1H), 3.65 (t, *J* = 6.0 Hz, 2H), 7.18-7.34 (m, 6H), 7.39-7.44 (m, 4H).

General procedure for Swern oxidation[278]

To a 0.5 M solution of oxalyl chloride (2 equiv.) in dry dichloromethane at -78°C and under a nitrogen atmosphere was added dry DMSO (4 equiv.). After stirring for 10 minutes at this temperature a solution of 4-methyl-1,4-pentanediol or 1,1-diphenyl-1,4-butanediol (1 equiv.) in anhydrous dichloromethane (10 mL / g of alcohol) was added. The solution was stirred for 1 hour at -78°C prior to the addition of triethylamine (4.5 equiv.). After stirring for 5 minutes at -78°C the solution was warmed to 22°C and stirred for a further 15 minutes at this temperature. The reaction was quenched by the addition of water. The

organic phase was separated and the aqueous phase further extracted with dichloromethane. The combined organic phases were washed with water, dried (Na_2SO_4), filtered and concentrated to give the crude aldehyde. The aldehyde was assumed to be in 100% yield and used without further purification in the next step.

5,5-Dimethyltetrahydro-2-furanol (233a) / 4-Hydroxy-4-methylpentanal (234a)
Pale yellow oil. The aldehyde was assumed to be in 100% yield and used without further purification in the next step.

5,5-Diphenyltetrahydro-2-furanol (233b) / 4-Hydroxy-4,4-diphenylbutanal (234b)
Pale yellow crystals. The aldehyde was assumed to be in 100% yield and used without further purification in the next step.

General procedure for Wittig reaction
Potassium *tert*-butoxide (1.05 equiv.) was added to a suspension of cinnamyl phosphonium salt **144a** (1.1 equiv.) in dry diethyl ether (10 mL / g of ylide salt) at 22°C and under an inert atmosphere (N_2). After stirring for 15 minutes the solution was cooled to 0°C and a solution of **233a-b / 234a-b** (1 equiv.) in dry diethyl ether or THF (10 mL / g of aldehyde) was added. After stirring for 48 hours at 22°C the solution was diluted by half with hexanes and filtered through silica (3 cm). The silica was washed with 2:3 ethyl acetate:hexanes until all diene had been removed. The combined filtrates were taken to dryness and the resulting residue was purified by flash chromatography.

(5*Z*,7*E*)- and (5*E*,7*E*)-2-Methyl-8-phenyl-5,7-octadien-2-ol (231d)
Yield: 0.92 g, 22% (two steps): Obtained as a 7:13 mixture of 5*Z*,7*E* : 5*E*,7*E* isomers. A small amount of each isomer was isolated. **(5*Z*,7*E*)-2-methyl-8-phenyl-5,7-octadien-2-ol:** Pale yellow oil; R_f 0.23 (1:4 ethyl acetate:hexanes); IR (neat) 3200-3600, 1594, 1574 cm^{-1}; ^1H NMR (300 MHz) δ 1.28 (s, 6H), 1.47 (s, 1H), 1.60-1.63 (m, 2H), 2.37-2.42 (m, 2H), 5.40 (dt, J = 10.8, 7.8 Hz, 1H), 6.14-6.19 (m, 1H), 6.40 (d, J = 15.6 Hz, 1H), 7.07 (ddd, J = 15.6, 11.4, 1.2 Hz, 1H), 7.20-7.23 (m, 1H), 7.30-7.33 (m, 2H), 7.40-7.42 (m, 2H); ^{13}C NMR (75 MHz) δ 23.0, 29.3, 43.5, 70.9, 124.1, 126.3, 127.4, 128.5, 128.8, 132.3, 132.7, 137.5; **(5*E*,7*E*)-2-methyl-8-phenyl-5,7-octadien-2-ol:** Pale yellow crystals; R_f 0.16 (1:4 ethyl acetate:hexanes); IR (nujol) 3100-3400, 1642 (weak), 1594, 1575 cm^{-1}; ^1H NMR (300 MHz) δ 1.25 (s, 6H), 1.45 (s, 1H), 1.60-1.63 (m, 2H), 2.23-2.27 (m, 2H), 5.85 (dt, J = 13.8, 7.2 Hz, 1H), 6.22-6.27 (m, 1H), 6.45 (d, J = 15.6 Hz, 1H), 6.74 (dd, J = 15.6, 10.2 Hz, 1H),

7.18-7.21 (m, 1H), 7.28-7.31 (m, 2H), 7.36-7.38 (m, 2H); ^{13}C NMR (300 MHz) δ 27.8, 29.3, 43.1, 70.8, 126.1, 127.1, 128.5, 129.2, 130.2, 130.6, 135.4, 137.6; **Analysis of mixture:** MS (EI) *m/z* (%): 216.2 (M^+, 25), 198.1 (44), 143.1 (100). HRMS Calcd for $C_{15}H_{20}O$ 216.1514, found 216.1524.

(4*Z*,6*E*)- and (4*E*,6*E*)-1,1,7-Triphenyl-4,6-heptadien-1-ol (231e)

Yield: 1.52 g, 34% (two steps); Pale yellow oil; 18:82 4*Z*,6*E*^{a} : 4*E*,6*E*^{b}; R_f 0.27 (1:9 ethyl acetate:hexanes); IR (neat) 3559, 3472, 1667, 1643, 1596 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.13-2.19 (m, 5H, includes OH^b)^{a,b}, 2.39-2.44 (m, 5H, includes OH^a)^{a,b}, 5.54-5.64 (m, 1H)^b, 5.83 (dt, *J* = 15.6, 7.8 Hz, 1H)^a, 6.11-6.22 (m, 2H)^{a,b}, 6.42 (d, *J* = 15.6 Hz, 1H)^b, 6.48 (d, *J* = 15.6 Hz, 1H)^a, 6.72 (dd, *J* = 15.6, 10.8 Hz, 1H)^b, 6.79 (ddd, *J* = 15.6, 10.8, 1.2 Hz, 1H)^a, 7.16-7.46 (m, 30H)^{a,b}; MS (EI) *m/z* (%): 340 (M^+, 17), 322 (13), 281 (10), 231 (38), 205 (19), 180 (40), 165 (18), 142 (12), 128 (19), 115 (23), 105 (100). HRMS Calcd for $C_{25}H_{24}O$ 340.1827, found 340.1830.

1,2-Dioxines 235a-e

Prepared by photolysis of the precursor 1,3-butadienes by the general procedure for 1,2-dioxine synthesis unless otherwise noted.

3-[6-(4-Methoxyphenyl)-3,6-dihydro-1,2-dioxin-3-yl]-1-propanol (235a)

Yield: 354 mg, 23%; Colourless oil; R_f 0.40 (1:1 ethyl acetate:hexanes); IR (neat) 3100-3600, 1611, 1586, 1514 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.69-1.85 (m, 5H), 3.64-3.68 (m, 2H), 3.79 (s, 3H), 4.53-4.56 (m, 1H), 5.49-5.51 (m, 1H), 6.02-6.14 (m, 2H), 6.86-6.91 (m, 2H), 7.28-7.33 (m, 2H); ^{13}C NMR (75 MHz) δ 28.8, 29.5, 55.3, 62.5, 78.3, 79.9, 113.9, 126.8, 128.5, 129.3, 130.1, 160.1; MS (EI) *m/z* (%): 250 (M^+, 16), 232 (68), 231 (63), 218 (100), 217 (4), 187 (67), 163 (26), 135 (98), 121 (62), 109 (39), 81 (38), 55 (35), 39 (33); HRMS (EI) calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1209.

3-[6-(4-Bromophenyl)-3,6-dihydro-1,2-dioxin-3-yl]-1-propanol (235b)

Yield: 1.31 g, 54%; Colourless oil; R_f 0.36 (9:11 ethyl acetate:hexanes); IR (neat) 3100-3600, 1592 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.69-1.78 (m, 4H), 2.04 (br s, OH), 3.61-3.67 (m, 2H), 4.55-4.67 (m. 1H), 5.44-5.46 (m, 1H), 6.05-6.11 (m, 2H), 7.23-7.27 (m, 2H), 7.47-7.51 (m, 2H); ^{13}C NMR (75 MHz) δ 28.5, 29.2, 62.3, 78.2, 79.4, 122.8, 125.9, 129.0. 130.1, 131.6, 136.6; MS (EI) *m/z* (%): 268 ([M-O_2]$^+$, 85), 266 (86), 221 (7), 209 (2), 185

(19), 169 (29), 142 (16), 128 (11), 97 (11), 84 (100), 55 (18), 43 (30); HRMS (EI) calcd for $C_{13}H_{15}O_3Br$ 298.0205, found 298.0209.

3-[6-(2-Naphthyl)-3,6-dihydro-1,2-dioxin-3-yl]-1-propanol (235c)

Yield: 0.44 g, 39%; Orange oil; R_f 0.28 (2:3 ethyl acetate:hexanes); IR (neat) 3100-3600, 1723, 1693, 1664, 1600, 1508 cm^{-1}; ^1H NMR (300 MHz) δ1.50-1.90 (m, 4H), 2.54 (br s, 1H), 3.55 (t, J = 6.0 Hz, 2H), 4.53-4.56 (m, 1H), 5.63 (br s, 1H), 6.02-6.11 (m, 2H), 7.40-7.46 (m, 3H), 7.74-7.82 (m, 4H); ^{13}C NMR (75 MHz) δ28.5, 29.2, 62.1, 78.2, 80.1, 125.7, 126.0, 126.2, 126.3, 127.5, 127.8, 128.0, 128.1, 128.6, 133.0, 133.3, 134.8; MS (EI) *m/z* (%): 252.1 (M^+-H_2O, 100), 238.1 (57). No HMRS Calcd for $C_{17}H_{18}O_3$ since M^+ was not observable.

2-Methyl-4-(6-phenyl-3,6-dihydro-1,2-dioxin-3-yl)-2-butanol (235d)

A solution of diene **231d** (0.75 g, 3.5 mmol) in $CDCl_3$ (6 mL) was photolysed with a 500W halogen lamp in the presence of rose bengal *bis*(triethylammonium) salt (30 mg) and oxygen for 6 hours. The solution was concentrated and the resulting residue purified by flash chromatography (3:7 ethyl acetate:hexanes). Yield: 0.40 g, 46%; Colourless oil; R_f 0.24 (3:7 ethyl acetate:hexanes); IR (neat) 3200-3600, 1603(weak) cm^{-1}; ^1H NMR (300 MHz) δ1.18 (s, 6H), 1.47-1.58 (m, 1H), 1.65-1.87 (m, 3H), 1.94 (br s, 1H), 4.50-4.55 (m, 1H), 5.50-5.52 (m, 1H), 6.02-6.13 (m, 2H), 7.32-7.38 (m, 5H); ^{13}C NMR (75 MHz) δ27.8, 29.0, 29.2, 39.2, 70.3, 78.6, 80.1, 126.4, 128.4, 128.4, 128.5, 128.6, 137.4; MS (LSIMS in mnba) *m/z* (%): 231.1 ([M-OH]$^+$, 100), 215.1 (33), 198.1 (36). HRMS Calcd for [$C_{15}H_{20}O_3$–H_2O] 230.1307, found 230.1307.

1,1-Diphenyl-3-(6-phenyl-3,6-dihydro-1,2-dioxin-3-yl)-1-propanol (235e)

Yield: 0.82 g, 49%; Pale yellow powder; A small amount was recrystallised from dichloromethane/hexanes; m.p.132-135°C. R_f 0.16 (1:9 ethyl acetate:hexanes); IR (nujol) 3551, 1598 (weak) cm^{-1}; ^1H NMR (300 MHz) δ1.61-1.86 (m, 2H), 2.21 (s, 1H), 2.35 (ddd, J = 14.1, 11.1, 4.8 Hz, 1H), 2.57 (ddd, J = 14.1, 11.1, 4.8 Hz, 1H), 4.52-4.56 (m, 1H), 5.50 (br s, 1H), 5.97-6.05 (m, 2H), 7.17-7.42 (m, 15H); ^{13}C NMR (75 MHz) δ27.8, 37.4, 77.9, 78.3, 80.2, 126.0, 126.1, 126.7, 126.8, 126.8, 128.2, 128.5, 128.5, 128.7,137.6, 146.7, 146.9; MS (EI) *m/z* (%): 372 (M^+, 0.8), 354 (58), 183 (100), 105 (59). HRMS Calcd for $C_{25}H_{24}O_3$ 372.1725, found 372.1735.

General procedure for synthesis of *trans* γ-hydroxy enones 236

To a 0.1 M solution of 1,2-dioxine **235** in acetone was added triphenylphosphine (0.5 equiv.) followed by triethylamine (1 drop / 10 mg of 1,2-dioxine). The solution was stirred for 2 hours, closely monitored by TLC, once complete the volatiles were removed *in vacuo* and the crude *trans* γ-hydroxy enone purified by column chromatography.

(*E*)-4,7-Dihydroxy-1-(4-methoxyphenyl)-2-hepten-1-one (236a)

Yield: 299 mg, 84%; Colourless oil; R_f 0.20 (1:3 ethyl acetate:diethyl ether). Purified by flash chromatography (7:13 ethyl acetate:diethyl ether).

(*E*)-1-(4-Bromophenyl)-4,7-dihydroxy-2-hepten-1-one (236b)

Yield: 302 mg, 58 %; Colourless oil; R_f 0.20 (1:3 ethyl acetate:diethyl ether). Purified by flash chromatography (1:3 ethyl acetate:diethyl ether).

(*E*)-4,7-Dihydroxy-1-(2-naphthyl)-2-hepten-1-one (236c)

Yield: 375 mg, 83%; R_f 0.40 (100% ethyl acetate). Purified by flash chromatography (100% ethyl acetate).

(*E*)-4,7-Dihydroxy-7-methyl-1-phenyl-2-octen-1-one (236d)

Yield: 47.7 mg, 80%; Colourless oil; R_f 0.47 (100% ethyl acetate). Purified by flash chromatography (100% ethyl acetate).

(*E*)-4,7-Dihydroxy-1,7,7-triphenyl-2-hepten-1-one (236e)

Yield: 30 mg, 55%; Pale yellow solid; R_f 0.35 (2:3 ethyl acetate:hexanes). Purified by flash chromatography (2:3 ethyl acetate:hexanes).

General procedure for LiOH mediated pyran synthesis.

To a 0.1 M solution of 1,2-dioxine **235** or *trans* γ-hydroxy enone **236** in THF was added lithium hydroxide (1 equiv.) and the mixture stirred for 2-4 days. The volatiles were removed *in vacuo* and the crude pyrans were then purified by column chromatography. Pyridine (15 equiv.), acetic anhydride (9 equiv.) and DMAP (0.2 equiv.) were then added to the combined pyrans and the solution stirred overnight. Dichloromethane was then added and the solution extracted with water and the organic layer dried ($MgSO_4$), filtered and the volatiles removed *in vacuo*. The crude pyrans were purified by column chromatography. Typical combined isolated yields 52-76% (two steps from 1,2-dioxine **235**) or 53-76% (two steps from *trans* enone **236**).

General procedure for DABCO mediated pyran synthesis.

To a 0.1 M solution of 1,2-dioxine in chloroform was added DABCO (0.4 equiv.) and the mixture stirred overnight. The volatiles were removed *in vacuo* and the crude pyrans were then purified by column chromatography. Pyridine (15 equiv.), acetic anhydride (9 equiv.) and DMAP (0.2 equiv.) were then added to the combined pyrans and the solution stirred overnight. Dichloromethane was then added and the solution extracted with water and the organic layer dried ($MgSO_4$), filtered and the volatiles removed *in vacuo*. The crude pyrans were purified by column chromatography. Typical combined isolated yields 48-71% (two steps from 1,2-dioxine **235**).

(±) (2*S*,3*R*)- 2-[2-(4-Methoxyphenyl)-2-oxoethyl]tetrahydro-2*H*-3-pyranyl acetate (237a)

Colourless oil; R_f 0.30 (1:3 ethyl acetate:hexanes); IR (neat) 1732 (split), 1682 (split), 1601, 1576, 1512 cm^{-1}; ^1H NMR (300 MHz) δ 1.45-1.58 (m, 1H), 1.65-1.85 (m, 2H), 1.96 (s, 3H), 2.16-2.25 (m, 1H), 2.97 (dd, J = 15.6, 3.6 Hz, 1H), 3.15 (dd, J = 15.6, 8.4 Hz, 1H), 3.42 (ddd, J = 11.4, 11.4, 3.0 Hz, 1H), 3.85-3.91 (m, 1H), 3.87 (s, 3H), 3.98 (ddd, J = 9.6, 8.4, 3.6 Hz, 1H), 4.64 (ddd, J = 10.8, 9.6, 4.5 Hz, 1H), 6.90-6.96 (m, 2H), 7.92-7.97 (m, 2H); ^{13}C NMR (75 MHz) δ 21.0, 25.1, 29.4, 41.1, 55.4, 67.7, 72.0, 76.4, 113.7, 130.4, 130.6, 163.5, 170.2, 196.3; MS (EI) *m/z* (%): 292 (M^+, 9), 256 (7), 232 (12), 135 (100), 92 (7), 77 (13), 55 (5), 43 (100); HRMS (EI) calcd for $C_{16}H_{20}O_5$ 292.1311, found 292.1307.

(±) (2*S*,3*S*)-2-[2-(4-Methoxyphenyl)-2-oxoethyl]tetrahydro-2*H*-3-pyranyl acetate (238a)

White solid; m.p. 74-75°C; R_f 0.15 (1:3 ethyl acetate:hexanes); IR (nujol) 1725, 1681 (split), 1601, 1578, 1515 cm^{-1}; ^1H NMR (300 MHz) δ 1.42-1.47 (m, 1H), 1.75-1.99 (m, 2H), 2.03-2.12 (m, 1H), 2.14 (s, 3H), 2.92 (dd, J = 16.5, 5.4 Hz, 1H), 3.25 (dd, J = 16.5, 6.9 Hz, 1H), 3.58 (ddd, J = 11.7, 11.7, 2.1 Hz, 1H), 3.87 (s, 3H), 3.98-4.04 (m, 1H), 4.18 (ddd, J = 6.9, 5.4, 1.5 Hz, 1H), 4.96-4.98 (m, 1H), 6.90-6.95 (m, 2H), 7.91-7.96 (m, 2H); ^{13}C NMR (75 MHz) δ 20.5, 21.1, 27.8, 40.2, 55.4, 68.3, 69.4, 74.7, 113.7, 130.2, 130.5, 163.6, 170.6, 195.8; MS (EI) *m/z* (%): 292 (M^+, 2), 279 (1), 256 (3), 232 (51), 204 (4), 179 (2), 163 (5), 135 (100), 121 (1), 92 (7), 77 (10), 55 (4), 43 (43); Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.89: Found: C, 65.69; H, 6.80.

7-(4-Methoxyphenyl)-4,7-dioxoheptyl acetate (239a)

White solid; m.p. 47-49°C; R_f 0.20 (1:3 ethyl acetate:hexanes); IR (neat) 1732 1715, 1704, 1674, 1599 cm^{-1}; ^1H NMR (300 MHz) δ 1.96 (m, 2H), 2.03 (s, 3H), 2.64 (t, J = 7.2 Hz, 2H), 2.84 (t, J = 6.6 Hz, 2H), 3.26 (t, J = 6.6 Hz, 2H), 3.87 (s, 3H), 4.09 (t, J = 6.6 Hz, 2H), 6.94 (dd, J = 6.9, 2.1 Hz, 2H), 7.96 (dd, J = 6.9, 2.1 Hz, 2H); ^{13}C NMR (75 MHz) δ20.9, 22.8, 32.1, 36.3, 39.2, 55.4, 63.6, 113.7, 129.8, 130.3, 163.6, 171.0, 197.0, 208.5; MS (EI) *m/z* (%): 292 (M^+, 6), 206 (5), 191 (22), 163 (10), 135 (100); HRMS (EI) calcd for $C_{16}H_{20}O_5$ 292.1311, found 292.1317.

(±) (2*S*,3*R*)-2-[2-(4-Bromophenyl)-2-oxoethyl]tetrahydro-2*H*-3-pyranyl acetate (237b)

Colourless oil; R_f 0.44 (1:3 ethyl acetate:hexanes); IR (neat) 1732 (split), 1682 (split), 1597, 1586 cm^{-1}; ^1H NMR (300 MHz) δ 1.45-1.58 (m, 1H), 1.67-1.83 (m, 2H), 1.99 (s, 3H), 2.17-2.26 (m, 1H), 2.96 (dd, J = 15.9, 3.3 Hz, 1H), 3.17 (dd, J = 15.9, 8.4 Hz, 1H), 3.40 (ddd, J = 11.4, 11.4, 3.3 Hz, 1H), 3.84-3.90 (m, 1H), 3.95 (ddd, J = 9.6, 8.4, 3.3 Hz, 1H), 4.63 (ddd, J = 10.8, 9.6, 4.5 Hz, 1H), 7.58-7.62 (m, 2H), 7.80-7.84 (m, 2H); ^{13}C NMR (75 MHz) δ 21.1, 25.1, 29.4, 41.4, 67.8, 71.9, 76.3, 128.3, 129.9, 131.9, 136.0, 170.2, 197.0; MS (EI) *m/z* (%): 342 ($[M+H]^+$, 3), 340 (3), 282 (15), 280 (16), 185 (61), 183 (58), 157 (6), 142 (7), 97 (11), 71 (15), 50 (4), 43 (100); HRMS (EI) calcd for $C_{15}H_{17}O_4Br$ 341.0389, found 341.0389.

(±) (2*S*,3*S*)-2-[2-(4-Bromophenyl)-2-oxoethyl]tetrahydro-2*H*-3-pyranyl acetate (238b)

Colourless oil; R_f 0.32 (1:3 ethyl acetate:hexanes); IR (neat) 1732 (split), 1688, 1643, 1586, 1568 cm^{-1}; ^1H NMR (300 MHz) δ 1.42-1.47 (m, 1H), 1.75-1.95 (m, 2H), 2.03-2.10 (m, 1H), 2.14 (s, 3H), 2.90 (dd, J = 16.8, 5.1 Hz, 1H), 3.26 (dd, J = 16.8, 7.5 Hz, 1H), 3.56 (ddd, J = 11.7, 11.7, 2.1 Hz, 1H), 3.97-4.02 (m, 1H), 4.16 (ddd, J = 7.5, 5.1, 1.2 Hz, 1H), 4.94-4.98 (m, 1H), 7.57-7.62 (m, 2H), 7.78-7.82 (m, 2H); ^{13}C NMR (75 MHz) δ20.4, 21.1, 27.8, 40.6, 68.2, 69.1, 74.4, 128.3, 129.6, 131.8, 135. 7, 170.5, 196.3; MS (EI) *m/z* (%): 343 (64), 341 (M^+, 65), 283 (53), 282 (59), 281 (56), 280 (54), 185 (100), 183 (100), 169 (7), 143 (26), 104 (4), 97 (10), 71 (18), 43 (40); HRMS (EI) calcd for $C_{15}H_{17}O_4Br$ 341.0389, found 341.0393.

7-(4-Bromophenyl)-4,7-dioxoheptyl acetate (239b)

White crystals; m.p. 73-75 °C; R_f 0.20 (1:3 ethyl acetate:hexanes); IR (neat) 1728, 1710, 1680, 1583 cm^{-1}; ^1H NMR (300 MHz) δ 1.95 (m, 2H), 2.05 (s, 3H), 2.64 (t, J = 7.2 Hz, 2H), 2.86 (t, J = 6.6 Hz, 2H), 3.24 (t, J = 6.6 Hz, 2H), 4.09 (t, J = 6.6 Hz, 2H), 7.61 (dd, J

= 6.9, 2.1 Hz, 2H), 7.83 (dd, *J* = 6.9, 2.1 Hz, 2H); ^{13}C NMR (75 MHz) δ 20.8, 22.7, 32.3, 36.1, 39.0, 63.5, 128.3, 129.5, 131.8, 135.3, 171.0, 197.4, 208.0; MS (EI) *m/z* (%): 342 ([M + H]$^+$, 5), 282 (14), 254 (48), 239 (70), 211 (13), 183 (98), 157 (18), 129 (13), 104 (10), 87 (87), 69 (18), 43 (100); Anal. Calcd for $C_{15}H_{17}O_4Br$: C, 52.80; H, 5.02: Found: C, 52.89; H, 5.02.

(±) (2*S*,3*R*)-2-[2-(2-Naphthyl)-2-oxoethyl]tetrahydro-2*H*-3-pyranyl acetate (237c)

Pale yellow oil; R_f 0.28 (1:4 ethyl acetate:hexanes); IR (neat) 1732, 1682, 1628, 1596, 1578, 1507 cm^{-1}; ^{1}H NMR (600 MHz) δ 1.54 (dddd, *J* = 12.6, 10.8, 10.8, 4.2 Hz, 1H), 1.67-1.72 (m, 1H), 1.74-1.82 (m, 1H), 1.98 (s, 3H), 2.21-2.25 (m, 1H), 3.13 (dd, *J* = 15.6, 3.6 Hz, 1H), 3.35 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.43 (ddd, *J* = 11.4, 11.4, 2.4 Hz, 1H), 3.86-3.91 (m, 1H), 4.05 (ddd, *J* = 9.6, 8.4, 3.6 Hz, 1H), 4.70 (ddd, *J* = 10.8, 9.6, 4.2 Hz, 1H), 7.53-7.56 (m, 1H), 7.57-7.60 (m, 1H), 7.86 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.97 (dd, *J* = 7.8, 0.6 Hz, 1H), 8.04 (dd, *J* = 9.0, 1.8 Hz, 1H), 8.46 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (75 MHz) δ 21.1, 25.1, 29.4, 41.4, 67.8, 72.0, 76.3, 123.9, 126.7, 127.7, 128.4, 128.4, 129.6, 130.1, 132.4,134.5, 135.5, 170.2, 197.7; MS (EI) *m/z* (%): 313 (M$^+$, 74), 253 (40), 155 (100), 127 (11), 43 (12); Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45; Found C, 72.54; H, 6.60.

(±) (2*S*,3*S*)-2-[2-(2-Naphthyl)-2-oxoethyl]tetrahydro-2*H*-3-pyranyl acetate (238c)

Colourless needles; Recrystallised by slow evaporation in CH_2Cl_2/heptane; m.p. 75-76.5°C; R_f 0.35 (1:3 ethyl acetate:hexanes); IR (nujol) 1726, 1677, 1628, 1597 (weak), 1578 (weak) cm^{-1}; ^{1}H NMR (600 MHz) δ 1.44-1.47 (m, 1H), 1.80-1.86 (m, 1H), 1.89-1.97 (m, 1H), 2.07-2.11 (m, 1H), 2.15 (s, 3H), 3.09 (dd, *J* = 16.8, 5.4 Hz, 1H), 3.43 (dd, *J* = 16.8, 7.2 Hz, 1H), 3.59 (ddd, *J* = 12.6, 12.0, 3.0 Hz, 1H), 4.00-4.04 (m, 1H), 4.24 (ddd, *J* = 7.2, 5.4, 1.8 Hz, 1H), 5.01-5.03 (m, 1H), 7.53-7.56 (m, 1H), 7.58-7.61 (m, 1H), 7.87 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.96 (dd, *J* = 7.8, 0.6 Hz, 1H), 8.01 (dd, *J* = 9.0, 1.8 Hz, 1H), 8.45 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (75 MHz) δ 20.5, 21.2, 27.8, 40.7, 68.3, 69.3, 74.6, 123.8, 126.7, 127.7, 128.4, 128.5, 129.6, 129.9, 132.5, 134.4, 135.6, 170.6, 197.3; MS (EI) *m/z* (%): 312.4 (M$^+$, 4), 252 (6), 155 (100), 127 (26); Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45; Found C, 73.11; H, 6.50.

Details of crystal structure determination of 238c.

Crystal data for $C_{19}H_{20}O_4$: *M* = 312.35, *T* = 223(2) K, monoclinic, $P2_1/c$, *a* = 35.331(3), *b* = 10.4015(8), *c* = 8.7744(7) Å, β = 96.181(2)°, *V* = 3205.8(4) Å^3, *Z* = 4, D_x = 1.294,

$F(000)$ = 1328, μ = 0.090 mm^{-1}, no. of unique data (Bruker AXS SMART CCD using Mo Kα radiation so that θ_{max} = 30.1°) = 9346, no. of parameters = 417, R (all data) = 0.154, wR (all data) = 0.179, ρ = 0.33 e $Å^{-3}$. The structure was solved by direct-methods (SIR92) and refined (anisotropic displacement parameters, H atoms in the riding model approximation and a weighting scheme $w = 1/[\sigma^2(F_o^2) + 0.0717P^2 + 0.4033P]$ where $P = (F_o^2 + 2F_c^2)/3$) with SHELXL-97 on F^2 using all reflections.

7-(2-Naphthyl)-4,7-dioxoheptyl acetate (239c)

White needles; Recrystallised by slow evaporation in CH_2Cl_2/heptane; m.p. 98-100°C; R_f 0.24 (1:3 ethyl acetate:hexanes); IR (nujol) 1731, 1712, 1681, 1624 cm^{-1}; ^1H NMR (300 MHz) δ 1.93-2.02 (m, 2H), 2.06 (s, 3H), 2.67 (t, J = 7.2 Hz, 2H), 2.92 (t, J = 6.3Hz, 2H), 3.45 (t, J = 6.3 Hz, 2H), 4.11 (t, J = 6.3 Hz, 2H), 7.53-7.63 (m, 2H), 7.86-7.91 (m, 2H), 7.95-7.98 (m, 1H), 8.03 (dd, J = 8.7, 1.8 Hz, 1H), 8.52 (br s, 1H); ^{13}C NMR (75 MHz) δ 20.8, 22.8, 32.4, 36.3, 39.1, 63.6, 123.7, 126.7, 127.7, 128.3, 128.4, 129.5, 129.7, 132.5, 133.9, 135.6, 170.9, 198.3, 208.3; MS (EI) *m/z* (%): 312.4 (M^+, 13), 211.2 (19), 155.1 (100), 127.2 (33). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45; Found C, 73.01; H, 6.36.

Details of crystal structure determination of 239c.

Crystal data for $C_{19}H_{20}O_4$: M = 312.35, T = 223(2) K, monoclinic, $P2_1/c$, a = 5.5546(5), b = 39.599(3), c = 7.3808(6) Å, β = 98.301(2)°, V = 1606.4(2) $Å^3$, Z = 4, D_x = 1.291, $F(000)$ = 664, μ = 0.090 mm^{-1}, no. of unique data (Bruker AXS SMART CCD using Mo Kα radiation so that θ_{max} = 30.1°) = 4688, no. of parameters = 210, R (all data) = 0.096, wR (all data) = 0.189, ρ = 0.51 e $Å^{-3}$. The structure was solved by direct-methods (SIR92) and refined (anisotropic displacement parameters, H atoms in the riding model approximation and a weighting scheme $w = 1/[\sigma^2(F_o^2) + 0.1068P^2 + 0.097P]$ where $P = (F_o^2 + 2F_c^2)/3$) with SHELXL-97 on F^2 using all reflections.

(±) (2*S*,3*R*)-6,6-Dimethyl-2-(2-oxo-2-phenylethyl)tetrahydro-2*H*-3-pyranyl acetate (237d)

Colourless oil; R_f 0.33 (3:17 ethyl acetate:hexanes); IR (neat) 1740, 1690, 1598, 1581 cm^{-1}; ^1H NMR (600 MHz) δ 1.16 (s, 3H), 1.26 (s, 3H), 1.57-1.74 (m, 3H), 1.94 (s, 3H), 2.00-2.04 (m, 1H), 2.98 (dd, J = 15.6, 3.6 Hz, 1H), 3.12 (dd, J = 15.6, 7.8 Hz, 1H), 4.26 (ddd, J = 10.2, 7.8, 3.6 Hz, 1H), 4.57 (ddd, J = 10.2, 10.2, 4.8 Hz, 1H), 7.43-7.47 (m, 2H), 7.53-7.56 (m, 1H), 7.94-7.96 (m, 2H); ^{13}C NMR (150 MHz) δ 21.1, 21.5, 26.0, 30.7, 35.4, 42.2, 69.2, 72.2, 72.9, 128.3, 128.5, 132.9, 137.5, 170.4, 198.1; MS (EI) *m/z* (%): 291 (M^+, 23),

230 (60), 175 (15), 157 (20), 149 (16), 120 (11), 105 (100). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64; Found C, 70.40; H, 7.44.

(±) (2*S*,3*S*)-6,6-Dimethyl-2-(2-oxo-2-phenylethyl)tetrahydro-2*H*-3-pyranyl acetate (238d)

Colourless oil; R_f 0.21 (3:17 ethyl acetate:hexanes); IR (neat) 1736, 1687, 1598, 1581 cm^{-1}; ^1H NMR (600 MHz) δ 1.23 (s, 3H), 1.26 (s, 3H), 1.34 (ddd, J = 13.2, 7.2, 1.2 Hz, 1H), 1.73 (ddd, J = 13.2, 13.2, 5.4 Hz, 1H), 1.90-1.99 (m, 2H), 2.09 (s, 3H), 3.04 (dd, J = 16.8, 6.0 Hz, 1H), 3.21 (dd, J = 16.8, 6.0 Hz, 1H), 4.41 (ddd, J = 6.0, 6.0, 1.2 Hz, 1H), 4.90-4.92 (m, 1H), 7.43-7.46 (m, 2H), 7.53-7.56 (m, 1H), 7.93-7.96 (m, 2H); ^{13}C NMR (150 MHz) δ 21.2, 21.3, 24.7, 30.6, 31.2, 40.9, 67.7, 68.5, 72.4, 128.1, 128.5, 133.1, 137.1, 170.8, 197.7; MS (EI) *m/z* (%): 291 (M^+, 84), 273 (4), 231 (84), 213 (75), 175 (18), 157 (56), 147 (13), 110 (27), 105 (100); Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64; Found C, 70.06; H, 7.87.

2-(2-Oxo-2-phenylethyl)-6,6-diphenyltetrahydro-2*H*-3-pyranyl acetate (237e and 238e)

Cis and *trans* isomers were inseparable and were obtained as a 3:2 mixture, respectively. Pale yellow fluffy crystals; m.p.45-50°C; R_f 0.55 (3:7 ethyl acetate:hexanes); IR (nujol) 1734, 1683, 1597, 1580 cm^{-1}; ^1H NMR (300 MHz) δ 1.92 and 2.12 (both s, 3H), 1.97-2.21 (m, 3H), 2.57 and 2.84 (both ddd, J = 14.1, 3.3, 3.3 Hz and J = 14.1, 3.6, 3.6 Hz, 1H), 3.01 and 3.08 (both dd, J = 16.2, 5.1 Hz and J = 14.7, 3.6 Hz, 1H), 3.41 and 3.52 (both dd, J = 14.7, 8.7 Hz and J = 16.2, 8.1 Hz, 1H), 4.15 and 4.26 (both ddd, J = 9.6, 8.7, 3.6 Hz and J = 8.1, 5.1, 1.5 Hz, 1H), 4.81 and 4.83-4.86 (ddd, J = 10.5, 9.6, 4.8 Hz and m, 1H), 7.05-7.37 (m, 20H), 7.44-7.49 (m, 4H), 7.55-7.60 (m, 2H), 8.04-8.06 (m, 4H); ^{13}C NMR (75 MHz) δ 20.9, 21.1, 25.5, 26.5, 28.6, 33.8, 40.9, 42.1, 68.5, 69.5, 70.8, 72.6, 80.2, 80.4, 124.6, 124.7, 126.3, 127.1, 127.1, 127.2, 127.8, 128.2, 128.4, 128.5, 128.5, 128.6, 132.9, 133.0, 137.3, 137.5, 141.3, 147.5, 148.3, 170.1, 170.5, 197.8, 198.1; MS (EI) *m/z* (%): 414 (M^+, 17), 373 (40), 354 (6), 180 (44), 157 (19), 105 (84), 77 (39), 43 (100). Anal. Calcd for $C_{27}H_{26}O_4$: C, 78.24; H, 6.32; Found C, 77.96; H, 6.43.

(4*Z*, 6*E*)- and (4*E*,6*E*)-4,6-Octadien-1-ol (247)

Prepared by a Wittig reaction of 4-hydroxybutanal **214b** and the ylide obtained from the crotyl phosphonium salt **144b** using the procedure as for 1,3-butadienes **216**. Yield: 4.35 g, 72%; Colourless oil; Obtained as a 1:1 mixture of 4*Z*,6*E*[279,280] : 4*E*,6E[281] isomers; R_f 0.23 (1:4 ethyl acetate:hexanes); ^1H NMR (300 MHz) δ 1.61-1.79 (m, 5H), 1.88 (br s, 1H),

2.11-2.27 (m, 2H), 3.62-3.68 (m, 2H), 5.25-5.75 (m, 2H), 5.94-6.42 (m, 2H); MS (EI) *m/z* (%): 126 (M^+, 21), 108 (8), 93 (100), 79 (46), 67 (40), 55 (85), 43 (94); HRMS (EI) calcd for $C_8H_{14}O$ 126.1045, found 126.1042.

3-(6-Methyl-3,6-dihydro-1,2-dioxin-3-yl)-1-propanol (248)

Prepared by photolysis of 1,3-butadienes **247** by the general procedure for 1,2-dioxine synthesis. Yield: 3.0 g, 68%; Colourless oil; R_f 0.31 (2:3 ethyl acetate:hexanes); IR (neat) 1732 (split), 1688, 1643, 1586, 1568 cm^{-1}; ^1H NMR (300 MHz) δ1.27 (dd, J = 0.6, 6.6 Hz, 3H), 1.64-1.82 (m, 4H), 2.02 (br s, 1H), 3.68 (t, J = 6.0 Hz, 2H), 4.43-4.47 (m, 1H), 4.63-4.70 (m, 1H), 5.84-5.91 (m, 2H); ^{13}C NMR (75 MHz) δ18.2, 28.7, 29.4, 62.4, 74.3, 78.1, 127.3, 129.0; MS (EI) *m/z* (%): 159 ($[M+ H]^+$, 39), 139 (45), 126 (100), 108 (4), 98 (4), 87 (12), 71 (11), 69 (11), 55 (12), 43 (27); HRMS (EI) calcd for $C_8H_{14}O_3$ 158.0943, found 158.0945.

Attempted synthesis of THP 249

Method 1: A solution of 1,2-dioxine **248** (172 mg, 1.09 mmol) in THF (11 mL) was treated with LiOH (26 mg, 1.09 mmol) and the reaction mixture heated under reflux for 40 hours. The solution was taken to dryness and the residue purified by flash chromatography to afford 27.5 mg, 16% of a 7:3 mixture of compounds **248**^{a} and **253**^{b}, respectively, as a colourless oil; ^1H NMR (300 MHz) δ 1.35-1.49 (m, 1H)^a, 1.64-1.73 (m, 2H)^a, 1.84-2.01 (m, 4H, includes 2H^b and OH for both compounds), 2.10-2.17 (m, 1H)^a, 2.22 (s, 3H)^a, 2.25 (s, 3H)^b, 2.65 (dd, J = 7.2, 15.9 Hz, 1H)^a, 2.68 (t, J = 7.2 Hz, 2H)^b, 2.90 (dd, J = 4.5, 15.9 Hz, 1H)^a, 3.26-3.39 (m, 2H)^a, 3.47-3.54 (m, 1H)^a, 3.69 (t, J = 3.6 Hz, 2H)^b, 3.83-3.90 (m, 1H)^a, 5.83-5.88 (m, 2H)^b. Full characterisation of both compounds was not possible as they were inseparable by flash chromatgraphy.

Method 2: $Co(SALEN)_2$ (102.8 mg, 0.32 mmol) was stirred in THF (27 mL) for 40 minutes and then a solution of 1,2-dioxine (500 mg, 3.2 mmol) in THF (27 mL) added. The reaction was monitored until all dioxine had been consumed (4-5 hours) and the solution was then treated with LiOH (75.7 mg, 3.2 mmol). After 16 hours at ambient temperature the solution was taken to dryness under reduced pressure and the residue purified by flash chromatography (3:2 ethyl acetate:hexanes). A brown oil was obtained consisting of a mixture of unidentified decomposition products.

***tert*-Butyl(dimethyl)[(4*Z*,6*E*)-4,6-octadienyloxy]silane and *tert*-butyl(dimethyl) [(4*E*,6*E*)-4,6-octadienyloxy]silane (250)**

Prepared by a Wittig reaction of crotonaldehyde and the ylide obtained from phosphonium salt **229** using the procedure as for 1,3-butadienes **230**. Yield: 1.02 g, 58%; Colourless oil; Obtained as a 7:3 mixture of $4Z,6E^a$: $4E,6E^b$ isomers; R_f 0.43 (1:99 ethyl acetate:hexanes); IR (neat) 1472, 1462, 1446 cm^{-1}; ^1H NMR (600 MHz) δ 0.04 (s, 6H)^b, 0.05 (s, 6H)^a, 0.89 (s, 9H)^b, 0.90 (s, 9H)^a, 1.57-1.62 (m, 4H)^{a,b}, 1.72 (d, J = 6.0 Hz, 3H)^b, 1.76 (d, J = 6.6 Hz, 3H)^a, 2.10 (q, J = 7.2 Hz, 2H)^b, 2.22 (q, J = 7.2 Hz, 2H)^a, 3.60 (t, J = 6.0 Hz, 2H)^b, 3.61 (t, J = 6.6 Hz, 2H)^a, 5.28 (dt, J = 10.8, 7.8 Hz, 1H)^a, 5.52-5.59 (m, 2H)^b, 5.62-5.68 (m, 1H)^a, 5.95 (dd, J = 10.8, 10.8 Hz, 1H)^a, 5.98-6.03 (m, 2H)^b, 6.31-6.36 (m, 1H)^a; ^{13}C NMR (75 MHz) δ -5.3, 17.9, 18.2, 18.3, 23.9, 26.0, 28.8, 32.5, 32.9, 62.4, 62.6, 126.8, 127.1, 129.0, 129.1, 130.6, 131.4, 131.7; MS (EI) *m/z* (%): 240 (M^+, 6), 225 (46), 183 (69), 153 (25), 141 (13), 127 (7), 108 (43), 89 (67), 75 (100); HRMS (EI) calcd for $C_{14}H_{28}OSi$ 240.1909, found 240.1906.

1-(*tert*-Butyl)-1,1-dimethylsilyl [3-(6-methyl-3,6-dihydro-1,2-dioxin-3-yl)propyl] ether (251)

Prepared by photolysis of 1,3-butadienes **250** by the general procedure for 1,2-dioxine synthesis. Yield: 0.62 g, 57%; Colourless oil; R_f 0.34 (1:19 ethyl acetate:hexanes); IR (neat) 2952, 2930, 2885, 2858, 1472, 1463, 1445 cm^{-1}; ^1H NMR (300 MHz) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.27 (d, J = 6.6 Hz, 3H), 1.55-1.79 (m, 4H), 3.60-3.68 (m, 2H), 4.43-4.47 (m, 1H), 4.63-4.66 (m, 1H), 5.83-5.91 (m, 2H); ^{13}C NMR (75 MHz) δ -5.3, 18.29, 18.34, 25.9, 28.6, 29.5, 62.8, 74.3, 78.1, 127.6, 129.0; MS (EI) *m/z* (%): 272 (M^+, 7), 254 (35), 239 (63), 197 (86), 183 (14), 169 (72), 145 (35), 122 (22), 95 (55), 75 (100), 57 (21), 43 (22); HRMS (EI) calcd for $C_{14}H_{28}O_3Si$ 295.1705, found 292.1700.

Attempted synthesis of THP 249

Method 1: To a solution of 1,2-dioxine **250** (52 mg, 0.19 mmol) in $CDCl_3$ (0.6 mL) was added a solution of $Co(SALEN)_2$ (1.2 mg, 3.82 x 10^{-3} mmol) in $CDCl_3$ (0.1 mL) which had been allowed to equilibrate for 30 minutes prior to its addition. The reaction was monitored by ^1H NMR until all dioxine had been consumed (10 days). The solution was filtered through a pad of silica (0.5-1.0 cm) and the silica washed with dichloromethane (5 mL). The filtrate was concentrated and the residue (42.1 mg) reconstituted in THF (2 mL) and treated with TBAF (61 mg, 0.23 mmol). After stirring at ambient temperature for 16 hours TLC analysis (1:19 ethyl acetate:hexane) indicated that all enone had been consumed. The

solution was concentrated *in vacuo* and the residue purified by flash chromatography to afford 17.4 mg, 72% (from enone) of compound **253** as a colourless oil; ^{1}H NMR (200 MHz) δ 1.55 (br s, 1H), 1.88 (dt, J = 7.4, 6.4 Hz, 2H), 2.25 (s, 3H), 2.68 (t, J = 7.4 Hz, 2H), 3.69 (t, J = 6.4 Hz, 2H), 5.83-5.89 (m, 2H); ^{13}C NMR (50 MHz) δ 13.4, 24.4, 31.1, 62.2, 105.6, 105.8, 150.4, 153.7. This compound was unable to be fully characterised as it was unstable and decomposed in $CDCl_3$.

Method 2: To a solution of 1,2-dioxine **250** (180 mg, 0.66 mmol) in THF (7 mL) was added Co(SALEN)$_2$ (16.1 mg, 0.05 mmol) and triphenylphosphine (86.6 mg, 0.33 mmol). Once all dioxine had been converted to *trans* enone **254**, the solution was filtered through silica and the silica washed with dichloromethane. The filtrate was concentrated and the residue placed in THF (5 mL) and treated with TBAF (260 mg, 1.0 mmol). After stirring at ambient temperature for 16 hours, the solution was taken to dryness under reduced pressure and the residue purified by flash chromatography (3:2 ethyl acetate:hexanes) to afford 5.4 mg, 5% of compound **248** as a colourless oil; ^{1}H NMR (300 MHz) δ 1.35-1.49 (m, 1H), 1.64-1.73 (m, 2H), 1.83 (br s, 1H), 2.10-2.17 (m, 1H), 2.22 (s, 3H), 2.65 (dd, J = 7.2, 15.9 Hz, 1H), 2.90 (dd, J = 4.5, 15.9 Hz, 1H), 3.26-3.39 (m, 2H), 3.47-3.54 (m, 1H), 3.83-3.90 (m, 1H); ^{13}C NMR (50 MHz) δ 25.6, 33.1, 47.1, 62.2, 67.7, 70.5, 78.8, 149.8.

5-Methyltetrahydro-2-furanol / 4-hydroxypentanal (255)

To a solution of γ-valerolactone (6.0 g, 60 mmol) in dry THF (60 mL) at –78°C was added a 1.0M solution of DIBAL-H in hexanes (66 mL, 66 mmol) dropwise over 20 minutes. After the addition of DIBAL-H was complete the solution was stirred for a further 60 minutes at –78°C. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (20 mL). Once all the aluminium salt had precipitated out the solution was warmed to ambient temperature. The precipitate was removed by vacuum filtration and washed with dichloromethane (3 x 50 mL). The filtrate was concentrated to give 5.91 g, 97% of the crude aldehyde **255** as a colourless liquid. The aldehyde was used in the next step without further purification.

(5*Z*,7*E*)- and (5*E*,7*E*)-8-Phenyl-5,7-octadien-2-ol (256)

Prepared by a Wittig reaction of **255** and the ylide obtained from phosphonium salt **144a** using the procedure as for 1,3-butadienes **216**.Yield: 6.24 g, 53%; Colourless oil; Obtained as a mixture of 5*Z*,7*E* : 5*E*,7*E* isomers. A small amount of each isomer was isolated. **(5*Z*,7*E*)-8-phenyl-5,7-octadien-2-ol:** R_f 0.30 (2:3 ethyl acetate:hexanes); IR (neat) 3100-

3600, 1594, 1574 cm^{-1}; ^1H NMR (600 MHz) δ 1.20 (d, J = 6.0 Hz, 3H), 1.51-1.62 (m, 2H), 1.75 (br s, 1H), 2.36-2.40 (m, 2H), 3.81-3.86 (m, 1H), 5.51 (dt, J = 10.8, 7.8 Hz, 1H), 1.67 (ddd, J = 10.8, 10.8, 1.2 Hz, 1H), 6.52 (d, J = 15.6 Hz, 1H), 7.08 (ddd, J = 15.6, 10.8, 1.2 Hz, 1H), 7.19-7.21 (m, 1H), 7.28-7.31 (m, 2H), 7.39-7.41 (m, 2H); ^{13}C NMR (75 MHz) δ 23.6, 24.4, 38.9, 67.5, 124.1, 126.3, 127.4, 128.6, 129.2, 132.2, 132.4, 137.5; **(5*E*,7*E*)-8-phenyl-5,7-octadien-2-ol:** Colourless oil; R_f 0.25 (2:3 ethyl acetate:hexanes); IR (neat) 3100-3600, 1643, 1596, 1574 cm^{-1}; ^1H NMR (600 MHz) δ 1.19 (d, J = 6.0 Hz, 3H), 1.51-1.61 (m, 2H), 1.87 (br s, 1H), 2.18-2.27 (m, 2H), 3.80 (sextet J = 6.0 Hz, 1H), 5.81 (dt, J = 15.0, 7.2 Hz, 1H), 6.22 (ddd, J = 15.0, 10.8, 1.2 Hz, 1H), 6.43 (d, J = 15.6 Hz, 1H), 6.73 (dd, J = 15.6, 10.8 Hz, 1H), 7.16-7.19 (m, 1H), 7.26-7.29 (m, 2H), 7.34-7.36 (m, 2H); ^{13}C NMR (75 MHz) δ 23.5, 29.2, 38.6, 67.6, 126.1, 127.1, 128.5, 129.1, 130.3, 130.9, 134.9, 137.5; **Analysis of mixture:** MS (EI) *m/z* 202.8 (M^+, 76), 169.7 (16), 155.6 (100), 132.5 (67), 129.5 (78), 104.4 (39), 91.3 (85), 56.2 (23), 45.2 (44); HRMS Calcd for $C_{14}H_{18}O$ 202.1358, found 202.1357.

4-(6-Phenyl-3,6-dihydro-1,2-dioxin-3-yl)-2-butanol (257)

Prepared by photolysis of 1,3-butadienes **256** by the general procedure for 1,2-dioxine synthesis. Yield: 1.46 g, 70%; Colourless oil; R_f 0.4 (2:3 ethyl acetate:hexanes); IR (neat) 3100-3600 cm^{-1}; ^1H NMR (75 MHz) δ 1.19 (d, J = 6.3 Hz, 3H), 1.45-1.97 (m, 5H), 3.77-3.87 (m, 1H), 4.52-4.62, (m, 1H), 5.52-5.55 (m, 1H), 6.04-6.15 (m, 2H), 7.33-7.40 (m, 5H); ^{13}C NMR (300 MHz) δ 23.5, 23.6, 29.2, 29.4, 34.9, 35.2, 67.6, 67.8, 78.2, 78.7, 80.2, 80.3, 126.5, 126.6, 128.5, 128.5, 128.5, 128.6, 128.7, 128.8, 137.3, 137.4. MS (EI) *m/z* (%): 235 ($[M+H]^+$, 9), 216 (4), 202 (100), 184 (9), 155 (29), 133 (25), 117 (15), 105 (36), 81 (60), 45 (35). HRMS Calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1256.

(*E*)-4,7-Dihydroxy-1-phenyl-2-octen-1-one

Prepared from 1,2-dioxine **257** by the general procedure for *trans* γ-hydroxy enone formation. Yield: 793 mg, 85%; Colourless oil.

Preparation of THP's 258a-d

To a 0.1 M solution of 1,2-dioxine **257** or its *trans* enone in THF or $CHCl_3$ was added LiOH (1 equiv.) or DABCO (0.4 equiv.), respectively. After stirring for 16 hours at ambient temperature the volatiles were removed *in vacuo* and the crude pyrans were then purified by column chromatography. Pyridine (15 equiv.), acetic anhydride (9 equiv.) and DMAP (0.2 equiv.) were then added to the combined pyrans and the solution stirred

overnight. Dichloromethane was then added and the solution extracted with water and the organic layer dried ($MgSO_4$), filtered and the volatiles removed *in vacuo*. The crude pyrans were purified by column chromatography.

(±) (2*R*,3*S*,6*R*)-6-Methyl-2-(2-oxo-2-phenylethyl)tetrahydro-2*H*-3-pyranyl acetate (258a)

Yield: 60 mg, 8%; Colourless oil; R_f 0.35 (1:4 ethyl acetate:hexane); IR (neat) 1738, 1687, 1597, 1581, 1449, 1374, 1240 cm^{-1}; ^1H NMR (600 MHz) δ 1.23 (d, J = 6.0 Hz, 3H), 1.34 (dddd, J = 13.2, 6.0, 3.6, 3.6 Hz, 1H), 1.83 (dddd, J = 13.2, 7.2, 3.6, 3.6 Hz, 1H), 1.92-2.01 (m, 2H), 2.02 (s, 3H), 3.15 (dd, J = 16.2, 6.0 Hz, 1H), 3,24 (dd, J = 16.2, 6.6 Hz, 1H), 4.02 (ddq, J = 7.2, 6.0, 6.0 Hz, 1H), 4.61 (ddd, J = 6.6, 6.0, 3.6 Hz, 1H), 4.99 (ddd, J = 7.2, 3.6, 3.6 Hz, 1H), 7.45-7.48 (m, 2H), 7.55-7.58 (m, 1H), 7.93-7.95 (m, 2H); ^{13}C NMR (150 MHz) δ 18.3, 21.1, 23.5, 27.3, 28.7, 67.6, 67.9, 69.4, 128.1, 128.6, 133.1, 137.1, 170.3, 197.6; MS (EI) *m/z* (%): 277 ($[M+H]^+$, 5), 216 (24), 105 (100), 77 (21), 43 (42); HRMS (ESI) found *m/z* 299.1263 ($M+Na^+$), $C_{16}H_{20}O_4$ + Na requires 299.1259.

(±) (2*R*,3*S*,6*S*)-6-Methyl-2-(2-oxo-2-phenylethyl)tetrahydro-2*H*-3-pyranyl acetate (258b).

Yield: 232 mg, 29%; Colourless oil; R_f 0.60 (1:4 ethyl acetate:hexane); IR (neat) 1738, 1690, 1597, 1580, 1449, 1239 cm^{-1}; ^1H NMR (600 MHz) δ 1.12 (d, J = 6.6 Hz, 3H), 1.44 (dddd, J = 13.8, 13.2, 10.8, 4.8 Hz, 1H), 1.55 (dddd, J = 13.2, 12.0, 10.2, 2.4 Hz, 1H), 1.73 (dddd, J = 13.8, 4.8, 2.4, 2.4 Hz, 1H), 1.92 (s, 3H), 2.17 (dddd, J = 12.0, 4.8, 4.8, 4.8 Hz, 1H), 3.02 (dd, J = 15.6, 4.2 Hz, 1H), 3.18 (dd, J = 15.6, 7.8 Hz, 1H), 3.54 (ddq, J = 10.8, 6.6, 2.4 Hz, 1H), 4.05 (ddd, J = 9.6, 7.8, 4.2 Hz, 1H), 4.60 (ddd, J = 10.2, 9.6, 4.8 Hz, 1H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 7.95-7.97 (m, 2H); ^{13}C NMR (150 MHz) δ 21.0, 21.2, 29.5, 32.4, 41.8, 72.2, 73.8, 75.8, 128.3, 128.5, 133.0, 137.3, 170.4, 197.9; MS (EI) *m/z* (%): 277 ($[M+H]^+$, 33), 216 (65), 105 (100), 77 (25), 43 (68); Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29; Found: C, 69.35; H, 7.39.

(±) (2*S*,3*S*,6*S*)-6-Methyl-2-(2-oxo-2-phenylethyl)tetrahydro-2*H*-3-pyranyl acetate (258c)

Yield: 11 mg, 1%; Colourless oil; R_f 0.37 (1:4 ethyl acetate:hexane); IR (neat) 1731, 1681, 1597, 1580, 1449, 1243, 754 cm^{-1}; ^1H NMR (600 MHz) δ 1.22 (d, J = 6.6 Hz, 3H), 1.57 (dddd, J = 13.8, 7.2, 6.6, 4.2 Hz, 1H), 1.73 (dddd, J = 13.8, 4.2, 4.2, 4.2 Hz, 1H), 1.83

(dddd, J = 13.8, 7.2, 6.6, 4.2 Hz, 1H), 1.97 (dddd, J = 13.8, 4.2, 4.2, 4.2 Hz, 1H), 2.03 (s, 3H), 3.10 (dd, J = 15.6, 5.4 Hz, 1H), 3.23 (dd, J = 15.6, 7.8 Hz, 1H), 3.96 (ddq, J = 6.6, 6.6, 4.2 Hz, 1H), 4.43 (ddd, J = 7.8, 5.4, 5.4 Hz, 1H), 4.70 (ddd, J = 6.6, 5.4, 4.2 Hz, 1H), 7.44-7.48 (m, 2H), 7.54-7.57 (m, 1H), 7.93-7.95 (m, 2H); ^{13}C NMR (150 MHz) δ 18.9, 21.2, 24.0, 28.1, 40.4, 70.1, 70.8, 128.2, 128.6, 133.1, 136.9, 170.4, 197.5; MS (EI) *m/z* (%): 277 ([M+H]$^+$, 27), 216 (45), 105 (100), 77 (24), 43 (39); HRMS (ESI) found *m/z* 299.1263 (M+Na$^+$), $C_{16}H_{20}O_4$ + Na requires 299.1259.

(±) (2*S*,3*S*,6*R*)-6-Methyl-2-(2-oxo-2-phenylethyl)tetrahydro-2*H*-3-pyranyl acetate (258d).

Yield: 326 mg, 42%; Colourless oil; R_f 0.40 (1:4 ethyl acetate:hexane); IR (neat) 1732, 1688, 1597, 1580, 1449, 1244 cm^{-1}; ^{1}H NMR (600 MHz) δ 1.20 (d, J = 6.6 Hz, 3H) 1.48 (dddd, J = 13.8, 5.4, 3.0, 3.0 Hz, 1H), 1.54 (dddd, J = 13.8, 13.8, 10.8, 3.0 Hz, 1H), 1.82 (dddd, J = 14.4, 13.8, 5.4, 3.0 Hz, 1H), 2.05 (dddd, J = 14.4, 3.0, 3.0, 3.0 Hz, 1H), 2.11 (s, 3H), 3.05 (dd, J = 16.8, 6.0 Hz, 1H), 3.28 (dd, J = 16.8, 6.0 Hz, 1H), 3.60 (ddq, J = 10.8, 6.6, 3.0 Hz, 1H), 4.22 (ddd, J = 6.0, 6.0, 1.2 Hz, 1H), 4.94 (ddd, J = 3.0, 3.0, 1.2 Hz, 1H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 7.93-7.95 (m, 2H); ^{13}C NMR (150 MHz) δ 21.2, 21.8, 27.7, 28.1, 40.7, 68.5, 74.2, 74.4, 128.1, 128.5, 133.1, 137.1, 170.7, 197.4; MS (EI) *m/z* (%): 277 ([M+H]$^+$, 27), 216 (25), 105 (100), 77 (22), 43 (55); Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29; Found: C, 69.23; H, 7.41.

6.5 Compounds discussed in Chapter 5

(3-Hydroxypropyl)(triphenyl)phosphonium chloride (259a)

Triphenylphosphine (30.52 g, 116.4 mmol) and 3-chloro-1-propanol (10.0 g, 105.8 mmol) were heated together neat at 130°C for 2 hours. The mixture was cooled and diethyl ether (150 mL) added to the resulting solid. The solid was finely broken up, the solvent decanted and the solid stirred for 16 hours in fresh diethyl ether (150 mL). The precipitate was collected, washed with diethyl ether (2 x 50 mL) and dried to give 31.56 g, 84% of phosphonium salt **259a** as a white powder; m.p. 222–225 °C (lit.[282] 228–229 °C);

(3-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxypropyl)(triphenyl)phosphonium iodide (259b)

3-Chloro-1-propanol was protected by TBDMS using the procedure of Corey and Venkateswarlu[166] to give *tert*-butyl(3-chloropropoxy)dimethylsilane. As the phosphonium salt would not form from *tert*-butyl(3-chloropropoxy)dimethylsilane it was converted to the more reactive iodo derivative, *tert*-butyl(3-iodopropoxy)dimethylsilane, using the method of Molander and St. Jean Jr.[283] *tert*-Butyl(3-iodopropoxy)dimethylsilane (20.0 g, 73.5 mmol) and triphenylphosphine (20.24 g, 77.2 mmol) were melted together at 80°C for 1.5 hours. To the cooled reaction vessel was added diethyl ether (120 mL) and the solid was finely broken up. The solvent was decanted and the precipitate stirred for 16 hours in fresh diethyl ether (120 mL). The precipitate was collected, washed with diethyl ether (2 x 50 mL) and dried to give 32.0 g, 81% (over two steps) of phosphonium salt **259b** as a white powder. Decomposed below its m.p.

6-Phenyl-3,5-hexadien-1-ol (261a)

Prepared by a Wittig reaction of *trans*-cinnamaldehyde and the ylide obtained from phosphonium salt **259a** using the procedure as for 1,3-butadienes **216** (Method 2). Yield: 1.50 g, 32%; Colourless oil; 64:36 $3Z,5E^a$: $3E,5E^b$; R_f 0.51 (2:3 ethyl acetate:hexanes); IR (neat) 3100-3600, 1666, 1596, 1576 cm^{-1}; ^1H NMR (200 MHz) δ 1.54 (br s, 2H)^{a,b}; 2.33-2.44 (m, 2H)^a, 2.49-2.61 (m, 2H)^b, 3.68 (t, J = 6.6 Hz, 2H)^a, 3.69 (t, J = 6.6 Hz, 2H)^b, 5.44-5.58 (m, 1H)^b, 5.77 (dt, J = 15.2, 7.2 Hz, 1H)^a, 6.22-6.35 (m, 2H)^{a,b}, 6.46 (d, J = 15.8 Hz, 1H)^b, 6.55 (d, J = 15.6 Hz, 1H)^b, 6.74 (dd, J = 15.8, 10.4 Hz, 1H)^a, 7.06 (ddd, J = 15.6, 11.2, 1.0 Hz, 1H)^b, 7.14-7.43 (m, 10H)^{a,b}; ^{13}C NMR (50 MHz) δ 31.4, 36.1, 61.9, 62.1, 123.9, 126.2, 126.4, 127.2, 127.5, 128.0, 128.5, 128.8, 130.7, 131.1, 131.4, 133.1, 133.2, 137.3; MS (EI) *m/z* (%): 174 (M^+, 74), 143 (79), 128 (100), 115 (21), 91 (25), 77 (6), 65 (10); HRMS (EI) calcd for $C_{12}H_{14}O$ 174.1045, found 174.1040.

***tert*-Butyl(dimethyl)[(3*E*,5*E*)-6-(2-naphthyl)-3,5-hexadienyl]oxysilane and *tert*-Butyl(dimethyl)[(3*Z*,5*E*)-6-(2-naphthyl)-3,5-hexadienyl]oxysilane (260)**

Prepared by a Wittig reaction of α,β-unsaturated aldehyde **228c** and the ylide obtained from phosphonium salt **259b** using the procedure as for 1,3-butadienes **230a-c**. Yield: 2.90 g, 40%; Colourless oil; Obtained as a 3:2 mixture of $3Z,5E^a$: $3E,5E^b$ isomers; R_f 0.18 (1:49 ethyl acetate:hexanes); IR (neat) 1737, 1686, 1598, 1580 cm^{-1}; ^1H NMR (200 MHz) δ 0.07 (s, 12H)^{a,b}, 0.91 (s, 18H)^{a,b}, 2.37-2.51 (m, 2H)^a, 2.52-2.63 (m, 2H)^b, 3.67-3.77 (m, 4H)^{a,b}, 5.58 (dt, J = 10.6, 6.6 Hz, 1H)^b, 5.87 (dt, J = 13.2, 6.6 Hz, 1H)^a, 6.24-6.38 (m, 2H)^{a,b}, 6.61 (d, J = 16.2 Hz, 1H)^a, 6.69 (d, J = 16.2 Hz, 1H)^b, 6.88 (dd, J = 16.2, 10.0 Hz, 1H)^a, 7.20 (ddd, J = 15.6, 11.2, 1.2 Hz, 1H)^b, 7.39-7.49 (m, 4H)^{a,b}, 7.57-7.66 (m, 2H)^{a,b}, 7.71-7.81 (m, 8H)^{a,b}; MS (EI) *m/z* (%): 339 ([M+ H]$^+$, 47), 282 (66), 156 (18), 206 (100), 192 (49), 165 (51), 141 (43), 115 (18), 89 (67), 75 (72), 73 (100), 59 (25); HRMS (EI) calcd for [$C_{22}H_{30}OSi$ + H] 339.2144, found 339.2142. Fully characterised as its corresponding hydroxy diene.

(3*Z*, 5*E*) and (3*E*,5*E*)-6-(2-Naphthyl)-3,5-hexadien-1-ol (261b)

Prepared by desilylation of **260** using the procedure as for 1,3-butadienes **231a-c**. Yield: 2.10 g, 84%; Colourless oil; Obtained as a 1:1 mixture of $3Z,5E^a$: $3E,5E^b$ isomers; R_f 0.36 and 0.45 (2:3 ethyl acetate:hexanes); IR (neat) 3090-3540, 2923, 1662, 1618 cm^{-1}; ^1H NMR (300 MHz) δ 2.43-2.49 (m, 2H)^a, 2.60-2.67 (m, 2H)^b, 3.72-3.83 (m, 4H)^{a,b}, 5.57 (dt, J = 10.8, 7.8 Hz, 1H)^b, 5.85 (dt, J = 15.0, 7.2 Hz, 1H)^a, 6.34-6.43 (m, 2H)^{a,b}, 6.66 (d, J = 15.6 Hz, 1H)^b, 6.74 (d, J = 15.6 Hz, 1H)^a, 6.90 (dd, J = 15.6, 10.2 Hz, 1H)^b, 7.21 (ddd, J = 15.6, 11.4, 1.2 Hz, 1H)^a, 7.39-7.49 (m, 4H)^{a,b}, 7.59-7.66 (m, 2H)^{a,b}, 7.73-7.81 (m, 8H)^{a,b}; ^{13}C NMR (75 MHz) δ 31.5, 36.2, 62.0, 62.2, 123.4, 123.5, 124.3, 125.7, 125.8, 126.1, 126.2, 126.3, 126.4, 127.62, 127.63, 127.87, 127.93, 128.1, 128.15, 128.2, 129.2, 130.9, 131.3, 131.7, 132.9, 133.0, 133.3, 133.4, 133.7, 134.8, 134.9; MS (EI) *m/z* (%): 225 ([M+H]$^+$, 11), 224 (63), 193 (83), 178 (100), 165 (43), 141 (25), 128 (24); HRMS (EI) calcd for [$C_{16}H_{16}O$ + Na] 247.1099, found 247.1101.

2-(6-Phenyl-3,6-dihydro-1,2-dioxin-3-yl)-1-ethanol (262a)

Prepared by photolysis of 1,3-butadienes **261a** by the general procedure for 1,2-dioxine synthesis. Yield: 0.738 g, 44%; Colourless oil; R_f 0.35 (2:3 ethyl acetate:hexanes); IR (neat) 3120-3610, 1676 (weak), 1602 (weak) cm^{-1}; ^1H NMR (300 MHz) δ 1.87-1.98 (m, 1H), 2.00-2.12 (m, 2H), 3.73-3.87 (m, 2H), 4.74-4.78 (m, 1H), 5.77-5.59 (m, 1H), 6.06-

6.15 (m, 2H), 7.33-7.39 (m, 5H); ^{13}C NMR (75 MHz) δ 35.7, 59.3, 76.5, 80.4, 126.8, 128.2, 128.6, 129.0, 136.9; MS (EI) *m/z* (%): 206 (M^+, 6), 204 (28), 188 (9), 174 (100), 157 (33), 143 (73), 128 (45), 115 (17), 105 (41), 83 (33), 77 (56); HRMS (EI) calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0943.

2-[6-(2-Naphthyl)-3,6-dihydro-1,2-dioxin-3-yl]-1-ethanol (262b)

Prepared by photolysis of 1,3-butadienes **261b** by the general procedure for 1,2-dioxine synthesis. Yield: 1.16 g, 48%; Pale orange oil; R_f 0.29 (2:3 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 1.90-2.15 (m, 3H), 3.75-3.90 (m, 2H), 4.78-4.82 (m, 1H), 5.72-5.74 (m, 1H), 6.12-6.20 (m, 2H), 7.45-7.51 (m, 3H), 7.81-7.85 (m, 4H); ^{13}C NMR (75 MHz) δ 35.8, 59.4, 76.6, 80.4, 125.8, 126.2, 126.5, 126.9, 127.6, 128.0, 128.1, 128.4, 128.5, 133.1, 133.5, 134.5; MS (EI) *m/z* (%): 256 (M^+, 14), 238 (67), 224 (18), 207 (100), 193 (13), 178 (38), 165 (38), 155 (83), 141 (29), 127 (55); HRMS Calcd for [$C_{16}H_{16}O_3$ + Na] 279.0997, found 279.0998.

(*E*)-4,6-Dihydroxy-1-phenyl-2-hexen-1-one (263a)

Prepared by general procedure for *trans* γ-hydroxy enone synthesis. Yield: 246 mg, 70%; Colourless oil; R_f 0.40 (100% ethyl acetate). Unstable and therefore used immediately.

(*E*)-4,6-Dihydroxy-1-(2-naphthyl)-2-hexen-1-one (263b)

Prepared by general procedure for *trans* γ-hydroxy enone synthesis. Yield: 50 mg, 50%; Pale yellow solid; R_f 0.39 (100% ethyl acetate). Unstable and therefore used immediately.

General procedure for the preparation of THF's 264 and 265

To a 0.1 M solution of 1,2-dioxine **262** or *trans* enone **263** in THF or $CHCl_3$ was added LiOH (1 equiv.) or DABCO (0.4 equiv.), respectively. After stirring for 16 hours at ambient temperature the volatiles were removed *in vacuo* and the crude furans were then purified by column chromatography. Pyridine (15 equiv.), acetic anhydride (9 equiv.) and DMAP (0.2 equiv.) were then added to the combined pyrans and the solution stirred overnight. Dichloromethane was then added and the solution extracted with water and the organic layer dried ($MgSO_4$), filtered and the volatiles removed *in vacuo*. The crude pyrans were purified by column chromatography.

2-(2-Oxo-2-phenylethyl)tetrahydro-3-furanyl acetate (268a) and (269a)

Prepared by treatment of 1,2-dioxine **262a** with LiOH, by the general procedure followed by acetylation of the reaction products. Yield: 86.4 mg, 46% (two steps); Obtained as a

mixture of isomers, *trans*:*cis*, 42:58; R_f 0.52 (2:3 ethyl acetate:hexanes); IR (neat) 1737, 1686, 1598, 1580 cm^{-1}; ^1H NMR (300 MHz) δ 1.97 (s, 3H)^b, 1.96-2.06 (m, 2H)^{a,b}, 2.08 (s, 3H)^a, 2.22-2.44 (m, 2H)^{a,b}, 3.26-3.38 (m, 4H)^{a,b}, 3.82 (ddd, J = 8.4, 8.4, 5.1 Hz, 1H)^b, 3.88 (ddd, J = 9.6, 9.0, 6.3 Hz, 1H)^a, 3.98-4.06 (m, 2H)^{a,b}, 4.39-4.45 (m, 2H)^{a,b}, 5.11 (ddd, J = 6.6, 2.4, 2.4 Hz, 1H)^a, 5.45 (ddd, J = 6.0, 3.9, 1.8 Hz, 1H)^b, 7.43-7.50 (m, 4H)^{a,b}, 7.53-7.60 (m, 2H)^{a,b}, 7.94-7.99 (m, 4H)^{a,b}; ^{13}C NMR (75 MHz) δ 20.7, 20.9, 32.1, 33.4, 38.1, 42.1, 65.9, 66.9, 74.6, 77.2, 78.2, 80.3, 127.9, 128.1, 128.4, 128.5, 133.0, 133.1, 136.8, 136.9, 170.0, 170.6, 197.2, 197.3; MS (EI) *m/z* (%): 249 ($[M+H]^+$, 20), 230 (6), 188 (18), 105 (100), 77 (16), 43 (13); Anal.Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50: Found : C, 67.50; H, 6.66.

Isolation of tetrahydrofuranols 264a and 265a prior to acetylation

LiOH (22.1 mg, 0.92 mmol) was added to a solution of *trans* enone **263a** (190 mg, 0.92 mmol) in THF (9 mL). After stirring for 16 hours at ambient temperature the solution was filtered over silica to remove the LiOH and the eluting solvent removed in *vacuo*. 40 mg of the residue was acetylated without further purification in order to obtain a ratio of isomers by ^1H NMR. The remaining residue was purified by flash chromatography to give 31 mg, 21% of **265a**, 46.4 mg, 31% of **264a** and 10 mg, 7% as a mixture of the two. R_f 0.12 (*trans* isomer) and 0.20 (*cis* isomer) (2:3 ethyl acetate:hexanes). Degradation of the *cis* THF **265a** to furan was evident by ^1H NMR. Tetrahydrofuranols **264a** (31.0 mg, 0.15mmol) and **265a** (36.1 mg, 0.18 mmol) were immediately acetylated under the general conditions to afford 26 mg (70%) of **268a** and 33 mg (76%) of **269a**, respectively, as colourless oils.

(±) (2*R*,3*S*)-2-(2-Oxo-2-phenylethyl)tetrahydro-3-furanyl acetate (268a)

Colourless oil; R_f 0.33 (3:7 ethyl acetate:hexanes); IR (neat) 2984, 2968, 2877, 1737, 1687, 1598, 1581 cm^{-1}; ^1H NMR (600 MHz) δ 2.00 (dddd, J = 13.8, 6.0, 2.4, 2.4 Hz, 1H), 2.08 (s, 3H), 2.26 (dddd, J = 13.8, 10.2, 8.4, 6.6 Hz, 1H), 3.26 (dd, J = 16.2, 7.2 Hz, 1H), 3.29 (dd, J = 16.2, 5.4 Hz, 1H), 3.88 (ddd, J = 10.2, 8.4, 6.0 Hz, 1H), 4.02 (ddd, J = 8.4, 8.4, 2.4 Hz, 1H), 4.42 (ddd, J = 7.2, 5.4, 2.4 Hz, 1H), 5.11 (ddd, J = 6.6, 2.4, 2.4 Hz, 1H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 7.94-7.96 (m, 2H); ^{13}C NMR (150 MHz) δ 21.0, 32.2, 42.2, 67.0, 78.3, 80.4, 128.2, 128.5, 133.2, 136.9, 170.8, 197.3.

(±) (2*R*,3*R*)- (2-Oxo-2-phenylethyl)tetrahydro-3-furanyl acetate (269a)

Colourless oil; R_f 0.33 (3:7 ethyl acetate:hexanes); IR (neat) 2981, 2947, 2880, 1739, 1686, 1598, 1580 cm^{-1}; ^1H NMR (600 MHz) δ 1.98 (s, 3H), 2.01 (dddd, J = 13.2, 7.8, 5.4, 1.8

Hz, 1H), 2.39 (dddd, J = 13.2, 8.4, 7.8, 6.0 Hz, 1H), 3.31 (dd, J = 16.8, 6.6 Hz, 1H), 3.38 (dd, J = 16.8, 6.6 Hz, 1H), 3.82 (ddd, J = 8.4, 8.4, 5.4 Hz, 1H), 4.03 (ddd, J = 8.4, 7.8, 7.8 Hz, 1H), 4.42 (ddd, J = 6.6, 6.6, 3.6 Hz, 1H), 5.45 (ddd, J = 6.0, 3.6, 1.8 Hz, 1H), 7.46-7.49 (m, 2H), 7.56-7.59 (m, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR (150 MHz) δ 20.9, 33.5, 38.2, 66.0, 74.8, 77.3, 128.2, 128.6, 133.2, 136.8, 170.2, 197.5; MS (EI) *m/z* (%): 249 ([M+ H]$^+$, 36), 189 (26), 171 (24), 129 (10), 105 (100), 83 (9), 43 (12).

Isolation of tetrahydrofuranols 264b and furanol 267b prior to acetylation

LiOH (28.1 mg, 1.17 mmol) was added to a solution of 1,2-dioxine **262b** (301 mg, 1.17 mmol) in THF (12 mL). After stirring for 16 hours at ambient temperature the solution was concentrated in *vacuo* and the residue purified by flash chromatography to give 87.8 mg, 29% of **267b** and 71.9 mg, 24% of **265b**. R_f 0.43 (furan **267b**) and 0.32 (*trans* THF **265b**) (3:2 ethyl acetate:hexanes). Compounds **265b** and **267b** were immediately acetylated under the general conditions.

(±)-(2*S*,3*R*)-2-[2-(2-Naphthyl)-2-oxoethyl]tetrahydro-3-furanyl acetate (268b)

Colourless oil; R_f 0.34 (1:4 ethyl acetate:hexanes); IR (neat) 3060, 2984, 2908, 2877, 2252, 1737, 1681, 1628, 1597 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.02 (dddd, J = 13.8, 6.6, 2.4, 2.4 Hz, 1H), 2.09 (s, 3H), 2.28 (dddd, J = 13.8, 9.9, 8.7, 6.9 Hz, 1H), 3.38 (dd, J = 16.2, 7.2 Hz, 1H), 3.44 (dd, J = 16.2, 5.4 Hz, 1H), 3.90 (ddd, J = 9.9, 8.7, 6.6 Hz, 1H), 4.04 (ddd, J = 8.7, 8.7, 2.4 Hz, 1H), 4.48 (ddd, J = 7.2, 5.4, 2.4 Hz, 1H), 5.16 (ddd, J = 6.9, 2.4, 2.4 Hz, 1H), 7.52-7.62 (m, 2H), 7.85-7.90 (m, 2H), 7.94-7.97 (m, 1H), 8.03 (dd, J = 8.7, 1.8 Hz, 1H), 8.47 (s, 1H); ^{13}C NMR (75 MHz) δ 21.0, 32.2, 42.3, 67.0, 78.3, 80.5, 123.8, 126.7, 127.7, 128.4, 128.5, 129.6, 130.0, 132.5, 134.2, 135.6, 170.8, 197.3; MS (EI) *m/z* (%): 298 (M$^+$, 13), 280 (39), 255 (14), 238 (20), 155 (100), 127 (38), 84 (71), 47 (21), 43 (62); HRMS Calcd for [$C_{18}H_{18}O_4$ + Na] 321.1103, found 321.1099.

2-[5-(2-Naphthyl)-2-furyl]ethyl acetate (271b)

Colourless oil; R_f 0.38 (1:9 ethyl acetate:hexanes); IR (neat) 3058, 2962, 1739, 1630, 1594, 1551, 1509 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.07 (s, 3H), 3.07 (t, J = 6.6 Hz, 2H), 4.00 (t, J = 6.6 Hz, 2H), 6.20 (dt, J = 3.3, 0.9 Hz, 1H), 6.67 (d, J = 3.3 Hz, 1H), 7.39-7.49 (m, 2H), 7.71 (dd, J = 8.7, 1.8 Hz, 1H), 7.76-7.85 (m, 3H), 8.08 (s, 1H); ^{13}C NMR (75 MHz) δ 20.9, 27.9, 62.3, 106.4, 108.7, 121.6, 122.1, 125.7, 126.4, 127.7, 128.0, 128.2, 128.3, 132.5, 133.6, 151.9, 153.0, 170.9; MS (EI) *m/z* (%): 280 (M$^+$, 100), 220 (76), 207 (12), 178 (6), 165 (10), 127 (7); HRMS Calcd for [$C_{18}H_{16}O_3$ + Na] 303.0997, found 303.0990.

(±) 3-[(1a*R*,2*S*,5*R*,5a*S*)-5-Phenylperhydrooxireno[2,3-*d*][1,2]dioxin-2-yl]-1-propanol (274).

To a solution of 1,2-dioxine **211** (366 mg, 1.66 mmol) in dichloromethane (15 mL) was added 70% 3-chloroperbenzoic acid (1.229 g, 4.98) and the solution stirred for 3 days at ambient temperature. Dichloromethane (10 mL) was then added and the solution extracted with sat. $Na_2S_2O_3$ (20 mL) followed by $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$, filtered and volatiles removed *in vacuo*. The crude epoxides were purified by column chromatography to yield major epoxide **274** (347 mg, 84%) as a colourless oil; R_f 0.50 (3:2 ethyl acetate:hexanes); IR (neat) 3392, 1597, 1580, 1493, 1455, 1049 cm^{-1}; ^1H NMR (300 MHz) δ 1.66-1.87 (m, 3H), 1.93-2.06 (m, 2H), 3.35 (d, J = 4.5 Hz, 1H), 3.55 (d, J = 4.5 Hz, 1H), 3.66-3.70 (m, 2H), 4.37 (dd, J = 9.6, 3.9 Hz, 1H), 5.31 (br s, 1H), 7.38-7.41 (m, 5H); ^{13}C NMR (75 MHz) δ 26.5, 28.4, 52.1, 52.8, 62.0, 77.9, 80.4, 128.0, 128.7, 129.1, 135.8; MS (EI) *m/z* (%): 236 (M^+, 3), 204 (11), 131 (27), 120 (100), 105 (78), 77 (94), 71 (74); Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; Found: C, 65.90; H, 6.75. And

(±) 3-[(1a*S*,2*S*,5*R*,5a*R*)-5-Phenylperhydrooxireno[2,3-*d*][1,2]dioxin-2-yl]-1-propanol (275) (17 mg, 4%) as a colourless oil; R_f 0.47 (3:2 ethyl acetate:hexanes); IR (neat) 3368, 1661, 1495, 1455, 1050 cm^{-1}; ^1H NMR (300 MHz) δ 1.64-2.13 (m, 5H), 3.57 (d, J = 4.2 Hz, 1H), 3.62 (dd, J = 4.2, 4.2 Hz, 1H), 3.72 (m, 2H), 4.36 (ddd, J = 9.0, 5.1, 4.2 Hz, 1H), 5.32 (bs, 1H), 7.36-7.43 (m, 3H), 7.51-7.54 (m, 2H); ^{13}C NMR (75 MHz) δ 25.6, 28.6, 51.8, 53.2, 62.7, 79.5, 128.5, 128.6, 129.2, 135.1. MS (EI) *m/z* (%): 236 (M^+, 1), 131 (40), 120 (81), 105 (100), 91 (71), 77 (75), 71 (56); HRMS (ESI) found *m/z* 259.0942 ($M+Na^+$), $C_{13}H_{16}O_4$ + Na requires 259.0946.

(±) (3*R*,4*S*,4a*S*,8a*S*)-3-Phenylperhydrpyrano[3,2-*c*][1,2]dioxin-4-ol (276)

To a solution of epoxide **274** (340 mg, 1.44 mmol) in dry dichloromethane (10 mL) was added *p*-toluene sulfonic acid (137 mg, 0.72 mmol) and the solution stirred overnight. After this time the volatiles were removed *in vacuo* and the crude pyran purified by column chromatography to yield pyran **276** (160 mg, 47%) as a colourless oil; R_f 0.25 (2:3 ethyl acetate:hexanes); IR (neat) 3401, 1602, 1585, 1496, 1455, 1096 cm^{-1}; ^1H NMR (600 MHz) δ 1.69 (ddddd, J = 13.8, 11.4, 10.2, 4.2, 1.2 Hz, 1H), 1.81 (ddddd, J = 13.8, 4.2, 4.2, 4.2, 4.2 Hz, 1H), 2.01 (dddd, J = 13.8, 4.2, 4.2, 4.2 Hz, 1H) 2.23 (dddd, J = 13.8, 10.8, 10.2, 4.2 Hz, 1H), 2.29 (bs, 1H), 3.63 (ddd, J = 11.4, 4.2, 1.2 Hz, 1H), 3.68 (ddd, J = 11.4, 11.4, 4.2 Hz, 1H), 3.99 (dd, J = 8.4, 5.4 Hz, 1H), 4.38 (ddd, J = 10.8, 5.4, 4.2 Hz, 1H), 4.44

(dd, J = 8.4, 8.4 Hz, 1H), 4.91 (d, J = 8.4 Hz, 1H), 7.34-7.40 (m, 3H), 7.41-7.44 (m, 2H); ^{13}C NMR (150 MHz) δ 24.2, 24.6, 61.6, 65.6, 75.1, 77.7, 86.5, 127.6, 128.5, 128.9, 135.4; MS (EI) *m/z* (%): 236 (M^+, 13), 105 (26), 71 (100), 60 (35), 43 (71); HRMS (ESI) found *m/z* 259.0942 ($M+Na^+$), $C_{13}H_{16}O_4$ + Na requires 259.0946.

(±) (2*R*,3*S*)-2-[(1*S*)-1-(Acetyloxy)-2-oxo-2-phenylethyl]tetrahydro-2*H*-3-pyranyl acetate (278)

To a solution of pyran **276** (160mg, 0.68 mmol) in dry dichloromethane (10 mL) was added triethylamine (10 drops) and the solution stirred overnight. The volatiles were then removed *in vacuo* and pyridine (0.82 mL, 10.16 mmol), acetic anhydride (0.68 mL, 6.78 mmol) and 4-DMAP (33mg, 0.27 mmol) were added and the solution stirred overnight. Dichloromethane (10 mL) was then added and the solution extracted with water (10 mL) and the organic layer dried ($MgSO_4$), filtered and the volatiles removed *in vacuo*. The crude pyran was purified by column chromatography to yield pyran **278** (150 mg, 69%) as a colourless solid; m.p. 70-71°C; R_f 0.36 (2:3 ethyl acetate:hexanes); IR (nujol) 1739, 1729, 1687, 1597, 1580, 1234, 1092, 720 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.39-1.42 (m, 1H), 1.63-1.68 (m, 1H), 1.81 (s, 3H), 1.83-1.91 (m, 1H), 1.99-2.04 (m, 1H), 2.12 (s, 3H), 3.53 (ddd, J = 12.6, 12.6, 2.4 Hz, 1H), 3.91 (dd, J = 7.2, 1.2 Hz, 1H), 4.09 (ddd, J = 12.6, 4.8, 2.4 Hz, 1H), 4.67 (bs, 1H), 6.02 (d, J = 7.2 Hz, 1H), 7.45-7.48 (m, 2H), 7.57-7.60 (m, 1H), 8.00-8.01 (m, 2H); ^{13}C NMR (75 MHz) δ 20.5, 20.8, 20.9, 27.5, 67.1, 68.7, 74.3, 78.0, 128.8, 129.1, 133.9, 136.1, 169.9, 170.6, 196.2; MS (EI) *m/z* (%): 321 ($M+H^+$,18), 277 (35), 261 (39), 218 (45), 105 (100); HRMS (ESI) found *m/z* 343.1157 ($M+Na^+$), $C_{17}H_{20}O_6$ + Na requires 343.1157.

Synthesis of 1,2-Dioxine 279

***tert*-Butyl[(3*Z*,5*E*)-3,5-heptadienyloxy]dimethylsilane and *tert*-butyl[(3*E*,5*E*)-3,5-heptadienyloxy]dimethylsilane**

Prepared by a Wittig reaction of crotonaldehyde and the ylide generated from phosphonium salt **259b** using the procedure as for 1,3-butadiene **230a-c** synthesis. Colourless oil; Yield: 3.67 g, 72%; Obtained as a 33:17 mixture of 3*Z*,5*E*^{a} and 3*E*,5*E*^{b} isomers; R_f 0.40 (1:99 ethyl acetate:hexanes); IR (neat) 3021, 2930, 2858, 1655 (weak) cm^{-1}; ^{1}H NMR (600 MHz) δ 0.05 (s, 6H)^b, 0.06 (s, 6H)^a, 0.89 (s, 9H)^{a,b}, 1.73 (d, J = 6.6 Hz, 3H)^b, 1.77 (d, J = 6.6 Hz, 3H)^a, 2.27 (q, J = 7.2 Hz, 2H)^b, 2.37-2.41 (m, 2H)^a, 3.63 (t, J = 7.2 Hz, 2H)^{a,b}, 5.30 (dt, J = 10.8, 7.8 Hz, 1H)^a, 5.51-5.56 (m, 1H)^b, 5.57-5.62 (m, 1H)^b,

5.65-5.71 (m, 1H)^a, 5.99-6.07 (m, 2H)^{a,b}, 6.30-6.35 (m, 1H)^a; ^{13}C NMR (50 MHz) δ-5.3, 17.9, 18.2, 18.4, 26.0, 31.5, 36.3, 62.9, 63.1, 125.3, 127.1, 127.3, 127.9, 129.5, 130.3, 131.6, 132.2; MS (EI) *m/z* (%): 226 (M^+, 6), 211 (31), 169 (100), 141 (7), 115 (10), 95 (13), 89 (29), 75 (66), 73 (53), 41 (10); HRMS Calcd for [$C_{13}H_{26}OSi$ + Na] 249.1651, found 249.1648.

(3*Z*,5*E*) and (3*E*,5*E*)-3,5-Heptadien-1-ol

Prepared by desilylation of the above compound using the procedure as for 1,3-butadienes **231a-c** synthesis. Colourless oil; Yield: 1.51 g, 83%; Obtained as a 67:33 mixture of 3*Z*,5*E*^{a} and 3*E*,5*E*^{b} isomers; R_f 0.28 (1:4 ethyl acetate:hexanes); IR (neat) 3130-3560, 3018, 2930, 1678 cm^{-1}; ^{1}H NMR (600 MHz) δ 1.74 (d, J = 6.6 Hz, 3H)^b, 1.78 (d, J = 6.9 Hz, 3H)^a, 2.33 (q, J = 6.6 Hz, 2H)^b, 2.45 (q, J = 6.6 Hz, 2H)^a, 2.46 (br s, 1H)^{a,b}, 3.62-3.70 (m, 2H)^{a,b}, 2.29 (dt, J = 10.2, 8.1 Hz, 1H)^a, 5.47-5.67 (m, 2H)^b, 5.67-5.79 (m, 1H)^a, 5.99-6.07 (m, 1H)^b, 6.07-6.15 (m, 1H)^a, 6.30-6.40 (m, 1H)^a; ^{13}C NMR (75 MHz) δ 17.9, 18.2, 31.2, 35.9, 62.0, 62.2, 124.5, 126.7, 127.0, 128.1, 130.4, 131.2, 131.6, 133.3; MS (EI) *m/z* (%): 112 (M^+, 72), 107 (14), 95 (56), 94 (59), 91 (14), 81 (100), 79 (47), 67 (24), 55 (28), 41 (30); HRMS Calcd for [$C_7H_{12}O + O_2$ + Na] 167.0684, found 167.0680.

2-(6-Methyl-3,6-dihydro-1,2-dioxin-3-yl)-1-ethanol (279)

Prepared by photolysis of (3*Z*,5*E*)- and (3*E*,5*E*)-3,5-heptadien-1-ol by the general procedure for 1,2-dioxine synthesis. Colourless oil; Yield: 1.01 g, 52%; R_f 0.38 (2:3 ethyl acetate:hexanes); IR (neat) 3100-3580, 3043, 2932, 2876, 1657 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.25 (d, J = 6.6 Hz, 3H), 1.80-2.05 (m, 2H), 2.44 (br s, 1H), 3.73-3.86 (m, 2H), 4.60-4.65 (m, 1H), 4.68-4.76 (m, 1H), 5.86-5.94 (m, 2H); ^{13}C NMR (75 MHz) δ 18.0, 35.7, 59.3, 74.3, 76.3, 127.0, 129.2; MS (EI) *m/z* (%): 145 ([M + H]$^+$, 9), 128 (4), 112 (100), 99 (13), 95 (13), 81 (58), 71 (7), 55 (4), 43 (4);

(±)-(3*R*,4*R*,4a*S*,7a*R*)-4-Iodo-3-phenylperhydrofuro[3,2-*c*][1,2]dioxine (280)

To a solution of 1,2-dioxine **262** (149 mg, 0.72 mmol) in acetonitrile (15 mL) was added $NaHCO_3$ (182 mg, 2.17 mmol) and iodine (0.55 g, 2.17 mmol). After stirring for 8 days at ambient temperature the reaction was quenched with the addition of sat. aqueous sodium thiosulfate until the iodine colour subsided. The organic phase was separated and washed with H_2O (30 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography to give 89.2 mg, 38% of **280** as a colourless solid; m.p. 60-66°C; R_f 0.25 (1:9 ethyl acetate:hexanes); IR (nujol) 3100-3580, 3043, 2932, 2876,

1657 cm^{-1}; ^1H NMR (600 MHz) δ2.22 (dddd, J = 13.8, 8.4, 7.2, 7.2 Hz, 1H), 2.28 (dddd, J = 13.8, 7.8, 6.0, 4.8 Hz, 1H), 3.92 (ddd, J = 8.4, 8.4, 6.0 Hz, 1H), 4.02 (ddd, J = 8.4, 8.4, 7.2 Hz, 1H), 4.55 (dd, J = 6.0, 6.0 Hz, 1H), 4.60 (dd, J = 6.0, 5.4 Hz, 1H), 5.01 (ddd, J = 7.2, 5.4, 4.8 Hz, 1H), 5.43 (d, J = 6.6 Hz, 1H), 7.34-7.39 (m, 3H), 7.44-7.46 (m, 2H); ^{13}C NMR (150 MHz) δ27.4, 29.4, 66.5, 80.4, 81.7, 86.9, 127.6, 128.5, 128.9, 137.0; MS (EI) *m/z* (%): 333 ($[M + H]^+$, 76), 315 (73), 299 (10), 239 (89), 206 (84), 191 (100), 174 (33), 161 (56), 151 (79), 145 (34), 105 (9), 91 (15); HRMS Calcd for [$C_{12}H_{13}O_3I$ + Na] 331.9910, found 331.9894.

(±)-(3*R*,4*R*,4a*S*,7a*R*)-4-Iodo-3-methylperhydrofuro[3,2-*c*][1,2]dioxine (281)

Procedure as for the synthesis of compound **280** except the reaction contents were heated under reflux for 48 hours. Yield: 333mg, 71%; Colourless oil; R_f 0.36 (1:9 ethyl acetate:hexanes); IR (neat) 2935, 2886, 1439, 1372 cm^{-1}; ^1H NMR (300 MHz) δ1.52 (d, J = 6.6 Hz, 3H), 2.05-2.22 (m, 2H), 3.91 (ddd, J = 8.4, 8.4, 5.4 Hz, 1H), 4.08 (ddd, J = 8.4, 7.8, 7.8 Hz, 1H), 4.23 (dd, J = 3.6, 3.6 Hz, 1H), 4.30 (dd, J = 3.6, 3.6 Hz, 1H), 4.44-4.52 (m, 1H), 4.97-5.01 (m, 1H); ^{13}C NMR (75 MHz) δ19.2, 27.5, 29.6, 66.7, 79.6, 80.1, 81.1; MS (EI) *m/z* (%): 271 ($[M + H]^+$, 51), 253 (38), 226 (13), 209 (8), 197 (35), 170 (55), 143 (59), 127 (94), 99 (46), 88 (70), 74 (86), 60 (85), 45 (100); HRMS Calcd for [$C_7H_{11}O_3I$ + Na] 292.9651, found 292.9647.

Attempted synthesis of 282a

Method 1: To a solution of 1,2-dioxine **211** (0.4 g, 1.8 mmol) in acetonitrile (50 mL) was added $NaHCO_3$ (0.46 g, 5.5 mmol) and I_2 (1.38 g, 5.5 mmol). The reaction mixture was stirred at ambient temperature and monitored by TLC for consumption of the dioxine. After 5 days the reaction was quenched with the addition of sat. aqueous sodium thiosulfate until the iodine colour subsided. The organic phase was separated and washed with H_2O (30 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo*. ^1H NMR analysis of the residue indicated that 1,2-dioxine had been recovered along with small amounts of an aldehyde by-product, most likely a result of oxidation of **211**.

Method 2: 1,2-Dioxine **211** (0.15 g, 0.7 mmol), $NaHCO_3$ (0.45 g, 5.3 mmol) and distilled water (25 mL) were stirred together until a homogeneous solution was obtained. Chloroform (25 mL) was added and the resulting solution cooled to 0°C as I_2 (1.62 g, 6.4 mmol) was added. The reaction mixture was allowed to warm to ambient temperature and

vigorously stirred at this temperature. No dioxine had reacted after 7 days and the reaction was subsequently abandoned.

Attempted synthesis of 282b

To a solution of 1,2-dioxine **235c** (0.5 g, 1.85 mmol) in acetonitrile (50 mL) was added $NaHCO_3$ (0.47 g, 5.6 mmol) and I_2 (1.41 g, 5.56 mmol). The reaction mixture was stirred at ambient temperature and monitored by TLC for consumption of the dioxine. No dioxine had reacted after 7 days and the reaction was subsequently abandoned.

2-[(1*E*,3*E*)-4-Phenyl-1,3-butadienyl]phenol (283)[284]

To a solution of salicylaldehyde (2.0 g, 16.4 mmol) in anhydrous diethyl ether (50 mL) under N_2 was added potassium *tert*-butoxide (1.84 g, 16.4 mmol). After stirring for 10 minutes at 20°C cinnamyl phosphonium salt **144a** (6.80 g, 16.4 mmol) and anhydrous diethyl ether (30 mL) was added and the reaction mixture stirred for an additional 16 hours at 20°C. The solution was diluted with hexanes (80 mL) and filtered over a silica pad (2-3 cm), which was washed with 2:3 ethyl acetate:hexanes (2 x 100 mL). The combined filtrates were concentrated *in vacuo* to give 2.58 g, 71% of 1,3-butadiene **283** as yellow crystals; The 1,3-butadiene **283** was used without further purification. A small amount was recrystallised from dichloromethane to give yellow needles; m.p. 163–165 °C (lit.[284] 164–165 °C); R_f 0.43 (1:4 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ 4.94 (br s, 1H), 6.61-6.70 (m, 1H), 6.76 (dd, J = 7.8, 1.2 Hz, 1H), 6.88-7.04 (m, 4H), 7.09-7.14 (m, 1H), 7.20-7.25 (m, 1H), 7.30-7.35 (m, 2H), 7.42-7.48 (m, 3H); ^{13}C NMR (75 MHz) δ 115.9, 121.2, 124.7, 126.4, 127.0, 127.1, 127.5, 128.5, 128.6, 129.7, 130.7, 132.7, 137.4, 152.8; MS (EI) *m/z* (%): 222 (M^+, 65), 207 (12), 202 (10), 178 (9), 165 (9), 145 (24), 131 (54), 115 (48), 107 (100), 91 (42), 77 (46), 51 (16), 39 (15).

2-(6-Phenyl-3,6-dihydro-1,2-dioxin-3-yl)phenol (284)

Prepared by photolysis of 1,3-butadiene **283** by the general procedure for 1,2-dioxine synthesis. Yield: 372 mg, 19%; Pale yellow oil; R_f 0.30 (1:4 ethyl acetate:hexanes); IR (neat) 3170-3550, 3063, 3034, 2874, 1702, 1674, 1605, 1598, 1486, 1456 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.66-5.68 (m, 1H), 5.82-5.84 (m, 1H), 6.26-6.34 (m, 2H), 6.78 (br s, 1H), 6.80-6.91 (m, 2H), 7.15-7.25 (m, 2H), 7.31-7.41 (m, 5H); ^{13}C NMR (75 MHz) δ 78.2, 80.4, 116.8, 120.4, 123.3, 126.6, 127.4, 128.3, 128.7, 129.0, 129.3, 130.2, 136.6, 154.9; MS (EI) *m/z* (%): 254 (M^+, 9), 236 (29), 222 (24), 161 (10), 145 (100), 131 (37), 121 (35), 117 (51),

115 (61), 105 (53), 91 (28), 77 (56), 65 (19), 39 (22); HRMS Calcd for $C_{16}H_{14}O_3$ 254.0943, found 254.0942.

Preparation of 2-substituted 1,3-benzodioxole 285

To a 0.1 M solution of 1,2-dioxine **284** in THF or $CHCl_3$ was added LiOH (1 equiv.) or DABCO (0.4 equiv.), respectively. After stirring for 16 hours at ambient temperature the reaction mixture was taken to dryness and the residue purified by flash chromatography.

(*E*)-3-(1,3-Benzodioxol-2-yl)-1-phenyl-2-propen-1-ol (285)

Major product obtained when 1,2-dioxine **284** is treated with LiOH. Yield: 89.9 mg, 55%; Pale yellow oily crystals; R_f 0.37 (1:4 ethyl acetate:hexanes); IR (neat) 3120-3550, 1667, 1627, 1602 cm^{-1}; ^1H NMR (300 MHz) δ 2.35 (br s, 1H), 5.65 (d, J = 8.1 Hz, 1H), 5.82 (ddd, J = 11.1, 6.9, 1.2 Hz, 1H), 6.02 (ddd, J = 11.1, 8.1, 0.9 Hz, 1H), 6.75-6.84 (m, 4H), 6.96 (dd, J = 6.9, 1.2 Hz, 1H), 7.26-7.46 (m, 5H); ^{13}C NMR (75 MHz) δ 70.4, 105.7, 108.62, 108.63, 121.60, 121.62, 125.1, 126.1, 128.0, 128.7, 139.3, 141.9, 147.32, 147.33; MS (EI) *m/z* (%): 254 (M^+, 9), 237 (4), 145 (100), 117 (33), 105 (21), 77 (23), 63 (10), 39 (11); Compound was unstable and appeared to decompose to furan. Therefore it was acetylated.

(*E*)-3-(1,3-Benzodioxol-2-yl)-1-phenyl-2-propenyl acetate (286)

Pyridine (0.9 mL), acetic anhydride (0.55 mL) and 4-DMAP (8.6 mg, 7.01 x 10^{-2} mmol) were added to compound **285** (90 mg, 0.35 mmol) and the solution stirred for 16 hours at 20°C. Dichloromethane was then added and the solution extracted with water and the organic layer dried ($MgSO_4$), filtered and the volatiles removed *in vacuo*. The residue was purified by flash chromatography to give 15.3 mg, 16% of acetate **286** as a pale yellow oil; R_f 0.24 (1:19 ethyl acetate:hexanes); ^1H NMR (600 MHz) δ 2.14 (s, 3H), 5.88 (ddd, J = 11.4, 6.6, 0.6 Hz, 1H), 5.98 (ddd, J = 11.4, 9.0, 1.2 Hz, 1H), 6.67 (d, J = 9.0 Hz, 1H), 6.78-6.83 (m, 4H), 7.03 (dd, J = 6.6, 1.2 Hz, 1H), 7.32-7.34 (m, 1H), 7.37-7.43 (m, 4H); ^{13}C NMR (150 MHz) δ 21.2, 71.3, 105.6, 108.6, 108.7, 121.59, 121.61, 126.7, 127.0, 128.4, 128.8, 134.8, 138.2, 147.3, 147.4, 169.9; MS (EI) *m/z* (%): 296 (M^+, 6), 267 (4), 236 (100), 221 (10), 163 (5), 145 (24), 121 (92), 115 (89), 84 (21), 51 (39), 49 (80).

1-(2-Hydroxyphenyl)-4-phenyl-1,4-butanedione (291)

Major product obtained when 1,2-dioxine **284** is treated with DABCO. Yield: 48.9 mg, 60%. White solid; m.p. 105–108 °C (lit.[285] 107 °C); R_f 0.42 (1:4 ethyl acetate:hexanes); IR

(nujol) 1684, 1640, 1576 cm^{-1}; ^1H NMR (300 MHz) δ 3.42-3.53 (m, 4H), 6.90-7.00 (m, 2H), 7.26-7.50 (m, 3H), 7.51-7.61 (m, 1H), 7.89-7.92 (m, 1H), 8.02-8.05 (m, 2H), 12.13 (s, 1H); ^{13}C NMR (75 MHz) δ 32.1, 32.2, 118.4, 119.0, 119.3, 128.1, 128.6, 129.9, 133.2, 136.3, 136.6, 162.3, 198.2, 204.5; MS (EI) *m/z* (%): 254 (M^+, 28), 236 (6), 149 (100), 121 (77), 105 (44), 77 (26), 65 (10), 43 (6).

Attempted in situ generation and cyclisation of 1,2-dioxine 295

A solution of the methyl ester of 1,2-dioxine **295** (100 mg, 0.43 mmol) in 3:1 MeOH / H_2O (40 mL) was treated with LiOH (48.3 mg, 2.0 mmol) for 16 hours at 4°C. MeOH was removed *in vacuo* and the aqueous layer acidified to pH 1 with dilute HCl (10%). The precipitate was extracted into dichloromethane (20 mL) and the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL), PTSA (25 mg) added and the solution then heated under reflux for 2 hours. MeOH was removed *in vacuo* and the residue taken up into dichloromethane (15 mL). The organic layer was washed with $NaHCO_3$ (10%, 15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. ^1H NMR analysis of the crude residue showed characteristic peaks for the presence of furan and 1,4-diketone.

3-(6-Phenyl-3,6-dihydro-1,2-dioxin-3-yl)propanoic acid (295)

To a 0°C solution of 1,2-dioxine **211** (702 mg, 3.2 mmol) in acetone (50 mL) was added slowly, a solution of 2.67 M Jones' reagent (4.17 g CrO_3 was dissolved in 4.6 mL con. sulfuric acid and diluted with 11 mL H_2O). The solution was stirred at 20°C for 1.5 hours. The reaction mixture was diluted with chilled H_2O (30 mL), and extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to give 412 mg, 55% of dioxine **295** as a white powder. A small amount of product was recrystallised from heptane/dichloromethane to give **295** as white needles; m.p. 98.5-100.5 °C; R_f 0.27 (2:3 ethyl acetate:hexanes); IR (nujol) 3281-3575, 1691 cm^{-1}; ^1H NMR (300 MHz) δ 2.00-2.17 (m, 2H), 2.48-2.66 (m, 2H), 4.57-4.61 (m, 1H), 5.57-5.58 (m, 1H), 6.04-6.17 (m, 2H), 7.33-7.38 (m, 5H), 11.02 (br s, 1H); ^{13}C NMR (75 MHz) δ 27.9, 29.8, 77.1, 80.3, 127.4, 127.8, 128.6, 129.0, 130.1, 136.9, 179.5; MS (EI) *m/z* (%): 216 ($[M-H_2O]^+$, 31), 157 (94), 133 (10), 115 (14), 105 (100), 77 (55), 59 (14), 55 (31); Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02: Found : C, 66.93; H, 6.02.

Attempted synthesis of lactone 300 using LiOH as base

To a solution of 1,2-dioxine **295** (50 mg, 0.21 mmol) in anhydrous THF (2.4 mL) was added LiOH (5.1 mg, 0.21 mmol). The solution was stirred at ambient temperature for 3 days, after which time a white precipitate was present. The white precipitate was immiscible in organic solvents suggesting the lithium salt of the dioxine had formed. The solvent was removed *in vacuo* and the residue taken up in dichloromethane (20 mL). The organic layer was washed with dilute HCl (10%, 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to regenerate 1,2-dioxine **295**.

(±) (5*S*)-5-[(1*S*)-1-Hydroxy-3-oxo-3-phenylpropyl]tetrahydro-2-furanone (300)

To a solution of 1,2-dioxine **295** (52 mg, 0.22 mmol) in $CHCl_3$ (2 mL) was added DABCO (49.8 mg, 0.44 mmol). The solution was stirred at 20°C for 3 hours and then heated in a 70°C oil bath for 16 hours. The solvent was removed *in vacuo* and the residue purified by flash chromatography to afford 37.1 mg, 71% of crude **301** as a pale solid, m.p. 89-114°C (lit.[286] crude 87-107°C, recrystallised 112.5-114.5°C) and 14.0 mg, 27% of lactone **300** as a white solid; A small amount of **300** was recrystallised from heptane/dichloromethane to give white needles; m.p. 93-94°C; R_f 0.28 (3:2 ethyl acetate:hexanes); IR (nujol) 3144-3650, 2253 (weak), 1780, 1769, 1747, 1732, 1689, 1682, 1671, 1597, 1580 cm^{-1}; ^1H NMR (600 MHz) δ 2.30-2.41 (m, 3H), 2.50 (ddd, J = 17.4, 10.2, 6.0 Hz, 1H), 2.73 (ddd, J = 17.4, 9.6, 7.2 Hz, 1H), 3.25 (dd, J = 18.0, 3.0 Hz, 1H), 3.41 (dd, J = 18.0, 9.0 Hz, 1H), 4.32 (ddd, J = 9.0, 3.0, 3.0 Hz, 1H), 4.58 (ddd, J = 8.4, 6.0, 3.0 Hz, 1H), 7.47-7.50 (m, 2H), 7.59-7.62 (m, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR (75 MHz) δ 23.9, 28.4, 41.6, 69.3, 81.6, 128.1, 128.8, 133.8, 136.4, 177.5, 199.7; MS (EI) *m/z* (%): 235 ($[M+H]^+$, 20), 217 (35), 157 (37), 149 (58), 120 (14), 105 (100), 77 (88), 51 (52); Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02: Found: C, 66.73; H, 5.99.

Details of crystal structure determination for 300

Crystal data for $C_{13}H_{14}O_4$: M = 234.24, T = 223(2) K, monoclinic, $P2_1/n$, a = 14.6504(16), b = 5.5565(6), c = 14.7565(15) Å, β = 106.628(2)°, V = 1151.0(2) $Å^3$, Z = 4, D_x = 1.352, $F(000)$ = 496, μ = 0.100 mm^{-1}, no. of unique data (Bruker AXS SMART CCD using Mo Kα radiation so that θ_{max} = 30.0°) = 3342, no. of parameters = 157, R (all data) = 0.069, wR (all data) = 0.150, ρ = 0.35 e $Å^{-3}$. The structure was solved by direct-methods (SIR92) and refined (anisotropic displacement parameters, H atoms in the riding model approximation and a weighting scheme $w = 1/[\sigma^2(F_o^2) + 0.0849P^2 + 0.1183P]$ where $P = (F_o^2 + 2F_c^2)/3$) with SHELXL-97 on F^2 using all reflections.

Towards optically enriched cyclopropanes

4-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-butanol (304)

To a cooled solution (-78°C) of 1,4-butanediol (6.05 g, 67.1 mmol) in anhydrous THF (70 mL) under N_2 was added dropwise and with stirring *n*-BuLi (30 mL, 2.5 M, 75 mmol) A solution of TBDMSCl (10.12 g, 67.1 mmol) in anhydrous THF (20 mL) was then added at -78°C. The mixture was stirred for 30 minutes at -78°C, followed by 90 minutes at 20°C and finally heated under reflux for 3 hours. The cooled solution was concentrated and the resulting residue placed in dichloromethane (180 mL). The organic layer was washed with water (120 mL), dried (Na_2SO_4), filtered and concentrated in vacuo and the residue purified by flash chromatography to give 8.99 g, 77% of the monoprotected diol **304** as a colourless oil. (A known compound but no NMR data available[252]) R_f 0.31 (1:4 diethyl ether:hexanes); ^{1}H NMR (300 MHz): δ0.07 (s, 6H), 0.09 (s, 9H), 1.65 (m, 4H), 2.60 (br s, 1H), 3.66 (m, 4H); ^{13}C NMR (75 MHz): δ-5.4, 18.3, 25.9, 29.8, 30.2, 62.8, 63.3.

4-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxybutanal (305)[252]

Prepared by Swern oxidation of alcohol **304** using procedure as for aldehydes **234**. Yield: 3.08, 65%; Pale yellow oil; R_f 0.43 (1:9 ethyl acetate:hexanes); ^{1}H NMR (200 MHz): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.86 (m, 2H), 2.51 (t, J = 7.2Hz, 2H), 3.68 (t, J = 6.0Hz, 2H), 9.27 (t, J = 6.0Hz, 1H); ^{13}C NMR (50 MHz): δ-5.5, 18.3, 25.5, 25.9, 40.8, 62.1, 202.5.[252]

Methyl (*E*)-6-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-2-hexenoate (306)

Procedure as for α,β-unsaturated esters **226**. Yield: 2.52 g, 99%; Colourless oil; R_f 0.35 (1:19 ethyl acetate:hexanes); ^{1}H NMR (300 MHz) δ0.05 (s, 6H), 0.89 (s, 9H), 1.62-1.72 (m, 2H), 2.24-2.32 (m, 2H), 3.63 (t, J = 6.0 Hz, 2H), 3.73 (s, 3H), 5.84 (dt, J = 15.6, 1.5 Hz, 1H), 7.00 (dt, J = 15.6, 6.9 Hz, 1H); ^{13}C NMR (50 MHz) δ-5.4, 18.3, 25.9, 28.7, 31.1, 51.3, 62.1, 121.1, 149.3, 167.1.

(*E*)-6-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-2-hexen-1-ol (307)

Prepared by DIBAL-H reduction of ester **306** using the procedure as for α,β-unsaturated alcohols **227**. Yield: 8.64 g, 98%; ^{1}H NMR (300 MHz) δ0.05 (s, 6H), 0.89 (s, 9H), 1.50 (br s, 1H), 1.56-1.65 (m, 2H), 2.07-2.14 (m, 2H), 3.62 (t, J = 6.3 Hz, 2H), 4.09 (d, J = 5.1 Hz, 2H), 5.60-5.78 (m, 2H); ^{13}C NMR (75 MHz) δ-5.3, 18.3, 15.9, 28.5, 32.2, 62.5, 63.8, 129.1, 132.9.

(*E*)-6-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-2-hexenal (308)

Prepared by Swern oxidation of alcohol **307** using procedure as for aldehydes **234**. Yield: Assumed to be 100% yield and used immediately in next step.

***tert*-Butyl[((4*Z*,6*E*)-10-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-4,6-decadienyl)oxy]dimethylsilane and *tert*-Butyl[((4*E*,6*E*)-10-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-4,6-decadienyl)oxy]dimethylsilane (309)**

Prepared by a Wittig reaction of aldehyde **308** and the ylide obtained from phosphonium salt **229** using the procedure as for 1,3-butadienes **230a-c**. Yield: 8.38 g, 57%; Colourless oil; Obtained as a 9:11 mixture of 4*Z*,6*E* : 4*E*,6E isomers; R_f 0.25 (1:49 ethyl acetate:hexanes); IR (neat) 2929, 2857, 1471, 1465 cm^{-1}; ^1H NMR (600 MHz) δ 0.04 (s, 12H)^b, 0.05 (s, 12H)^a, 0.89 (s, 18H)^b, 0.90 (s, 18H)^a, 1.56-1.64 (m, 8H)^{a,b}, 2.11 (q, J = 7.2 Hz, 4H)^b, 2.13-2.17 (m, 2H)^a, 2.20-2.24 (m, 2H)^a, 3.59-3.63 (m, 8H)^{a,b}, 5.30 (dt, J = 10.8, 7.8 Hz, 1H)^a, 5.54-5.59 (m, 2H)^b, 5.65 (dt, J = 15.0, 7.8 Hz, 1H)^a, 5.97 (dd, J = 10.8, 10.8 Hz, 1H)^a, 5.98-6.03 (m, 2H)^b, 6.30-6.35 (m, 1H)^a; ^{13}C NMR (75 MHz) δ -5.3, 18.3, 24.0, 26.0, 28.8, 29.2, 32.5, 32.8, 62.5, 62.6, 125.9, 129.0, 129.4, 130.6, 131.8, 134.1; MS (EI) *m/z* (%): 341 ([M-C_4H_9]$^+$, 67), 315 (40), 265 (35), 251 (24), 209 (100), 189 (57); HRMS Calcd for [$C_{22}H_{46}O_2Si_2$-C_4H_9] 341.2332, found 341.2337.

(4*Z*,6*E*)- and (4*E*,6*E*)-4,6-Decadiene-1,10-diol (310)

Prepared by desilylation of **309** using the procedure as for 1,3-butadienes **231a-c**. Yield: 264 g, 87%; Colourless oil; Obtained as a 77:23 mixture of 4*Z*,6*E* : 4*E*,6*E* isomers; R_f 0.52 and 0.56 (100% ethyl acetate); IR (neat) 3050-3550, 3018, 2935, 2868, 1470, 1445 cm^{-1}; ^1H NMR (600 MHz) δ 1.44 (br s, 1H)^b, 1.56 (br s, 2H)^a, 1.64-1.70 (m, 4H)^{a,b}, 2.16 (q, J = 7.2 Hz, 2H)^b, 2.19-2.23 (m, 1H)^a, 2.25-2.29 (m, 1H)^a, 3.64-3.67 (m, 4H)^{a,b}, 5.33 (dt, J = 10.8, 7.8 Hz, 1H)^a, 5.57-5.61 (m, 2H)^b, 5.68 (dt, J = 15.0, 7.2 Hz, 1H)^a, 5.99 (dd, J = 10.8, 10.8 Hz, 1H)^a, 6.03-6.05 (m, 2H)^b, 6.35-6.40 (m, 1H)^a; ^{13}C NMR (75 MHz) δ 23.9, 28.8, 29.1, 32.1, 32.2, 32.4, 62.2, 62.3, 62.4, 126.1, 129.2, 129.3, 130.7, 131.7, 133.9; HRMS Calcd for $C_{10}H_{19}O_2$ 171.1385, found 171.1379.

***tert*-Butyl 3-[(±)-(3*S*,6*R*)-6-(3-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxypropyl)-3,6-dihydro-1,2-dioxin-3-yl]propoxydimethylsilane (311)**

Prepared by photolysis of 1,3-butadienes **310** by the general procedure for 1,2-dioxine synthesis. Yield: 1.44 g, 32%; Colourless oil; R_f 0.30 (3:97 ethyl acetate:hexanes); IR (neat) 2953, 2858, 1472, 1462, 1445 cm^{-1}; ^1H NMR (600 MHz) δ 0.04 (s, 12 H), 0.89 (s,

18H), 1.58-1.71 (m, 8H), 3.59-3.67 (m, 4H), 4.45-4.49 (m, 2H), 5.88-5.91 (m, 2H); ^{13}C NMR (75 MHz) δ -5.3, 18.3, 25.9, 28.5, 29.5, 62.8, 78.1, 127.9; MS (EI) *m/z* (%): 429 ([M-H]+, 5), 373 (5), 317 (3), 281 (16), 241 (18), 201 (100); HRMS Calcd for $C_{22}H_{46}O_4Si$-H 429.2856, found 429.2862.

Attempted synthesis of THP 313

To a solution of 1,2-dioxine **311** (11.4 mg, 2.6 x 10^{-2} mmol) in $CDCl_3$ (0.6 mL) was added a solution of $Co(SALEN)_2$ (0.4 mg, 1.2 x 10^{-3} mmol) in $CDCl_3$ (0.1 mL) (Note: catalyst was allowed to equilibriate in the solvent for 10 minutes prior to its addition). After 48 hours at ambient temperature ^1H NMR analysis indicated that all dioxine had ring-opened to *cis* enone **312**. TBAF (10.4 mg, 4.0 x 10^{-2} mmol) was added to the solution and the reaction progress monitored by ^1H NMR. Despite consumption of the enone the ^1H NMR spectrum did not correspond to that expected for THP **313**. The product obtained is yet to be identified.

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Corrections and Additional Remarks

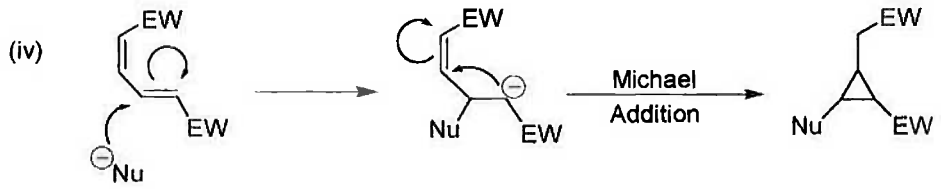
Pg 9 'muti' should be multi.

Pg 11 'miotic' should be mitotic.

Pg 12 'bioactivites' should be bioactivities.

Pg 18 'Furthermore, usually only one enantiomer of a compound will exhibit biological activity' should read that usually one enantiomer is far more potent than the other and/or may exhibit immensely different biological function.

Pg 30 Scheme 1.13: entries (iii) and (iv) are identical but entry (iv) should consist of the following:



Pg 34 'Since enantiomers possess very similar physical properties' should read since enantiomers possess identical physical properties.

Pg 48 The statement 'The presence of the *E* double bond is clearly evident by the large coupling constant of 17.4 Hz between the vinylic protons' is incorrect. There is only one vinylic proton present in compound **131** and it couples to the adjacent alkyl proton with a coupling constant of 10.2 Hz, in addition to a long range coupling to the alkyl methyl group. The ROSEY spectrum of **131** suggests *trans* orientation between the vinylic proton and vinylic methyl group as there is no through space interaction between these two substituents.

Pg 63 The ratio of Compound **159** relative to **158** was approximately 1:2.

Pg 77 In 'For instance, (*E*)-Unsaturated esters' the capital U should be replaced by a lower case u.

Pg 86 'deutrated' should be deuterated.

Pg 90 The ratio of products illustrated in Chart 4.1 was determined by ^{1}H NMR analysis.

Pg 114 In '...required to prepare the 2-Naphthyl...' the capital N should be replaced by a lower case n.

Pg 122 'mass spectroscopy' should be mass spectrometry.

Pg 160 For compound **181b**, the 'I' located after (300 MHz) and (75 MHz) should be δ.

Pg 171 Although compound **229** has been utilised by a number of researchers, no information has been given in the literature for its preparation and/or its characterisation.

Pg 178 Due to the instability of *trans* γ-hydroxy enones, compounds **236** were reacted immediately and therefore they were not characterised. Hence, the lack of experimental data for these compounds.

Pg 186 Method 2: compound **248** should be **249**.

Pg 200 Missing data for compound **285**: HRMS (ESI) Calcd for [$C_{22}H_{28}O_3Si$ + Na] 277.0841, found 277.0834.

The work pertaining to the synthesis of natural and non-natural grenadamide (Chapter 3) and the preparation of tetrahydropyrans from 1,2-dioxines containing tethered hydroxy groups (Chapter 4) have been submitted for publication.