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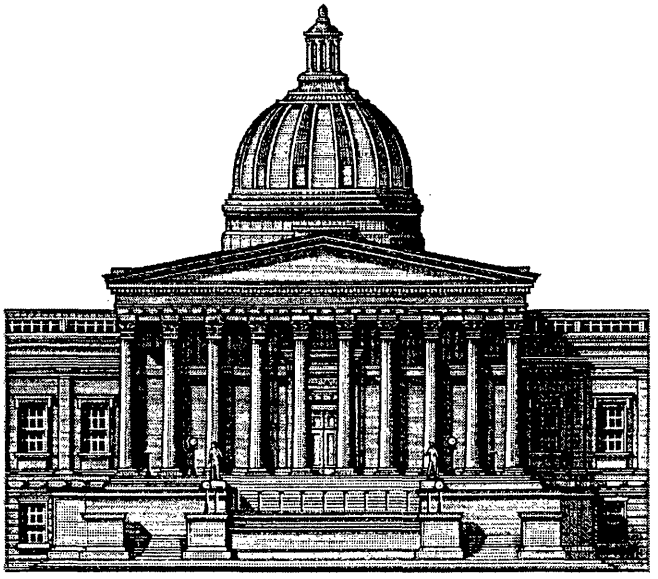

The Asymmetric Synthesis of Several Fragrant Natural Products

A thesis presented by

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Abstract

The thesis covers the synthetic routes to the jasmonoids, in particular the methyl jasmonates. It is divided into several chapters. The initial chapter covers background on the jasmonates including the discovery, occurrence in nature and the biosynthesis of these compounds along with the more recent research into their biological activity as plant pheromones. This section also focuses in more detail, using selected examples from the chemical literature, on the various syntheses to methyl dihydrojasmonates (hedione), methyl *trans*-jasmonates and methyl *epi*-jasmonates together with the problems associated with these.

Chapter 2 explores synthetic routes to the *trans*-jasmonoids in particular methyl dihydrojasmonate. A particular emphasis is placed upon the asymmetric conjugate addition reaction, using extended enolates of homochiral phospholidinone templates (derived from homochiral ephedrine), to afford methyl *trans*-dihydrojasmonates (hedione) in high enantioselectivity. This asymmetric conjugate reaction is further explored in Chapter 3 where we use this synthetic asymmetric methodology is used to prepare both enantiomers of methyl *trans*-jasmonates proceeding *via* a functionalised enone system. The synthesis of the intermediates required for the conjugate additions are also presented.

In Chapter 4 a novel route to racemic *epi*-jasmonate is discussed. The synthetic routes concentrate on a Diels-Alder strategy. It includes our initial investigations comprising, the cycloaddition reactions of 2-cyclopenten-1-one with 2-methoxybutadiene and isoprene using various Lewis acids, together with a synthetic route to a racemic mixture *epi*-jasmonate using concentrated solutions of lithium perchlorate to catalyse the Diels-Alder reaction of 2-cyclopenten-1-one spiroketals with isoprene. This synthetic route was developed further by using chiral spiroketals of 2-cyclopenten-1-one derived from tartaric acid, in an attempt to introduce chirality during the cycloaddition. This work also provided an insight into the mechanism of this particular cycloaddition reaction.

Chapter 5 highlights the two synthetic routes to the calythrone analogue (*n*-butyl-3,4-dimethylcyclopent-3-en-2,3-dione). The first route is based upon the rearrangement of a derivative of 2,3-dimethylmaleic anhydride. The latter comprises the Pauson-Khand reaction to establish the functionalised cyclopentendione skeleton.

Finally a formal description of the experimental results and procedures is presented.

Abbreviations

Ac	Acetyl
AIBN	Azoisobutyronitrile
Ar	Unspecified aromatic group
B	Base
BTEAC	Benzyl triethyl ammonium chloride
BINOL	(*R* or *S*)-1,1'-binapthol
Bn	Benzyl
Bp	Boiling point
br	Broad
(br)	Broad intensity (Infra Red)
Bu	Butyl
CH_2Cl_2	Dichloromethane
CSA	10-Camphorsulfonic acid
CTAB	Cetyltrimethylammonium bromide
$Co_2(CO)_8$	Dicobalt octacarbonyl
Δ	Heat
D	Deuterium
d	doublet
DCM	Dichloromethane
DIPA	Diisopropylamine
DMAP	4-(Dimethylamino)pyridine
DME	Ethylene glycol dimethyl ether
DMF	*N,N*-dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethylsulfoxide
E^+	Unspecified electrophile
ee	Enantiomeric excess
equiv	Molar equivalents
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
h	hour(s)

HCl	Hydrochloric acid
HMPA	Hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
HPLC	High Performance liquid chromotogrpahy
i	iso
i.r.	Infra-red
LDA	Lithium diisopropylamide
Lit.	Literature value
LUMO	Lowest unoccupied molecular orbital
M	Molar concentration
m	Multiplet
(m)	Medium intensity (Infra Red)
mesityl	2,4,6-trimethylphenyl
$MgSO_4$	Magnesium sulfate
min	Minutes
Mp	Melting point
Me	Methyl
n	neo
Na_2SO_4	Sodium sulfate
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance spectroscopy
P	Quin
Pen	Pentyl
PPTS	Pyridinium *p*-toluenesulfonate
p-TsCl	*p*-Toluenesulfonyl chloride (4-methylbenzenesulfonyl chloride)
p-TsOH	*p*-Toluenesulfonic acid
Pr	propyl
q	Quartet
R	Unspecified carbon substituent
rt	Room temperature
s	Singlet
(s)	Strong intensity (Infra Red)
t	Triplet
t	tert

TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
Tf	Triflate
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMS	Trimethylsilyl
(w)	Weak intensity (Infra Red)
X	Unspecified hetroatom substituent

CONTENTS

Chapter 2

Methyl dihydrojasmonate (Hedione®)

Chapter 3

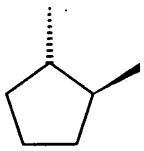
Methyl *trans*-jasmonates

Chapter 4

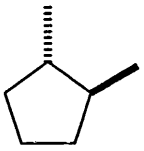
Methyl *epi*-jasmonates

Stereochemical Notation

Throughout this thesis, the graphical representation of stereochemistry is in accord with the convention proposed by Maehr.[1] Thus, solid and broken wedges denote absolute configuration and the solid and broken lines denote racemates. For the former, greater narrowing of both solid and broken wedges indicates distance from the viewer.



Absolute



Relative

Acknowledgements

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Special thanks also to the people, past and present, who have made working on the 4th floor a sheer delight, especially: Allen (Ying Yang) Jensen, Andy (MIT) Peak, Gupreet (I'm Back!) Bhatia, Bod (The anima!l) Haque. J. (No Problem) Cai, Darren (The Guzzler) Greening, Imran (Top Boy) Shah, James (The Blagger!) Madden, John (Argh Yeah!) Lennon, Kamal (Michael J) Uddin, Maria Christofi, Martin Wilmshurst, Matt (Lightening ?) Popkin, Pierre (The Big Guy!) Jung, Patrick (What No Work!) Elford, Phil (I'm having a smoke in my Fumehood!) Heggerty, Rodney, Ruk, Saj (Ooh! REEAALLYY!) Malik, Michael (BT 553) Morris, Sameer (Shushi) Bamberi, Simon Robinson, Vern (No Worries!) Delisser, Vic (Kickass) Gupta, Yau-Fai Ng to name but a few....

I would also like to thank my industrial co-workers, John James, Ben Isaac, Peter Whips, Jack Chan, Amir Yusif, and Jerry Usher for all their help and support throughout my placement at Bush Boake Allen Ltd.

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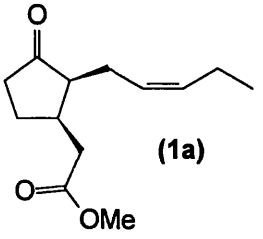
Chapter One

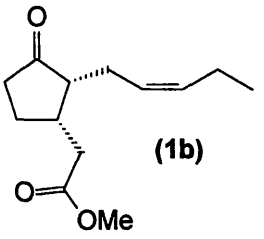
Introduction to the methyl jasmonates and calythrone analogues

1.1 Introduction to the jasmonoids

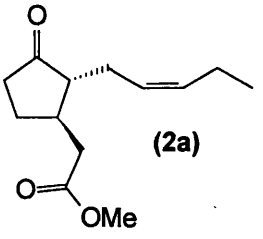
The methyl jasmonates are of great importance in the fragrance industry and are used widely in the formulation of many perfumes.[2] These natural products have strong jasmine odour characteristics and are found naturally occurring in the blossoms of many flowers,[3] and fruits, such as, tomatoes, lemons and apples. The four isomers of methyl jasmonate (**1** & **2**) are shown below.



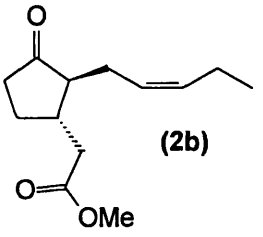
(+)-methyl *epi*-jasmonate



(-)-methyl *epi*-jasmonate

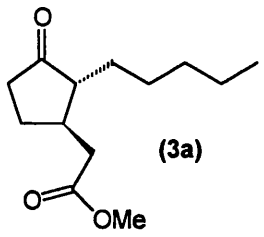


(-)-methyl *trans*-jasmonate



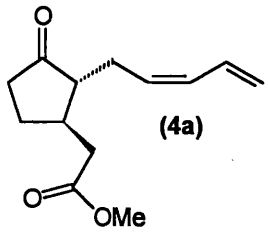
(+)-methyl *trans*-jasmonate

The methyl jasmonates fall into the category of compounds more commonly known as 'jasmonoids'. These molecules are responsible for the strong characteristic odour of jasmine oil[4] isolated from the plant '*Jasminum grandiflorum* L.'. Among the jasmonoids are the methyl dihydrojasmonates (such as **3**) which are commercially known as '*hedione*'. These cheaper analogues of methyl jasmonates are widely used as a substitute to jasmine and are found naturally in tea leaves and lemons.[5] Other jasmonoids include methyl dehydrojasmonates (**4**) and *cis*-jasmone (**5**). It is predominately a combination of these compounds that contribute to the subtle-sweet fragrance of '*Jasminum grandiflorum* L.'.



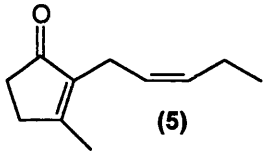
(3a)

(-)-methyl dihydrojasmonate



(4a)

(-)-methyl dehydrojasmonate



(5)

cis-jasmone

The odoriferous white blossoms of the jasmine plant have been used in India for ceremonial purposes and for the scenting of ointments for many centuries. Today, jasmine flower oil and its synthetic substitutes are key ingredients employed universally in the manufacture of high-grade perfumes.

The genus *Jasminum*, *fam.* Oleaceae comprises about 100 species of shrubs or climbers native to Northern India, of which 40 or more occur in North America and Great Britain. Jasmine was grown in gardens before its large-scale cultivation in fields for the perfume industry. This began in reality in the late 19th century in the Grasse area of Southern France where the local climatic conditions led to a frost resisting variety[2] (obtained by grafting *Jasminum. grandiflorum* L. on *J. officinale*). In the early 1920's further industrial plantations of jasmine appeared in warmer parts of the world, in particular Egypt. The cultivation of jasmine and the extraction of its flower oil has been decisive in the establishment of the French perfumery industry,[6] and is very important still today in the global perfumery industry.

1.2 The Extraction Process

In the Grasse region of Southern France, jasmine flower oil was obtained by the so-called '*enfleurage*' process,[2] which uses the fact that the jasmine flowers continue to give off their unique, high quality odour long after picking. The odoriferous material released can then readily be absorbed into a suitable fat base *via* natural diffusion at room temperature. In practice, freshly gathered jasmine flowers are spread over the

surface of the fat base, left in contact for 24 hours, and then replaced by fresh flowers. This process is repeated during the entire period of the jasmine harvest (about 10 weeks) without renewing the fat base. The base then becomes impregnated with the volatile oil, which is extracted with ethanol and isolated as a concentrate ('*concrete*'). Although the *enfleurage* method gives relatively high yields of jasmine flower oil, it also requires a great deal of costly labour.

Today this process has been replaced by the direct extraction of the oil from jasmine flowers with petroleum ether, which affords an oil known as jasmine '*concrete*'. The '*concrete*' is delipified with alcohol to afford between 53 -63 % by weight of jasmine oil, known as jasmine '*absolute*'. A cultivated area of 1500 m^2 gives rise to approximately 600 Kg of jasmine flowers, which after the extraction process gives 1 litre of the jasmine *absolute* and has a commercial value of approximately £8,000.[7]

1.3 Uses of Jasmine oil

In contrast to the '*absolute*', the '*concrete*' of jasmine is not commonly used in perfumery, except in certain soap perfumes where the waxes and other non-volatile lipid constituents are advantageous. By far the greatest part of the jasmine *concrete* producted is processed into the '*absolute*', which, due to its outstanding fragrance properties, has found almost universal use in perfumery applications. At least 80 % of all perfumes on the market today contain the base note of jasmine which contains high proportions of methyl jasmonates (**1a** & **2a**), methyl dihydrojasmonate (**3a**) and *cis*-jasmone (**5**). However, in many perfume compositions natural jasmine '*absolute*' is partly replaced by cheaper synthetic substitutes. These substitutes provide a jasmine-like odour at a fraction of the price of methyl jasmonates.[2]

1.4 The Chemical Composition of the Jasmine Flower oil

Interest in "jasmine chemistry" started about 100 years ago with Hesse,[8] who identified benzyl acetate, linalyl acetate, (+)-linalool, benzyl alcohol, indole and, methyl anthranilate as the chief constituents of jasmine oil. He later identified a ketonic constituent comprising 5 % of jasmine oil. This cyclopentanone derivative, *cis*-jasmone (**5**) had a fruity, celery-like odour and was thought to be the chief component responsible for the jasmine odour. In 1924, Hesse determined the empirical formula to be $C_{11}H_{16}O$ and in 1927 Ruzicka and Pfeifer confirmed the structure as *cis*-jasmone (**5**).

In 1933, the structure that Ruzicka and Pfeifer proposed was universally accepted.[9] Various syntheses of *cis*-jasmone have subsequently appeared in literature.

Demole *et al* in 1962 made the first discovery that the methyl jasmonates are a major component of natural Egyptian jasmine oil.[10] Natural Egyptian jasmine oil was distilled under reduced pressure and the fraction, boiling at 100-160 °C / 0.05 (mm), was further purified by chromatography. They were able to isolate *cis*-jasmone (**5**) and another compound rich in jasmine odour, which they determined to be methyl jasmonate (**2**).

The odour of (-)-methyl jasmonate (**2a**) is considerably sweeter than that of *cis*-jasmone (**5**) and has been highly desired by perfumers. However, methyl jasmonate has two asymmetric centres with the odour characteristics of each diastereoisomer being slightly different for example (+)-methyl *epi*-jasmonate (**1a**) has an odour threshold some 200 times greater than that of the corresponding (-)-methyl jasmonate (**2a**).[2]

Among the 97 compounds listed as components of jasmine oil *cis*-jasmone (**5**), (-)-methyl *trans*-jasmonate (**2a**) and (+)-methyl *epi*-jasmonate (**1a**), constituting 3-4 % of absolute jasmine oil, are said to be the specific carriers of the true natural jasmine fragrance.

1.5 The chemical composition of the *absolute* jasmine oil from (*Jasminum grandiflorum* L.)[2]

Chemical	Formula	Weight	Year isolated
Acids			
Benzoic acid	$C_7H_6O_2$	122	1942
Nonanoic acid	$C_9H_{18}O_2$	158	1980
Dodecanoic acid	$C_{12}H_{24}O_2$	200	1980
Tridecanoic acid	$C_{13}H_{26}O_2$	214	1980
Tetradecanoic acid	$C_{14}H_{28}O_2$	228	1980
Palmitoleic acid	$C_{16}H_{30}O_2$	254	1980
Hexadecanoic acid	$C_{18}H_{30}O_2$	278	1980
Linoleic acid	$C_{18}H_{32}O_2$	280	1980
Oleic acid	$C_{18}H_{34}O_2$	282	1980
Octadecanoic acid	$C_{18}H_{36}O_2$	284	1980
Eicos-9-enoic acid	$C_{20}H_{38}O_2$	310	1980
Eicosanoic acid	$C_{20}H_{40}O_2$	312	1980
Heneicosanoic acid	$C_{21}H_{42}O_2$	326	1980
Docosanic acid	$C_{22}H_{44}O_2$	340	1980
Tricosanoic acid	$C_{23}H_{46}O_2$	354	1980
Tetracosanoic acid	$C_{24}H_{48}O_2$	368	1980
Ursolic acid	$C_{30}H_{48}O_2$	456	1980

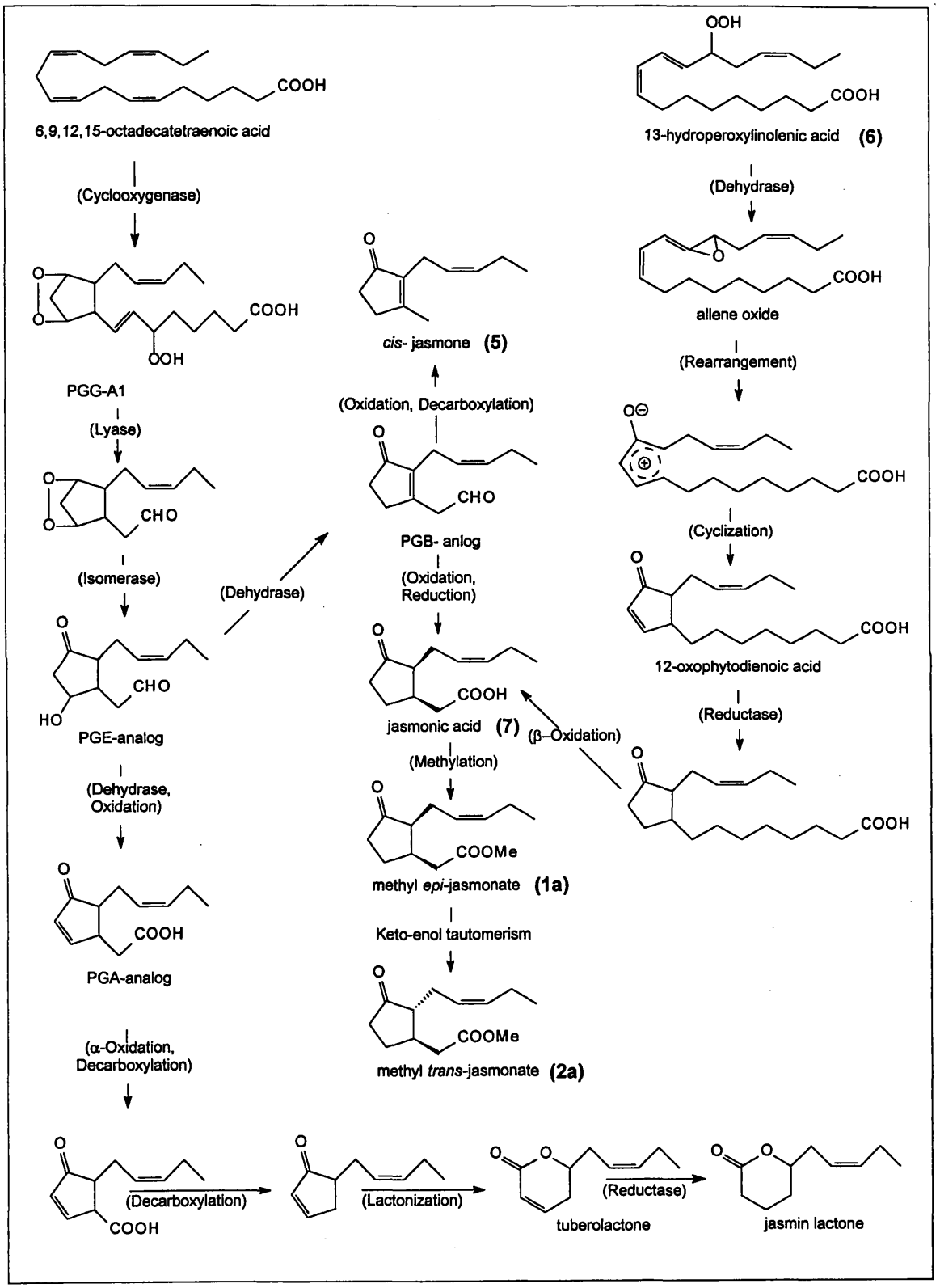
Alcohol			
(*Z*)-Hex-3-en-1-ol	$C_6H_{12}O$	100	1974
Benzyl alcohol	C_7H_8O	108	1899
(+)-Linalool	$C_{10}H_{18}O$	154	1899
Geraniol	$C_{10}H_{18}O$	154	1942
α-Terpineol	$C_{10}H_{18}O$	154	1942
Farnesol	$C_{15}H_{26}O$	222	1926
Nerolidol	$C_{15}H_{26}O$	222	1942
Geranyl-linalool	$C_{20}H_{40}O$	290	1958
Isophytol	$C_{20}H_{40}O$	296	1956
Phytol	$C_{20}H_{40}O$	296	1958
Esters			
Methyl benzoate	$C_8H_8O_2$	136	1974
(*Z*)-Hex-3-enyl acetate	$C_8H_{14}O_2$	142	1974
Benzyl acetate	$C_9H_{10}O_2$	150	1899
(*Z*)-Hex-3-enyl butyrate	$C_{10}H_{18}O_2$	170	1974
(*Z*)-Hex-3-enyl isobutyrate	$C_{10}H_{18}O_2$	170	1972
(*Z*)-Hex-3-enyl benzoate	$C_{13}H_{16}O_2$	204	1962
Benzyl benzoate	$C_{14}H_{12}O_2$	212	1942
Methyl hexadecanoate	$C_{17}H_{34}O_2$	270	1958
Methyl linolenate	$C_{19}H_{34}O_2$	292	1958
Phytyl acetate	$C_{22}H_{42}O_2$	338	1958
Isophytyl acetate	$C_{22}H_{42}O_2$	338	1958
Phytyl hexadecanoate	$C_{36}H_{70}O_2$	534	1977
Phytyl linolenate	$C_{38}H_{68}O_2$	556	1977
Phytyl oleate	$C_{38}H_{72}O_2$	560	1977
Ketoesters			
Methyl *trans*-(*Z*)-4,5-dehydrojasmonate	$C_{13}H_{18}O_3$	222	1974
Methyl (-)-*trans*-(*Z*)-jasmonate (**2a**)	$C_{13}H_{18}O_3$	224	1962
Ethyl (-)-*trans*-(*Z*)-jasmonate	$C_{14}H_{22}O_3$	224	1974
Methyl (-)-*cis*-(*Z*)-jasmonate (**1a**)	$C_{13}H_{18}O_3$	224	1962
Ketoester	$C_{14}H_{22}O_3$	238	1974
Ketones			
6-Methylhept-5-en-2-one	$C_8H_{14}O$	126	1962
Cis-(*Z*)-jasmone (**5**)	$C_{11}H_{16}O$	164	1899
6,10,14,Trimethylpentadecan-2-one	$C_{18}H_{36}O$	268	1962
Lactones			
Hexan-4-olide	$C_6H_{10}O_2$	114	1973
4-Methylhex-5-en-4-olide	$C_7H_{10}O_2$	126	1973
Heptan-4-olide	$C_7H_{12}O_2$	128	1973
Octan-4-olide	$C_8H_{14}O_2$	142	1973
Nonan-4-olide	$C_9H_{16}O_2$	156	1973
(-)-(*R*)-(*Z*)-Ded-7-en-5-olide	$C_{10}H_{16}O_2$	168	1962
(*Z*)-Dec-7-en-4-olide	$C_{10}H_{16}O_2$	168	1973
Bicyclic lactone	$C_{12}H_{18}O_2$	194	1974
Phenols			
p-Cresol	C_7H_8O	108	1910
Cresol	$C_8H_{10}O_2$	138	1942
Vanillin	$C_8H_8O_3$	152	1962
Eugenol	$C_{10}H_{12}O_2$	164	1939

Nitrogen-Containing compounds			
3-Vinylpyridine	C_7H_7N	105	1973
3-Ethylpyridine	C_7H_9N	107	1978
Indole	C_8H_7N	117	1899
Phenylacetonitrile	C_8H_7N	117	1973
3-Vinyl-4-methylpyridine	C_8H_9N	119	1978
3-Ethyl-4-methylpyridine	$C_8H_{11}N$	121	1978
Quinoline	C_9H_7N	129	1973
2-Methylquinoline	$C_{10}H_9N$	143	1973
Methyl nicotinate	$C_7H_7NO_2$	151	1978
Methyl anthranilate	$C_8H_9NO_2$	151	1978
Methyl 4-methyl-nicotinate	$C_8H_9NO_2$	151	1978
2-Phenylnitroethane	$C_8H_9NO_2$	151	1973
Methyl 5-vinyl nicotinate	$C_9H_9NO_2$	163	1978
Methyl 5-ethyl nicotinate	$C_9H_{11}NO_2$	165	1978
Methyl *N*-methyl-anthranilate	$C_9H_{11}NO_2$	165	1965
Ethyl 5-vinyl nicotinate	$C_{10}H_{11}NO_2$	177	1978
Methyl 4-methyl 5-vinyl nicotinate	$C_{10}H_{11}NO_2$	177	1978
Ethyl 5-ethyl nicotinate	$C_{10}H_{13}NO_2$	179	1978
Methyl 4methyl-5-ethyl-nicotinate	$C_{10}H_{13}NO_2$	179	1978
Ethyl 4-methyl 5-ethyl-nicotinate	$C_{11}H_{15}NO_2$	193	1978
Methyl *N*-acetylanthranilate	$C_{10}H_{11}NO_3$	193	1964
Miscellaneous			
Benzaldehyde	C_7H_6O	106	1942
'Linalool oxides' *cis* & *trans*	$C_{10}H_{18}O_2$	170	1974
(*E*)-Farnesene (α & β)	$C_{15}H_{24}$	204	1980
Ketolactone	$C_{12}H_{16}O_2$	208	1942
Neophytdiene	$C_{20}H_{38}$	278	1980
(*E*)-Phyta-1,3-diene	$C_{20}H_{38}$	278	1980
(*Z*)-Phyta-1,3-diene	$C_{20}H_{38}$	278	1980
Phyta-2,4-diene	$C_{20}H_{38}$	278	1980
Squalene	$C_{30}H_{50}$	410	1977

1.6 Biosynthetic pathway

In nature it is thought that C-13 hydroperoxylinolenic acid (**6**),[11] an intermediate found in prostaglandin synthesis, is also the precursor to jasmonic acid. The biosynthetic pathway (Scheme **1.01**) has been extensively studied and it is widely accepted that methyl *epi*-jasmonate (**1**) is formed directly by this pathway. It is also thought that methyl *trans*-jasmonate (**2**) is derived from methyl *epi*-jasmonate (**1**) by keto-enol tautomerism.

The biosynthetic pathway to the jasmonoids **Scheme 1.01**



1.7 The Biological Activity of Methyl Jasmonate

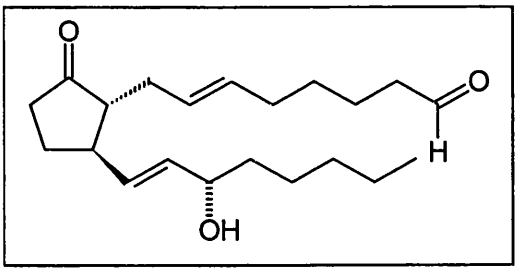
Recent reports have suggested that jasmonic acid (**7**) and its derivatives play a key role as phytohormones (pheromones).[12] It was found that only one of the four isomers of methyl jasmonate (**1a**, **1b**, **2a** & **2b**) is biologically active, the (+)-methyl *epi*-jasmonate (**1a**).[13] The biological activity of this compound includes tomato and potato tuber induction, tendril coiling and a key role in the induction of secondary metabolite production for growth promotion.[14]

It has been shown that the addition of racemic methyl *epi*-jasmonate (**1**) to potato plants can also reduce microtubules but significantly increase the formation of tubers.[15] Other effects include signal transduction[16,17,18] as a plant's defence against herbivores by stimulating the release of volatile substances that act as 'SOS signals'[19] attracting predators that prey upon herbivores.[20,21]

1.8 The Structural relationship to Prostaglandins

As mentioned earlier, the prostaglandins (for example see Structure **1.02**) share structural similarities with the jasmonates. They are both comprised of a cyclopentanone ring with alkyl groups at α and β-positions.

$\Delta^{5,6}$-*trans*-11-deoxy PGE_2 **Structure 1.02**



The potent and diverse biological activity of prostaglandins has attracted the attention of numerous scientists from academic and industrial laboratories. Many novel synthetic routes to the natural material have been devised following the pioneering work of Corey and Fried,[22] and of these, the most adaptable syntheses have been used to prepare a host of analogues including both *epi* and *trans*-jasmonates.

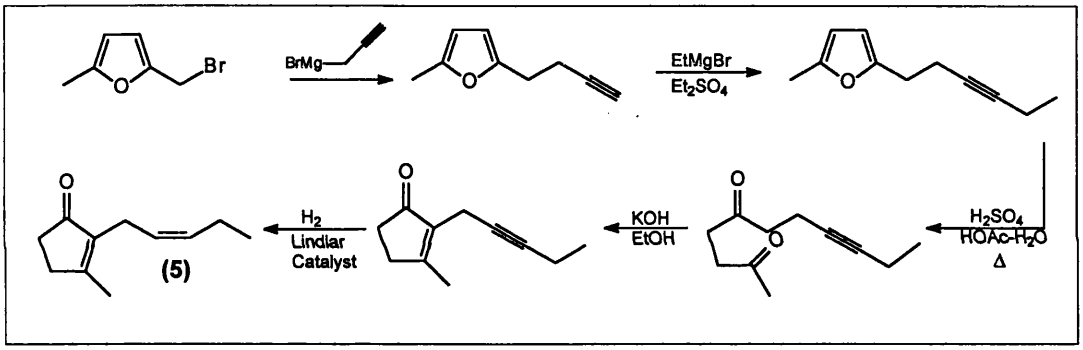
1.9 The Most Prevalent Syntheses of Jasmonoids

Over the past 30 years there have been over 150 synthetic methods reported for the synthesis of methyl jasmonate (**2a**),[23,24] methyl dihydrojasmonate (**5**) and *cis*-

jasmone (**5**). In the late 1980's and early 1990's, with the development of novel asymmetric methodology in organic synthesis, elaborate synthetic routes to enantioselective methyl *trans*-jasmonates and methyl *epi*-jasmonates appeared in the literature.

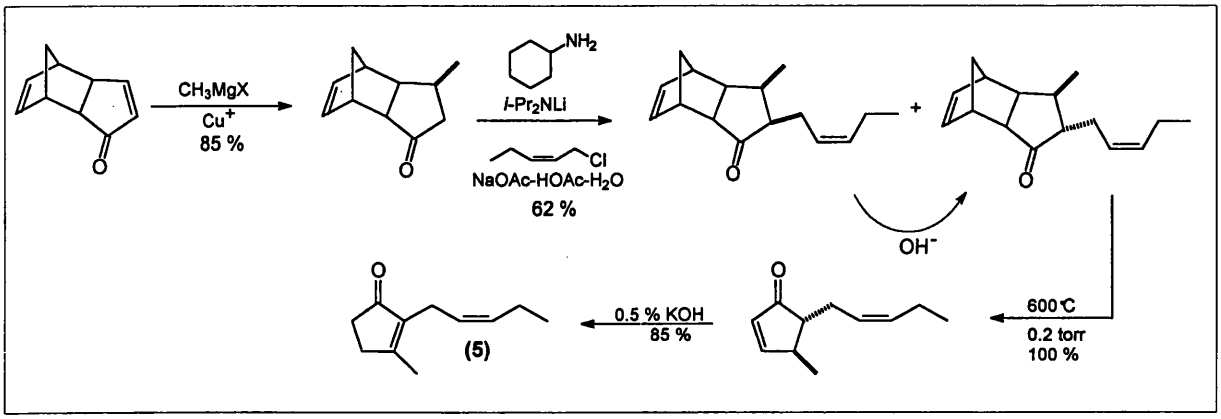
In the early 1970's *cis*-jasmone (**5**) was the focus of continuous attention owing to its economic value and as a convenient target to test many new methodologies. Many key discoveries were made, including the fact that furans were latent 1,4 dicarbonyl compounds, which were readily converted by acid treatment to diketones. This protocol has been exploited in many subsequent syntheses of *cis*-jasmone (**5**) and other related compounds. Sisdo's synthesis of *cis*-jasmone is one such example[25] (Scheme **1.02**).

Sisido's synthesis of cis-jasmone (**5**) **Scheme 1.02**



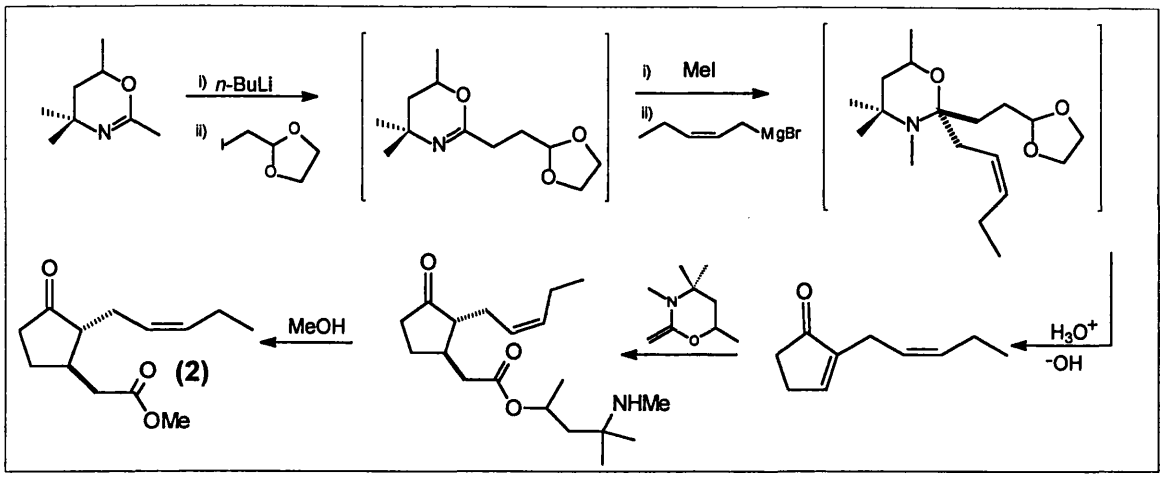
Another synthesis of *cis*-jasmone (**5**) that has received much attention was by Stork.[26] Stork demonstrated complete control over alkylation at α and β positions of a tricyclic cyclopentenone. This procedure opened the way to different 4,5-disubstituted cyclopentenone derivatives (Scheme **1.03**).

Stork's synthesis of cis-jasmone (**5**) **Scheme 1.03**



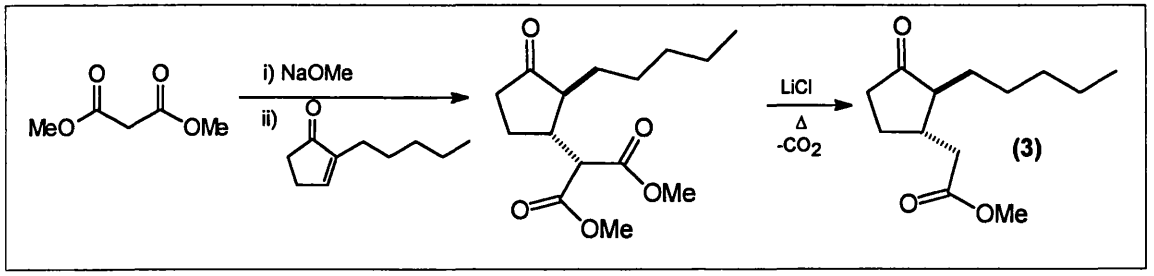
In the late 1970's syntheses of the methyl jasmonates started appearing in the literature. These syntheses reported novel methodologies such as the use of dihydrooxazine derivatives which offered both nucleophilic and electrophilic sites for carbon-carbon bond formation which is amply demonstrated in the Meyer's-Nazarenko[27] synthesis (Scheme **1.04**).

Meyers - Nazarenko synthesis using dihydrooxazine **Scheme 1.04**



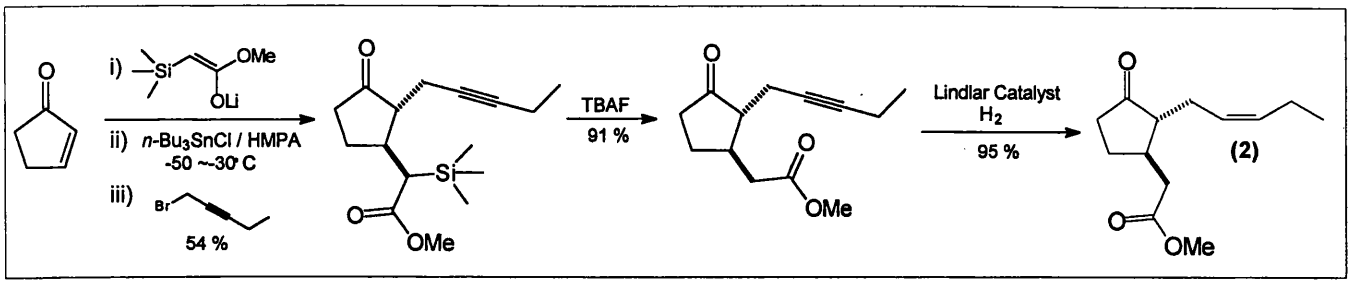
By the end of the 1980's a convenient racemic preparation of methyl dihydrojasmonate (**2**) based upon the conjugate addition of methyl malonate to a saturated 2-alkyl cyclopentenone was used by industry to synthesise large quantities of methyl dihydrojasmonate[28] (Scheme **1.05**).

Conjugate addition of methyl malonate to a functionalised enone **Scheme 1.05**



Various other similar racemic syntheses also appeared including a short 3 step synthesis by Nishiyama[29] which utilised a conjugate addition of lithiotrimethylsilyl acetate to cyclopentenone followed by a sequential vicinal alkylation using stannyl enolate trapping (Scheme **1.06**).

Nishiyama's short three step synthesis of racemic methyl jasmonate **Scheme 1.06**



1.10 Asymmetric Routes

Prior to the start of this Ph.D. research programme there were only nine published asymmetric routes to the methyl jasmonates. A further four asymmetric routes to both the methyl jasmonates and methyl *epi*-jasmonates have been published during the last three years which highlights their importance as excellent fragrance compounds and plant pheromones.

The enantioselective synthetic routes to the methyl *epi* and *trans*-jasmonates can be categorised into the following 5 groups:-

i) The use of chiral auxiliaries / templates to establish the chiral centres.

ii) The use of chiral synthons, where the stereochemistry is conserved throughout the synthesis.

iii) Syntheses utilising a Diels-Alder cycloaddition reaction to establish the *syn* relationship.

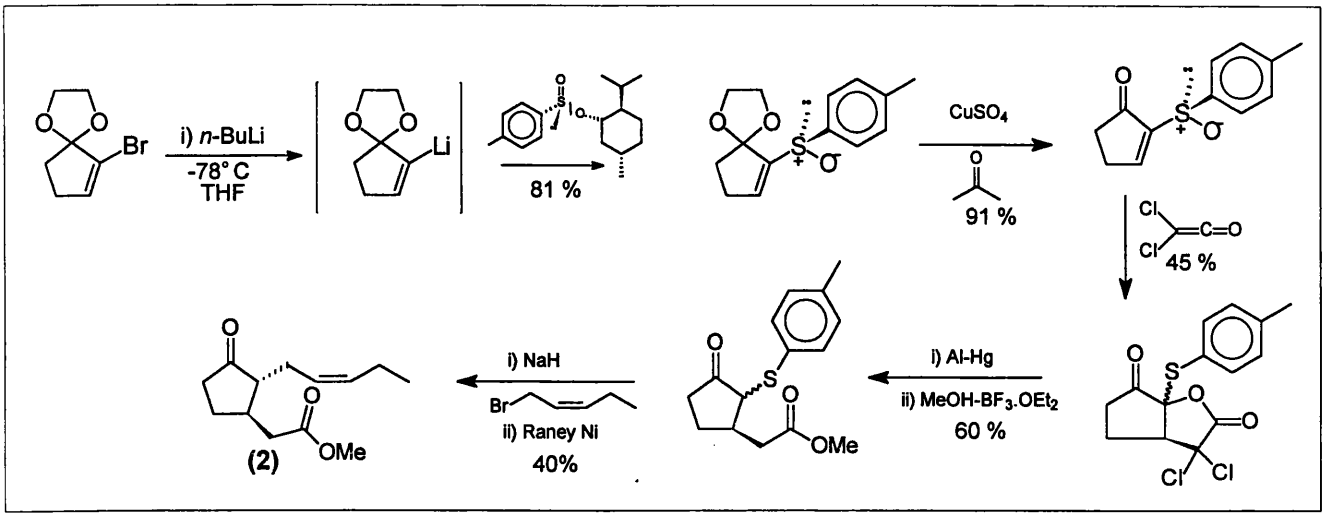
iv) The use of a bicyclic lactone, which has been used extensively in prostaglandin syntheses in the 1980's.

v) The use of a free radical cyclization approach.

1.11 i) Use of Asymmetric Auxiliaries to establish stereogenic centres

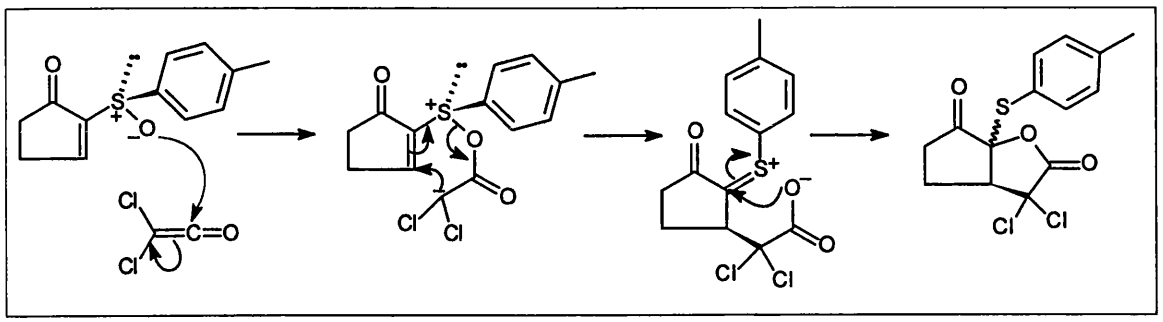
In 1985 Posner utilised an additive Pummerer rearrangement involving direct conversion of α,β-unsaturated sulfoxides into α,β-disubstituted sulfides[30] (Scheme **1.07**).

Synthesis of chiral methyl *trans*-jasmonates **Scheme 1.07**



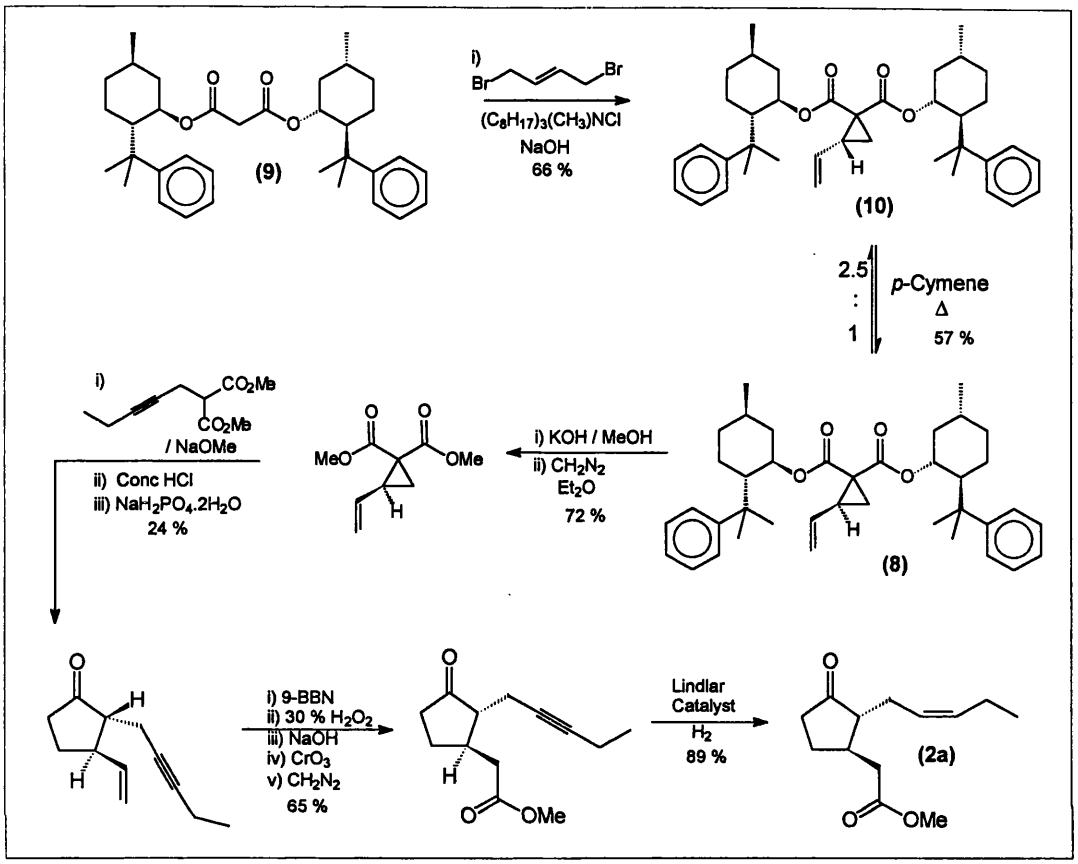
The Pummerer rearrangement[31] proceeded *via* a [3,3]-sigmatropic rearrangement (Scheme **1.08**). The (-)-methyl jasmonate (**3**) was synthesised with a 20 % enantiomeric purity. This synthesis although producing (**3**), in low enantiomeric excess, showed how the presence of a chiral auxiliary in the form of sulfoxide could be used to direct neighbouring groups with facial selectivity.

Mechanism of the asymmetric induction step **Scheme 1.08**



In 1982 Quinkert used an enantiomerically pure cyclopropane (**8**) as a convenient building block for (-)-methyl jasmonate (**2a**).[32] The cyclopropane was prepared using an asymmetry inducing reaction of (*E*)-1,4-dihalo-2-butene with chiral menthol derivative (**9**) (Scheme **1.09**). This lead to a separable equilibrium mixture of the two cyclopropanes (**8** &**10**) in a ratio of 1 : 2.5.

Quinkert's synthesis of enantioselectively pure (-)-methyl jasmonate (**2a**) **Scheme 1.09**

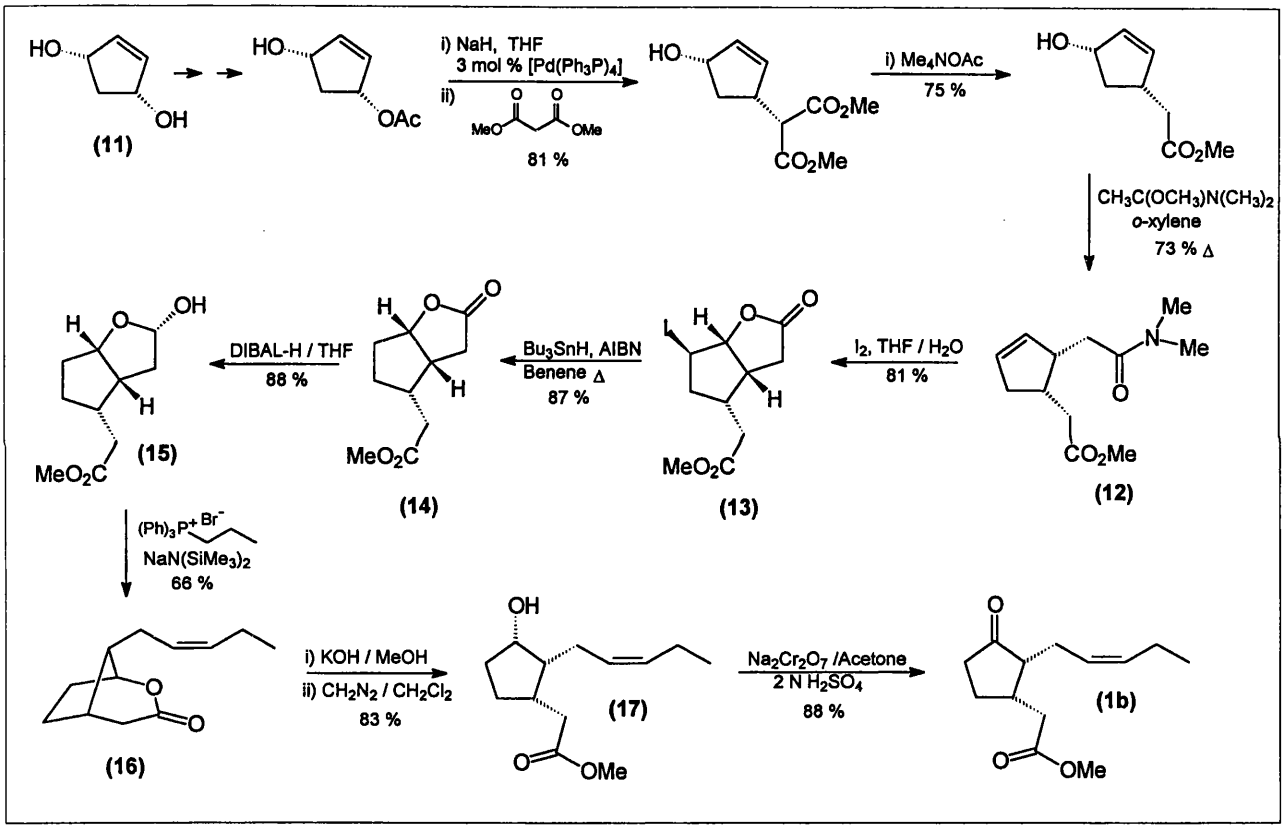


Saponifcation of the diester (**8**) followed by esterification with diazomethane proceeded to give the corresponding methyl ester. Alkylation using a functionalised alkyne lead to ring opening of the cyclopropane followed by subsequent ring closure to a functionalised cyclopentanone after decarboxylation. Hydroboration of the primary olefin was followed by oxidation of the primary alcohol with chromium trioxide and esterification with diazomethane, and this lead to methyl *trans*-dehydrojasmonate. Regiospecific hydrogenation was achieved with a Lindlar catalyst, which lead to enantiomericllay pure (-)-methyl *trans*-jasmonate (**2a**). Although the synthesis produced the desired methyl *trans*-jasmonate in excellent enantioselectivity, two equivalents of the chiral auxiliary were required to form the chiral malonate ester (**10**) and the overall yield of (-)-methyl *trans*-jasmonate (**2a**) was only 5 % based upon the starting malonate (**9**).

1.12 ii) Using a chiral synthon approach

In 1989 Montforts reported an enantiodivergent alkylation of cyclopent-2-ene-1,3-diol (**11**), using a palladium (0)-induced reaction.[33] The stereochemistry of the chiral synthon was conserved throughout the nine step synthesis and methyl *epi*-jasmonate (**1b**) was synthesised in an overall yield of 13 % from the cyclopentene-1,3-diol (**11**) precursor (Scheme **1.10**).

Montforts's synthesis of (-)-methyl *epi*-jasmonate **Scheme 1.10**

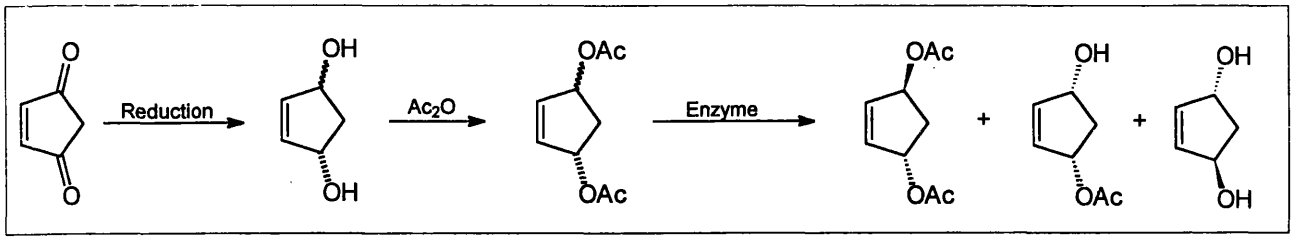


The key step in the synthesis was the lactonization of the amide (**12**), which was achieved *via* the electrophilic addition of molecular iodine to the amide (**12**) affording the *cis*-fused bicyclic lactone (**13**). Treatment with tributyltin hydride lead to dehydroiodination to lactone (**14**). Selective reduction of the lactone (**14**) to lactol (**15**) proceeded with one equivalent of diisobutylaluminium hydride. A subsequent Wittig reaction using conditions laid out by Bestmann[34] then produced the bridged lactone (**16**), with almost exclusive (*Z*) olefin geometry (96 : 4). Then, hydrolysis of the lactone with potassium hydroxide followed by methylation of the free acid resulted in the

formation of a *cis*-fused methyl cucurbate (**17**). Mild oxidation of the methyl cucurbate (**17**), using sodium dichromate, gave methyl *epi*-jasmonate (**1b**) in > 99 % optical purity.

The high enantioselectivity of the *epi*-jasmonate was a direct result of the enantiomeric purity of the starting synthon since the stereochemistry of the stereocentre was conserved throughout. However, the enantiomerically pure cyclopentenediol (**11**) was not readily available and extremely expensive to prepare. Montforts obtained the chiral diol from the resolution of racemic cyclopentenediol[35] (Scheme **1.11**).

Resolution / separation by enzymatic hydrolysis of the corresponding di-acetate (Scheme **1.11**)

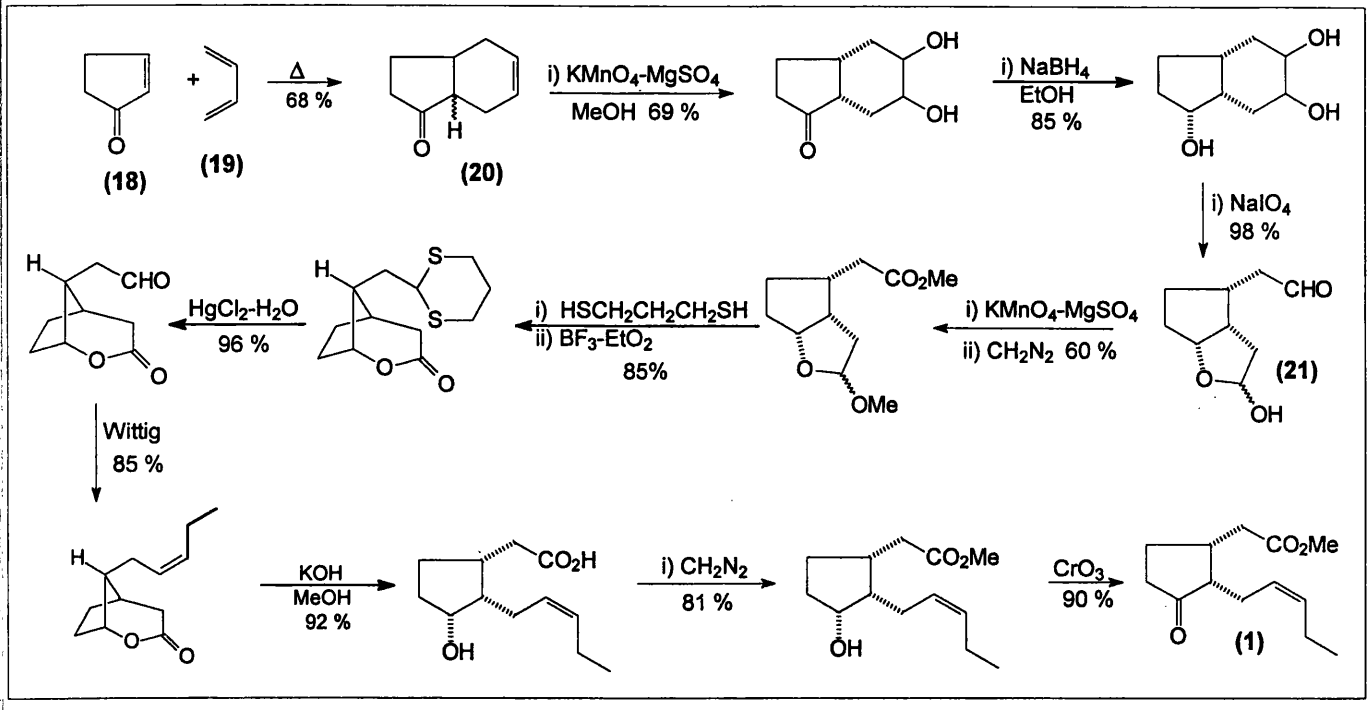


The separation of the diastereoisomers was achieved by enzymatic hydrolysis of the corresponding diacetoxy compound, which meant a significant amount of the cyclopentenediol had to be discarded and recycled. The availability of, for example, resin bound recyclable enzymes would now of course simplify the practical aspect of the resolution step.

1.13 iii) Use of a Diels-Alder Cycloaddition Strategy to Synthesise *epi*-Jasmonates

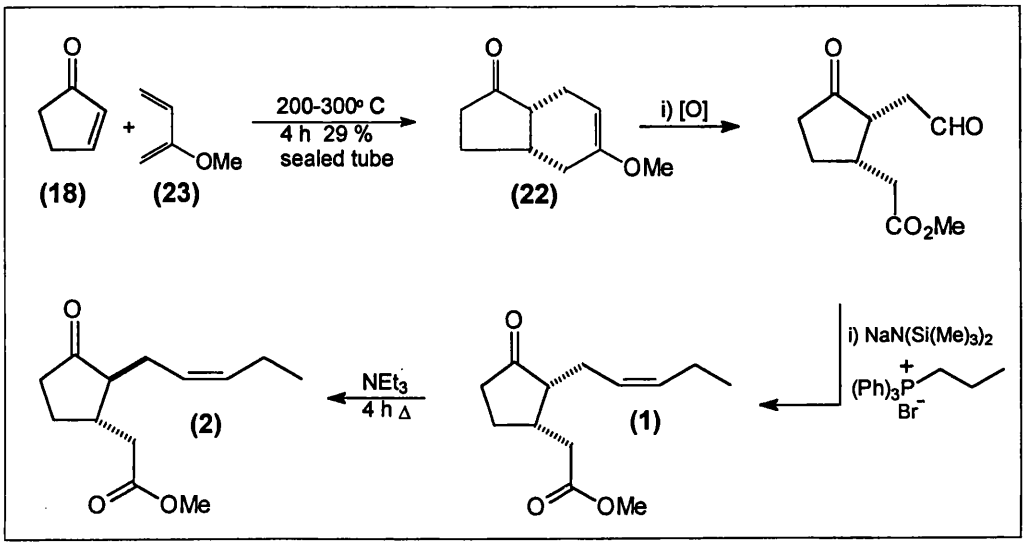
In 1975 Torii reported the first synthesis of racemic methyl *epi*-jasmonate.[36] He proceeded *via* a Diels-Alder cycloaddition reaction between 2-cyclopenten-1-one (**18**) and butadiene (**19**) (Scheme **1.12**). The tetrahydroindanone (**20**) was dihydroxylated with $KMnO_4$-$MgSO_4$, [37] selectively reduced with sodium borohydride, and then converted to the hemiacetal (**21**). This route then lead to a racemic mixture of the methyl *epi*-jasmonates (**1**).

Torii's 12 step synthesis of racemic methyl *epi*-jasmonate (**1**) **Scheme 1.12**



A year later a Japanese patent[38] appeared which included a short three step synthesis to a racemic mixture of methyl *epi*-jasmonate proceeding *via* a Diels-Alder cycloaddition reaction. 2-Cyclopenten-1-one (**18**) and 2-methoxybutadiene (**23**) were heated at 200- 300 °C under high pressure (Scheme **1.13**).

Japanese patented route to racemic methyl jasmonate (**2**) **Scheme 1.13**.

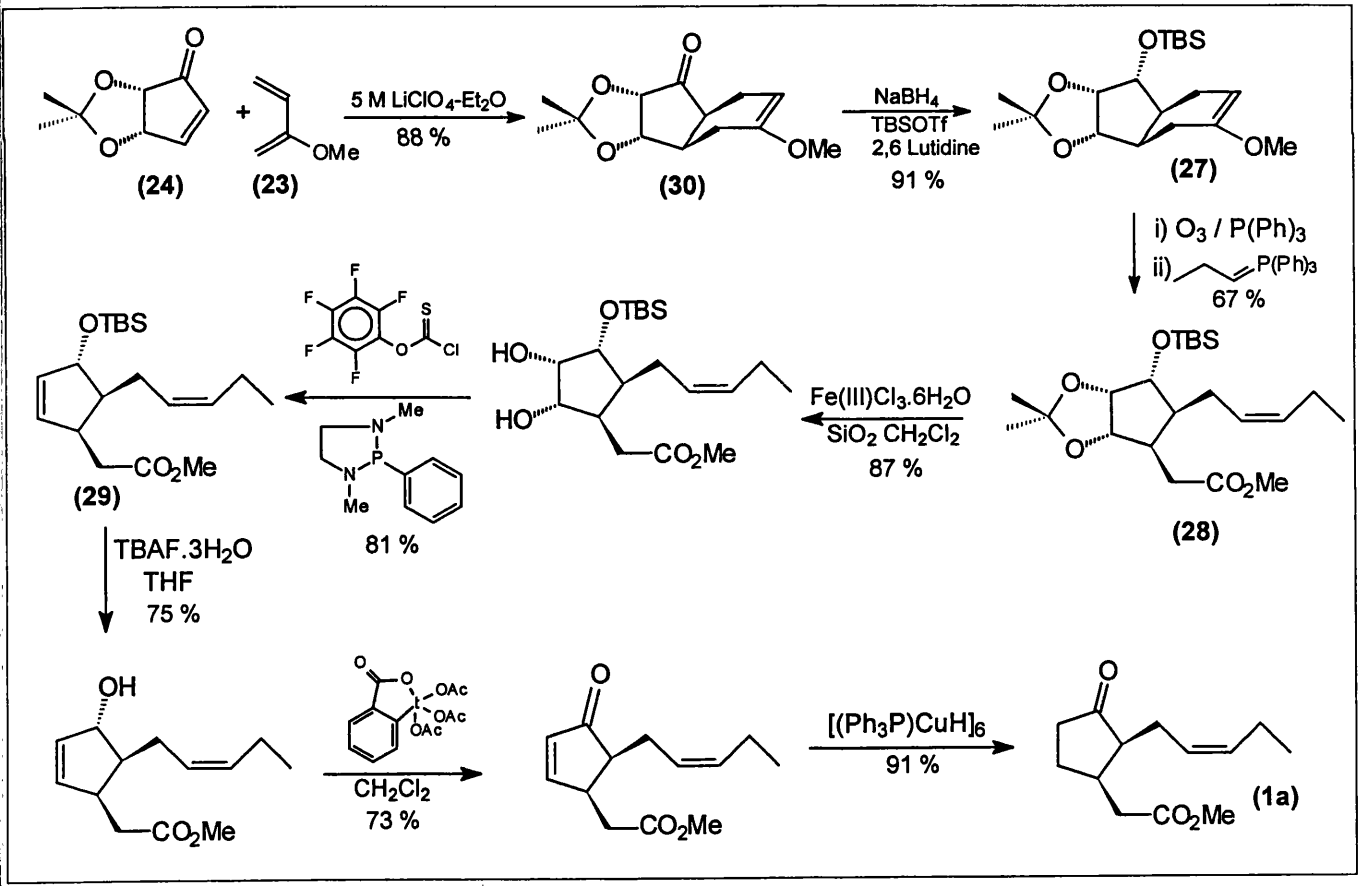


These harsh conditions resulted in a 22 % yield of the cycloaddition products. Subsequent oxidative cleavage of the olefin (**22**) followed by a Wittig reaction, resulted in the formation of methyl *epi*-jasmonate (**1**) in an overall yield of 2 %. The *epi*-jasmonate was then epimerized in the presence of triethylamine to afford racemic methyl *trans*-jasmonate (**2**), their desired target.

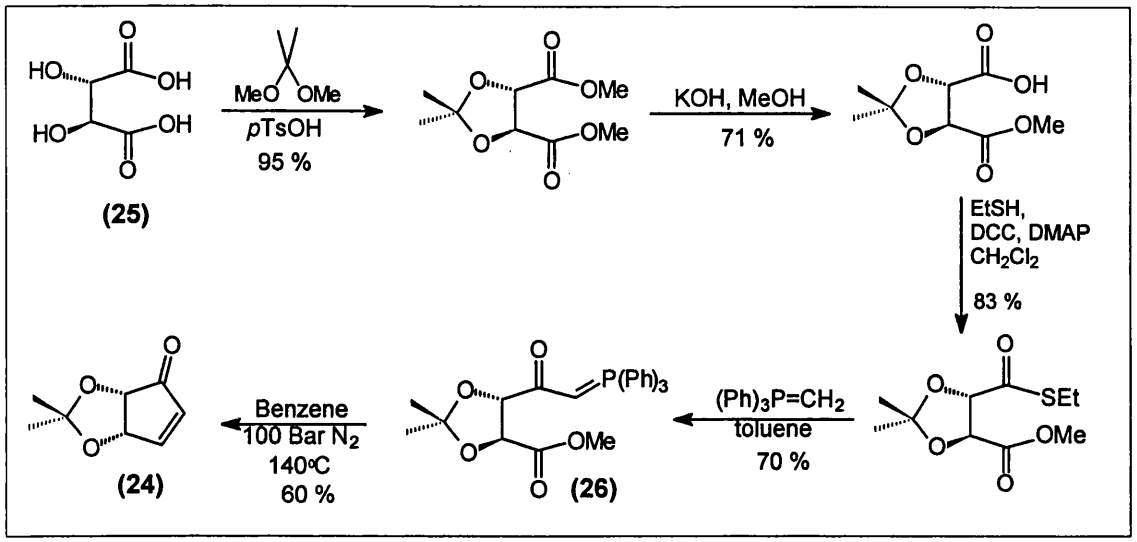
More recently, towards the end of this Ph.D. Bestmann published a similar Diels-Alder strategy to (+)-methyl *epi*-jasmonate (**1a**), in 10 % overall yield and 97 % *ee* (Scheme **1.14**).[39] The synthesis used a chiral cyclopentenoid synthon (**24**), previously used in the preparation of prostaglandins.

The chiral cyclopentenoid (**24**) was synthesised from chiral tartaric acid (**25**), *via* a stereo inversion of the cyclic ketal (**26**)[40] (Scheme **1.15**). This was then used in the stereoselective Diels-Alder cycloaddition that established the two chiral centres.

Asymmetric route to (+)-methyl *epi*-jasmonate (**1a**) **Scheme 1.14**



Synthesis of cyclopentenoid (**24**) *from tartaric acid* (**25**) **Scheme 1.15**



Oxidation of the cyclohexene (**27**) with ozone afforded an aldehyde that underwent the Wittig reaction to give almost exclusively the (*Z*)-olefin (**28**) in 67 % yield. Removal of the ketal by treatment with pentaflurorophenylchlorothionoformiate and *N,N*-dimethyl-2-phenyl-1,3-diazaphospholidine gave the silylether (**29**). Then, hydrogenation using a triphenylphosphine copper (I) hydride hexamer (Stryker's reagent), proceeded with remarkable chemoselectivity to give (+)-methyl *epi*-jasmonate (**1a**) in an overall yield of 6 % with an *ee* of 97 % from enantiomerically pure ketal (**24**). This route also provided a synthetic route to (-)-methyl jasmonate (**2a**) in 7 % overall yield and 96 % *ee*. This was achieved by ozonolysis of the cycloadduct (**30**) directly without reduction to the alcohol. Whilst these routes had many advantages, the removal of the chiral auxiliary was not straightforward and required three different steps involving costly reagents.

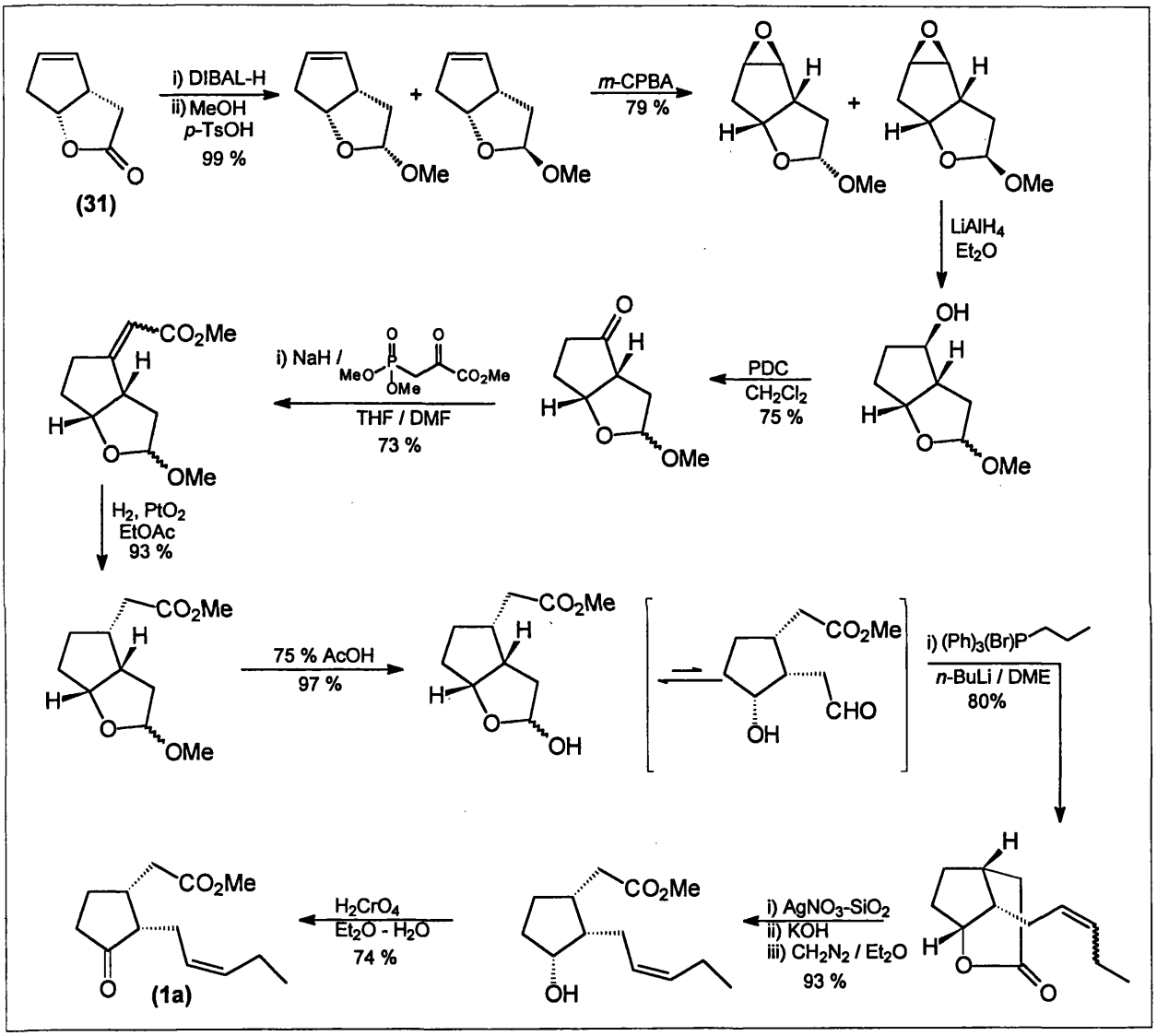
1.14 iv) Use of a 'bicyclic lactone' to synthesise homochiral *epi*-jasmonoids

In 1991 Kitahara successfully converted the chiral bicyclic lactone (**31**)[41] (a useful building block for the synthesis of prostaglandins) into (-)-methyl *epi*-jasmonate (**1a**). This synthesis was accomplished in 20 % overall yield through 11 steps from the lactone (Scheme **1.16**).

The synthesis is complicated by the fact that the starting chiral synthon was commercially expensive, (prepared by the kinetic resolution of racemic 2-oxacyclopentanetanecarboxylic acid).[42] Another disappointing fact was the number of

synthetic transformations in the synthesis. Several manipulations were hampered by the generation of diastereoisomeric mixtures.

Kitahara's synthesis of (+)-methyl *epi*-jasmonate (**1a**) **Scheme 1.16**

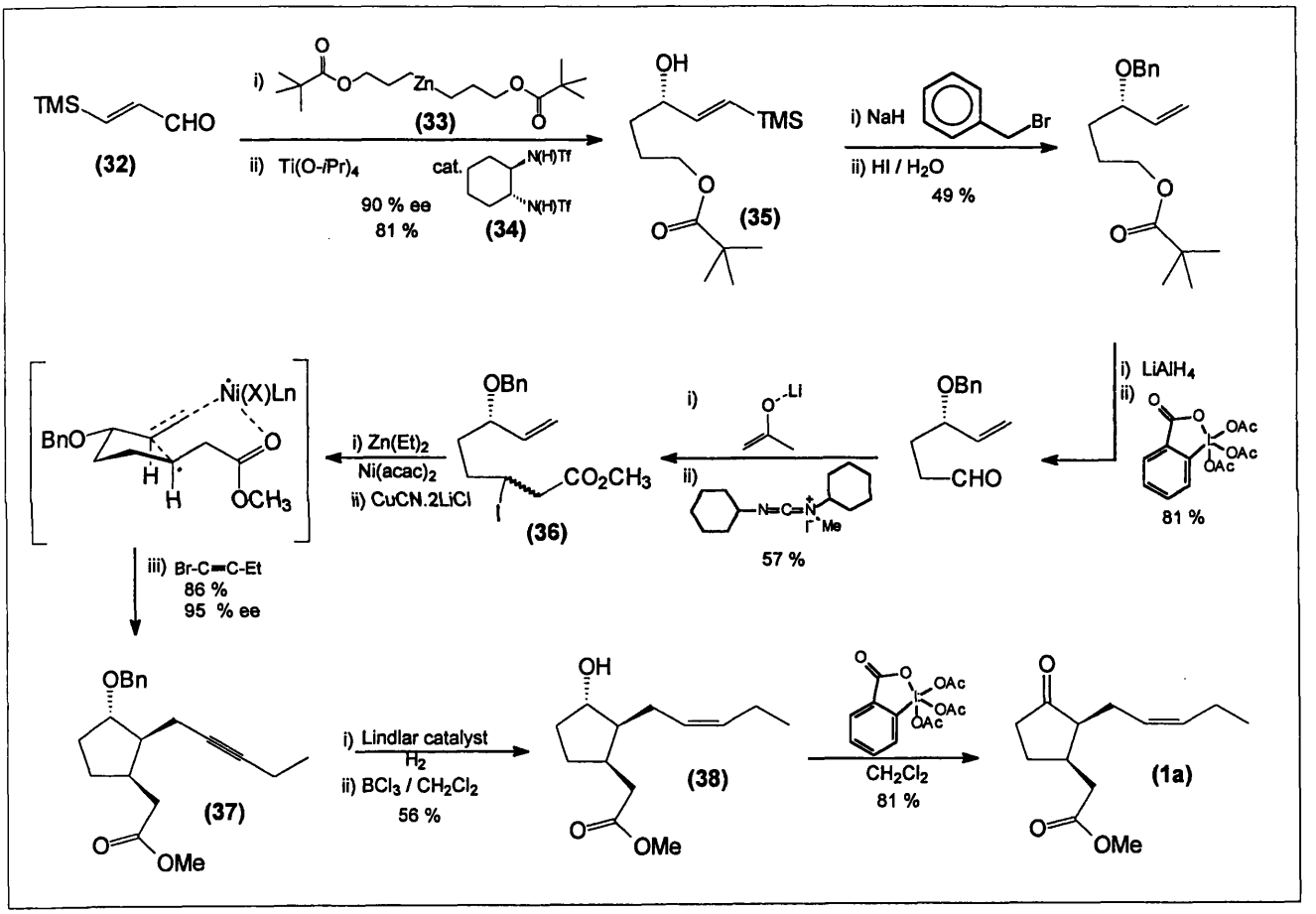


1.15 v) Free radical cyclization approach to methyl jasmonate

In 1995, Knochel's synthesis of (+)-methyl *epi*-jasmonate (**1a**) was the first free radical cyclization approach to provide an *epi*-jasmonate in 89 % optical purity[43] (Scheme **1.17**). The key step was the asymmetric alkylation of aldehyde (**32**) with the dialkylzinc species (**33**) using a chiral amine catalyst (**34**), which produced the

enatiomerically pure secondary alcohol (**35**). Subsequent free radical cyclization was achieved using a nickel catalyst that was able to chelate in a regioselective manner to both the carbonyl group and π-electrons of the olefin (**36**) affording the *syn* functionalised cyclopentanone (**37**). Hydrolysis of the benzyl protecting group gave (-)-methyl *epi*-cucurbate (**38**).

Knochel's asymmetric synthesis of (+)-methyl *epi*-jasmonate (**1a**) **Scheme 1.17**



Finally, (-)-methyl *epi*-cucurbate (**38**) was oxidised to (+)-methyl *epi*-jasmonate (**1a**) *via* a Dess-Martin oxidation.[44] This afforded the jasmonoid (**1a**) in an overall combined yield of 7 % over seven synthetic steps from the α,β-unsaturated aldehyde synthon.

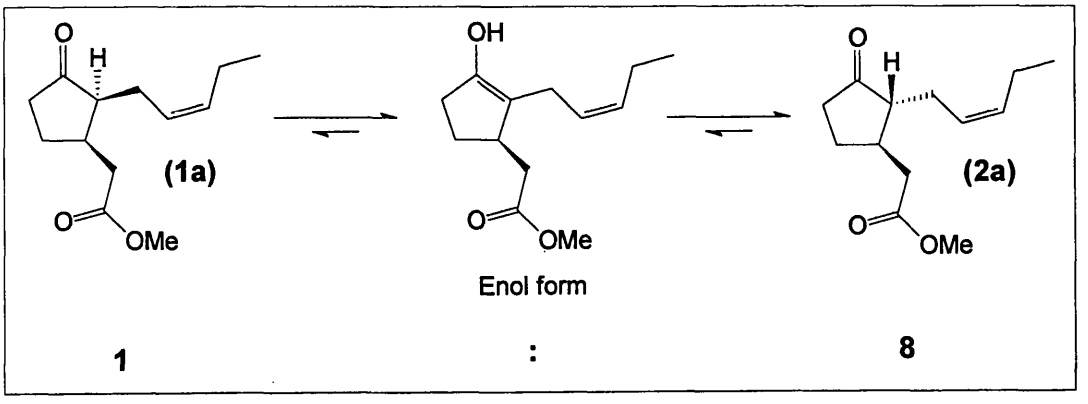
By studying the five different strategies used to prepare methyl jasmonates, it was clear that the Diels-Alder cycloaddition route offered a quick synthetic pathway to the *epi*-jasmonoids. It was also apparent that the cycloaddition reaction had not been fully exploited to give enantiomerically pure *epi*-jasmonates (prior to last year). The other

key synthetic route was the use of a homochiral bicylic lactone (**31**), already featured in five different synthetic preparations of both chiral *epi*-prostaglandins and chiral methyl *epi*-jasmonates (**1a** & **1b**), several having been patented. We felt that there was more scope with an alternative approach based upon the Diels-Alder cycloaddition reaction to the methyl *epi*-jasmonates (**1a** & **1b**) and concentrated on this option. For the methyl *trans*-jasmonates (**2a** & **2b**) we decided to investigate asymmetric conjugate addition reactions onto functionalised enones, since there have been several reports on new methodologies of this type.

1.16 Problems associated with the synthesis of *epi*-jasmonates

The properties of methyl *epi*-jasmonate were first studied by Demole in 1962.[9] He found that (+)-methyl *epi*-jasmonate (**1a**) was not stable at room temperature, and underwent epimerization at the α (chiral) centre to give (-) methyl *trans*-jasmonate (**2a**). The thermal energy required for this epimerization process was calculated experimentally to be approximately 5 Kcal mol^{-1}. In nature the methyl jasmonates are found in a ratio of 1:8, where most of the material is in the thermodynamically more stable (*trans*) configuration (Scheme **1.18**).

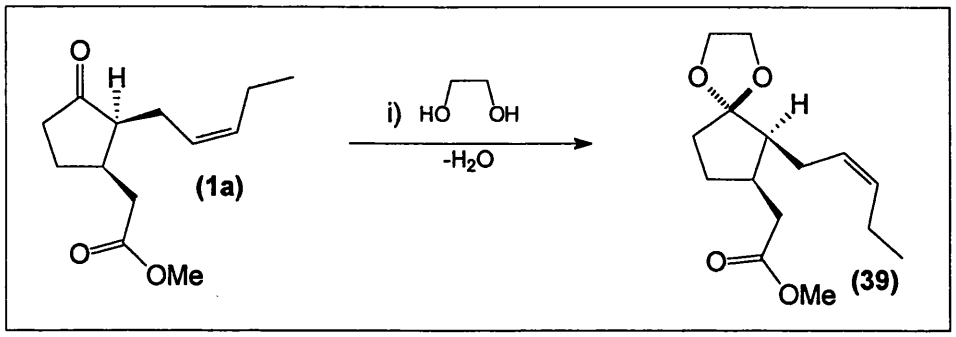
Tautomerism of methyl *epi*-jasmonate (**1a**) *to* methyl *trans*-jasmonate (**2a**) **Scheme 1.18**



To overcome this problem of keto-enol tautomerism, methyl *epi*-jasmonate (**1**) will have to be derivatized to either reduce the rate of, or stop the epimerization process. Some methods for achieving this are outlined below.

One option is to derivatize the *epi*-product, by making the ethylene glycol ketal of the ketone (**39**). This would stop the epimerization process (Scheme **1.19a**) by not allowing keto-enol tautomerism to take place.

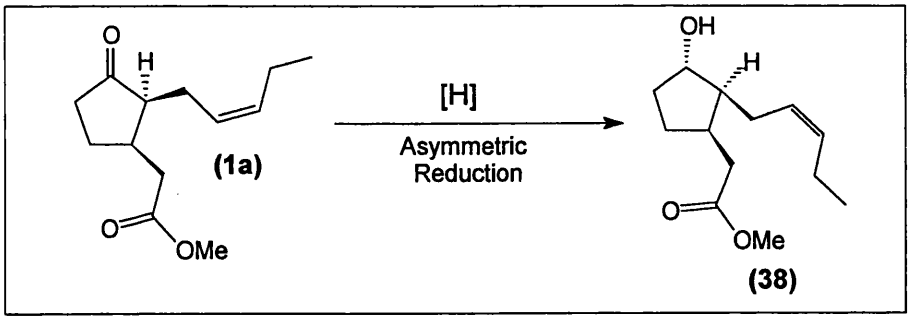
Protection of methyl *epi*-jasmonate (**1a**) *with ethylene glycol* **Scheme 1.19a**.



Typically, the deprotection of acetals requires the use of a proton source or Lewis acid, which as a consequence are not compatible with the sensitive functionality. Mild hydrolysis conditions using iron (III) chloride hexahydrate[45] have however been shown to be compatible with acid sensitive functionalities, and could feasibly be used.

A second option could be to selectively reduce the ketone to a secondary alcohol (*ie* methyl *epi*-cucurbate). Methyl *epi*-cucurbate is also naturally occurring and could be used to unequivocally prove the absolute configuration (Scheme **1.19b**).

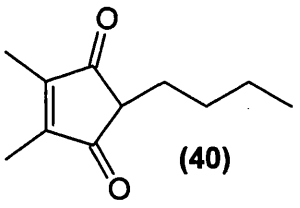
Reduction of methyl *epi*-jasmonate (**1a**) *to a secondary alcohol* (**38**) **Scheme 1.19b**.



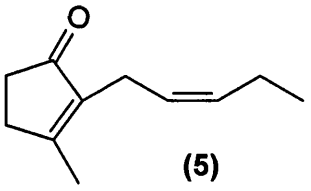
However, oxidation back to the ketone may prove difficult due to the delicate functionality that this molecule possesses. A neutral oxidising agent would have to be used. A Dess-Martin periodinane oxidation[44] has been shown in Knochel's synthesis to be ideal due to the mild reaction conditions.

1.17 Introduction to the Calythrone analogue

1,2-Dimethyl-4-butyl-cyclopenten-4,5-dione (**40**), is an extremely interesting compound with a strong butter / jasmine odour. The structure has a plane of symmetry and harbours several similarities to *cis*-jasmine (**5**). Both are unsaturated cyclic ketones with vinyl methylene groups and have acyclic alkyl groups at positions α to the ketone.



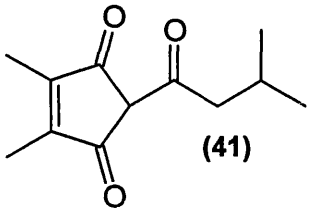
(40)



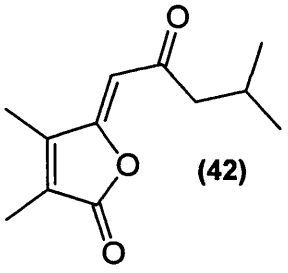
(5)

The structure of dione (**40**), is similar to a natural product more commonly known as 'calythrone'. Calythrone (**41**) has a floral odour, not reminiscent of jasmine.

In 1940 Penfold first tried to isolate this rare β-triketone from the essential oil of *Calythrix tetragona*,[46] a plant native to Queensland, Australia. The β-triketone was given the name of 'calythrone' and Penfold endeavoured to elucidate its structure by chemical oxidation. The 4-ylidenebutenolide structure (**42**) was proposed.



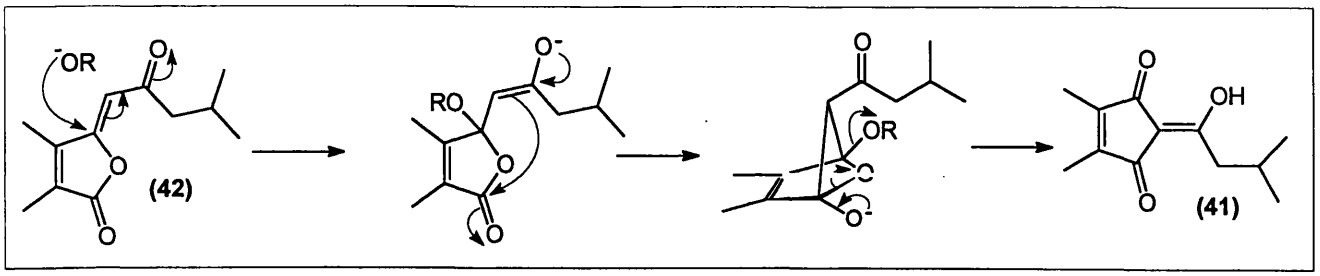
(41)



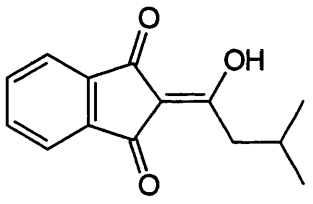
(42)

In 1951 Birch proposed a different structure for calythrone (**41**) largely on the basis of ultraviolet and infra red absorption data.[47] In 1978 Pattenden then demonstrated the ease with which (**42**) rearranged to (**41**) in sodium methoxide-methanol (Scheme **1.20**), and suggested that it may be that natural calythrone actually has the ylidenebutenolide structure and that cyclopentenedione is an artifact produced during its basic extraction and isolation.[48]

Rearrangement of (**42**) *to* (**41**) *with sodium methoxide* **Scheme 1.20**

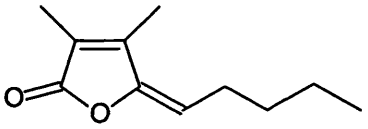


In 1958 Moore had revealed that calythrone (**41**) and valone (**43**), a related natural product, had mild insecticidal properties proving toxic to both adult *Phaedon cochleariae* (mustard beetles) and *Alphitobius leavigatus* (lesser mealworm beetles).[49]



(43)

The calythrone analogue (**40**) was first identified as an artifact in the mini-scale preparation of bovolide (**44**),[50] a 4-ylidenebutenolide found in bovine milk.



(44)

It seems that a similar rearrangement of bovolide (**44**) under basic conditions, may be a plausible route to the calythrone analogue (**40**).

The calythrone analogue (**40**) is of great importance to Bush Boake Allen as it offers a unique jasmine odour which can be used in formulations to create new synthetic fragrances. A small quantity of the calythrone analogue (**40**) had previously been synthesised at Bush Boake Allen *via* a 4-ylidenebutenolide.[51] However, further quantities were required together with a larger range of analogues for fragrance evaluation. In addition, the route previously used was low yielding and expensive. Our aim was to devise an alternative route or improve the current route so that the synthesis is less expensive and therefore more applicable to synthesis on a large scale.

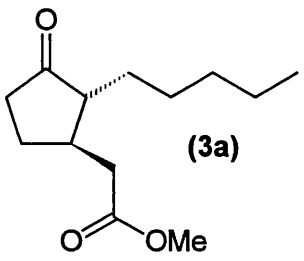
Chapter Two

Methyl dihydrojasmonates
'Hedione®'

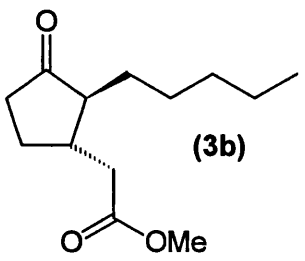
2.1 Aim

The aim of this project was to devise an efficient and cheap synthetic route to enantiomericly pure *trans*-jasmonoids in particular the dihydrojasmonates (**3a** & **3b**). An extensive literature search revealed that there were several synthetic approaches that could be used to the *trans*-jasmonoids. Most of the synthetic routes reported have utilised some sort of 1,4 Michael addition. Several routes to methyl-*trans*-jasmonate (**2**) have proceeded *via* the epimeration of methyl *epi*-jasmonate (**1**).

Racemic methyl dihydrojasmonate is known commercially as 'hedione'.



(-)-methyl dihydrojasmonate



(+)-methyl dihydrojasmonate

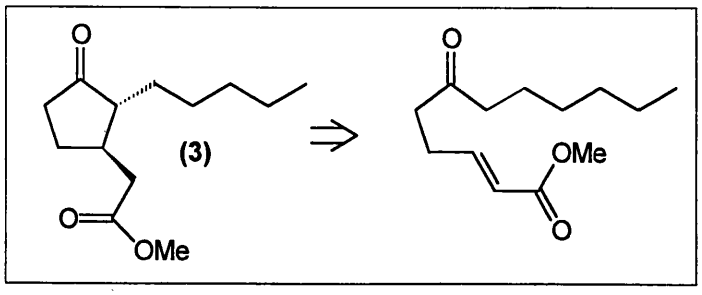
This chapter is divided into the following subsections:

i) An introduction to synthetic strategies to methyl *trans*-dihydrojasmonate (**3a** & **3b**).
ii) The selection of the synthetic strategy.
iii) The synthesis of 2-pentyl-2-cyclopentenone (**45**).
iv) The synthesis of a racemic sample of methyl *trans*-dihydrojasmonate (**3**) for analytical purposes.
v) The synthesis of homochiral methyl dihydrojasmonate (**3a** & **3b**) derived from chiral organo phosphorous templates (**46** & **47**).
vi) Summary.

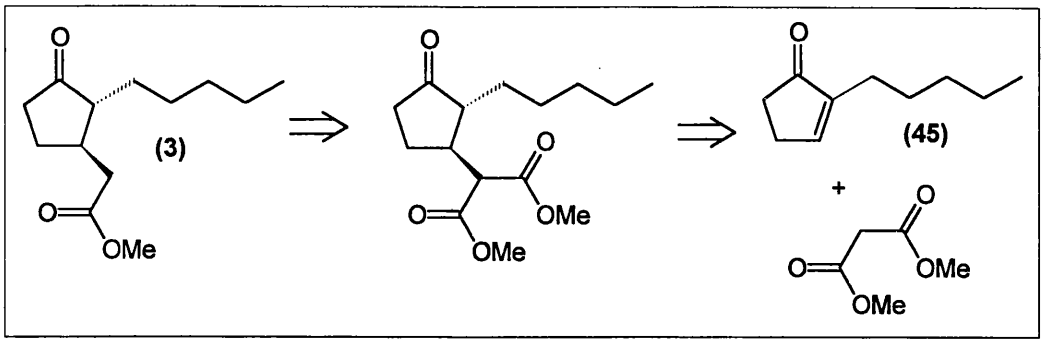
2.2 i) Introduction to various strategies available

Several synthetic routes have been outlined above (see introduction). In addition, the equilibration of the *epi*-jasmonates has been used in some routes. The key approaches to hedione are shown below. The intramolecular cyclisation of a suitably functionalised α,β-unsaturated ester (Strategy **2.01a**) and the 1,4 Michael addition of a malonate equivalent to a functionalised enone (Strategy **2.01b**).

Intramolecular cyclisation of α,β-unsaturated ester **Strategy 2.01a**



Michael addition of α,β unsaturated ketone with a malonate equivalent **Strategy 2.01b**



These two types of approaches both involve conjugate addition reactions of some type that have been used successfully in short syntheses to racemic dihydrojasmonate.[28]

2.3 Synthetic plan to a enantioselective synthesis

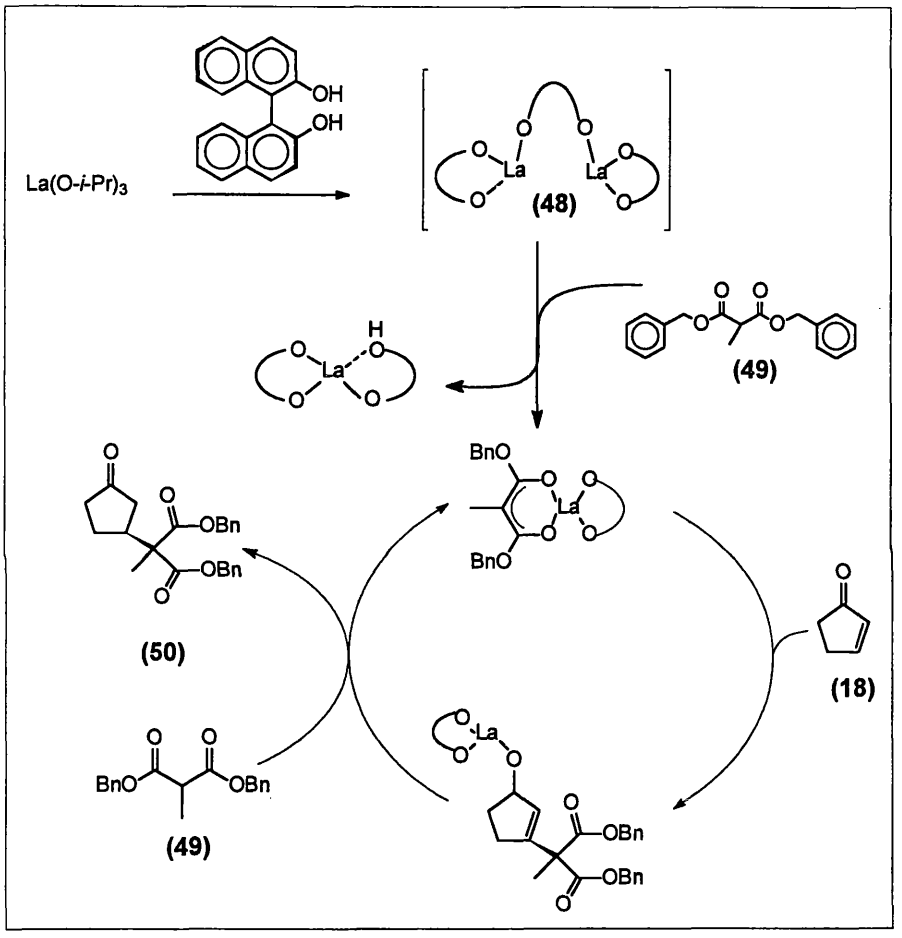
The key to an enantioselective synthesis revolves around the establishment of the stereochemistry at the β-centre. Once the β-stereocentre has been set the keto-enol properties will bring about tautomerism to the thermodynamically more stable *trans* stereochemistry. An in depth literature search revealed several asymmetric Michael addition methods. The most suitable asymmetric methodologies have been selected and are discussed below.

2.4 Current asymmetric methods

In 1994 Shibasaki succeeded in developing new asymmetric (*S*)-BINOL-lanthanum metallic complexes,[52] which have been quite effective in catalytic asymmetric Michael additions of a malonate group β to the ketone of 2-cyclopenten-1-one (**18**). The BINOL-lanthanum metallic complex (**48**) was able to ligate to dibenzylmethylmalonate

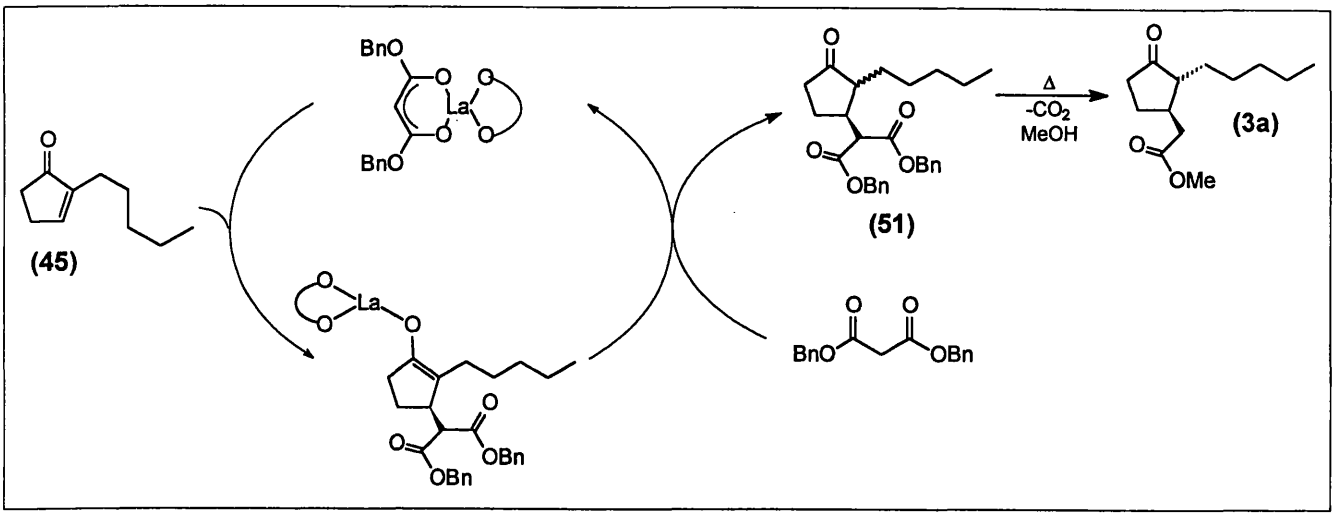
(**49**), and the carbonyl of the enone, resulting in addition from the least hindered face (Scheme **2.02**). The yields for the Michael addition product (**50**) were excellent, 90-97 % with impressive *ee*'s of 80-87 %.

Asymmetric Michael addition of dibenzylmethylmalonate (**49**) *using BINOL* (**48**) *metal complex* **Scheme 2.02**



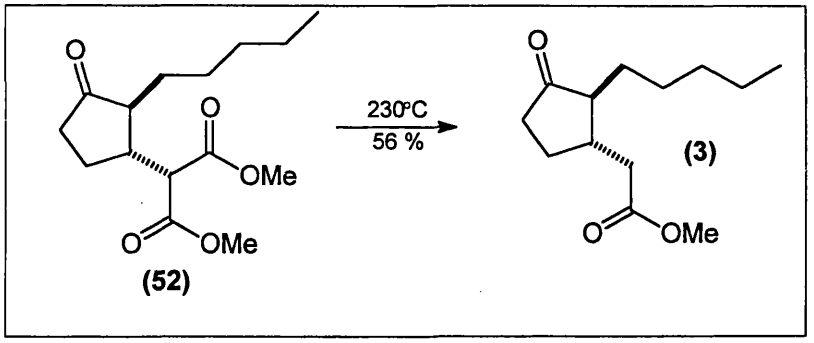
This methodology could also be applied to the synthesis of homochiral *trans*-jasmonate by asymmetric conjugate addition of the BINOL lanthanum metallic complex (**48**) to a functionalised cyclopenten-1-one instead of cyclopenten-1-one (**18**) (Scheme **2.03**), similar to strategy **2.01b**.

Proposed route to chiral trans-dihydrojasmonate (**3a**) *based on BINOL lanthanum* (**48**) *methodology* **Scheme 2.03**



Such a synthetic strategy however has had its problems during the subsequent decarboxylation steps. In a reported synthesis to methyl jasmonate by Wilson,[28] the diester (**52**) was decarboxylated to the monoester (**3**) in only a 56 % yield (Scheme **2.04**).

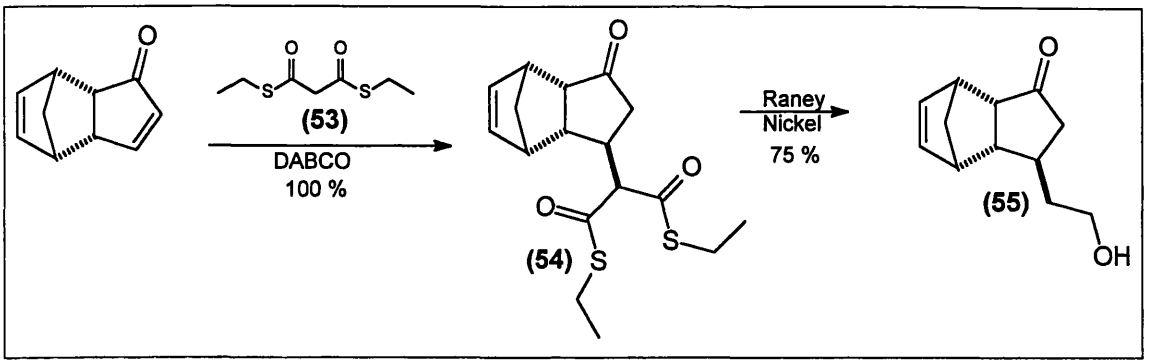
Decarboxylation of diester **Scheme 2.04**



It was found that the thermal energy required was also sufficient to cause the retro Michael addition reaction. The overall yield, reported by Wilson, for methyl dihydrojasmonate (**3**) from cyclopentanone (**66**) was then only 7 %.

To get around this problem, the conjugate addition of *S,S*-dithiomalonate (**53**) followed by reduction of the dithioester (**54**) with raney nickel has been reported on a similar diester giving the corresponding alcohol (**55**) in an efficient two step process of 75 % yield over the two steps[53] (Scheme **2.05**).

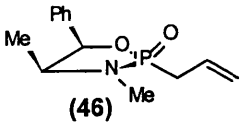
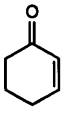
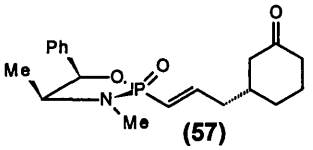
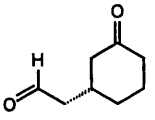
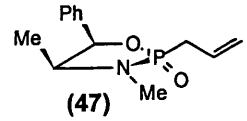
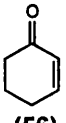
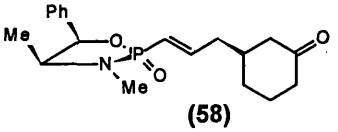
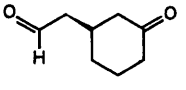
Michael addition using ethyl thiomalonate (**53**) */ reduction to alcohol* (**55**) **Scheme 2.05**



This method would overcome the decarboxylation problems involved in malonate systems, due to the milder conditions used. Subsequent oxidation of the alcohol to the acid followed by esterification would lead to the desired monoester. Despite these advantages it was felt that the presence of trace impurities of a sulfur residue could contaminate the odour of the final product. This was a significant problem encountered by Posner[30] who used chiral sulfoxides to synthesise chiral methyl jasmonate (*see chapter 1*).

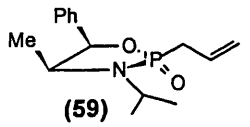
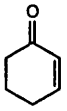
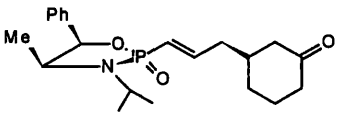
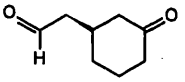
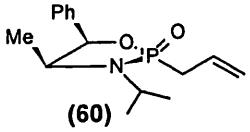
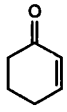
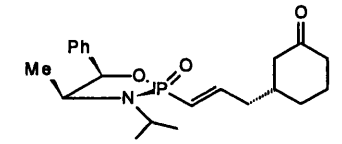
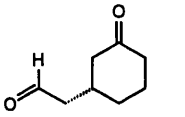
Another novel asymmetric protcol was reported by Hua in 1986. He reported an interesting conjugate addition, using extended lithium anions of chiral phospholidinones (derived from chiral ephedrine) (**46** & **47**) which successfully induced chirality in 1,4 Michael addition reactions to cyclohexenone (**56**).[54] This approach lead to cyclohexanone acids and aldehydes in high yields and good enantioselectivites (> 70 % *ee*) (Table **2.06a**).

Results of 1,4 addition of chiral phospholidinones to cyclohexenone (**56**) **Table 2.06a**

Phospholidinone	enone	1,4-γ–adduct	aldehyde	Yield %	Opt yield % *ee*
 (46)	 (56)	 (57)		82	73
 (47)	 (56)	 (58)		82	74

In their work, they noted that the substitution of an *N*-methyl group with an *N*-isopropyl group led to a higher enantioselectivities with one of the phospholidinones (**59**) but lower enantioselectivities for the corresponding diastereoisomer (**60**) (Table **4.5b**). It was also noted that inversion of the stereochemistry at the methyl group, (pseudo-ephedrine)[55] gave remarkable selectivity for one of the 1,4-γ-adducts, however the corresponding diastereoisomer of the phospholidinone gave an extremely low enantioselectivity of 28 % (Table **2.06b**).

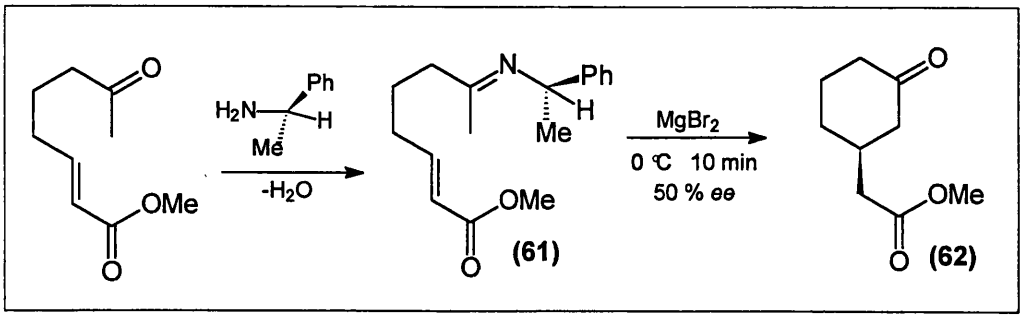
Results of 1,4 addition of using N-isopropyl substituted chiral phospholidinones **Table 2.06b**

Phospholidinone	enone	1,4-γ–adduct	aldehyde	Yield %	Opt yield % *ee*
 (59)	 (56)			82	88
 (60)	 (56)			62	28

The benefit of this approach was that it offered a quick synthetic method to asymmetric β-ester ketones. It was also felt that this methodology could also be applied to the synthesis of enantioselective methyl jasmonates by the asymmetric conjugate addition of chiral phospholidinones to a functionalised cyclopenten-1-one (**18**) instead of cyclohexenone (**56**) (Strategy **2.01b**).

In d'Angelo's 1988 review of asymmetric conjugate additions, he showed how chiral amines had been used to introduce chirality in intramolecular Michael-type additions to α,β-unsaturated esters[56] (Scheme **2.07**). One particular example showed how forming a chiral imine (**61**) could act as a directing group by blocking one face of the olefin resulting in the conjugate additions occurring from the other face of the molecule. Hydrolysis of the enamine afforded the cyclic ketone (**62**) in 35-60 % *ee*.

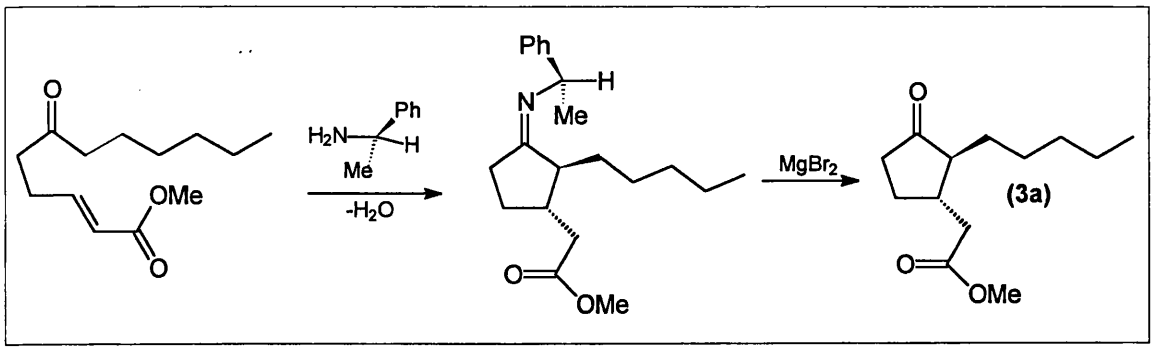
Intramolecular Michael addition **Scheme 2.07**



The low enantioselectivity of this type of reaction is thought to be due the distance between the chiral amine group and the olefin. Indeed, increasing the steric bulk of the amine only marginally increased the enantioselectivity. However, since the enantioselectivites of the reported reaction was only modest, 50 % *ee,* we were unsure whether this methodology could be adapted to give higher enantioselectivites.

Outlined below is a proposed route to chiral methyl dihydrojasmonate similar to Strategy **2.01a** proceeding *via* a similar intramolecular cyclisation of a functionalised α,β-unsaturated ester / chiral enamine (Scheme **2.08**).

Proposed route to chiral methyl dihydrojasmonate (Scheme **2.08**)



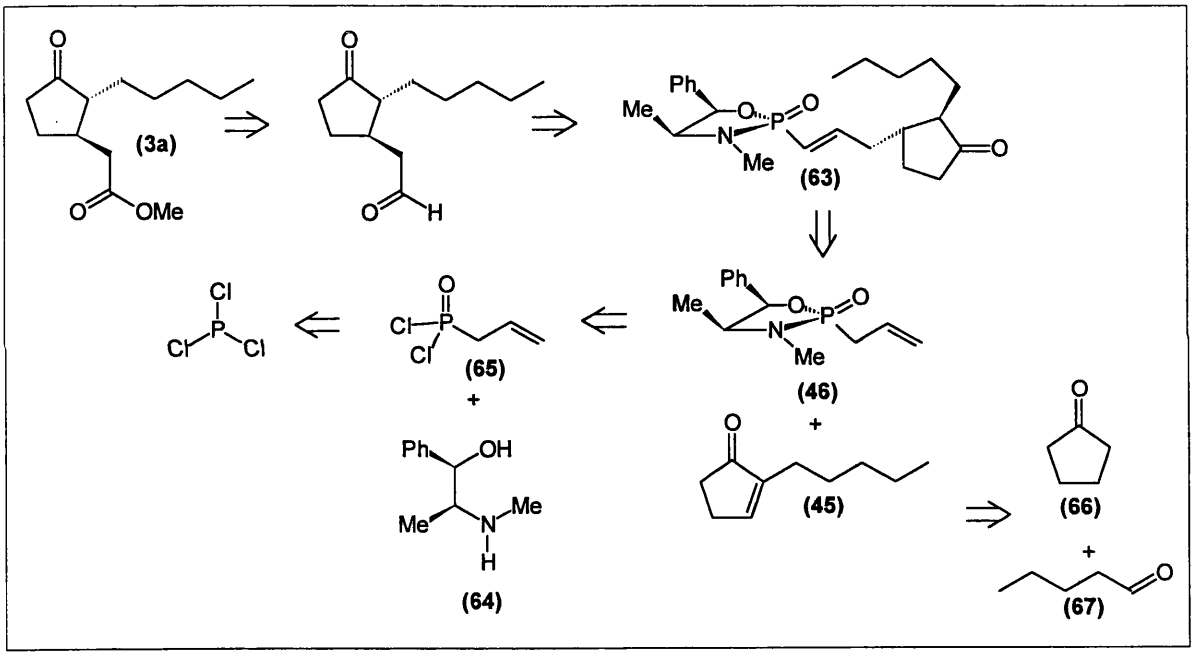
2.5 ii) Selection of the Synthetic Strategy

After careful deliberation we decided to investigate the chiral phospholidinone approach as an asymmetric route to methyl dihydrojasmonate. The main reason why we choose this synthetic strategy was its scope for optimisation. The chiral groups on the phospholidinone could always be modified to give (-) and (+)-methyl *trans*-dihydrojasmonate in the highest optical purity.

We devised a synthetic strategy to chiral methyl *trans*-dihydrojasmonates (**3a** & **3b**) using this 1,4 conjugate addition with a chiral phospholidinone template (**46** & **47**)

(Scheme **2.09**). We choose chiral ephedrine as our chiral amine to prepare the phospholidinone templates, since it gave good enantioselectivites for both of the diastereoisomeric phospholidinone templates (**46** & **47**) when used with 2-cyclohex-1-enone (**56**) but was also commercially readily available in >99 % enantiomeric purity. Olefinic cleavage of both 1,4-γ-adducts (**57** & **58**) was reported, by Hua, to proceed efficiently with ozone to afford the corresponding aldehyde. Oxidation of the resulting aldehyde followed by methylation would hopefully result in the formation of chiral *trans*-dihydrojasmonate (**3a** & **3b**).

Retrosynthetic analysis to chiral dihydrojasmonate via chiral phospholidinones **Scheme 2.09**



The synthetic routes to the fragments required for the chiral synthesis of dihydrojasmonates (**3a** & **3b**) are outlined above (Scheme **2.09**).

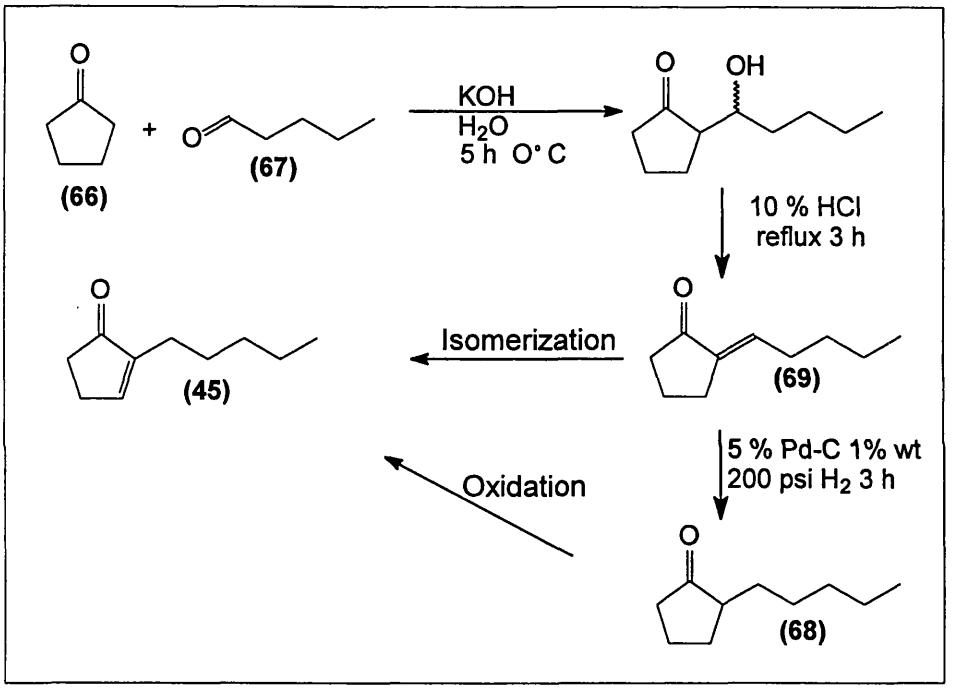
Chiral phospholidinones (**46** & **47**) can be synthesised by the addition of the chiral moiety, ephedrine (**64**), to allylphosphonyl dichloride (**65**) as reported in the literature.[54]

Previous work carried out at Bush Boake Allen has demonstrated that 2-pentyl-2-cyclopentanone (**68**), (commercially known as 'delphone'),[57] can be efficiently synthesised *via* an aldol condensation reaction between cyclopentanone (**66**) and

n-valeraldehyde (**67**), and the subsequent elimination followed by hydrogenation (Scheme **2.10**).

Analysis of the synthetic route to this compound outlines two possible routes to the desired enone (**45**), the first, an oxidation of 'delphone' (**68**) to give the desired enone (**45**) directly and the second, an isomerisation of the olefin (**69**), the precursor to 'delphone' (**68**).

Possible routes to the enone via a 'delphone' or a 'delphone' intermediate **Scheme 2.10**

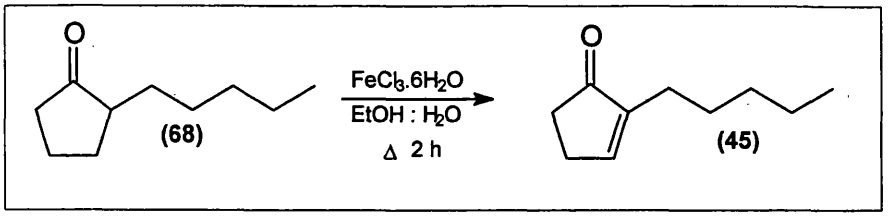


2.6 iii) Synthesis of enone 2-pentyl-2-cyclopenten-1-one

Initially we started by preparing racemic hedione, using strategy **2.01b**. For this synthesis we required an identical enone to that needed for the chiral synthesis.

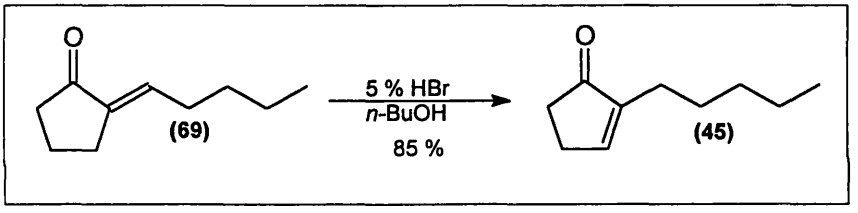
We used 2-pentyl-cyclopentanone (**68**), (provided by BBA), and used this as a convenient starting point for our enone synthesis. We initially investigated an iron (III) chloride oxidation[58] of 'delphone' (**68**). This proceeded to afford the desired endocyclic olefin (**45**) in 46 % yield (Scheme **2.11**). It was observed that a significant portion of the ketone (**68**) had polymerised due to the harsh reaction conditions.

Oxidation of ketone (**68**) *using iron trichloride to α,β-unsaturated ketone* (**45**) **Scheme 2.11**



The more direct route, by olefin isomerisation of the precursor to 'delphone' (**69**), was then explored. The endocyclic alkene (**69**), generated from the elimination of the aldol product, was isomerised to the desired endocyclic olefin (**45**) by refluxing with catalytic hydrobromic acid in ethanol.[59] This procedure afforded the desired enone (**45**) in 85 % yield (Scheme **2.12**), and was therefore the preferred route to our cyclopentenone moiety.

Isomerisation of exocyclic olefin (**69**) *to endocyclic olefin* (**45**) **Scheme 2.12**

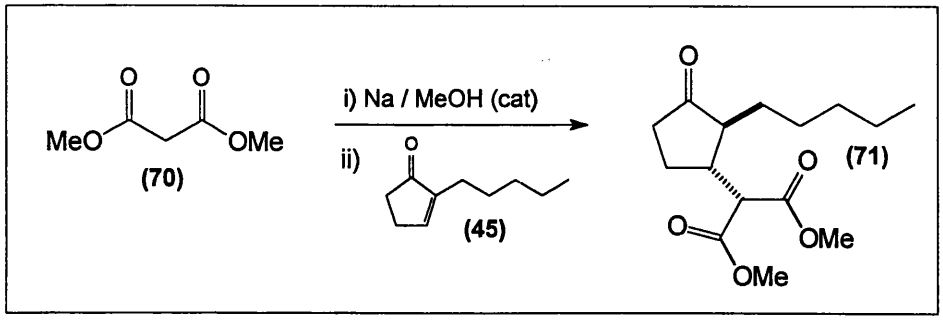


Now that we had devised an efficient route to the enone (**45**), we proceeded to prepare a racemic mixture of *trans*-dihydrojasmonate (**3**) using a literature route (outlined in *chapter 1*).

2.7 iv) Synthesis of racemic methyl dihydrojasmonate

Following Wilson's strategy to methyl jasmonate,[28] dimethyl malonate (**70**) was deprotonated with a stoichiometric amount of sodium hydride and added to the enone (**45**) over 2 hours. The reaction was stirred for a further for 4 h and then quenched using a protic source (methanol). The product (**71**) was isolated in only 12 % yield. It was thought that the Michael addition product (**71**) may also readily undergo the reverse reaction to give back the dimethyl malonate and enone, (**45**) based on our tlc analysis findings. When a catalytic amount of base was used in a protic solvent (methanol) and enone (**45**) added over a period of several hours, the resulting enolate was able to be quenched *in situ* giving a much higher yield of the product, 79 % (Scheme **2.13**). This yield compared well with that reported for methyl jasmonate, (83 %).

Michael addition using anion of dimethyl malonate (**70**) *as nucleophile* **Scheme 2.13**

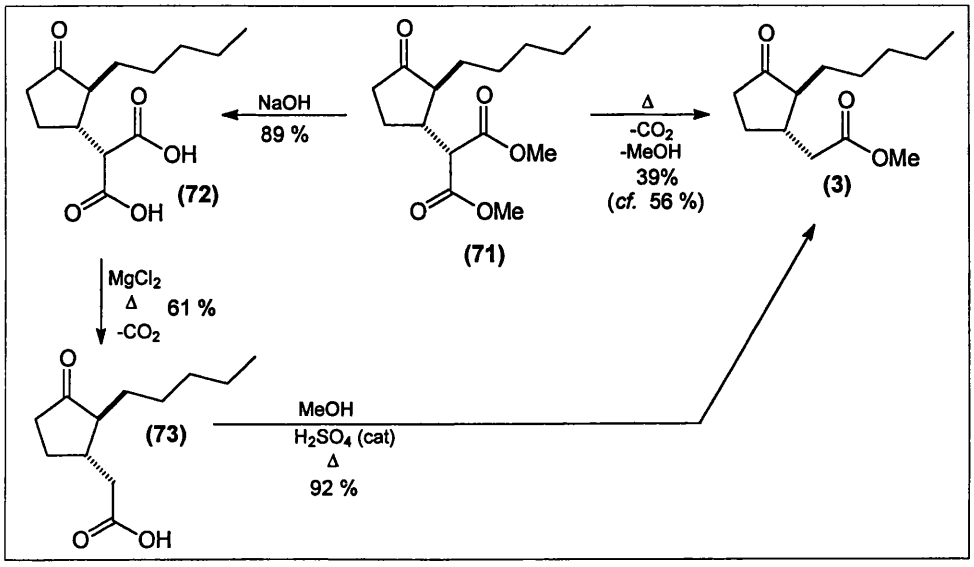


It was interesting to note that while the Michael addition adduct (**71**) had a higher R_f than the starting enone (**45**) on thin layer chromatography, during purification using flash chromatography grade silica gel, the enone (**45**) eluted first off the column, contrary to the expected order of elution. This observation may be attributable to the bulky nature of the diester (**71**).

Wilson reported a similar decarboxylation of a malonate species with a modest conversion, 56 %, to the monoester by thermal decomposition in the presence of water. This procedure was then followed to afford a poor yield, 39 % of racemic hedione (**3**). The majority of the product had undergone the retro-Michael addition reaction producing the enone (**45**) and dimethyl malonate in accordance with similar literature reports.[60]

A stepwise approach was then investigated, and diester (**71**) was first saponified with sodium hydroxide before the resulting diacid (**72**) was heated in the presence of magnesium chloride[61] (Scheme **2.14**).

Alternative decarboxylation approach **Scheme 2.14**

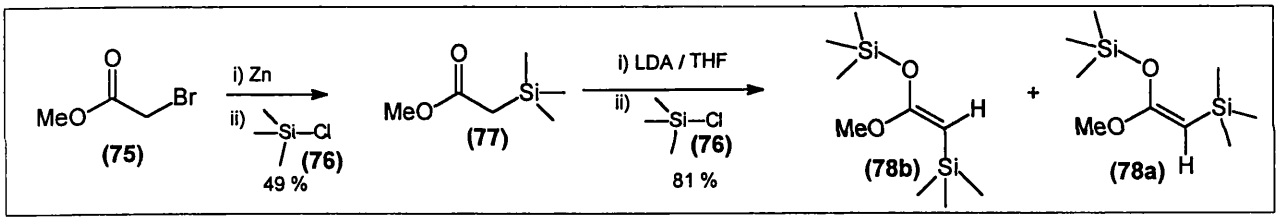


This resulted in chelation of the carbonyl groups with the magnesium, possibly reducing the energy barrier for the decarboxylation and giving the monoacid (**73**). The monoacid (**73**) produced was then esterified to give racemic dihydrojasmonate (**3**).

The jasmonoid was isolated in poor overall yield, 9 % together with an impurity inseparable by chromatographic methods. We therefore decided to improve this synthetic route by using an alternative synthetic equivalent to dimethyl malonate.

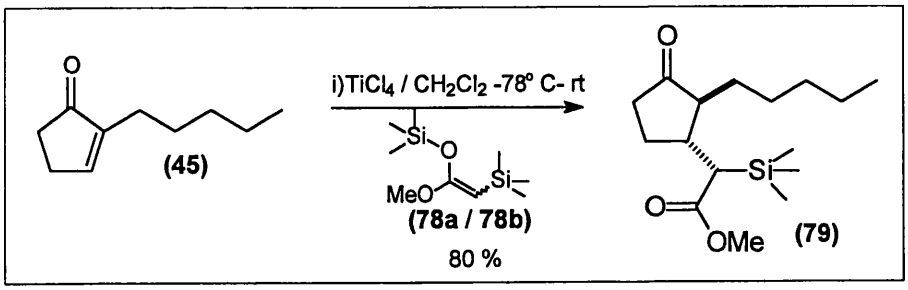
This involved the use of methyl trimethylsilylacetate (**74**), which was synthesised following Fessenden's procedure *via* a Reformatsky reaction between bromoacetate (**75**) and trimethylsilyl chloride (**76**).[62] The resulting methyl ester (**77**) was deprotonated to form the enolate anion. This was trapped using excess trimethylsilyl chloride (**76**) to generate a mixture of *cis* / *trans* enol ethers (**78a** & **78b**) in a combined yield of 65 % from the starting bromoacetate (**75**) (Scheme **2.15**), (*cf.* lit yield 71 %).[29]

Preparation of silyl enol ethers **Scheme 2.15**.



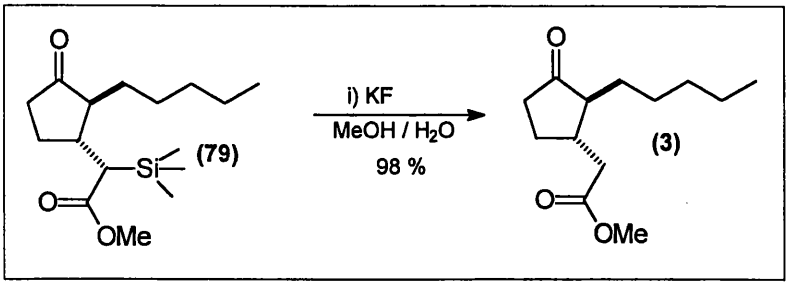
The enone (**45**) was then reacted with the silyl enol ethers (**78a** & **78b**) in the presence of the Lewis acid, titanium tetrachloride[63] (Scheme **2.16**). This afforded the racemic silylester (**79**) in 80 % yield.

Titanium tetrachloride catalysed Michael addition **Scheme 2.16**



The silicon functionality was removed in quantitative yield by stirring in a methanol solution of potassium fluoride (Scheme **2.17**), to afford racemic methyl dihydrojasmonate (**3**), required for analysis purposes.

Removal of trimethylsilyl group **Scheme 2.17**

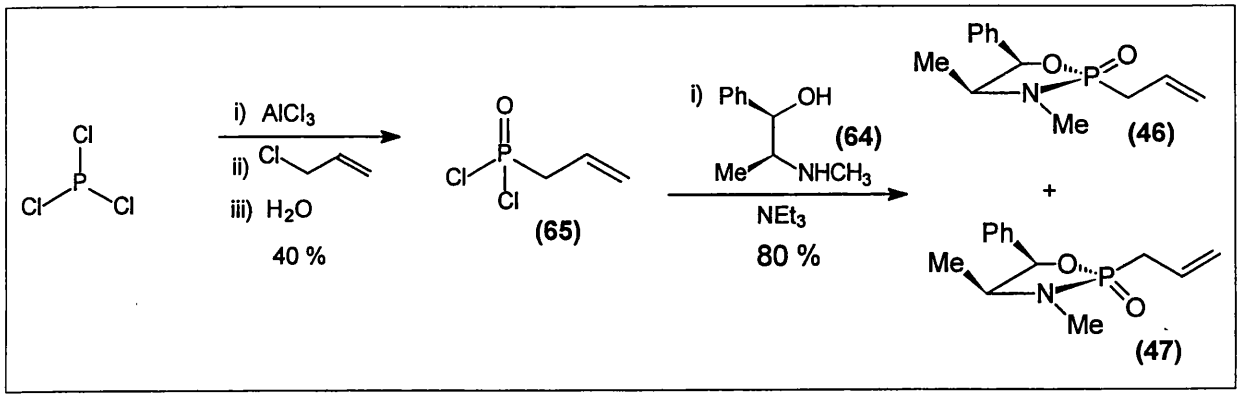


2.8 v) The preparation of enantioselective dihydrojasmonates

The chiral templates (**46** & **47**) were synthesised from allylphosphonyl dichloride (**65**) and (-)-(1*R*,2*S*)-ephedrine (**64**). Whilst other chiral substrates were considered, such as chiral diamines which have also shown similar asymmetric induction properties to ephedrine,[64] they are much more expensive.

Allylphosphonyl dichloride (**65**) was prepared following a literature preparation by reacting phosphorous trichloride with aluminium chloride in the presence of allyl chloride. The resulting phosphorous complex was then hydrolysed with water directly to give allylphosphonyl dichloride (**65**) in 40 % overall yield.[65] The chiral phospholidinones (**46** & **47**) were then synthesised by reacting allylphosphonyl dichloride (**69**) with two equivalents of triethylamine and (-)-(1*R*,2*S*)-ephedrine (**64**) at room temperature for 12 hours (Scheme **2.18**). The mixture was purified by flash chromatography to yield the two diastereoisomers, an oil (**46**) and a solid (**47**) in a ratio of 1:1, with a combined yield of 85 %.

Preparation of the enantioselectively pure organo phosphorous templates **Scheme 2.18**

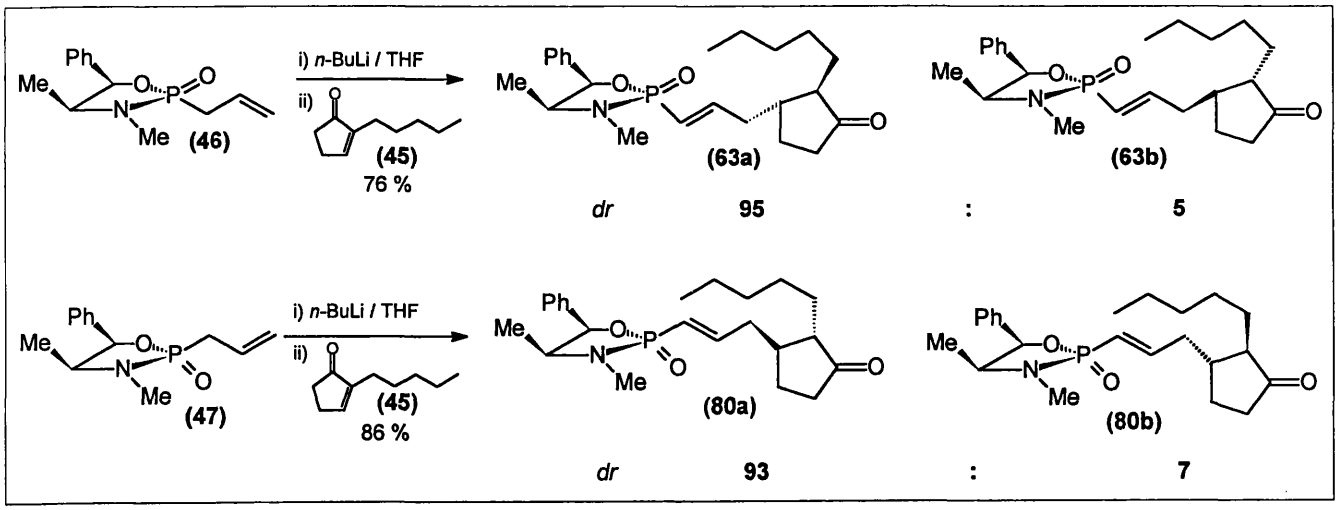


While phospholidinone (**46**) eluted first off the column and was isolated as a colourless viscous oil, phospholidinone (**47**) was isolated as a white solid and was recrystallised to >99 % purity.

Deprotonation of the chiral phosphorous template (**46**) by *n*-butyllithium at -78° C is believed to generate the kinetic anion resulting in the formation of the *trans* anion.[66] The enone (**45**) was then added at -78 °C and quenched after 30 minutes. The Michael adducts (**63a** & **63b**) were isolated in a combined yield of 76 %. The geometry of the alkene formed was determined to be exclusively *trans* (by ^{1}H NMR). The diastereomeric ratio of the Michael addition products (**63a** & **63 b**) were calculated from ^{1}H NMR to be 95 : 5. Attempts were made to separate these distereoisomers however, we were unable to achieve this through chromatographic techniques.

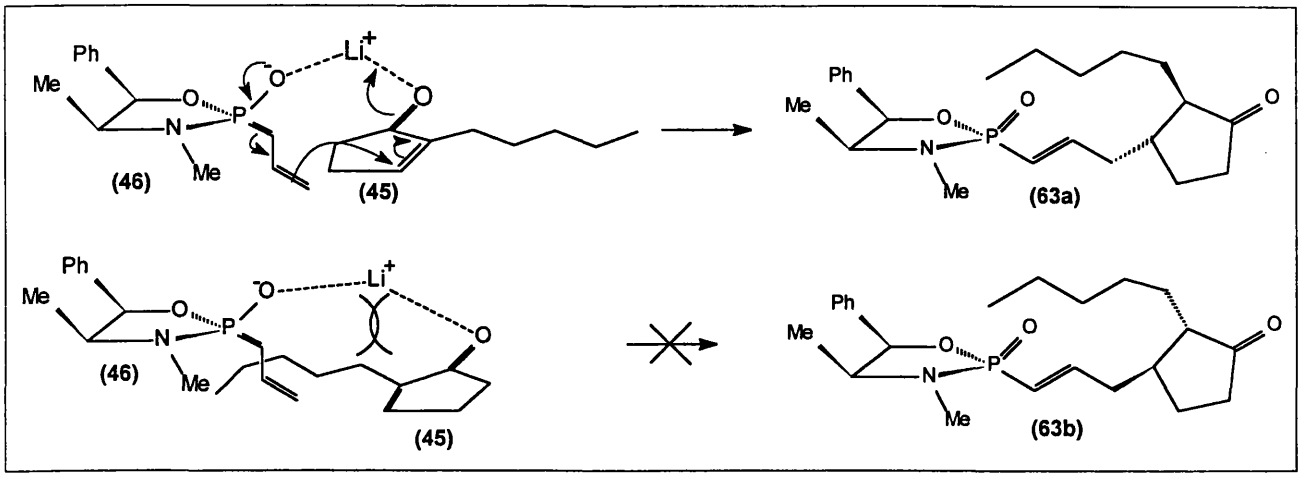
The chiral phospholidinone (**47**) similarly underwent the Michael addition to the enone (**45**) under identical conditions to give Michael adducts (**80a** & **80b**) in 86 % yield, the diastereomeric ratio was calculated from ^{1}H NMR to be 93 : 7 respectively. (Scheme **2.19**).

The Michael addition products of the allylphospholidinone (**46** & **47**) **Scheme 2.19**



The asymmetric induction occurs during this Michael addition. A rational theory can be proposed by studying the addition of the chiral phospholidinone from both faces of the enone (**45**) (Scheme **2.20**). It is apparent that addition to one face will bring about a sterically more congested transition state than that of the other.

Favoured and disfavoured Transition States for addition of phospholidinone anion (**46**) *to enone* (**45**) **Scheme 2.20**



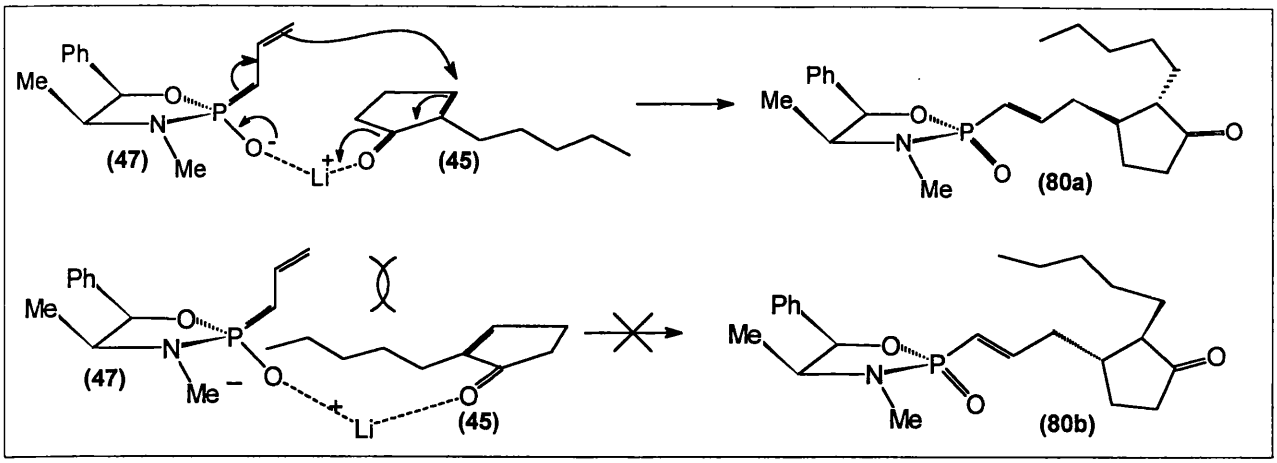
The anion of the chiral template reacts preferentially from one face of the enone (**45**), whereby the enone (**45**) is held by the lithium ion in such an orientation that the interactions between the phenyl group and the nitrogen methyl group are minimised. The anion is then able to react in a 1,4 Michael fashion from the least hindered face of enone (**45**), bringing about asymmetric induction.

The other homochiral phospholidinone template (**47**) reacted in a similar fashion but from the opposite face of the enone (**45**) bringing about the opposite stereochemistry at the asymmetric centres. In both cases the enone (**45**) had reacted almost exclusively from beneath the auxiliary. This was no doubt influenced by the steric nature of the phenyl group blocking the top face (Scheme **2.21**).

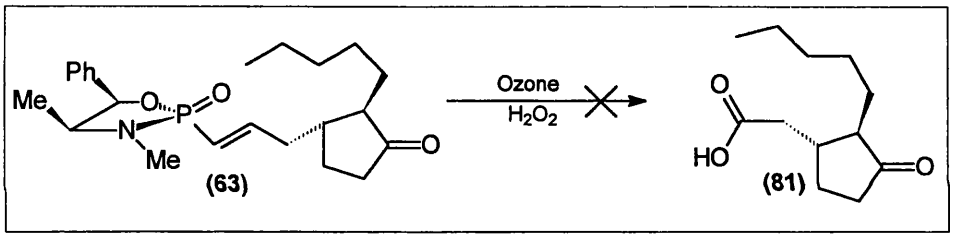
The isolated yields of the two Michael adducts (**63** & **80**) were 80 % and 79 % respectively. We first attempted to remove the chiral template by oxidative cleavage of the *trans* olefin with ozone followed by an oxidative work-up with hydrogen peroxide.[67] However, this failed to produce the desired acid (Scheme **2.22**), instead a mixture of several unknown compounds were detected.

Favoured and disfavoured Transition States for addition of template (**47**) *to enone* (**45**)

Scheme 2.21

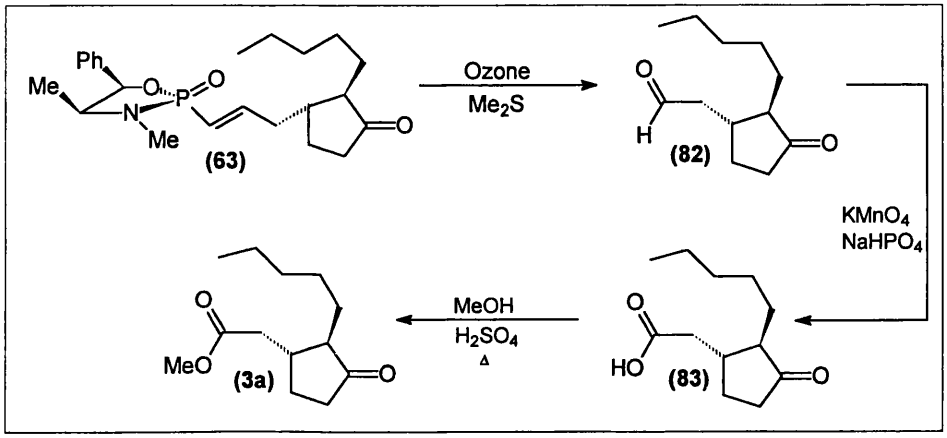


Attempted oxidative ozonolysis of Michael adduct **Scheme 2.22**



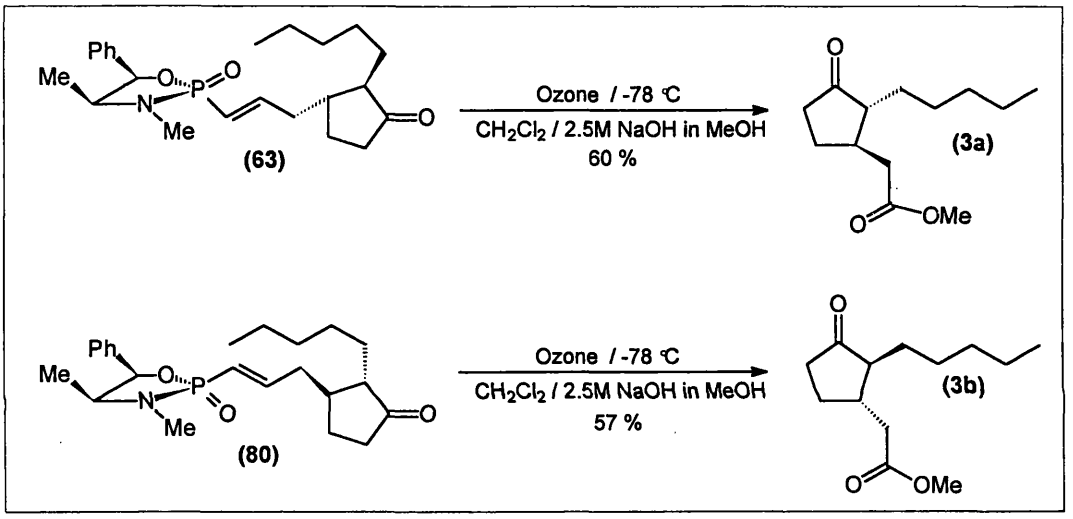
The ozonolysis was repeated with a reductive work-up and this gave the aldehyde (**82**) in 62 % yield. The aldehyde (**82**) was then oxidised with potassium permanganate[68] to the corresponding acid (**83**) in 71 % yield (Scheme **2.23**). Esterification of the acid (**83**) with methanol and catalytic sulfuric acid[69] gave (+)-methyl *trans*-dihydrojasmonate (**2a**) in an overall yield of 20 % from the Michael adduct (**63**).

Reductive work-up followed by oxidation and methylation **Scheme 2.23**



Attempts were made to improve the ozonolysis procedure and a literature precedent was found whereby ozonolysis in a 2.5 M solution of sodium hydroxide in methanol[70] was used together with dichloromethane at -78 °C to afford methyl dihydrojasmonate (**3a**) directly from the olefin (**63**). Treatment of the 1,4-γ-adducts (**63** & **80**) (derived from chiral templates **46** & **47**) under these (basic) conditions gave rise to methyl dihydrojasmonate (**3a** & **3b**) in overall yields of 60 % and 57 % respectively in a one step process (Scheme **2.24**).

Cleavage of templates using ozonolysis with sodium methoxide solution **Scheme 2.24**



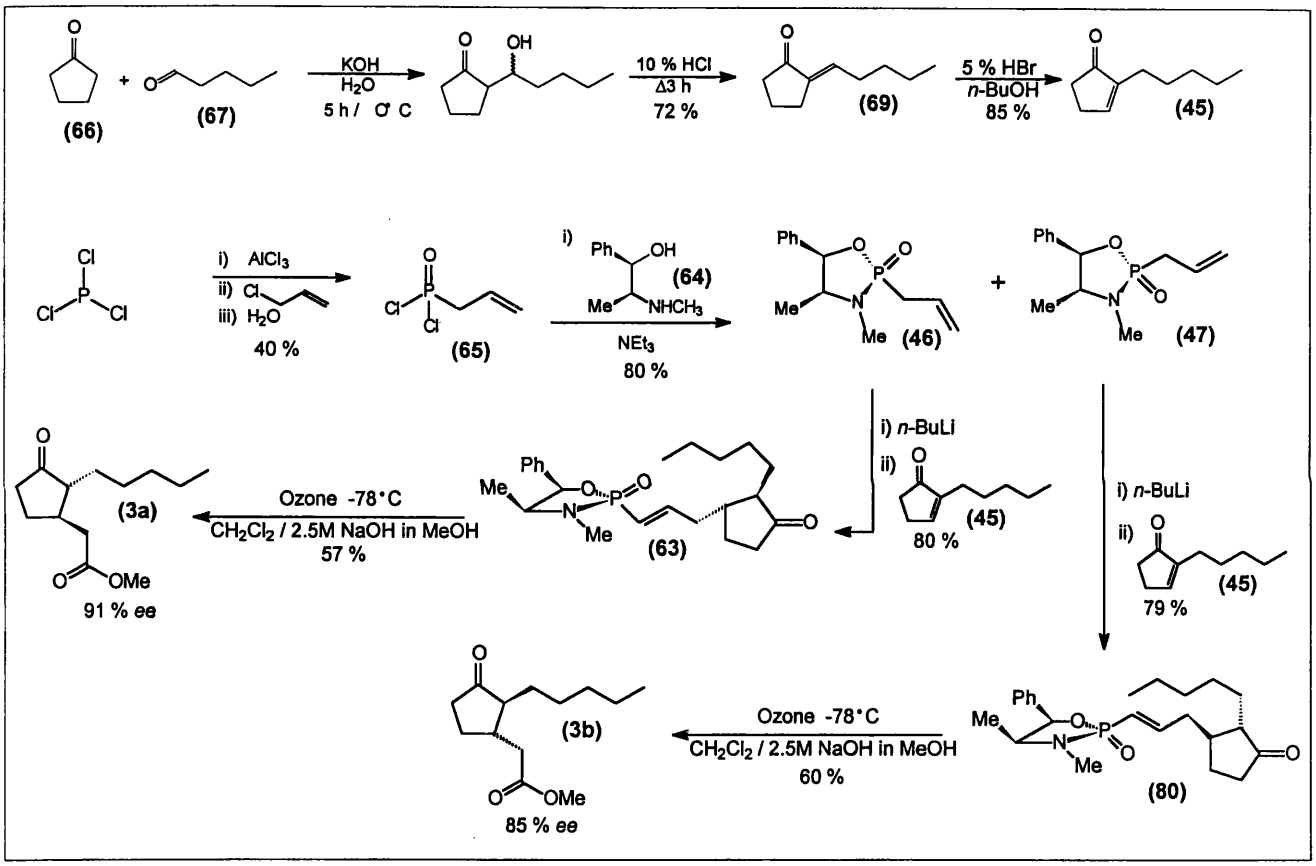
These methyl dihydrojasmonates were analysed by HPLC, using a chiralcel OD column. The results were detected using a U.V. detector operating at 227 nM wavelength. (+)-Methyl dihydrojasmonate (**3b**), derived from phospholidinone (**47**), was synthesised in 85 % *ee* and (-)- methyl *trans*-dihydrojasmonate (**3a**), the nature identical compound, was synthesised in 91 % *ee* from phospholidinone (**46**).

The observed optical rotations of the synthesised dihydrojasmonates (**3a** & **3b**) from our synthetic strategy were $[\alpha]_D^{25}$ +41.2 ° (*c* =0.810 in $CHCl_3$) for (**3a**) and $[\alpha]_D^{25}$ -48.2 ° (*c* =0.848 in $CHCl_3$) for (**3b**), which were consistent with the HPLC results.

2.9 vi) Summary

Overall, we were able to prepare enantiomerically enriched methyl dihydrojasmonates (**3a** & **3b**) in 85 % and 91 % *ee via* a Michael addition of the extended lithium anions of chiral allylphospholidinones (**46** & **47**), derived from allylphosphonyl dichloride (**65**) and chiral ephedrine (**64**) (Scheme **2.25**).

Summary of synthetic route **Scheme 2.25**



The overall yield of methyl dihydrojasmonates (**3a** & **3b**) based upon the (-)-(1*R*,2*S*)-ephedrine (**64**) was 36-37 % and 46-48% yield based upon 2-pentyl-2-cyclopenten-1-one (**45**). Since we were able to prepare both enantiomers of chiral methyl dihydrojasmonates (**3a** & **3b**) with high enantioselectivities, we were confident that this methodology could also be applied to the synthesis of certain prostaglandins and of interest to us, chiral methyl *trans*-jasmonates (**2a** & **2b**). (The latter of which is discussed in *chapter 3*).

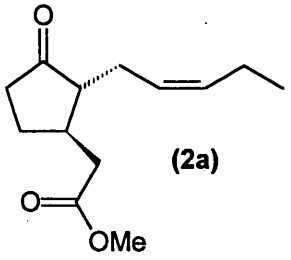
Chapter Three

Methyl *trans*-jasmonates

3.1 Aim

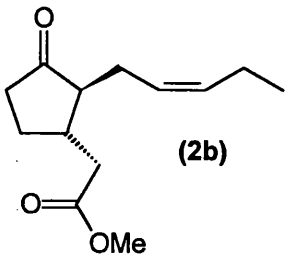
Our aim was to devise a straightforward, comparatively inexpensive and novel enantioselective synthesis of both methyl *trans*-jasmonates (**2a** & **2b**). On the basis of our chiral methyl *trans*-dihydrojasmonate (**3a** & **3b**) route we decided to follow an analogous synthetic approach (*see chapter 2*).

Methyl *trans*-jasmonates are more commonly referred to as 'methyl jasmonates'.



(2a)

(-)-methyl jasmonate



(2b)

(+)-methyl jasmonate

This chapter will be divided into the following subsections:

i) An introduction to previous synthetic strategies to the methyl jasmonates (**2**)
ii) The synthetic strategies to the enone, 2-(2-pentynyl)-2-cyclopenten-1-one (**84**)
iii) The synthetic strategies to 1-bromo-2-pentyne (**85**)
iv) The synthesis of 1-bromo-2-pentyne (**85**) and 2-(2-pentynyl)-2-cyclopenten-1-one (**84**)
v) The racemic synthesis of analytic samples of the methyl *trans*-jasmonates (**2**).
vi) The enantioselective synthesis of methyl jasmonates (**2a** & **2b**) derived from organophosphorous templates (**46** & **47**)
vii) Summary

3.2 i) Introduction to previous synthetic strategies

There are several synthetic routes currently available to the *trans*-jasmonates (*see chapter 1* & *chapter 2*), but they have either had low yielding steps as part of a multistep synthesis or used either reagents or starting materials which are prohibitively expensive.

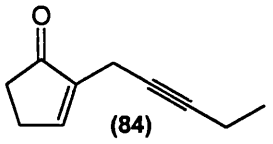
As discussed earlier with the dihydrojasmonate synthesis, the most significant routes have utilised a Michael addition reaction of some type. Although, some have used the

intramolecular cyclisation of an α,β-unsaturated ester, others have proceeded *via* the 1,4 Michael addition of malonate equivalents to a functionalised enone. Due to our success in terms of regioselective control with this latter strategy and its successful application to the synthesis of chiral methyl *trans*-dihydrojasmonates (**3a** & **3b**), we investigated this further by applying the same strategy to synthesise enantiomerically enriched methyl *trans*-jasmonates (**2a** & **2b**).

3.3 Synthetic strategy to methyl jasmonate

The presence of the *cis*-olefin in the methyl jasmonates, meant that a suitably functionalised enone had to be used. The most obvious choice was the enone, 2-(2-pentynyl)-2-cyclopenten-1-one (**84**). This could serve as a masked *cis*-olefin since reductions of alkynes in the presence of Lindlar catalyst are stereoselective producing exclusively the *cis*-olefin.[71] The alkyne was also selected due to the use of ozonolysis for the removal of the chiral templates, and alkynes have been reported by McCurry[72] to tolerate ozonolysis conditions in the presence of tertiary olefins.

3.4 ii) The synthetic strategies to the enone, 2-(2-pentynyl)-2-cyclopenten-1-one

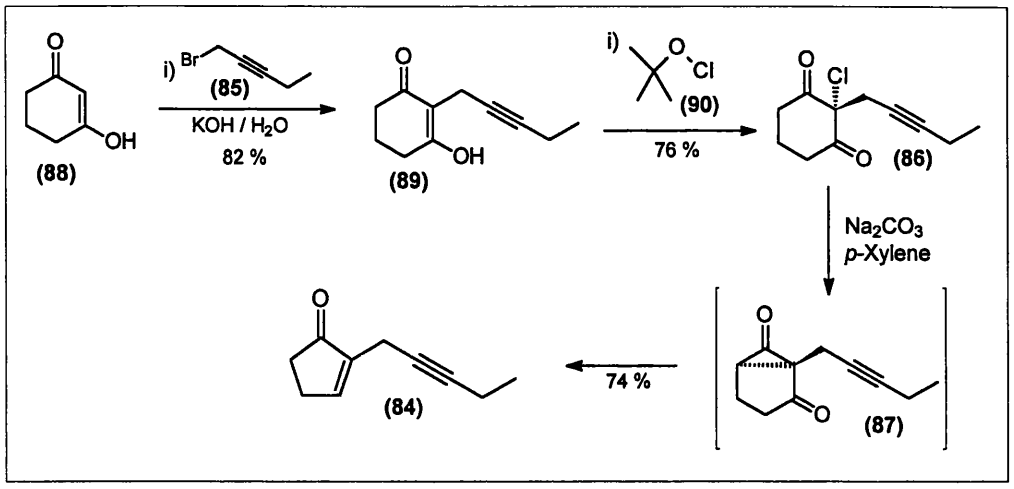


(84)

The reported synthetic routes for the preparation of such enones are neither simple nor versatile. We initially directed our attention to developing an efficient synthetic method for this enone from cheaply available materials. Of the synthetic routes to this enone in the literature, the most significant syntheses are outlined below.

In 1971 Buchi reported the first synthetic route to this enone (**84**).[73] (Scheme **3.01**). 2-(2-Pentynyl)-2-cyclopenten-1-one (**84**) was prepared by a ring contraction of an α-chlorodiketone (**86**) with sodium carbonate to a three membered ketone intermediate (**87**) which underwent the rapid cheletropic elimination of carbon monoxide.

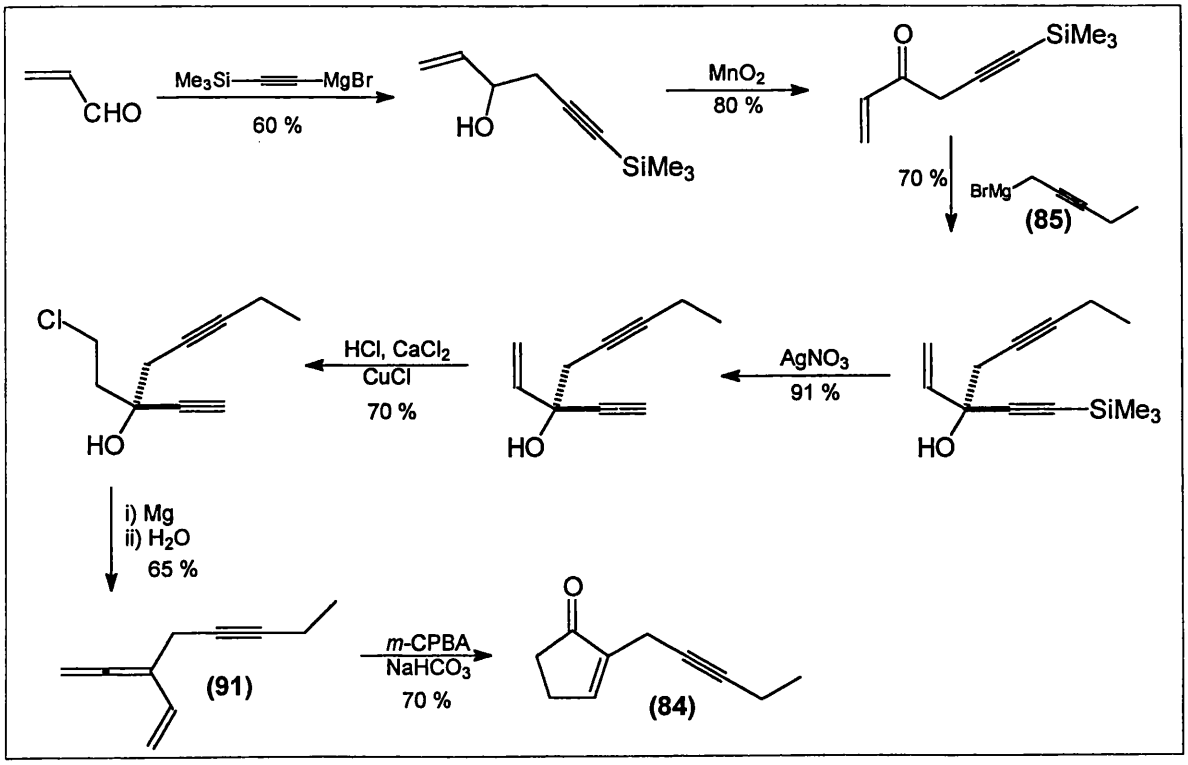
Buchi synthetic route to enone (**84**) **Scheme 3.01**



This route offered a simple route to the desired enone. However, the starting diketone (**88**) was expensive and also unstable at room temperature, undergoing self condensation.

Roumestant has reported a seven-step synthesis of the enone (**84**) (Scheme **3.02**).[74]

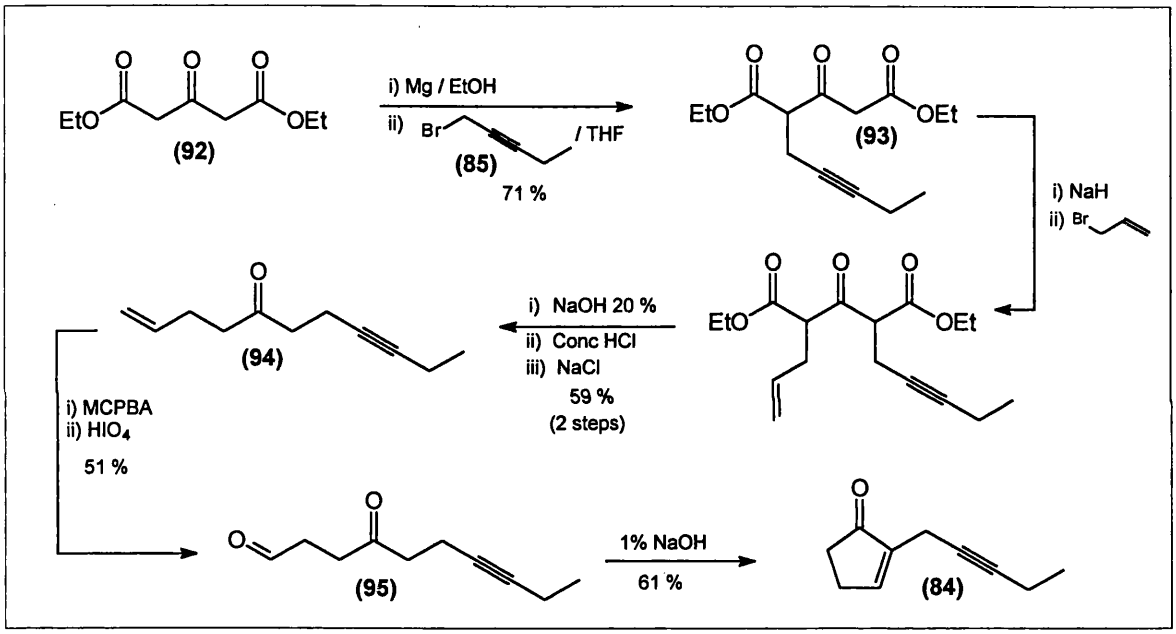
Synthesis of enone (**84**) *by treatment with peracid on an appropriately substituted vinylallene* (**91**) **Scheme 3.02**



He demonstrated how an appropriately substituted vinylallene (**91**) underwent conversion to the desired enone (**84**) by an oxidative process using *meta*-chloroperbenzoic acid. However, the overall yield from 1-bromo-2-pentyne (**85**) was a disappointing 19 % and he used some high cost starting materials.

Naoshima approached the synthesis *via* an intramolecular aldol condensation, using a functionalised keto-aldehyde (Scheme **3.03**).[75]

Naoshima's synthesis of enone (**84**), *using an intramolecular aldol condensation* **Scheme 3.03**

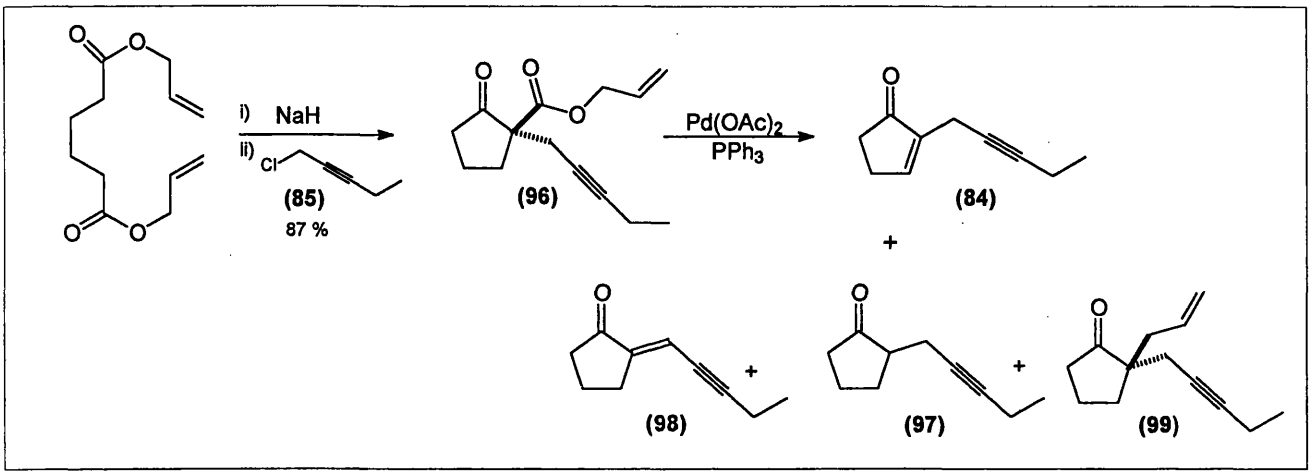


The monoalkyl 3-oxoglutarate (**93**) was prepared in 71 % yield from diethyloxoglutarate (**92**) by alkylation with 1-bromo-2-pentyne (**85**), and conversion to the olefin (**94**) in 59 % yield *via* a selective alkylation with allylbromide which was accompanied by a double decarboxylation. The primary olefin (**94**) was epoxidized with *meta*-chloroperbenzoic acid and subsequent periodic acid oxidation gave the keto-aldehyde (**95**) in 51 % yield. The keto-aldehyde (**95**) was cyclized using a 1 % sodium hydroxide solution to give 2-(2-pentynyl)-2-cyclopenten-1-one (**84**) in 61 % yield.

This route offered a simple intramolecular cyclization to form the enone (**84**). The starting materials were also cheap, however, the oxidation of the primary alkene (**94**) to the aldehyde (**95**) was poor yielding. There was however possible scope for improvement by using a different oxidation method, and improving the selectivity of the oxidation.

More recently, Tsuji has reported a novel synthetic method to α,β-unsaturated ketones (**84**) *via* a palladium catalyzed decarboxylation-dehydrogenation reaction using allyl β-ketocarboxylate (**96**) (Scheme **3.04**).[76]

Palladium acetate catalyzed conversion of β-keto ester (**96**) *into 2-(2-pentynyl)-2-cyclopenten-1-one* (**84**) **Scheme 3.04**

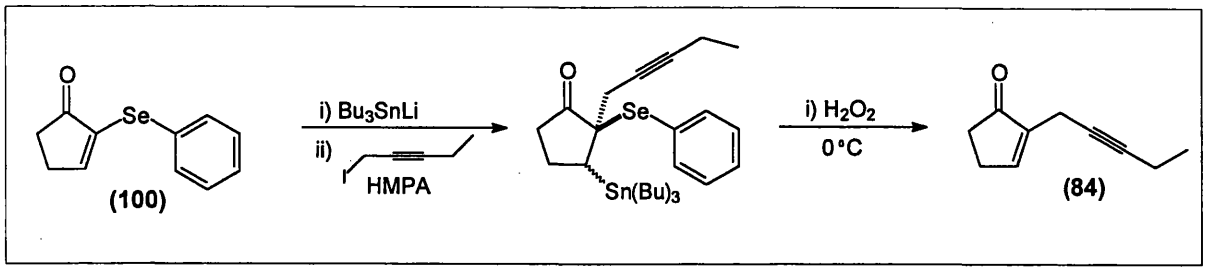


Three other reactions also competed with the desired palladium-catalyzed reaction of allyl 2-oxo-1-alkyl-2-cyclopentanecarboxylate (**96**). They were a decarboxylation-dehydrogenation to give 2-alkyl-2-cyclopentanone (**97**), the decarboxylation-protonation to 2-(2-pentynyl)-cyclopentanone (**98**) and the decarboxylation-alkylation to 2-allyl-(2-pentynyl)-cyclopentanone (**99**). The optimum conditions for selective formation of the required 2-(2-pentynyl)-2-cyclopenten-1-one (**84**) were when 5 mol % of the palladium catalyst was used at reflux in acetonitrile. This provided an isolated yield of nearly 80 % from the β-ketoester. However, the problem of separating the other by-product still posed a significant problem due to their structural similarity.

In 1991 Toru reported the use of a novel vinyl anion equivalent, accompanied by a new destannylselenenylation procedure to give the desired enone (**84**).[77] The reaction was achieved by the conjugate addition of (tributylstannyl)lithium to 2-(phenylseleno)-2-cyclopentenone (**100**), followed by trapping of the resulting enolate with 1-bromo-2-pentyne (**87**). Subsequent destannylselenenylation gave 2-(2-pentynyl)-2-cyclopenten-1-one (**84**) in 79 % yield (Scheme **3.05**).

Toru's synthesis of 2-(2-pentyne-2-)cyclopenten-1-one (**84**) *via destannylselenenylation*

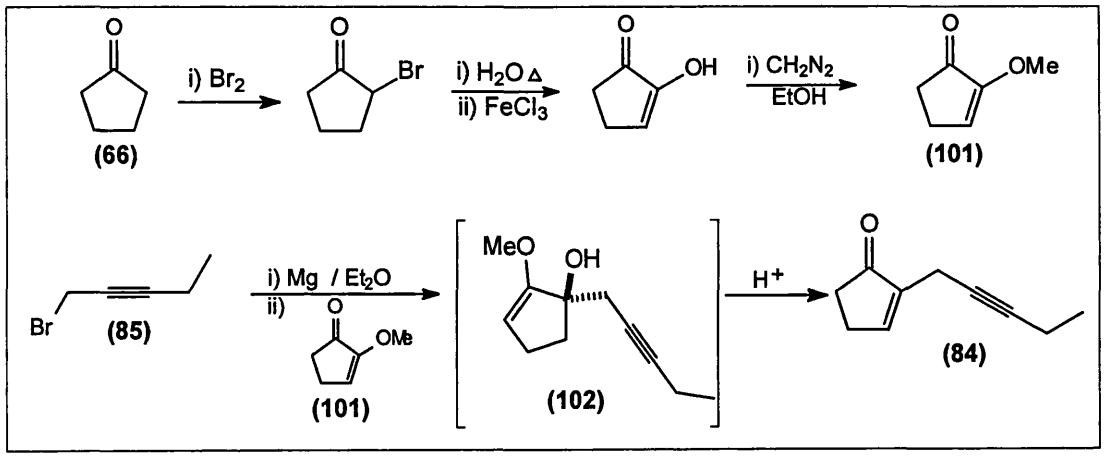
Scheme 3.05



This short synthetic approach held several attractions, but the reagents diphenydiselenide, tributylstannyllithium and hexamethylphosphoramide are extremely toxic and expensive, making this route unattractive for scale-up.

Several other routes were not considered due to either low yields or expensive synthons. Whilst Buchi's and Naoshima's syntheses were potential routes we wished to investigate alternative approaches first, which also used the same key halide intermediate (**85**). We considered our route, outlined in scheme **3.06** to potentially be more direct than all the others, with the exception of Buchi's. One major advantage was the cost of the starting materials, which were cheap and readily available.

Our proposed synthetic route to 2-(2-pentynyl)-2-cyclopenten-1-one (**84**) **Scheme 3.06**



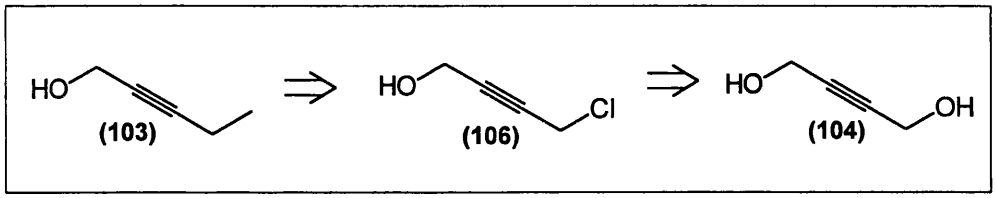
Synthesis of 2-(2-methoxy)-cyclopentenone (**101**) could be achieved using literature precedent.[78] We then envisaged nucleophilic attack of the Grignard (**85**) to the carbonyl of 2-(2-methoxy)-cyclopentenone (**101**), resulting in the formation of a tertiary alcohol (**102**). Based upon work by Ansell,[79] we anticipated a regioselective dehydration of (**102**) to 2-(2-pentynyl)-2-cyclopenten-1-one (**84**).

An efficient route to 1-iodo or 1-bromo-2-pentyne (**85**) was also required since this key intermediate was commercially not available. Since the conversions of alcohols to bromides have been well documented we concentrated on the synthesis to the corresponding 2-pentyn-1-ol (**103**).

3.5 iii) Synthetic strategies to 1-bromo-2-pentyne *via* 2-pentyn-1-ol

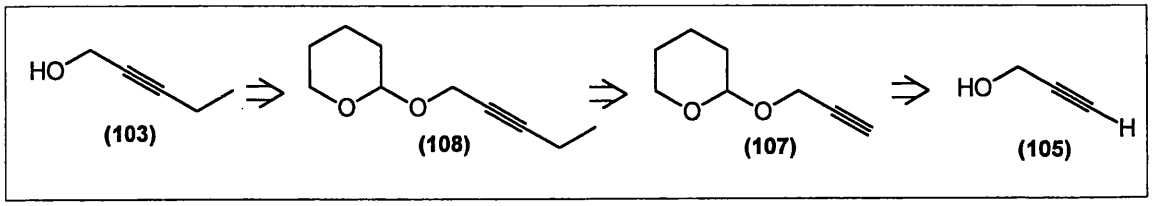
A literature search revealed two synthetic strategies to 2-pentyn-1-ol (**103**). The first was from 1,4-but-2-yne diol (**104**) (Scheme **3.07**) and the other from propargyl alcohol (**105**) (Scheme **3.08**).

Retrosynthetic outline showing the synthesis of 2-pentyn-1-ol (**103**) *from 1,4-but-2-ynediol* **Scheme 3.07**



1,4-But-2-ynediol (**104**) can be mono-chlorinated using thionyl chloride to the chloroalcohol (**106**). Treatment of the resulting chloroalcohol (**106**) with excess methyl magnesium bromide has been used to generate 2-pentyn-1-ol (**103**) in 45 % overall yield.[80]

Retro synthetic analysis of 2-pentyn-1-ol (**103**) *from propargyl alcohol* (**105**) **Scheme 3.08**

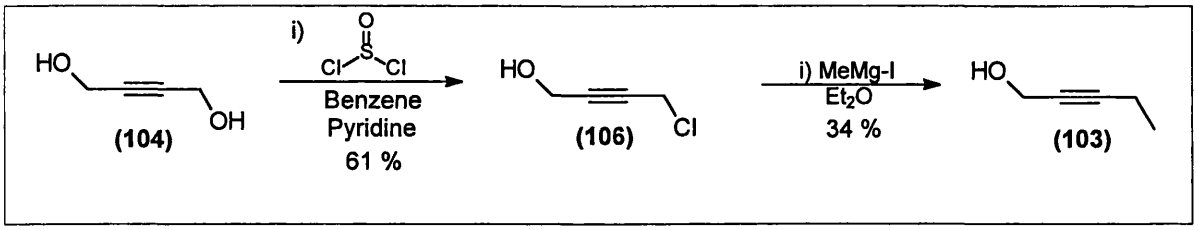


This alternative synthetic route starts with the protection of propargyl alcohol (**105**) using 2,3-dihydropyran.[81] Alkylation of the resulting pyran ether (**107**) with alkyl halide and hydrolysis of the protecting group will afford 2-pentyn-1-ol (**103**). Many of the reported syntheses described used this method to prepare the 2-pentyn-1-ol (**103**) in about 40 % yield from propargyl alcohol (**105**). However, initially we decided to investigate the 1,4-but-2-ynediol (**104**) route since this offered the desired alcohol (**103**) in a short two step process, avoiding any protection.

3.6 iv) Synthesis of 2-pentyn-1-ol (103) *via* 1,4 but-2-yne diol (104)

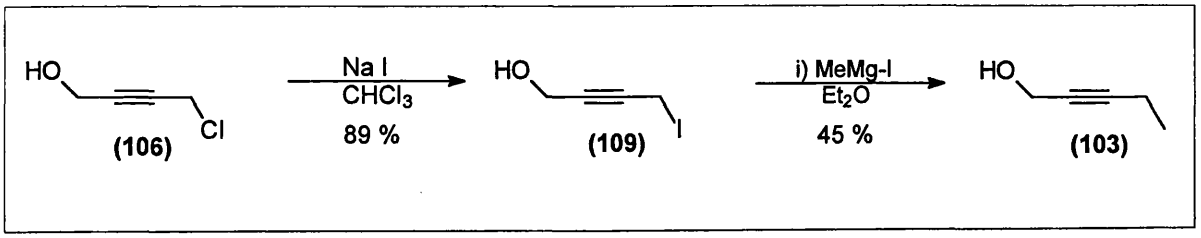
The mono-chlorination of diol 1,4 but-2-yne (**104**) was achieved using thionyl chloride and pyridine in 61 %. Then, methyl magnesium iodide (prepared by heating methyl iodide cautiously over magnesium turnings in diethyl ether), was added to a solution of 4-chlorobut-2-ynol (**106**) in diethyl ether. The reaction was heated for 2 hours before being quenched to afford the propargylic alcohol (**103**) in 34 % yield (Scheme **3.09**). The overall yield was found to be only 21 %, significantly lower than that reported in the literature.[80] This may be due to problems with the isolation of the 2-pentyn-1-ol (**103**), which was found to be volatile.

Synthetic route to 2-pentyn-1-ol (**103**) *from 1,4-but-2-yndiol* (**104**) **Scheme 3.09**



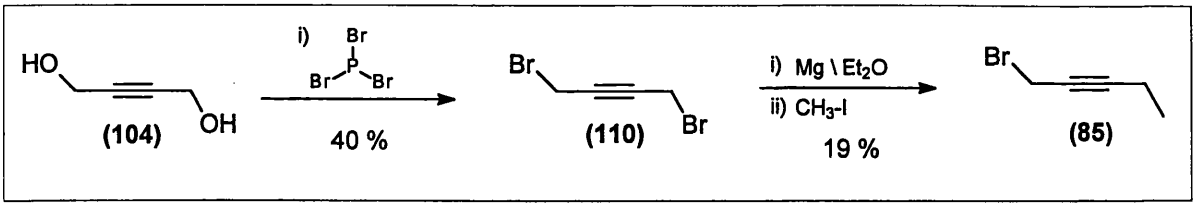
Slight improvements to the overall yield were achieved when the corresponding iodoalcohol (**109**)[82] was used instead of the chloroalcohol (**106**) as shown below (Scheme **3.10**), however the overall conversion of 1,4-but-2-ynediol (**104**) to 2-pentyn-1-ol (**103**) was still unsatisfactory.

Synthetic route to 2-pentyn-1-ol (**103**) *via iodoalcohol* (**109**) **Scheme 3.10**



Instead, an attempt was made to prepare 1,4-dibromobut-2-yne (**110**) *via* the reaction of 1,4-but-2-ynediol (**104**) with phosphorous tribromide (Scheme **3.11**).[83] Subsequent nucleophilic displacement using 1 equivalent of methyl magnesium iodide gave 1-bromo-2-pentyne (**87**) in only 19 % yield, an overall yield of 7 % from the starting diol (**104**).

Synthetic route to 2-pentyn-1-ol (**103**) *via dibromide* (**110**) **Scheme 3.11**



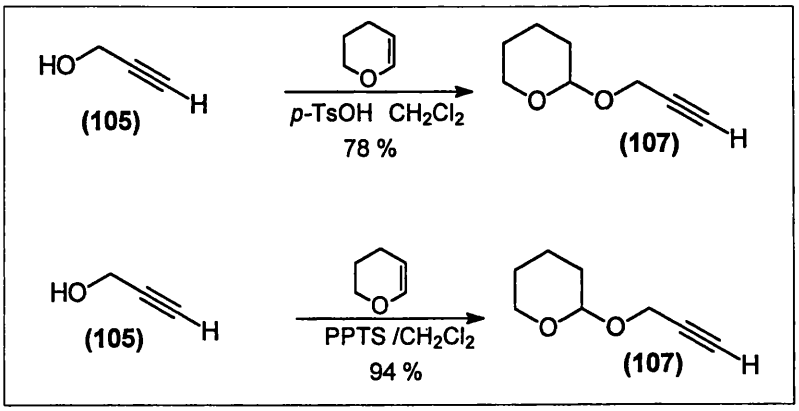
Not only was the yield of this conversion poor, but 4-chlorobut-2-ynol (**106**), 4-iodobut-2-ynol (**109**), and 1,4-dibromobut-2-yne (**110**) were found to be powerful skin irritants inducing TYPE IV allegeric skin reactions.[84] For these reasons these synthetic approaches were abandoned and we turned to the second synthetic route using propargyl alcohol. A recent publication has also warned of the explosive nature of the chloroalcohol (**106**) when purified by reduced pressure distillation.[85]

3.7 Synthesis of 2-pentyn-1-ol (103) *via* propargyl alcohol (105)

To avoid contact with the haloalkynes, the route *via* protection of propargyl alcohol (**105**) was then used.

The reaction of propargyl alcohol (**105**) with 2,3 dihydropyran, proceeded in 78 % yield (*cf* lit 91 %).[81] However, we improved this literature procedure by using pyridinium *p*-toluenesulfonate (PPTS)[86] instead of *p*-toluenesulfonic acid, which resulted in the formation of tetrahydropyran (**107**) in 94 % yield (Scheme **3.12**).

Protection of propargyl alcohol (**105**) *with 2,3 dihydropyran* **Scheme 3.12**



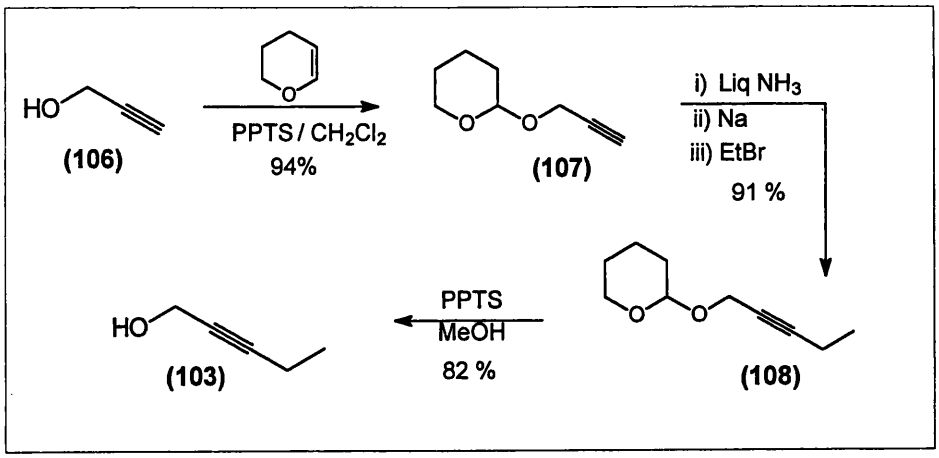
Kajiwara's reported alkylation of the protected alkyne (**107**) and ethyl bromide was achieved using *n*-butyllithium, with HMPA and at 0 °C, to give the alkylated tetrahydropyran ether (**108**) in only 45 % yield.[81]

We repeated this alkylation under similar conditions, without the use of HMPA, allowing the reaction to warm to room temperature instead. The reaction proceeded rather slowly and after 72 hours the reaction was quenched, to give the desired alkylated tetrahydropyran ether (**108**) in 39 % yield together with a by-product (alkylated in the propargylic position) which unfortunately possessed a similar R_f on tlc to the desired product, making purification difficult. We repeated the alkylation with ethyl iodide instead of ethyl bromide and reaction proceeded slightly faster, taking 18 hours to go to completion. The desired alkylated product (**108**) was then isolated in 78 % yield with only a trace amount of by-products by ^{1}H NMR.

Although we had improved the literature procedure, the reaction took 3 days to go to completion. We then used a liquid ammonia / sodium amide alkylation procedure that was reported by Komatsu[87] to give the desired alkylated tetrahydropyran ether (**108**) in 95 % yield. In our hands the reaction proceeded to give the desired alkylated tetrahydropyran ether (**108**) in 91 % yield. This procedure was the one used to prepare large quantities of tetrahydropyran ether (**108**).

The deprotection of the tetrahydropyran ether (**108**) proceeded in almost quantitative yield with PPTS. However, isolation of the alcohol (**103**) was difficult due to its volatility. The desired 2-pentyn-ol (**103**) was isolated in 82 % yield which was consistent with Kajiwara's reported yield of 85 %.

Synthetic route to 2-pentyn-1-ol (**103**) **Scheme 3.13.**



Our overall yield of the pent-2-yne-ol (**103**) was 70 %, based upon propargyl alcohol (**105**) (Scheme **3.13**). This was higher than that reported by Komatsu and Kadjiwara, which were 66 % and 30 % respectively

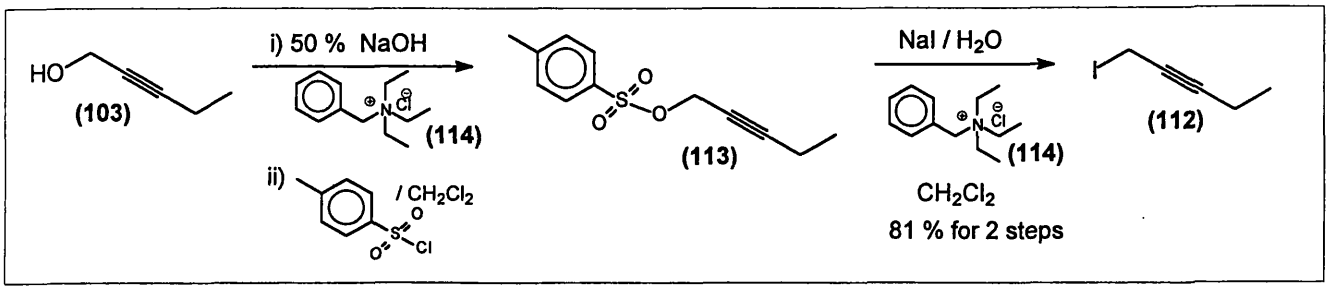
3.8 Halogenation reactions of the 2-pentyn-1-ol (103)

We aimed to prepared both 1-iodo and 1-bromo-2-pentyne for comparative purposes. Using literature procedure, we initially used an iodination method using triphenylphosphine, imidazole and molecular iodine in toluene.[88] Unfortunately this resulted in the formation of polymeric material (the substrate being insoluble in the solvent). The reaction was repeated in a mixed solvent system consisting of acetonitrile and diethyl ether (ratio 3: 1)[89] which overcame the solubility problem and gave the iodoalkyne (**112**) in 55 % yield after purification by chromatography. A two step iodination reaction was also investigated. The tosylate (**113**) was formed initially, in neat pyridine using tosyl chloride and then the tosylate (**113**) was heated in acetone with sodium iodide. The reaction conditions were however quite harsh and it is possible that 1-iodo-2-pentyne (**112**) decomposed upon prolonged heating. Small amounts of the 1-iodo-2-pentyne (**112**) were observed in the reaction mixture by ^{1}H NMR.

The iodination was further improved by following a biphasic procedure reported by Khusid.[90] The tosylate (**113**) was prepared under phase transfer conditions using a 50 % solution of aqueous sodium hydroxide in dichloromethane in the presence of the phase transfer catalyst benzyltriethylammonium chloride (**114**) (synthesised by the treatment of benzyl chloride with neat triethylamine). The tosylate (**113**), prepared in almost quantitative yield, was then taken though crude without purification to the next step and was stirred at room temperature with a saturated aqueous solution of saturated sodium iodide in dichloromethane containing the phase transfer catalyst (**114**) (BTEAC). The reaction proceeded in excellent yield to afford the *n*-iodinated 2-pentyne (**112**), purified by reduced pressure distillation, in 81 % yield, from the corresponding alcohol (**103**) (Scheme **3.14**).

It was noted that the1-iodo-2-pentyne (**112**) was light sensitive. The corresponding bromide (**85**) was prepared using an analogous procedure in 81 % yield.

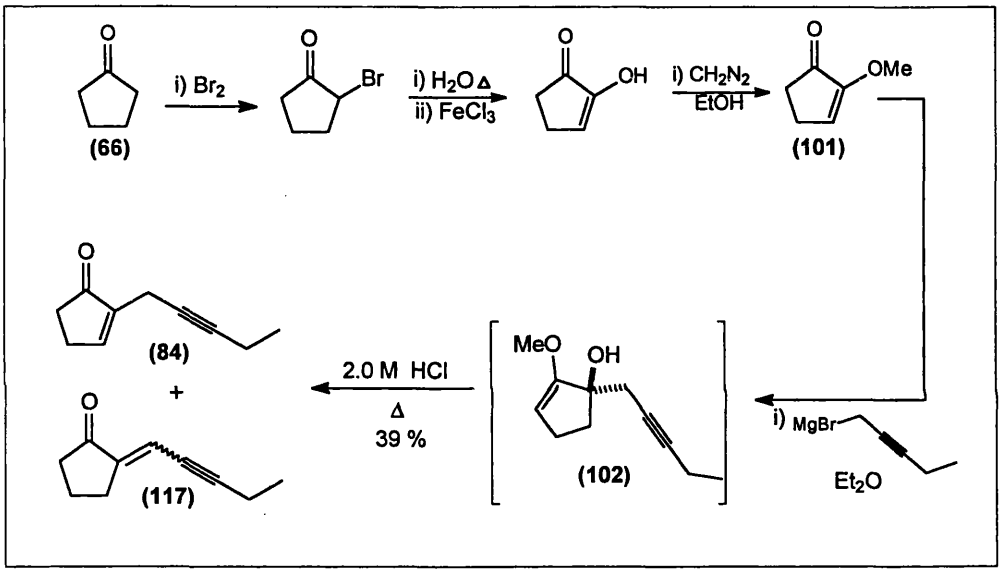
Conversion of unsaturated alcohol (**103**) *to corresponding iodide* (**142**) **Scheme 3.14**



3.9 Synthesis of 2-(2-pentynyl)-2-cyclopenten-1-one (84)

We then proceeded with the synthetic route to 2-(2-pentynyl)-2-cyclopenten-1-one (**86**). Cyclopentanone was converted to 2-(2-methoxy)-cyclopenten-1-one (**101**) *via* a three step one-pot process involving the bromination of the ketone (**20**) with molecular bromine, displacement of the bromine (**115**) with hydroxide anion and then oxidation to the dione (**116**) by treatment with ferric (III) chloride, in an overall 30 % yield. This was consistent with the literature reported yield of 37 % (Scheme **3.15**).[78]

Synthetic route to enone via nucleophilic addition of Grignard **Scheme 3.15**

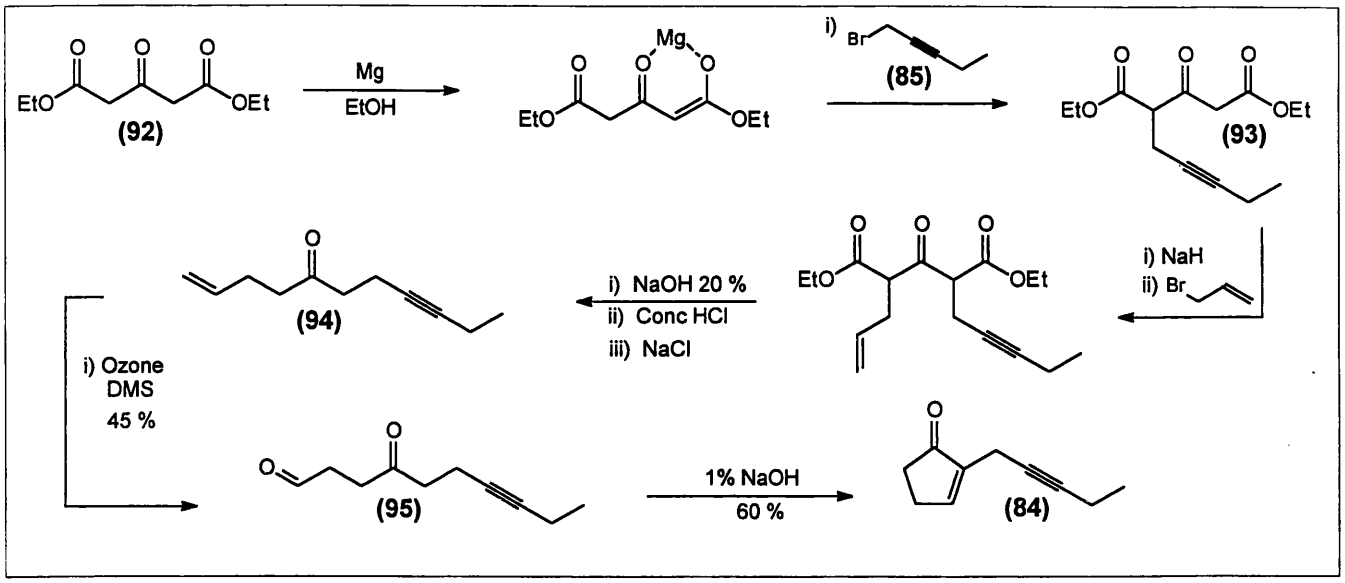


Methylation of the dione (**116**) with diazomethane (generated in situ from Diazald)[91] gave 2-(2-methoxy)-cyclopenten-1one (**101**) which was found to be acid sensitive and readily hydrolysed when subjected to column chromatography. This was therefore used crude.

The Grignard reaction between 1-bromo-2-pentyne (**87**) and 2-(2-methoxy) cyclopentenone (**101**) led to an inseparable mixture of endocyclic and exocyclic olefins (**86** & **117**) in a ratio of 4 : 1. The presence of the alkyne reduced the likelihood of the exocyclic olefin (**117**) isomerizing into the ring.

It was clear that an alternative route was required to overcome this problem and after careful consideration we decided to investigate Naoshima's route to the enone with our aim of improving the overall yield by refining the oxidation of the primary olefin (**94**) (Scheme **3.16**).

Synthesis of the enone using a modified synthetic route to Naoshima's **Scheme 3.16**



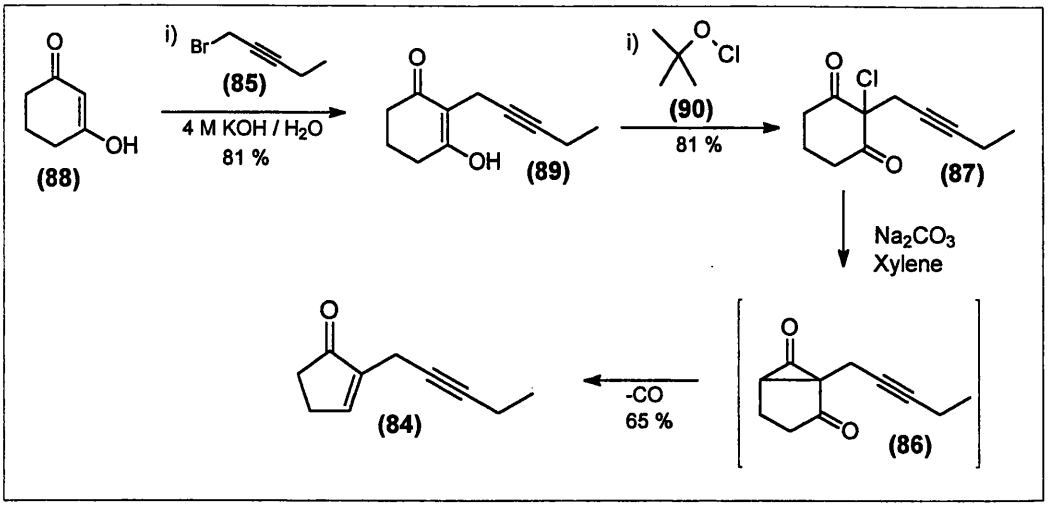
We managed to synthesise 2-(2-pentynyl)-2-cyclopenten-1-one (**84**) from this route, however, the overall yield was disappointingly low. The intramolecular aldol condensation proceeded in a good yield consistent with the literature, 60 %. The overall conversion to the enone (**84**) though was poor, hampered by several low yielding steps. Oxidation of the olefin (**94**) by treatment with catalytic osmium tetraoxide and sodium periodate gave a low yield of 45 % of the aldehyde (**95**) (*cf* lit. yield 55 %).[75]

An alternative oxidation method using ozonolysis, followed by a reductive work-up, was investigated, but the yield of the aldehyde (**94**) was not dramatically improved (47 % yield). It was thought that the presence of the alkyne resulted in side reactions.

Since multigram quantities of the bromide (**85**) were required for the enone (**84**) synthesis we decided to persue Buchi's synthetic route, which promised higher yields of the enone (**84**) and also used the same key 1-bromo-2-pentyne (**85**) intermediate, which we could readily synthesise in high yield.

Cyclohexan-1,3-dione (**88**) was alkylated with 1-bromo-2-pentyne (**85**) in potassium hydroxide solution. The alkyne dione (**89**) was isolated by recrystallization in 81 % yield and then successfully chlorinated using *t*-butyl hypochlorite[92] (**90**) in 81 % yield. The chloride underwent ring contraction by a cheletropic elimination of carbon monoxide using sodium carbonate in *p*-xylene to afford the desired enone (**84**) in 65 % (Scheme **3.17**).

Synthesis of the enone (**84**) *using Buchi's synthetic route* **Scheme 3.17**



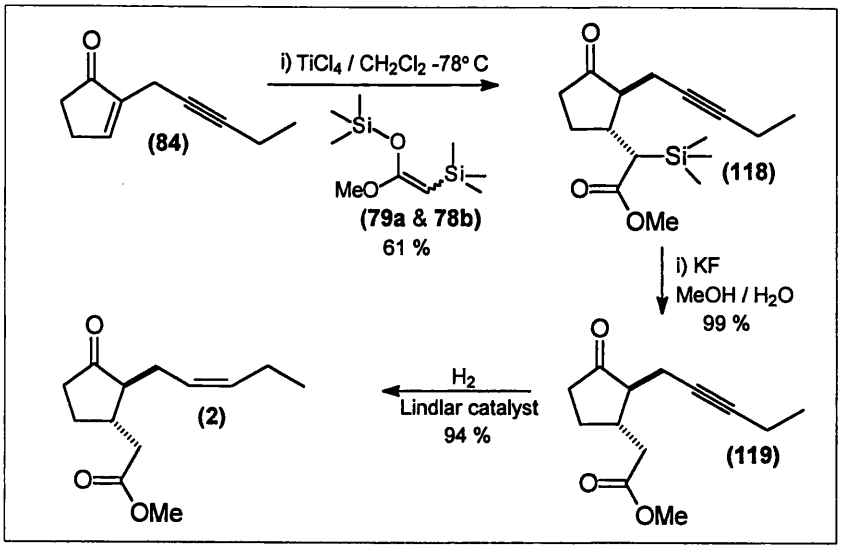
This method provided the desired enone (**84**) in 43 % overall yield from the bromide (**85**), (*cf* lit yield 46 %).[73]

3.10 v) Preparation of the racemic methyl jasmonate (2)

A similar procedure to that used to synthesise racemic methyl dihydrojasmonate (**2a** & **2b**) was utilised. The silylenol ether (**78a** & **78b**) was added to the enone (**84**) in the presence of titanium tetrachloride. This facilitated the formation of the Michael adduct (**118**) which underwent quantitative conversion to racemic methyl *trans*-dehydrojasmonates (**119**) by treatment with potassium fluoride in methanol.

The selective reduction of the alkyne (**119**) was achieved by using a Lindlar catalyst[71] and a stoichiometric amount of hydrogen. The hydrogen was accurately measured using a burette. The uptake of hydrogen was therefore controlled and afforded the *cis*-olefin as the sole product (by ^{1}H NMR) in 94 % yield. This afforded a racemic sample of methyl jasmonates (**2**), required for the HPLC determination of optical purity of enantiomerically enriched methyl jasmonates (**2a** & **2b**) (Scheme **3.18**).

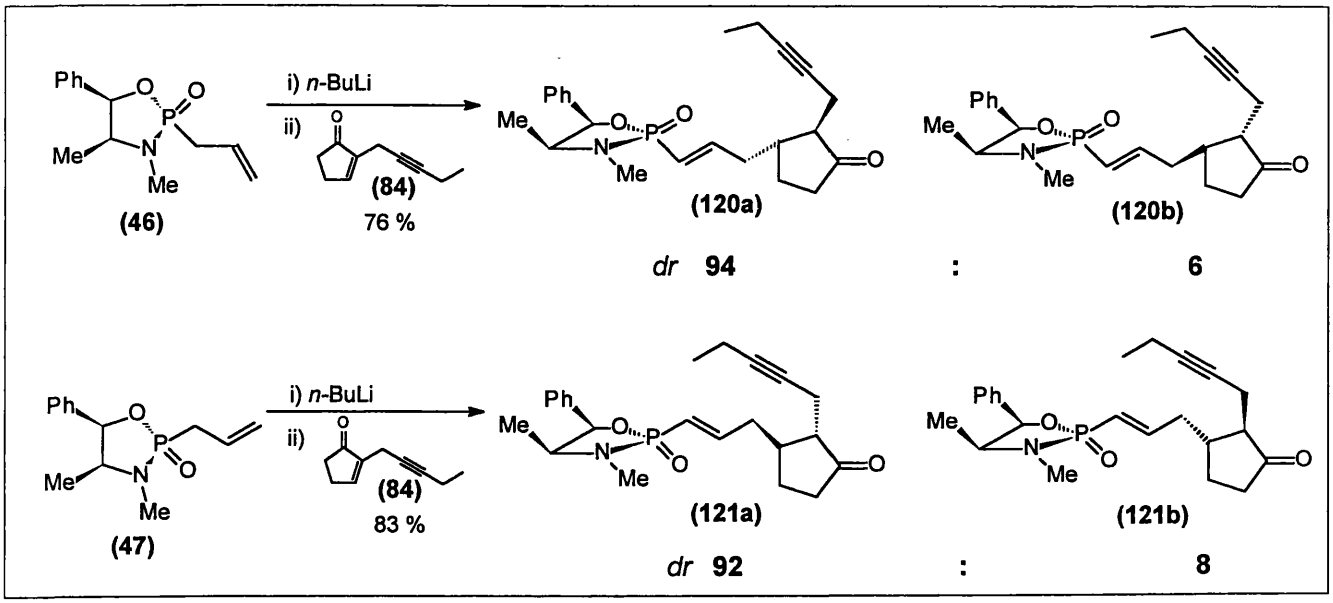
Synthetic route to racemic methyl jasmonate (**2**) **Scheme 3.18**



3.11 vi) Synthesis of chiral methyl jasmonate

An analogous method to dihydrojasmonate (*chapter 1*) was adopted to prepare enantiomerically enriched methyl jasmonates (**2a** & **2b**) (Scheme **3.19**).

Michael addition of phospholidinone to enone (**84**) **Scheme 3.19**



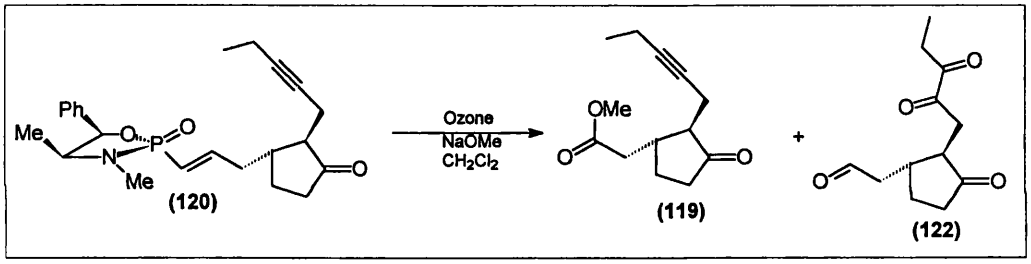
The Michael addition of the chiral phospholidinone template (**46** & **47**) introduced the asymmetric centre at the β-position of the cyclopentenone ring.

The extended anion of the chiral template (**46**) reacted preferentially from one face of the enone (**84**). A rational similar to that proposed for the dihydrojasmonate (**3a** & **3b**)

(*Chapter 2*), also applies with these analogues. The diastereoselectivities were also comparable to those obtained for the dihydrojasmonates. Template (**46**) gave rise to a diastereoratio of 94 : 6 for phospholidinones (**120a / 120b**) and template (**47**) gave a diastereoratio of 92 : 8 for phospholidinones (**121a / 121b**).

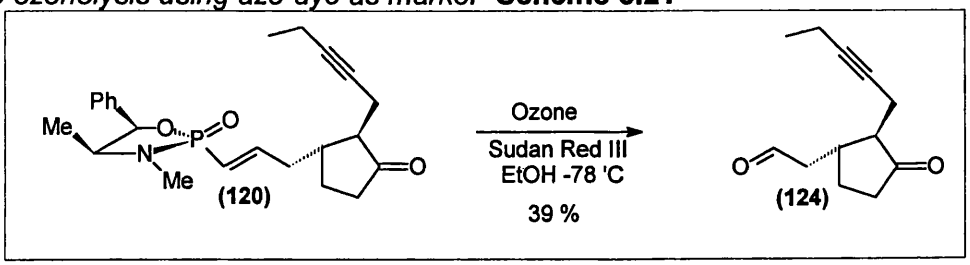
Having prepared the Michael adducts (**120** & **121**), we desired a mild oxidative method to oxidatively cleave the olefins (**120** & **121**) to the corresponding acid / methyl ester. However, the presence of the alkyne functionality complicated matters. Ozonolysis, in the dihydrojasmonate (**3**) case had a defined end point, when all of the olefin (**63** & **80**) had reacted excess ozone could be detected marking the end point of the reaction. In the case of the phospholidinones **120** & **121**, ozone can also react with the alkyne functionality to afford the corresponding triketone (**122**) (Scheme **3.20**).

Oxidative cleavage of the 1,4-γ-adduct (**122**) *using excess ozone* **Scheme 3.20**



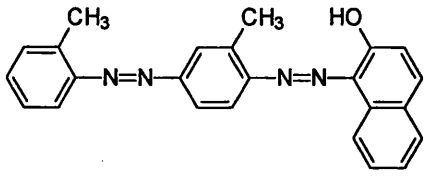
Under the standard ozone conditions it was found that the alkyne reacted as well as the hindered olefin giving a mixture of compounds. The reaction was then repeated using an azo-dye, Sudan Red III[93] (**123**), to indicate the cut-off point of the olefin cleavage and a 39 % yield of the desired aldehyde (**124**) was achieved (Scheme **3.21**).

Selective ozonolysis using azo-dye as marker **Scheme 3.21**



This gave us a good indication that the ozonolysis could be controlled to selectively oxidise the hindered olefin in preference to the less reactive alkyne. If this failed then the aldehyde (**124**) could always be taken forward and oxidised to the corresponding acid and esterified to give methyl jasmonate (**2a**).

Unfortunately the azo-dye (**123**) used was unstable in the presence of sodium methoxide due to the hydroxyl group, which meant that the direct oxidation of the olefin (**120**) to the methyl ester (**3a**) was not possible with the azo-dye (**123**).

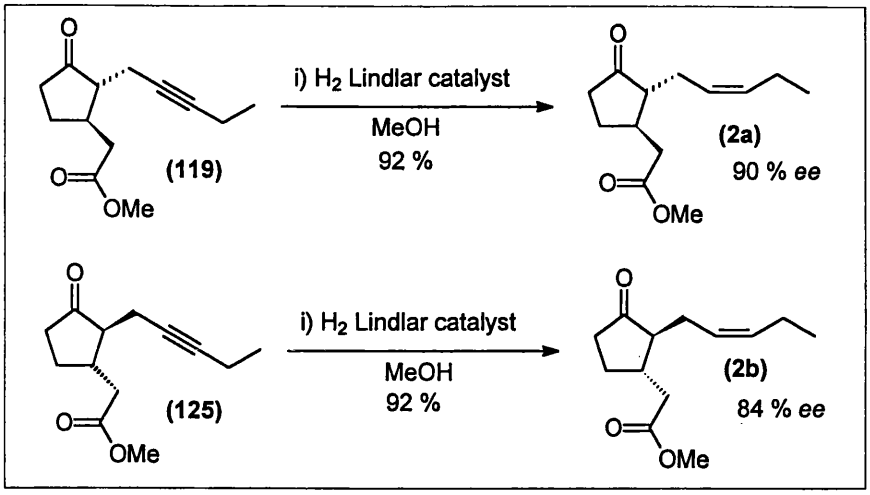


Sudan Red III (**123**)

We therefore tried to monitor whether the extent of the reaction could be assessed by tlc analysis. Since these reactions were carried out at -78 °C, analysis by tlc (developed at room temperature) was not an accurate representation of the extent of the reaction. The tlc sample taken from the reaction mixture (-78 °C) continued to react quickly while warming up to room temperature, and this gave a false indication as to the extent of the reaction. This was overcome by removing and quenching aliquots from the reaction mixture. From this we were able to predict the optimum time for quenching the reaction. This was just prior to all the starting material being consumed as determined by tlc analysis. It ensured that the excess dissolved ozone in the reaction mixture would not continue to react with the alkyne functionality. The corresponding methyl esters (**2a** & **2b**) were then isolated in yields of 39-41 %, after purification by column chromatography.

A similar reductive procedure to that used with the racemic methyl jasmonate was followed. This resulted in the formation of (-)-methyl jasmonates (**2a**) and (+)-methyl jasmonate (**2b**) in >90 % yield from the corresponding chiral alkynes (**119** & **125**) (Scheme 8.8). The odour characteristics of the (-)-methyl jasmonate (**2a**) (nature identical) was noted as being distinctively sweeter than the corresponding (+)-methyl jasmonate (**2b**) (Scheme **3.22**).

Selective reduction of alkynes by hydrogenation using Lindlar catalyst **Scheme 3.22**



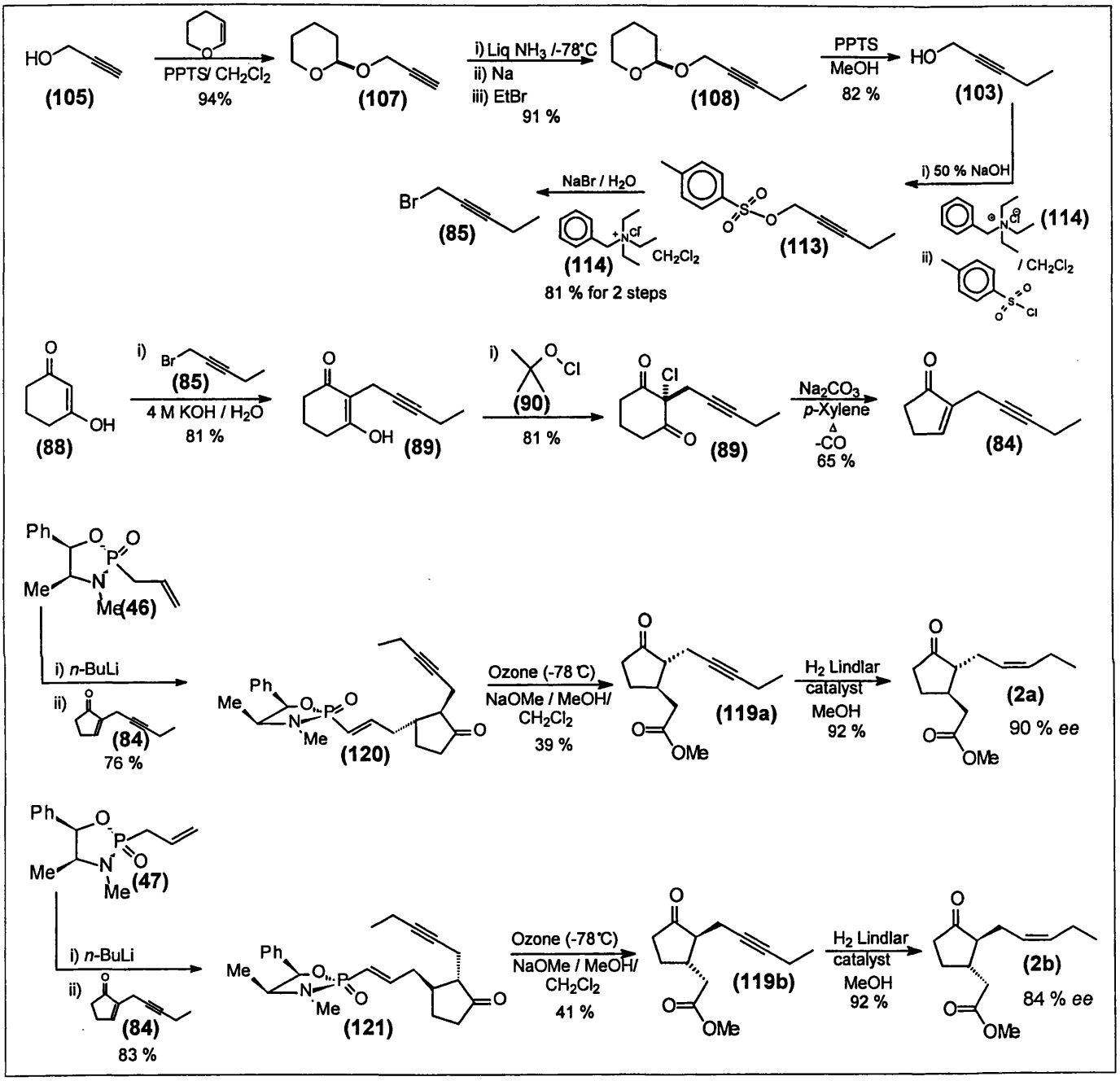
3.12 Optical purity

The enantiomeric purity was determined by HPLC, using an OD chiral phase column. The elution conditions were first established using a racemic sample of methyl jasmonate. The prepared enantiomerically enriched methyl *trans*-jasmonates (**2a** & **2b**) were then analysed using the same HPLC conditions and indicated that (**2a**) had an enantiomeric excess of 90 %, while (**2b**) was 85 % optically pure. This was consistent with the observed optical rotations of these compounds.

3.13 vii) Summary

Overall, we were able to prepare the enatiomerically enriched methyl *trans*-jasmonates (**2a** & **2b**) in 90 % and 85 % *ee* respectively (Scheme **3.23**). We developed an improved synthesis of the key bromide (**85**) intermediate used in the enone (**84**) synthesis, by modified reaction conditions compared to literature routes. Once we had synthesised the bromide (**85**), we investigated a novel route to 2-(2-pentynyl)-2-cyclopenten-1-one (**84**), which initially seemed more direct than the literature procedures. Unfortunately we encountered a problem during the dehydration stage, which gave the desired enone (**84**) as an inseparable mixture of isomers.

Summary of the synthetic routes to chiral methyl jasmonates (**2a** & **2b**) **Scheme 3.23**



We eventually used Buchi's synthetic route to 2-(2-pentynyl)-2-cyclopenten-1-one (**84**), which resulted in a 43 % overall yield based upon the bromide (**85**). The enantiomerically enriched methyl *trans*-jasmonates (**2a** & **2b**) were then synthesised in 28-31 % yield respectively from the enone, 2-(2-pentynyl)-2-cyclopenten-1-one (**84**).

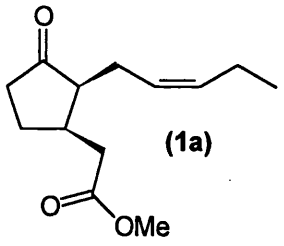
In summary we have demonstrated the usefulness of this asymmetric methodology, which has been used to prepare both chiral methyl *trans*-dihydrojasmonates (**3a** & **3b**) and chiral methyl *trans*-jasmonates (**2a** & **2b**) and are in no doubt that this methodology can also be extended to prepare related prostanoids.

Chapter Four

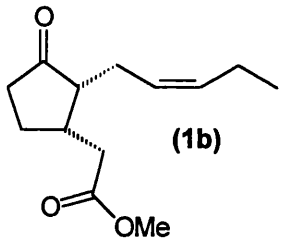
Methyl *epi*-jasmonates

4.1 Aim

Our aim was to devise a novel comparatively inexpensive synthetic route to the methyl *epi*-jasmonates (**1**) with a view to an industrial scale-up process.



(+)-methyl *epi*-jasmonate



(-)-methyl *epi*-jasmonate

This chapter is divided into the following subsections:

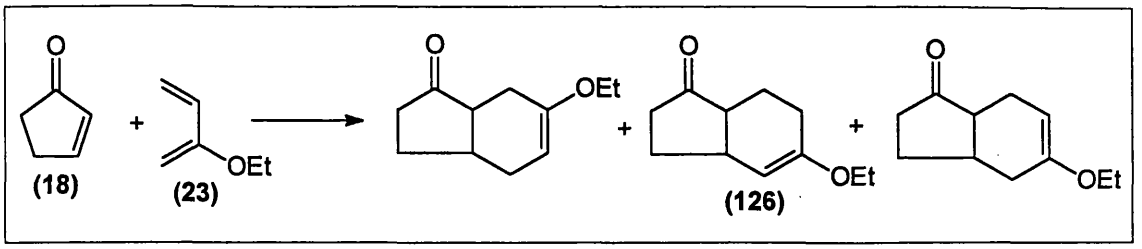
i) Introduction to the *epi*-jasmonoid chemistry, in particular the Diels-Alder reactions
ii) Synthetic approach using 2-methoxybutadiene (**23**) and 2-cyclopenten-1-one (**18**)
iii) Synthetic strategy to *epi*-jasmonate proceeding *via* the magnolia ketone (**136**)
iv) Synthetic strategy to chiral *epi*-jasmonates using homochiral ketals
v) Summary
vi) Future plans

4.2 i) Introduction to the *epi*-jasmonoid chemistry

Previous routes have been reported to the *epi*-jasmonates as described and (*chapters 1 & 2*) in some cases as part of a route to the *trans*-jasmonates. To establish the *syn*-stereochemistry on the 5-membered ring, Knochel[43] used a free radical stereoconvergent approach. Other approaches have used a Diels-Alder cycloaddition reaction. The first such approach was reported by Torii,[36] which gave a low yielding route to *epi*-jasmonate. Notably, a high temperature was used for the Diels-Alder reaction.

A more recent publication highlighted the difficulties of a related Diels-Alder cycloaddition strategy to this compound where the methyl *epi*-jasmonates (**1**) were synthesised in <4 % overall yield. The Diels-Alder reaction proceeded to give a mixture of cycloadducts and amongst the mixture was a significant portion of material withisomerised double bond[94] (**126**) (Scheme **4.01**).

Diels-Alder reaction, with cycloadduct undergoing bond isomerisation **Scheme 4.01**

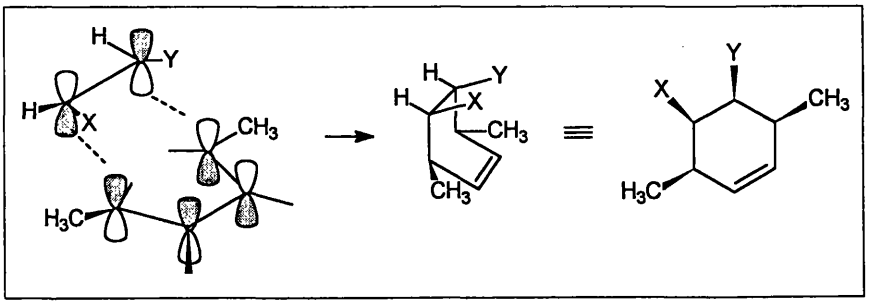


4.3 Advantages of a Diels-Alder strategy

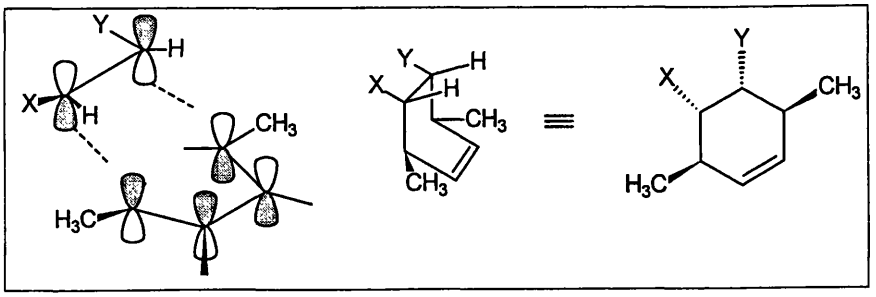
The Diels-Alder cycloaddition reaction is a useful method for forming substituted cyclohexenes. The concerted nature of the mechanism is generally accepted where the diene adopts the s-*cis* confirmation. For unsymmetrical dienophiles, there are two possible stereochemical orientations with respect to the diene. The two possible orientations are called '*endo*' and '*exo*' (Diagram **4.02a** & **4.02b**).

Cycloaddition of an alkene and a diene, showing interaction of LUMO of alkene with HOMO of diene.

Endo addition in a Diels-Alder reaction **Diagram 4.02a**



Exo addition in a Diels-Alder reaction **Diagram 4.02b**



In the *endo* transition state, the reference groups (X,Y) on the dieneophile are orientated towards the π system. In the *exo* transition state the substituent groups (X,Y) are orientated away from the π-system. The *endo* mode of addition is usually preferred when an unsaturated substituent on the dieneophile, such as a carbonyl group, can overlap with the π-system of the diene. The empirical statement which describes this preference is the Alder Rule.[95]

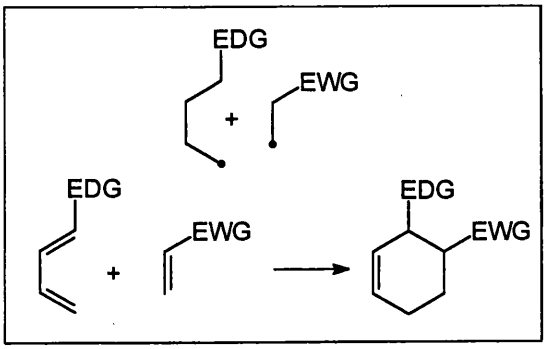
Frequently a mixture of both stereoisomers is formed and sometimes the *exo* product predominates, but the Alder rule is a useful initial guide to prediction of the stereochemistry of the Diels-Alder reaction. There is also a strong electronic substituent effect in the Diels-Alder addition that can influence the stereochemical nature of the product. These relationships are readily understood in terms of frontier orbital theory.

Electron-rich dienes have high-energy HOMOs and interact strongly with the LUMO of electron -poor dienophiles. The question of regioselectivity arises when both the diene and the alkene are unsymmetrically substituted. Generally, there is a preference for the '*ortho*' and the '*para*' orientations respectively. This preference can be understood in terms of frontier orbital theory.

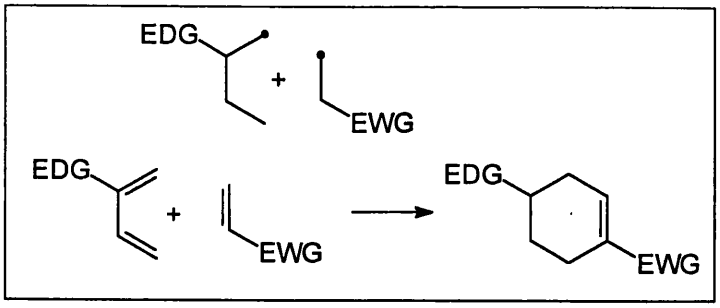
When the dieneophile bears an electron-withdrawing substituent (EWG) and the diene bears an electron-donating substituent (EDG), the strongest interaction is then between the HOMO of the diene and the LUMO of the dieneophile. Because of this interaction, the reactants will be orientated so that the carbons with the highest coefficients in the two frontier orbitals will begin the bonding process.

We hoped to use this '*para* effect' to provide us with high regioselectivities in the desired cycloaddition product which can be rationalised by the HOMO-LUMO interactions of the alkene and diene (Diagram **4.03a** & **4.03b**).

'Ortho' like orientation **Diagram 4.03a**



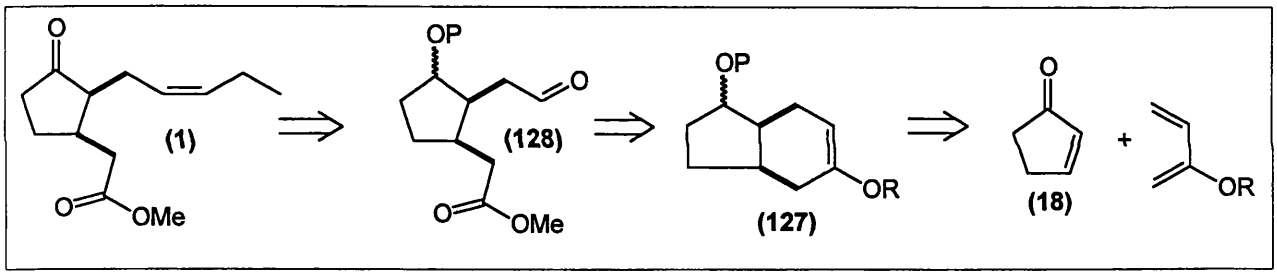
'Para' like orientation **Diagram 4.03b**



4.4 ii) Synthetic strategy using 2-methoxybutadiene & 2-cyclopenten-1-one

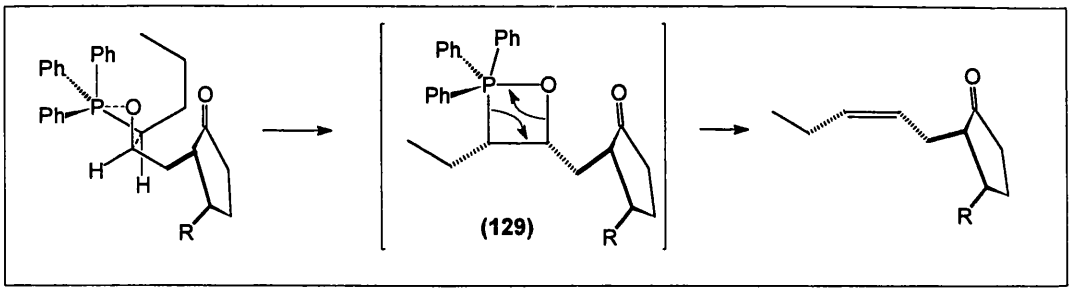
Our synthetic strategy is outlined below involving, as a key step, the Diels-Alder cycloaddition of a suitable diene with 2-cyclopenten-1-one (**18**) to give the *syn* bicyclic system (**127**), with the majority of the adduct as the '*para*' product (Strategy **4.04**).

Retrosynthetic analysis of proposed route to epi-jasmonate (**1**) **Strategy 4.04**



Oxidative cleavage of the olefin (**127**) would result in the formation of an aldehyde / ester carbonyl functionality (**128**). The Wittig reaction, using a non-stabilised ylid under 'salt free' conditions, would then result in the desired *cis*-olefin geometry. The geometry of the olefin can be explained by the non-stabilised ylid reacting in a non-reversible manner with an aldehyde to give mainly the *cis*-disubstituted cyclic 4-membered oxaphosphetane. The interactions between the R group and phosphorus substituents are minimised in the initial approach. The *cis*-stereochemistry of this favoured oxaphosphetane (**129**), retained within the product alkene, is believed to undergo a rapid decomposition *via* a *syn* 2s+2a cycloreversion, driven by relief of severe angular strain in the 4-membered ring (Scheme **4.05**).[96]

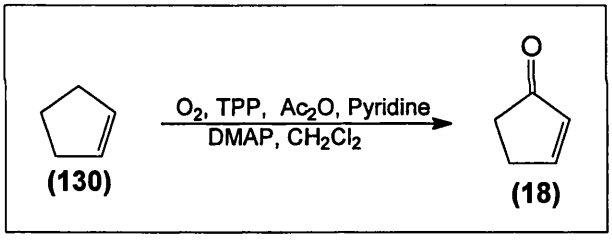
Transition state of the Wittig reaction using a non-stabilised ylid **Scheme 4.05**



4.5 Diels- Alder reactions using 2-cyclopenten-1-one & 2- methoxybutadiene

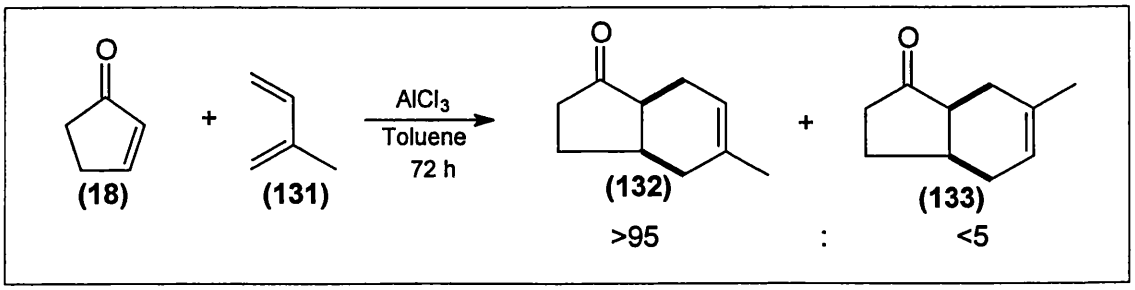
A compound required that was the key to the success of the *epi*-jasmonates route, was 2-cyclopenten-1-one (**18**). Whilst it was commercially available, small samples are expensive and it was therefore prepared in house. This enone was synthesised from cyclopentene (**130**) *via* a photooxygenation reaction[97] using tetraphenylphophyrin[98] in 71 % yield (Scheme **4.06**).

Photooxygenation of cyclopentene (**18**) **Scheme 4.06**



Fringuelli has reported the Diels-Alder cycloaddition reaction of cyclopenten-1-one (**18**) with a 10 fold excess of isoprene (**131**) reacting in a highly regioselective fashion,[99] with excellent isolated yields, 85 % in the presence of a Lewis acid (aluminium trichloride) (Scheme **4.07**).[100]

Fringuelli's Diels-Alders reaction of cyclopenten-1-one with isoprene **Scheme 4.07**



Initially we tried to repeat this work, using the same reaction conditions. The temperature was found to be an important variable governing the outcome of the regioselectivity. The reaction was repeated at four different temperatures, room temperature, 40 °C, 50 °C and 60 °C, (stirring under nitrogen for three days) and the results are summarised in table **4.08**.

Summary of Diels Alder reactions using Lewis acid (aluminium trichloride) **Table 4.08**

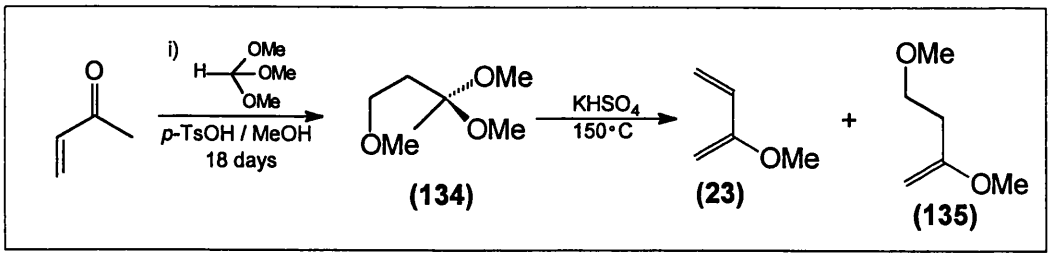
Temperature °C	Isolated % yield	'*Para* product' (**132**)	'*Meta* product' (**133**)
20	18	3	1
40	49	5	1
50	61	3	1
60	58	2	1
50 (Lit)	76	10	1

The reaction carried out at room temperature showed very little product after 72 hours, less than 20 % of the cycloaddition product formed. However the reaction at 40 °C showed the best regioselectivity. By ^{1}H NMR spectroscopy, it was found to be approximately, 5:1 (integral ratios of the vinyl protons), however, the isolated yield was only 49 %. The reactions carried out at higher temperatures were found to give lower regioselectivities 3:1 at 50 °C (*cf.* lit 10:1)[99] and 2:1 for the reaction at 60 °C. These results showed that at best we could only synthesise an enriched mixture of 5:1. Since these cycloadducts were regioisomers, separation by 'chromatographic' methods would be extremely difficult and would not serve as a convenient method for the preparation of the bicyclic coumpound (**132**), required for the synthesis of the *epi*-jasmonates. Tin tetrachloride was also used as an alternative Lewis acid, but this also caused degradtion of the diene (**131**).

We then decided to repeat these Diels-Alder reaction with 2-methoxybutadiene (**23**) in an attempt to see if the problems associated with isoprene (**131**) could be avoided.

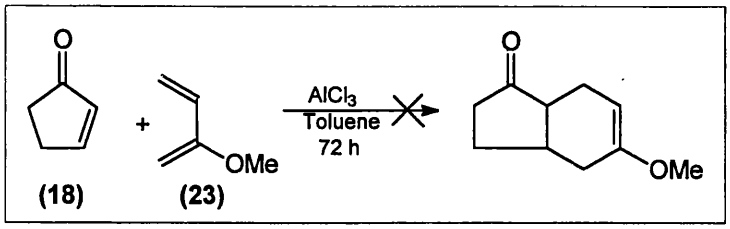
The synthesis of 2-methoxybutadiene (**23**) was explored following a literature preparation,[101] whereby methyl vinyl ketone was ketalised with methyl orthoformate for 18 days. The resulting ketal (**134**) was then pyrolized in the presence of potassium hydrogen sulfate to afford 2-methoxybutadiene (**23**) in a 40 % overall yield from methyl vinyl ketone (Scheme **4.09**). A 10 % yield of the semi-pyrolized olefin (**135**) was also formed. Handling the diene (**23**) was made difficult by its low boiling point.

Synthetic preparation of 2-methoxybutadiene (**23**) **Scheme 4.09**



The Diels-Alder cycloaddition reaction was performed with 2-cyclopenten-1-one (**18**) and 2-methoxybutadiene (**23**) under the conditions laid out by Fringuelli.[99] However it was noted that 2-methoxybutadiene (**23**) was not stable to the Lewis acid and underwent self-polymerisation almost immediately (Scheme **4.10**).

Cycloaddition reaction using 2-methoxybutadiene (**23**) **Scheme 4.10**



We then proceeded to prepare 2-trimethylsilyloxybutadiene, a synthetic equivalent to 2-methoxybutadiene (**23**). This was synthesised by trapping the enol of methyl vinyl ketone with trimethyl silyl chloride (**76**) in 47 % yield.[102]

Attempts to use 2-trimethylsilyloxybutadiene (**136**) with 2-cyclopenten-1-one (**18**) under similar Lewis acid conditions also proved fruitless.

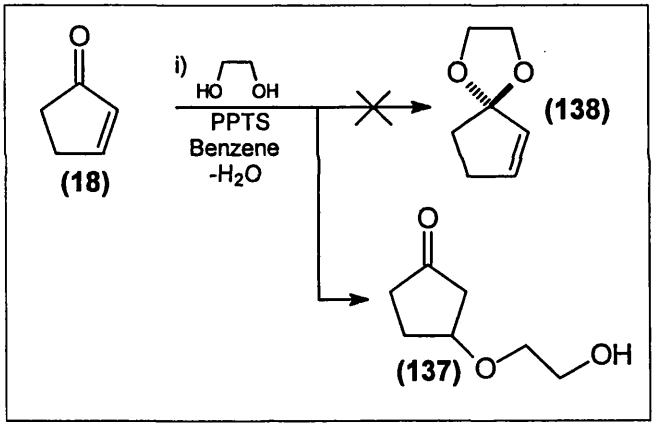
Since these dienes were not only cumbersome to prepare, but also were prone to polymerisation, we reverted to the use of isoprene (**131**), which has a similar electronic configuration to both 2-methoxybutadiene (**23**) and 2-trimethylsilyloxy butadiene (**136**) but is commercially readily available. The use of isoprene instead of 2-methoxybutadiene (**23**) in our strategy would however lead directly to another related jasmonoid, magnolia ketone (**136**). It was also conceivable that the corresponding methyl ketone could be converted to the desired methoxy functionality following a haloform reaction. With this in mind, we proceeded to use isoprene in our Diels-Alder investigations.

More recent work by Grieco, has shown that ionic Diels-Alder reactions can be carried out efficiently by using the ethylene ketals of masked enones as dieneophiles, in concentrated solutions of lithium perchlorate in diethyl ether with 1 mol % of camphor sulfonic acid.[103] The cycloadditions proceeded giving the Diels-Alder adduct in excellent yields (>95 %) and also extremely high regioselectivies, 90- 98%.

However, Grieco has only worked with six membered enones and has not shown any examples of this reaction with the ketals of 2-cyclopenten-1-one (**18**). Our initial aim was to establish if similar reaction yields and selectivities were achievable with the ethylene ketal of the five membered enone. Our first goal was to prepare the ethyl glycol ketal of 2-cyclopenten-1-one (**18**), to test whether the lithium perchlorate catalysed cycloaddition would be feasible for five membered ketals.

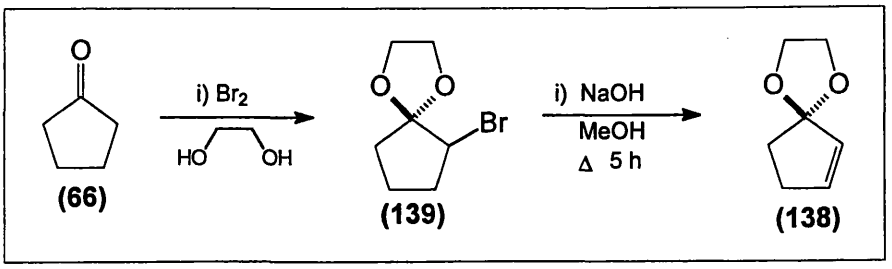
Using Grieco's procedure for preparing 2-cyclohexanone ethylene ketals, we tried to ketalize 2-cyclopenten-1-one (**18**) with ethylene diol using a mild acid catalyst (PPTS). Unfortunately this mainly led to decomposition of the enone although a small amount of the Michael addition product (**137**) was isolated in <5 % yield (Scheme **4.11**). Several acid catalysts were tried but with no success. It was thought that the strained nature of the five membered enone made it difficult for the diol to add to the strained carbonyl, in nucleophilic fashion.

Ketalisation of 2-cyclopenten-1-one with ethylene diol **Scheme 4.11**



We then embarked on a literature preparation involving the α-bromination of cyclopentanone (**66**) in ethylene glycol.[104] The synthetic route is outlined in scheme **4.12**.

Synthetic route to the ethylene ketal (**138**) **Scheme 4.12**

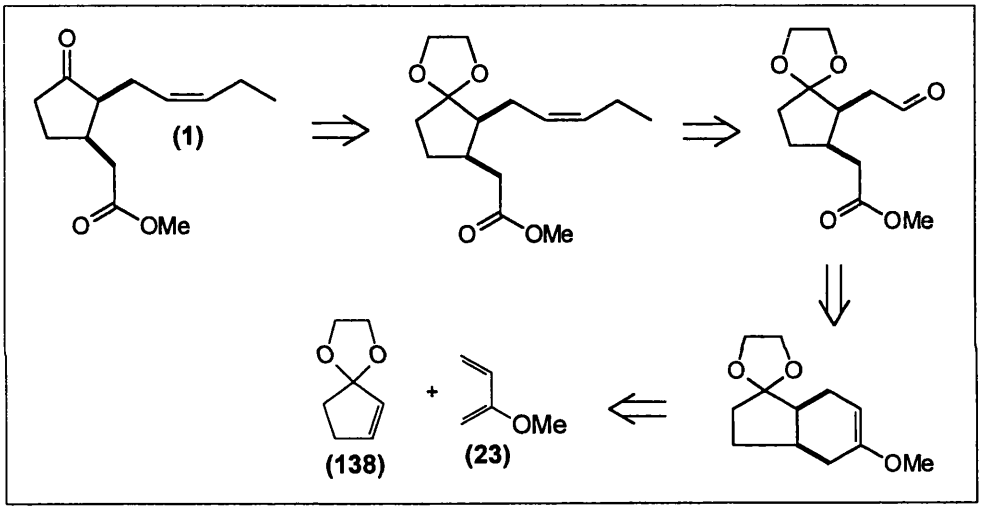


Elimination of the crude bromide (**139**) (isolated yield was much lower as the bromide was not stable at room temperature), by treatment of base afforded the ketal enone (**138**) in an overall yield of 51 % (lit. yield 58 %).[104]

4.6 Synthetic strategy to *epi*-jasmonates using enone (138)

We tried the Diels-Alder cycloaddition reaction initially with 2-methoxybutadiene (**23**) and 2-cyclopenten-1-one ethylene ketal (**138**) (Scheme **4.13**). However, it was again noted that the diene (**23**) decomposed almost immediately.

Synthetic plan to epi-jasmonates using enone (**138**) **Scheme 4.13**

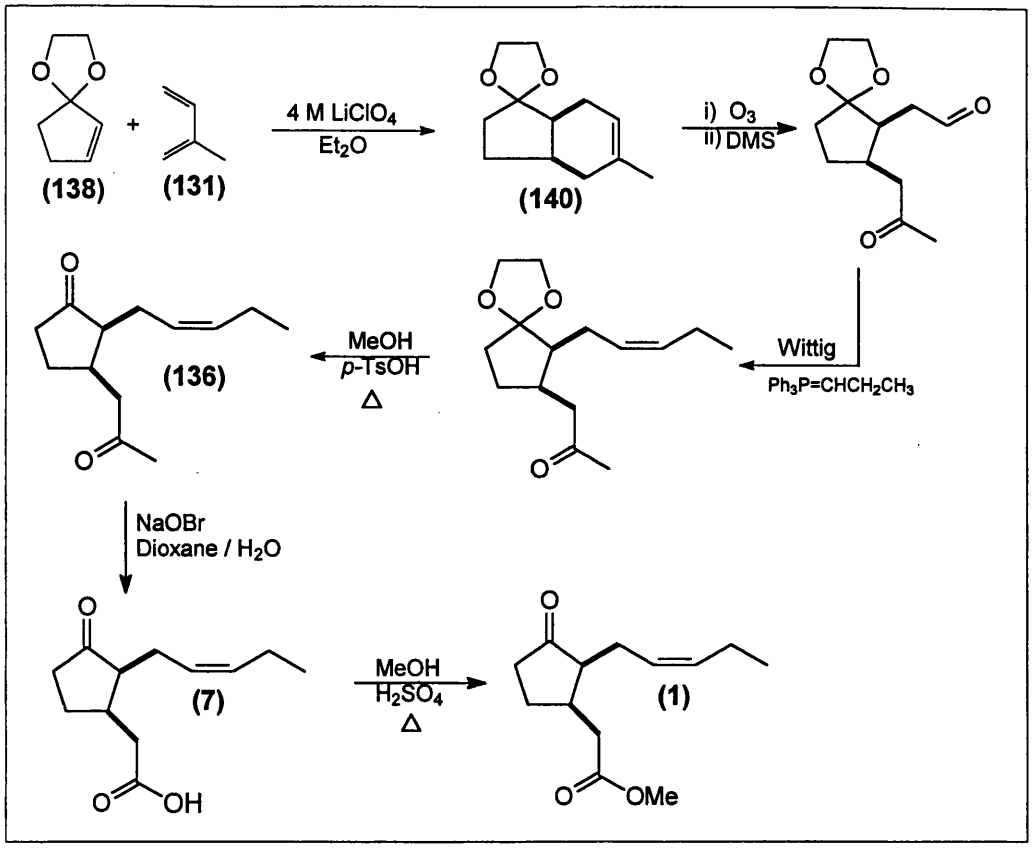


It was thought that the Lewis acid was causing spontaneous self-polymerisation of the diene (**38**). We then proceeded to use isoprene (**131**) for the reasons discussed earlier.

4.7 iii) Synthetic strategy to *epi*-jasmonate *via* magnolia ketone

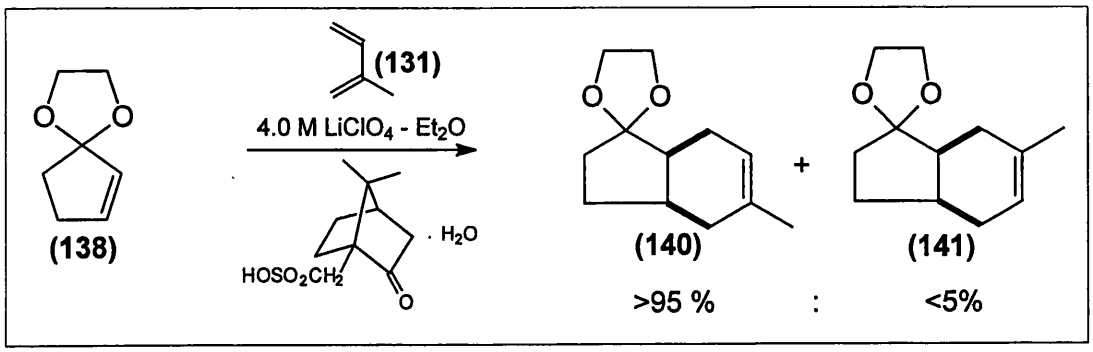
The synthetic strategy to the *epi*-jasmonates proceeding *via* the magnolia ketone (**136**) intermediate is shown in scheme **4.14**.

Synthetic route to methyl *epi*-jasmonate (**1**) *via magnolia ketone* (**136**) **Scheme 4.14**



The cycloaddition reaction with isoprene (**131**) and the ethylene ketal (**138**) in 4.0 M lithium perchlorate – diethyl ether solution with catalytic camphorsulfonic acid, proceeded in excellent yield (91 %), giving the *para*-isomer (**140**) in greater than 95 % regioselectivity (by ^{1}H NMR) (Scheme **4.15**).

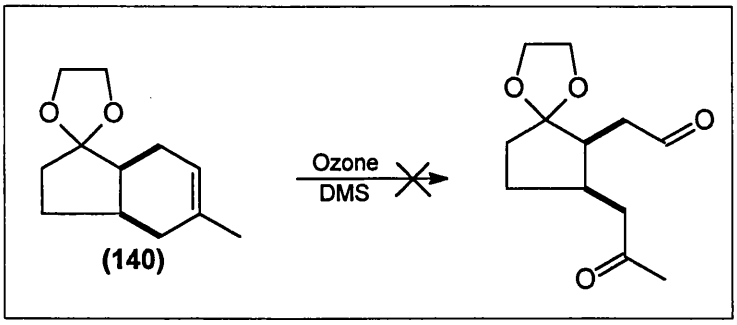
4.0 M Lithium perchlorate-diethyl ether catalyzed cycloaddition reaction **Scheme 4.15**



It was interesting to note that in the absence of the acid catalyst, the reaction mixture remained colourless, indicating that the reaction had failed to react, and it was only when 1 mol % was added that a pale yellow colouration resulted after 30 minutes. This disappeared immediately when the reaction was neutralised with triethylamine. The *para* and *meta* cycloadducts (**140** & **141**) were separated by column chromatography.

Ozonolysis of the *para* cycloadduct (**140**) resulted in the formation of several components. This was thought to be a result of the ketal breaking down and rearranging during the ozonolysis (Scheme **4.16**).

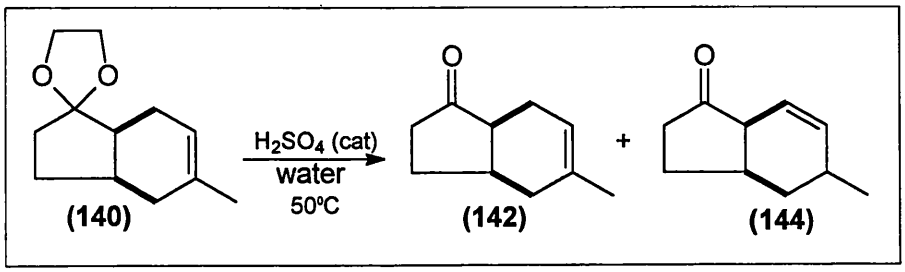
Ozonolysis of the para cycloadduct (**140**) **Scheme 4.16**



The presence of a ketone here would jeopardise the *syn* integrity. It was therefore decided to deprotect the ketal (**140**) and reduce the ketone (**142**) to an alcohol (**143**). This would ensure that no epimerization would take place during the remaining synthetic steps.

The ketal (**140**) was deprotected to ketone (**142**), under mild acid conditions (Scheme **4.17**), dilute sulfuric acid at 50 °C. The hydrolysis was complete after 2 hours, however the olefin also underwent bond migration to olefin (**144**) similar to that reported by Kitahara.[94] This presence of the bond migrated species (**144**) was evident from the crude ^{1}H NMR showing additional vinyl protons. These isomers were inseparable by chromatographic methods forcing us to adopt another hydrolysis procedure.

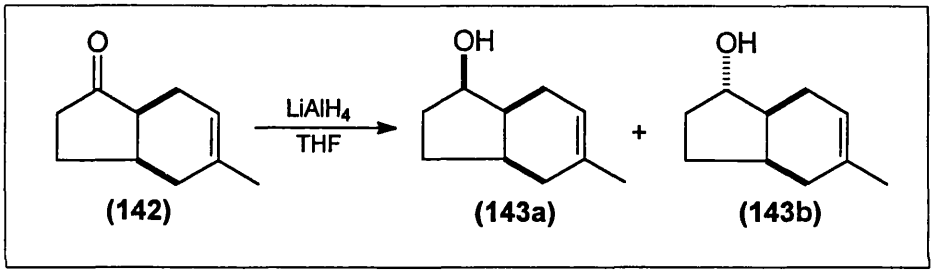
Hydrolysis of ketal (**140**) *using sulfuric acid* **Scheme 4.17**



A milder approach using dilute hydrochloric acid (2.7 M) at room temperature overcame the bond isomerization problem. The desired ketone (**142**) was isolated in almost quantitative yield (a trace of the bond migrated material was detected by ^{1}H NMR).

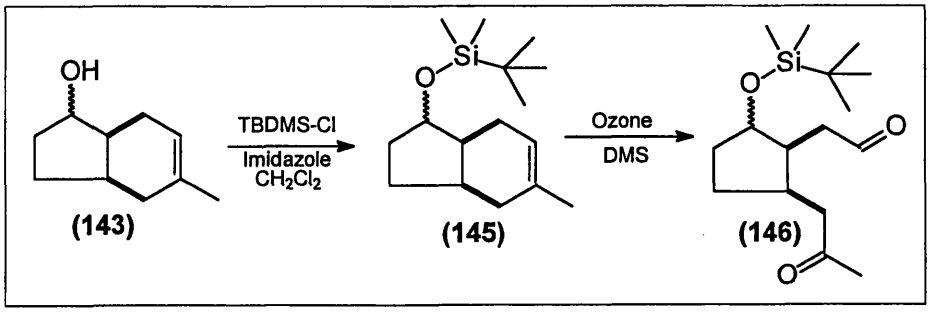
The ketone (**142**) was then reduced using lithium aluminium hydride and this proceeded to generate two diastereoisomeric alcohols (**143a** & **143b**) in equal proportions. To simplify product analysis during subsequent steps, a more stereoselective reduction was explored. Reduction using sodium borohydride at -30 °C also resulted in the formation of the two diastereoisomers. However when cerium(III)chloride heptahydrate[105] was used in conjunction with sodium borohydride a more selective reduction of 4:1 resulted. The rationale for this selectivity may be attributed to the chelation of the carbonyl with cerium from the least hindered face and delivery of the hydride from the opposite face of the cerium complex. Since the diastereoisomers had almost identical physical properties they were carried through as a mixture (Scheme **4.18**).

Unselective reduction of ketone (**142**) *using lithium aluminium hydride* **Scheme 4.18**



The alcohols (**143**) were protected with *t*-butyldimethylsilyl chloride. This provided us with an inert group that would tolerate ozonolysis conditions. The silyl ether (**145**) was then subjected to ozone treatment followed by a reductive work-up of the ozonide with dimethyl sulfide to afford the methyl ketone (**146**) intermediate in 71 % yield (Scheme **4.19**).[106]

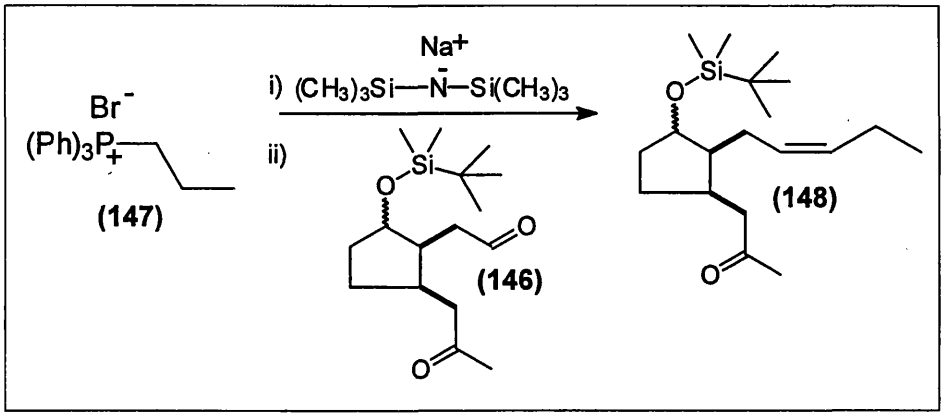
Protection of alcohol (**143**) *with t-butyldimethylsilyl chloride* **Scheme 4.19**



Non-stabilised ylids under 'salt-free' conditions are known to give rise to predominately (*Z*)-olefins (discussed in earlier synthetic strategy) and therefore these conditions were followed.[96]

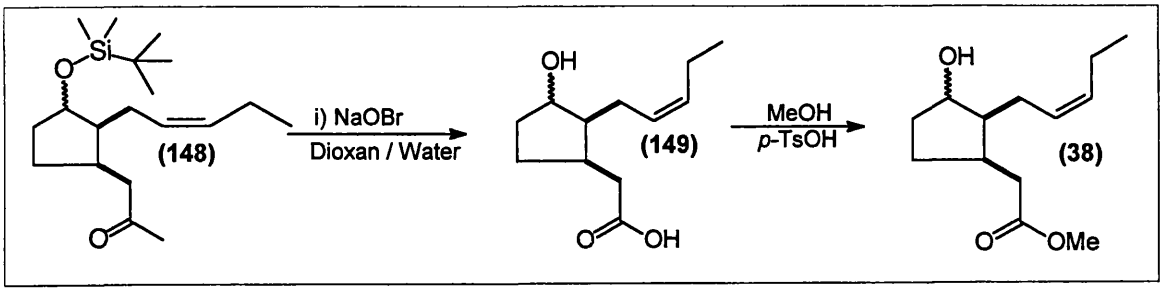
The aldehyde intermediate (**146**) was used immediately in the Wittig reaction. The unstabilised ylid was generated *in situ* by treatment of *n*-propyl phosphonium bromide (**147**) with sodium hexamethyldisilylazide in tetrahydrofuran.[107] The resulting salt that formed was allowed to settle in the solution. Addition of the supernatent ylid solution to aldehyde (**146**) then produced predominantly the *cis* olefin (**148**), (20 : 1 , *cis* / *trans* by ^{1}H NMR) after purification (Scheme **4.20**).

Wittig reaction using non-stabilsed salt free conditions **Scheme 4.20**



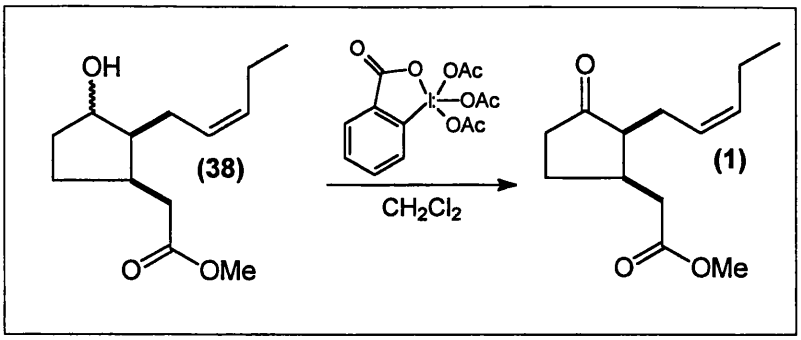
The methyl ketone (**148**) was then successfully converted to the corresponding acid (**149**) by the haloform reaction with sodium hypobromite in a dioxan / water mixture.[108] This also brought about the deprotection of the silyl protecting group to give the acid (**149**) in 61 % yield. The acid (**149**) was methylated by heating in methanol and catalytic sulfuric acid to afford a diastereoisomeric mixture of methyl *epi*-cucubrate in 84 % yield (Scheme **4.21**).

The haloform reaction converting magnolia ketone (**136**) *to epi-cucubric acid* (**149**)
Scheme 4.21



Finally, the cucubate (**38**) was oxidised under mild conditions, utilising freshly prepared Dess-Martin periodinane.[45] This oxidised the alcohol smoothly to methyl *epi*-jasmonate (**1**) (Scheme **4.22**). The *epi*-jasmonate was purified by chromatographic methods to afford a colourless oil, with a strong sweet jasmine odour.

Oxidation of epi-cucubrate (**38**) *to* methyl *epi*-jasmonate (**1**) **Scheme 4.22**

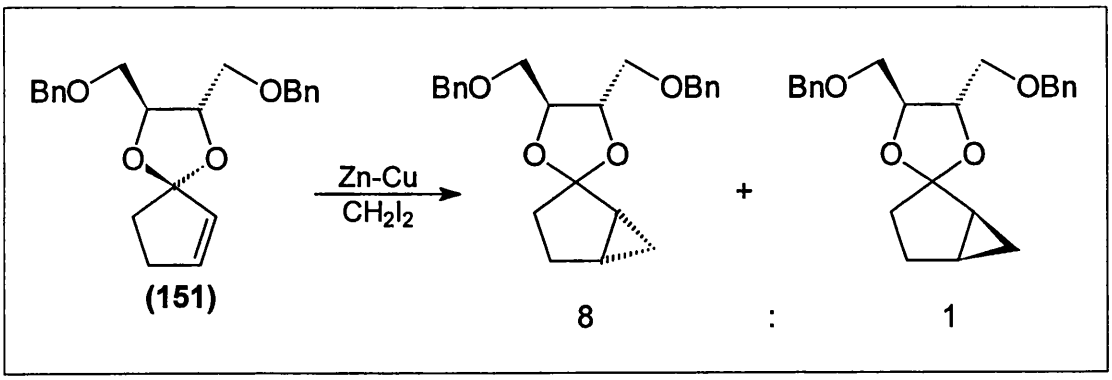


NMR analysis showed this to be similar to the *trans*-jasmonates (**2**), however, there was a marked difference in the α-H's chemical shift. The smell of this racemic mixture was noted to be considerably stronger than the (-)-methyl jasmonate (**2a**), this being consistent with reports made by Helmchen.[109]

4.8 iv) Synthetic strategy to chiral *epi*-jasmonates using homochiral ketals

After the success of the racemic route we decided to adapt it to explore whether an enantioselective synthesis to *epi*-jasmonates (**1a** & **1b**) could be achieved. It was possible that the presence of bulky chiral groups on the ketals could hinder the Diels-Alder cycloaddition from occurring from one face. Chiral ketals of enones have been synthesised previously and been used successfully in the enantioselective preparation of cyclopropanes by Mash[110] (Scheme **4.23**).

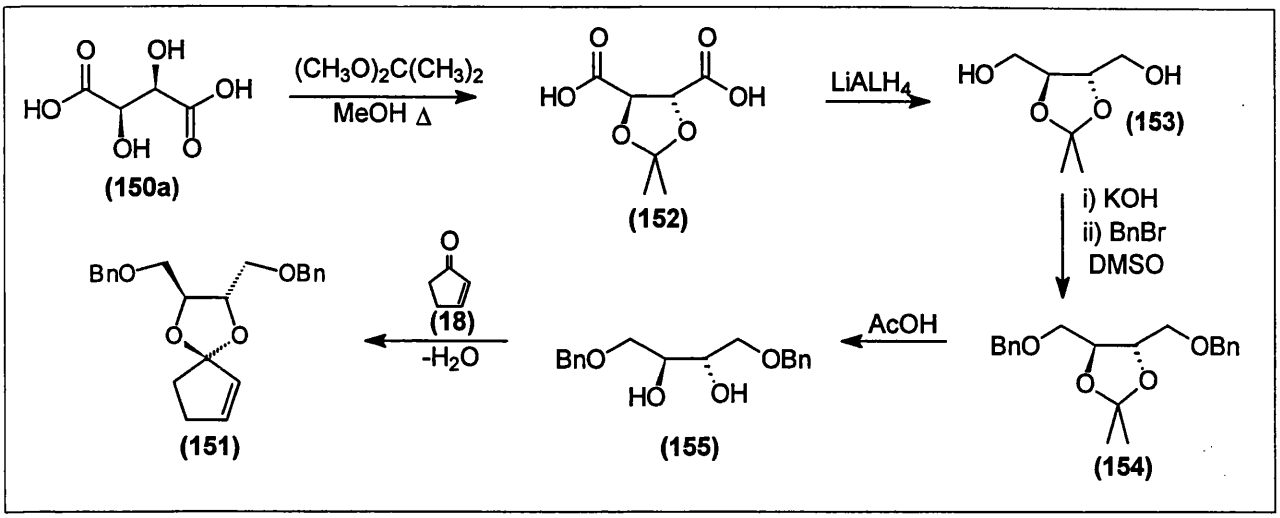
Regioselective cyclopropanation achieved by chiral ketals **Scheme 4.23**



Diastereoselective cyclopropanations are directed *via* chelation control by the homochiral ketal protecting groups, which are derived from enantiomerically pure tartaric acid (**150a**) (Scheme **4.24**).

Synthesis of enantioselective ketal (**151**) *via enantiomerically pure tartaric acid* (**150a**)

Scheme 4.24

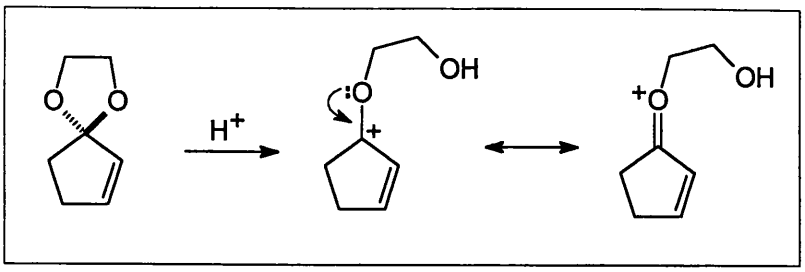


(-)-Tartaric acid (**150a**) was first protected using 2,2-dimethoxy propane in methanol to generate the isopropylidene diester (**152**). The diester (**152**) was then reduced using lithium aluminium hydride to afford the diol[111] (**153**) which underwent benzylation with potassium hydroxide and benzyl bromide in dimethyl sulphoxide. The isopropylidene group in (**154**) was then hydrolysed in acetic acid and the diol (**155**) ketalised with 2-cyclopenten-1-one (**18**). A literature precedent was followed whereby the ketalisation proceeded in 5 days in the presence of calcium carbide,[112] (used to remove the water generated). The dibenzylketal (**151**) was isolated in 60 % yield as a pale yellow viscous oil.

The Diels-Alder cycloaddition reaction using 4.0 M lithium perchlorate - diethyl ether solution was repeated with the dibenzylketal (**151**) and isoprene (**131**) at room temperature with 1 mol % of camphor sulfonic acid. The reaction mixture remained colourless (no yellow colouration was observed as in previous reactions) and the dibenzylketal (**151**) was isolated in an almost quantitative yield.

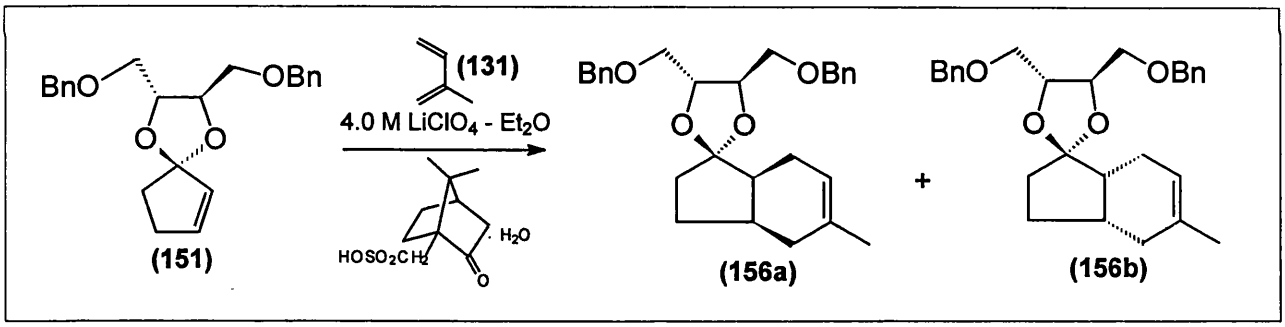
This reaction was repeated but the amount of camphor sulfonic acid was increased to 2 mol %, but still no reaction occurred. It was when we repeated the reaction with 3 mol % of camphor sulfonic acid that a faint yellow colouration was observed. Grieco proposed a mechanistic theory in his original paper indicating that the opening of the ketal under mild acid conditions gave a reactive carbocation intermediate, which rapidly undergoes the Diels-Alder cycloaddition reaction.[103] The yellow colouration observed in our reaction certainly agrees with his hypothesis, of a reactive carbocation intermediate (Scheme **4.25**).

Hydrolysis of ketal leading to a carbocation stabilised possibly by the perchlorate anion **Scheme 4.25**



The reaction mixture was then quenched with sufficient base to neutralise the acid and purified by column chromatography. The cycloaddition product (**156**) was isolated in 80 % yield (Scheme **4.26**). Although the ^{1}H NMR showed a broad single olefinic proton peak at δ 5.22 and no other protons signals in that region, the ^{13}C NMR showed clearly that this was a mixture of diastereoisomers of equal proportions. This indicated that the chiral benzyl groups had not directed the isoprene (**131**) to attack from the least hindered face.

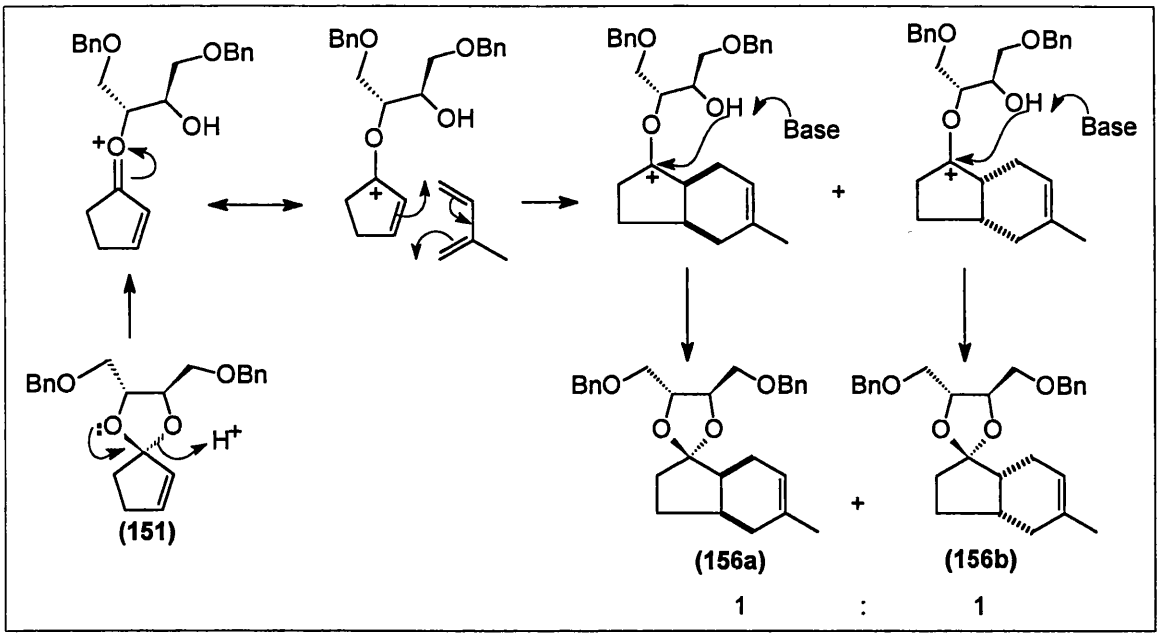
Diels-Alder cycloaddition reaction using a homochiral dieneophile **Scheme 4.26**



The ketal (**156**) was hydrolysed and the resulting ketone was found to have no optical rotation. To provide further information, and in case the ^{13}C NMR signals were due to different conformations we synthesised the racemic ketal from racemic tartaric acid.

The Diels-Alder cycloaddition reaction produced identical ^{1}H and ^{13}C NMR spectra to the cycloaddition product of the homochiral dibenzylketal (**151**). We therefore deduced that the conformation of the carbocation active species (scheme **4.25**) produced was such that the chiral groups on the dibenzylketal (**151**) were either too far removed to influence the cycloaddition or that the oxonium species had too short a lifetime. Such that the asymmetric environment created by the presence of the chiral groups on the ketal was destroyed due to the sp^2 carbocation intermediate (Scheme **4.27**).

Plausible mechanism of the cycloaddition reaction using ketal (**151**) **Scheme 4.27**



Grieco had also showed that 5.0 M lithium perchlorate - diethyl ether solutions can also catalyse these Diels-Alder reactions in the absence of a Brønsted acid. The reaction time was however much longer, in the order of several hours compared to minutes. The mechanism for these reactions was thought to proceed *via* the classical Diels-Alder reaction without the breaking of the ketal ring.

The cycloaddition reaction between the enatiomerically pure dibenzylketal (**151**) and isoprene was repeated using 5.0 M lithium perchlorate - diethyl ether for 24 hours at room temperature.[113] The reaction was worked up to find no Diels-Alder cycloaddition products. In fact the ketal was recovered in almost quantitative yield. It was thought that perphaps the presence of the bulky benzyl groups hindered attack of the dieneophile. Another important point was thatthere was no electron withdrawing group attached to the alkene, rather a ketal which could possibly retard the reaction rate.

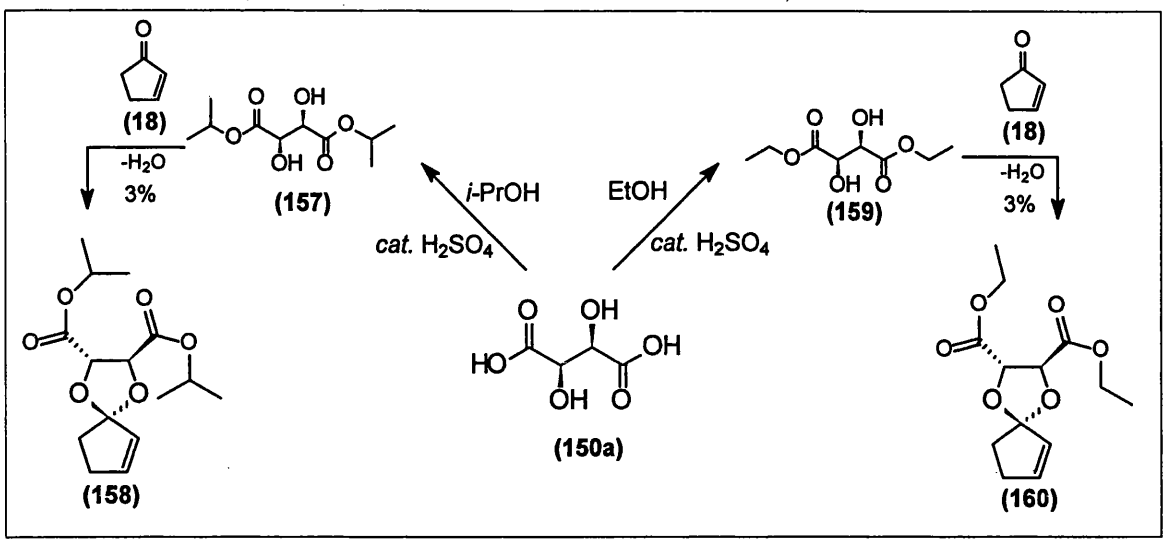
Whilst it was conceivable that the problem was carbocation formation, the size and distance between the chiral groups and the olefin may also have been important, and therefore we synthesised the chiral ester derivatives of tartaric acid (**150a**).

These ketals were prepared in a similar fashion to those from thretiol (**155**) by ketalizing the corresponding diol with 2-cyclopenten-1-one (**18**) in benzene using a soxhlet extractor and calcium carbide as the drying agent. The reaction was heated for 10 days with PPTS, however when the reaction was worked up, only 3 % of the desired ketal was formed, and the majority of the diol was recovered.

The reaction was repeated with *para*-toluene sulfonic acid, again only 2- 3 % of the ketals (**158**, **160**) were formed after 10 days (Scheme **4.28**). These findings were not

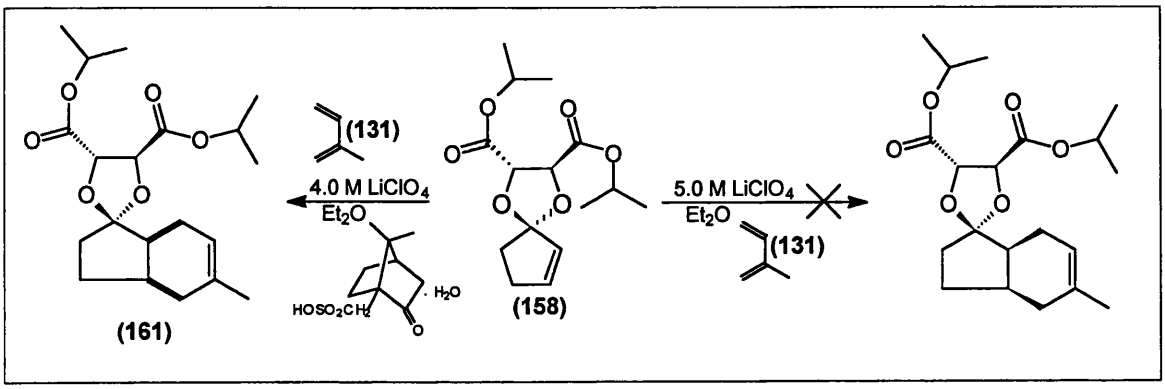
consistent with those reported by Lange[114] who had achieved yields of 57- 61% for ketals (**158** & **160**) using PPTS as the catalyst.

Preparation of enantioselective ketals (**158** & **160**) *derived from enantiomerically pure tartaric acid* (**150a**) **Scheme 4.28**



We repeated the Diels-Alder reaction using ketal (**158**) with isoprene (**131**), this time using 5.0 M lithium perchlorate - diethyl ether solutions at room temperature. However, after 24 hours of reaction time no Diels-Alder adduct was observed. The Diels-Alder cycloaddition in 4.0 M lithium perchlorate - diethyl ether solution, using 3 mol % of camphour sulfonic acid, afforded the cycloaddition product as a mixture of diastereoisomers, similar results to that observed with ketal (**151**) (Scheme **4.29**).

Diels-Alder reactions utilising homochiral ketals (**161**) **Scheme 4.29**



During the course of the PhD a communication by Bestmann reporting an efficient and flexible route to (-)-methyl jasmonate (**2a**) and (+)-methyl *epi*-jasmonate (**1a**) was published (*see page 17*).[39] His procedure made use of a chiral cyclopentenoid building block (**24**) that has been extensively used in the synthesis of enantioselective

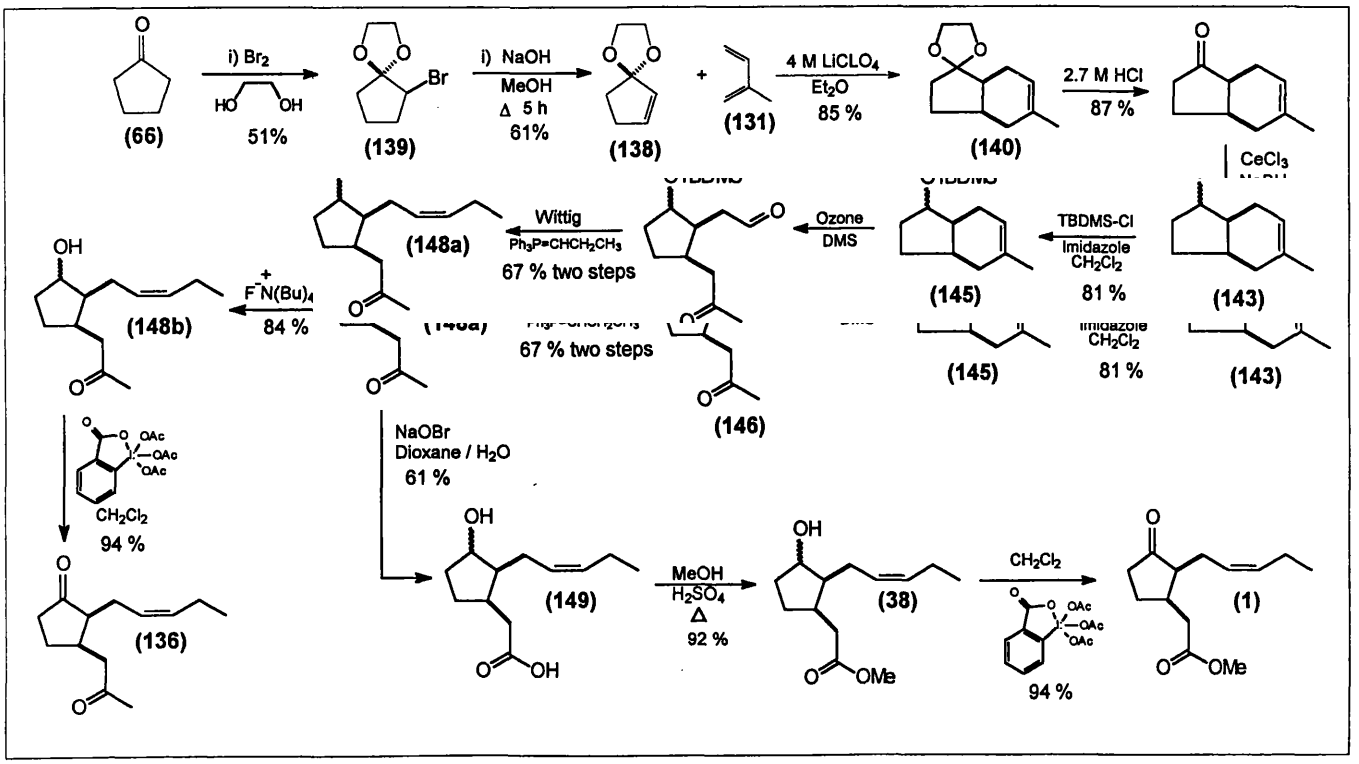
prostaglandins. His route also utilised the Diels-Alder cycloaddition reaction catalysed by lithium perchlorate.

The chiral starting block was prepared from enantiomerically pure tartaric acid (**150a**). The problem that Bestmann encountered was the removal of the chiral handle on the cyclopentanone ring. This was achieved by treatment with pentafluorophenylchloro thionoformate and then with 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine and proceeded in 72 % yield.

4.9 v) Summary

We managed to devise a new synthetic route to methyl *epi*-jasmonate (**1**) *via* a lithium perchlorate - diethyl ether catalysed Diels-Alder cycloaddition reaction. The Diels-Alder reaction proceeded in high yield with excellent regioselectivity. The resulting ketal cycloadduct (**140**) was hydrolysed to the ketone (**142**) and reduced to the alcohol (**143**). The alcohol was protected with *t*-butyldimethylsilyl chloride to give the *t*-butylsilylether (**145**), which underwent oxidative cleavage at the olefin by ozonolysis to the methyl ketone / aldehyde (**146**). *Cis* olefination was achieved using a classical Horner-Evans Wittig reaction providing us with a synthetic route to magnolia ketone (**136**) (Scheme **4.30**).

Synthetic route to methyl epi-jasmonate (**1**) *via magnolia ketone* (**136**) **Scheme 4.30**



A haloform reaction converted the methyl ketone (**148a**) to the corresponding acid (**149**), which was esterified to methyl cucubrate (**38**). A mild oxidation using Dess-Martin periodane gave racemic methyl *epi*-jasmonate (**1**).

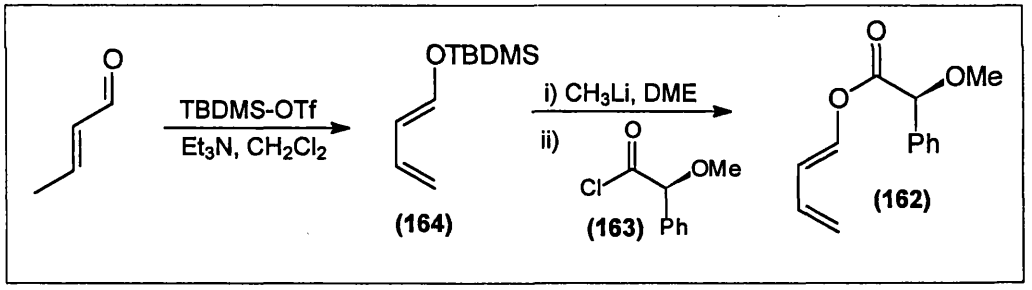
The overall yield of the 8 steps leading to racemic methyl *epi*-jasmonate (**1**), based on the starting 2-cyclopenten-1-one ethylene ketal (**138**) was 12 %.

We also explored this synthetic strategy using homochiral ketals, in an attempt to synthesise chiral methyl *epi*-jasmonates (**1a** & **1b**). Unfortunately we were unable to induce chirality using the chiral ketals (**151**, **158** & **160**). However, the Diels-Alder reactions gave us an insight into the mechanism of this reaction.

4.10 vi) Future work

The other chiral induction process briefly investigated involved the use of a chiral diene (**162**) derived from (*S*)-O-methylmandeloyl chloride (**163**) and 1-*t*-butyl dimethylsilyloxybutadiene (**164**) (Scheme **4.31**).[115]

Synthesis of chiral diene derived from (S)-O-methylmandelate (**163**) **Scheme 4.31**

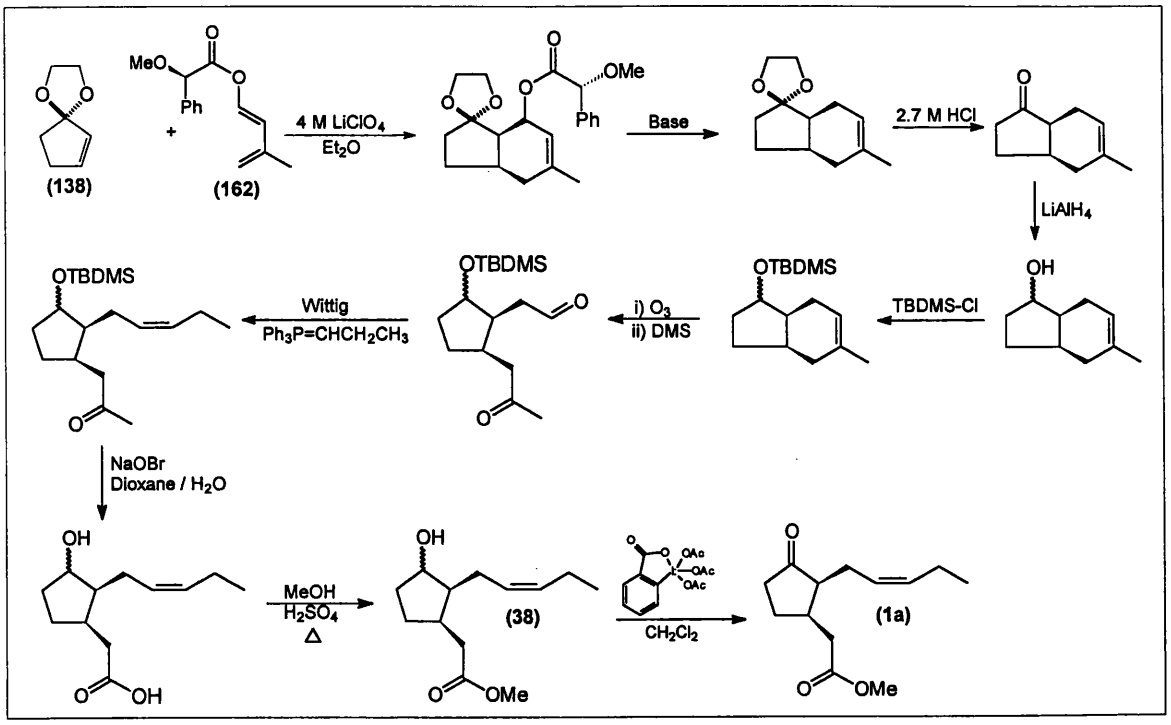


This diene (**162**) has been reported by Trost[115] to give high levels of diastereoselectivity in Diels-Alder reactions, which is thought to be due to the conformation of the ester and π-stacking in the transition state.

A similar chiral diene (**162**) could be used in our synthetic route to racemic *epi*-jasmonate (**1**) with the aim of an asymmetric induction in the Diels-Alder cycloaddition reaction. Outlined in scheme **4.32** is a potential synthetic strategy to chiral methyl *epi*-jasmonates (**1a** & **1b**).

*Proposed synthetic route to epi-*jasmonate (**1a**) *using chiral diene* (**162**) *to induce chirality*

Scheme 4.32

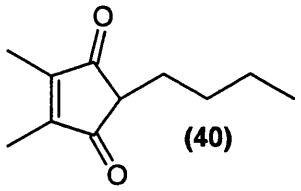


Chapter Five

Calythrone analogues

5.1 Aim

Our aim was to devise a straightforward, comparatively inexpensive synthetic route to the 'calythrone analogue', 2-butyl-4,5-dimethyl-4-cyclopenten-1,3-dione (**40**) and various other similar analogues.



(40)

2-Butyl-4,5-dimethyl-4-cyclopenten-1,3-dione

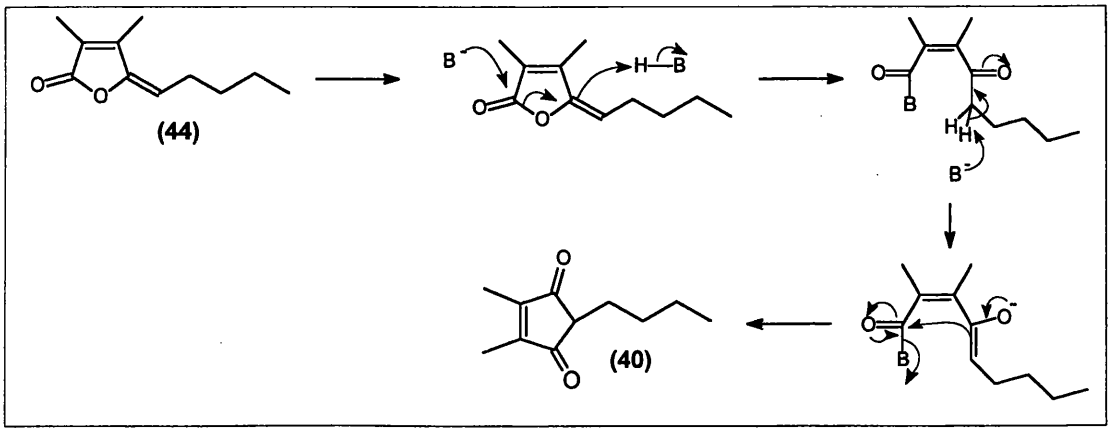
This chapter is divided into the following subsections:-

i) Introduction to the calythrone analogue (**40**)
ii) The optimization of the existing route to the calythrone analogue (**40**)
iii) The synthesis of related calythrone analogues
iv) Synthetic strategies to dimethylmaleic anhydride
v) The synthesis of the calythrone analogue (**40**) utilizing the Pauson-Khand reaction
vi) Summary

5.2 i) An introduction to the calythrone analogue (40)

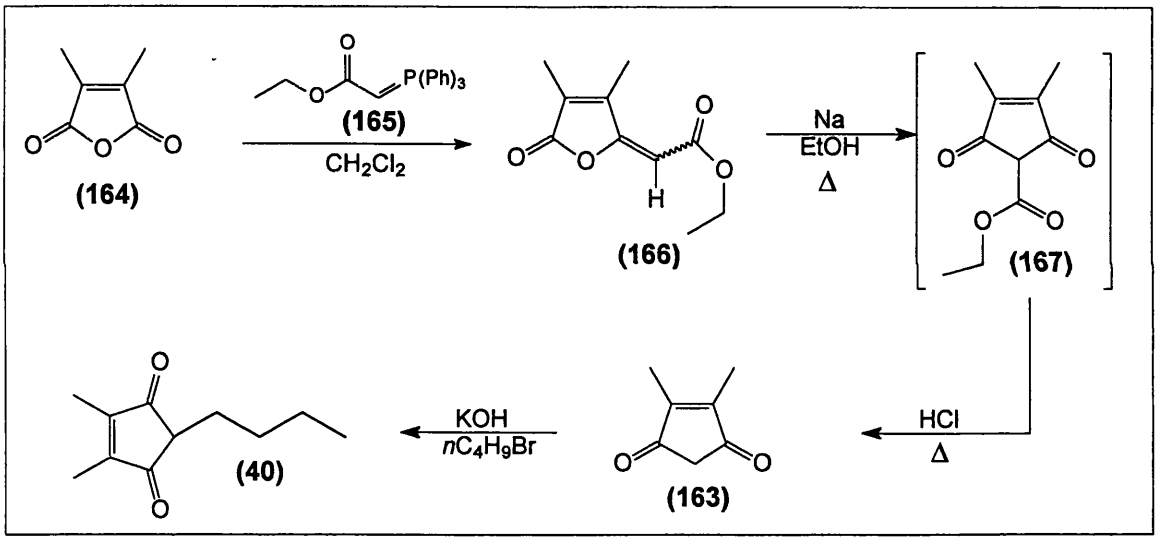
The calythrone analogue 2-butyl-4,5-dimethyl-4-cyclopenten-1,3-dione (**40**) was first identified as a minor trace impurity[116] in the synthetic preparation of bovolide (**44**). It is thought the calythrone analogue (**40**) was formed by the rearrangement shown in Scheme **5.01**.

Possible conversion of bovolide (**44**) *to the calythrone analogue* (**40**) **Scheme 5.01**



The calythrone analogue (**40**) is unusual in that it is has an axis of symmetry. The odour characteristic of this molecule has a distinct resemblance to that of jasmine oil. Initial attempts to synthesise (**40**) at Bush Boake Allen resulted in the preparation of a small amount of this material.[51] However, the route was expensive due to the cost of dimethylmaleic anhydride and the product was isolated in an overall yield of less than 5 %. The monoalkylation of diketone (**163**) had been found to be problematic, giving mixtures of mono and dialkylated material, and the reaction conditions utilized a ten fold excess of base, in the form of potassium hydroxide, using 1-bromobutane as the solvent (25 fold excess). This made the adopted route by Bush Boake Allen (Scheme **5.02**) unfeasible for the large-scale preparation required for extensive odour evaluation.

Synthetic route used to prepare calythrone analogue (**40**) **Scheme 5.02**



The aim of this aspect of the project was therefore to develop a feasible route to this compound and various other synthetic analogues. We tackled this in two ways, by optimizing the existing route and by seeking an alternative synthetic strategy.

5.3 ii) Optimization of the existing route

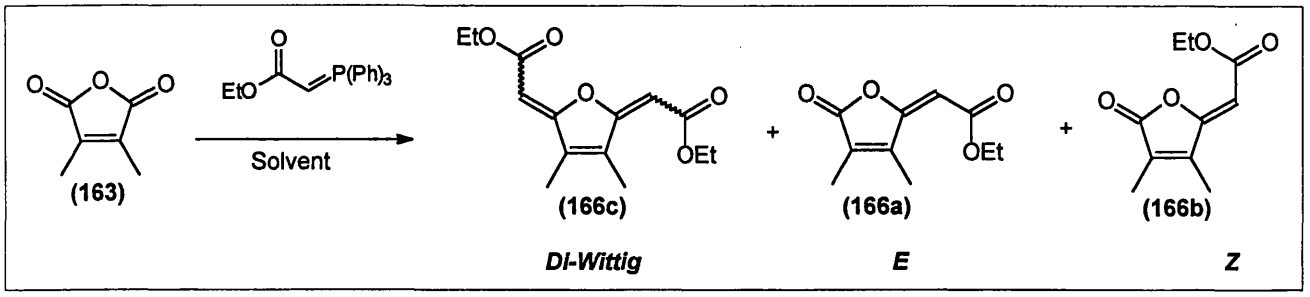
The first aim was to improve the yield of the Wittig reaction between 2,3-dimethylmaleic anhydride (**164**) and the phosphorane (**165**). Bohlmann first reported Wittig reactions between ylids and anhydrides / lactones.[117]

We carried out several reactions at room temperature in various organic solvents: ethyl acetate, tetrahydrofuran, toluene, and dichloromethane. Due to the cost of the anhydride, the reactions were performed with a slight excess of phosphorane

(**165**) (1.1 equiv) to ensure that all the anhydride was consumed (Scheme **5.03**). The results are summarized in table **5.04**.

The general Wittig reaction between 2,3-dimethylmaleic anhydride (**164**) and the ylid (**165**)

Scheme 5.03



The summary of the results from the Wittig reaction **Table 5.04**

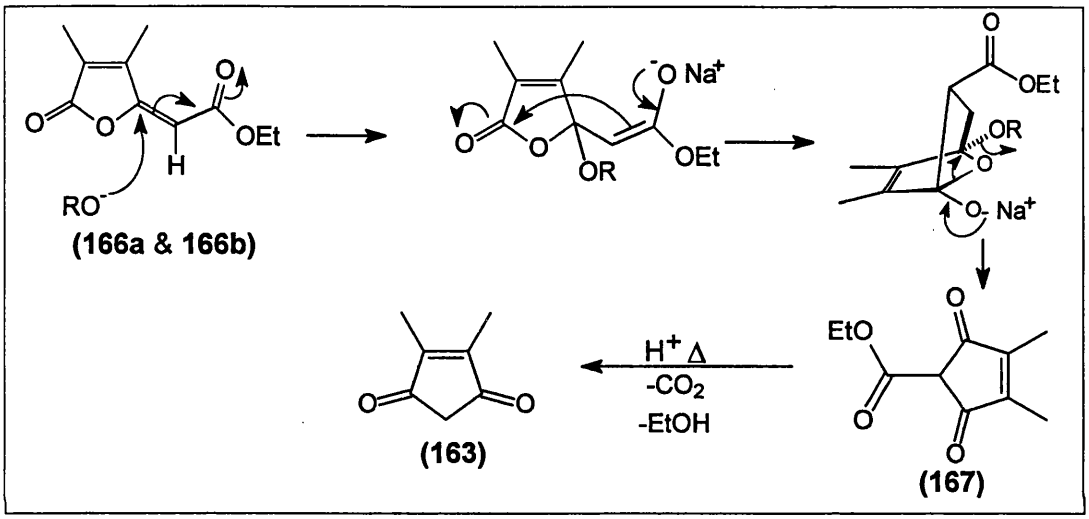
	% Yield of *E / Z*	DiWittig %	*Trans : Cis*
Ethyl acetate	52	5	3 : 2
Tetrahydrofuran	69	3	1 : 1
Toluene	76	0	3 : 2
Dichloromethane	65	2	3 : 2
Surfactant / water	52	9	2 : 3

The reactions proceeded in moderate to good yields, 50 -76 % (overall yield was based on combined yield of both *trans / cis* geometric isomers (**166a** & **166b**). The *trans* (**166a**) / *cis* (**166b**) ratio was obtained from the ^{1}H NMR spectrum. Toluene gave the highest combined yield of 76 % with a ratio of isomers *trans / cis*, 3 : 2) with no diWittig (**166c**) product being detected. The two geometric isomers had very different physical properties, (**166a**) was a colourless oil with a R_f of 0.45 in 7 : 1 petroleum spirits 40 - 60° C / ethyl acetate, where as (**166b**) was isolated as a waxy-solid, with a corresponding R_f of 0.75. The NMR ^{13}C signals also showed significant differences.

The use of a surfactant solution (CTAB) was found to give the highest *cis* olefin geometry in moderate combined yield of 52 % (*trans : cis*, 2 : 3) with the diWittig product (**166c**) formed in approximately 9 % yield. However, a notable amount of hydrolyzed anhydride was detected, approximately 10 %. A general trend was observed whereby the more polar the solvent the higher the quantity of the diWittig product (**166c**) formed.

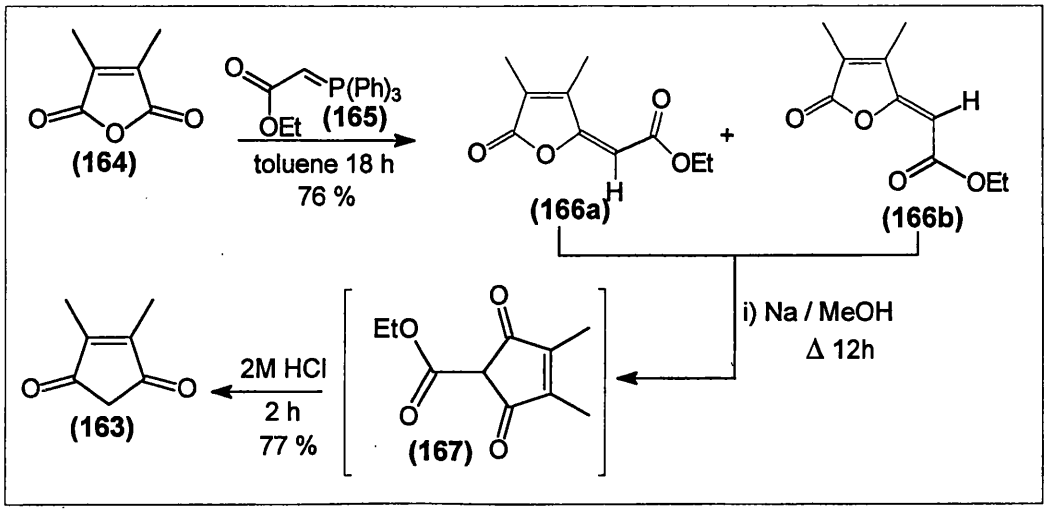
The lactones (**166a** & **166b**) underwent a base catalyzed intramolecular rearrangement to give a tricarbonyl species (**167**) (Scheme **5.05**). It was noted that sodium methoxide gave a higher yield, 81 %, of the tricarbonyl compound (**167**) as compared to sodium ethoxide, which only gave 71 %. This may be attributable to the higher nucleophilic nature of methoxide ions as compared to ethoxide.[118]

Mechanism of the based catalyzed intramolecular rearrangement **Scheme 5.05**



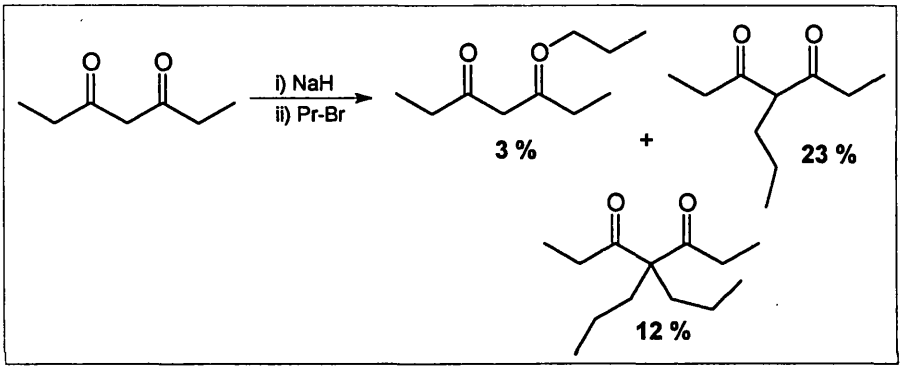
An orange precipitate was isolated by filtration, washed with dilute hydrochloric acid and then heated for a further 2 hours. This ensured that all of the tricarbonyl material had been decarboxylated to give an almost quantitative conversion to diketone (**163**). The overall yield of the diketone (**163**) from the anhydride (**164**) was 59 % (Scheme **5.06**).

Summary of synthetic route to key diketone (**163**) *intermediate* **Scheme 5.06**



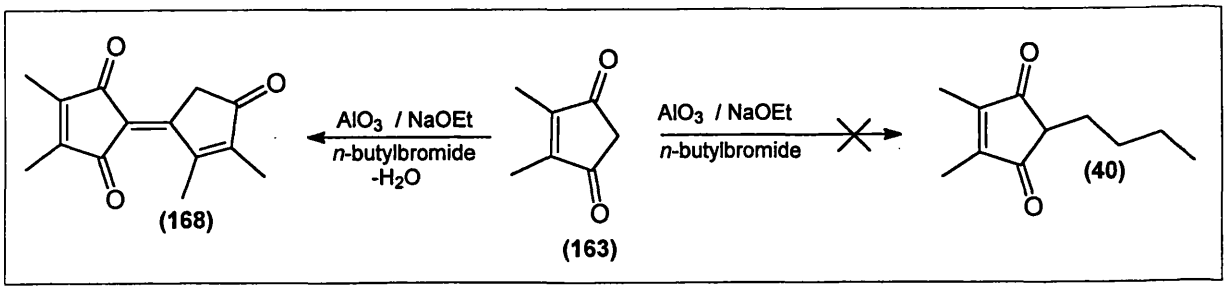
Selective C-alkylation of 1,3 dicarbonyl compounds, having two active hydrogen atoms, has often been a problem using conventional methods of protons abstraction / alkylation. This is because other side reactions can predominate; e.g. *O*-alkylation, di*C*-alkylation and Claisen condensations. Generally poor yields of the mono alkylated product are obtained, with significant mixtures of the dialkylated product and starting material. Scheme **5.07** shows the result of the alkylation of hepta-1,3-dione reported by Johnson.[119]

Example showing alkylation of diketone systems using conventional techniques **Scheme 5.07**



The selective monoalkylation of similar systems have been reported, by performing the reaction on the surface of alumina impregnated with sodium ethoxide.[120] When these alkylation conditions were tried with the diketone, a deep red colour formed (indicating proton abstraction and anion formation), which remained when 1-bromobutane was added to the reaction. The diketone (**163**) was recovered in 20 % yield together with polymeric material and a white solid resembling the self-condensation product of the diketone (**168**) (confirmed by ^{1}H NMR and mass spectroscopy). No mono-alkylated material was detected (Scheme **5.08**).

Alkylation using solid phase / sodium ethoxide technique **Scheme 5.08**

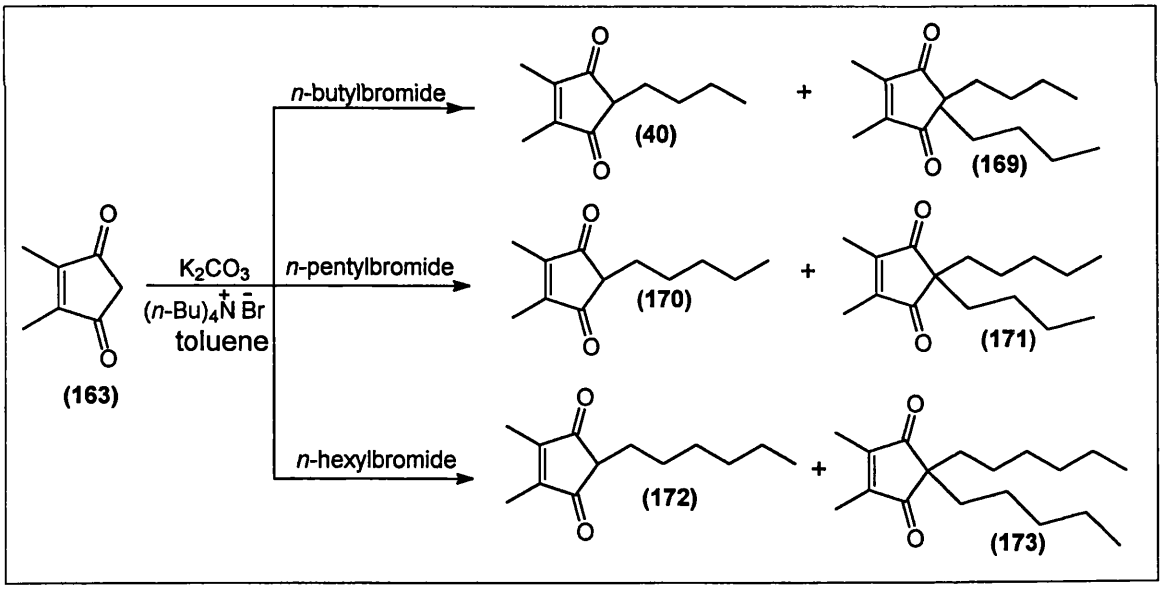


A bi-phasic mono-alkylation procedure was then explored. This involved the use of potassium carbonate and *n*-tetrabutylammonium bromide as the phase transfer catalyst.[121] The diketone (**163**) was first heated in the presence of base (4.5 equiv) in toluene and the phase transfer catalyst for 2 hours before the alkyl halide was added, this produced the mono and dialkylated products in a ratio of 5 : 1 in a moderate yield of 56 % based on consumed diketone (**163**). Various conditions were tried, including increasing the reaction time and reducing the amount of base, which only resulted in an increase in the amount of dialkylated material formed.

5.4 iii) The synthesis of various calythrone analogues

The corresponding pentyl and hexyl mono- and dialkylated materials were also synthesised using this alkylation procedure and they were also isolated in similar proportions to those obtained with the butyl compound (Scheme **5.09**).

Summary of the calythrone analogues synthesised **Scheme 5.09**



We noted that the pentyl mono-alkylated diketone (**170**) possessed a much weaker jasmine odour than the corresponding butyl material (**40**) and the corresponding hexyl mono-alkylated diketone (**172**) was odourless. The dialkylated materials (**169**, **171** & **173**) had weak buttery / fatty odour characteristics.[122]

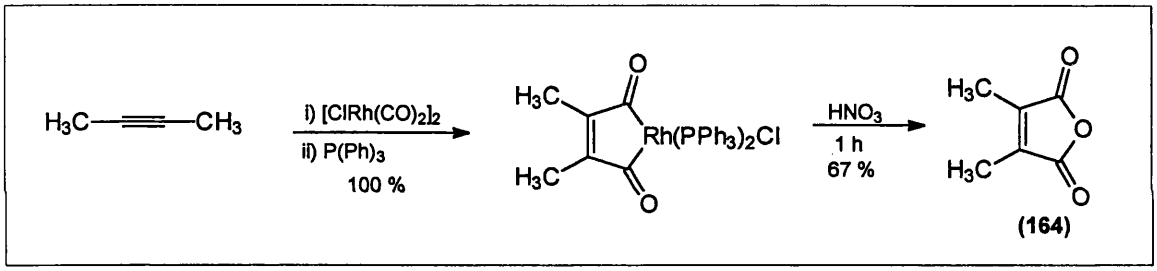
The problems associated with this route were cost and feasibility. The 2,3-dimethylmaleic anhydride is nearly £10 / gram and the fact that the alkylation was not as

selective as one would like poses a substantial problem for larger scale preparations. To reduce the cost of the synthesis it was therefore decided to explore synthetic routes to 2,3-dimethylmaleic anhydride. The routes explored are outlined below.

5.5 iv) Synthetic strategies to dimethylmaleic anhydride (164)

A search in the literature for preparations of dimethylmaleic anhydride (**164**) highlighted Maitlis's route. He reported a costly procedure which involved the complexation of alkynes with Rh(I). This has led to high yields of the disubstituted maleic anhydrides by nitric acid oxidation of the rhodacyclopentenedione[123] (Scheme **5.10**).

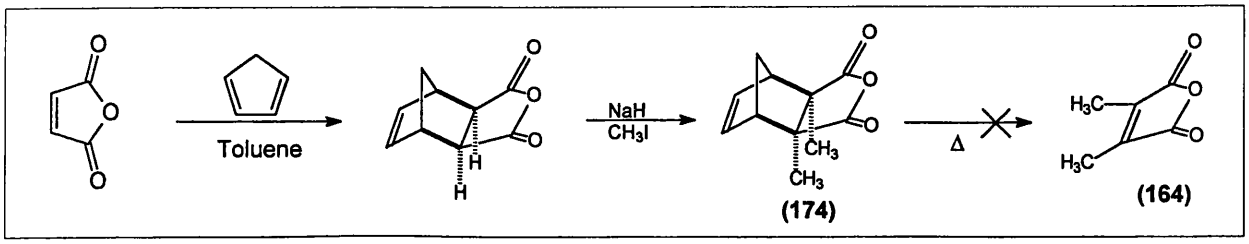
Malitis's synthetic route to dimethylmaleic anhydride (**164**) **Scheme 5.10**



5.6 Alternative approaches to 2,3-dimethylmaleic anhydride (164)

We explored a couple of alternative routes that we envisaged might generate the required anhydride. The first involved the preparation of 2,3-dimethylmaleic anhydride from maleic anhydride. Maleic anhydride was stirred with freshly cracked cyclopentadiene in toluene at 0 °C to afford a white crystalline solid. The Diels-Alder cycloadduct was then treated with sodium hydride (2.2 equiv) and methyl iodide (2.5 equiv) to form the dimethylated anhydride (**174**) (yellow foam) in 19 % yield (Scheme **5.11**).

Synthetic plan to 2,3-dimethylmaleic anhydride (**164**) **Scheme 5.11**

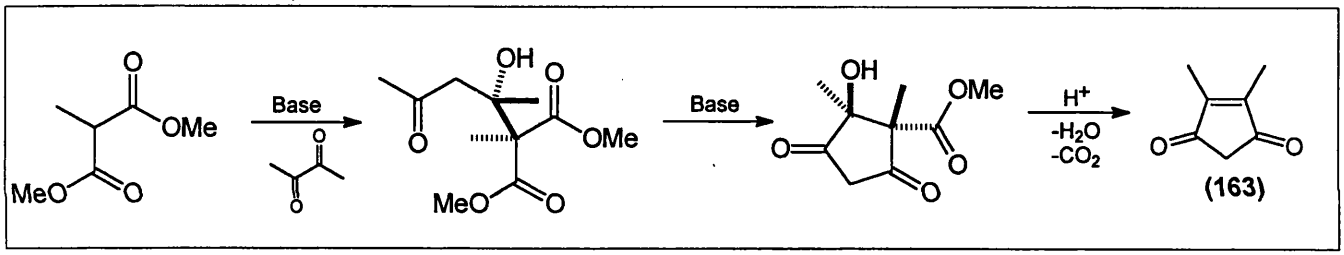


Since the Diels-Alder reaction is reversible, we planned to use this property to force a retro Diels-Alder reaction on the dialkylated anhydride (**174**). The dimethylated anhydride was heated neat for several hours. Results from these experiments showed that the retro Diels-Alder had not proceeded, but instead, the anhydride had broken down.

5.7 Alternative synthetic equivalent to 2,3-diemthylmaleic anhydride

We also looked at a one step condensation approach between methyldiethyl malonate and 2,3-butanedione (Scheme **5.12**). The initial alkylation was performed using a variety of different bases. However, it was noted that 2,3-butanedione readily underwent self polymerization.

Synthetic outline to diketone (**163**) **Scheme 5.12**



It was later apparent that the malonate anion generated was acting competitively as a base as well as a nucleophile, readily deprotonating the α-protons of 2,3-butadione rather than nucleophilically attacking the electrophilic carbonyl as desired.

It was clear that the synthesis of 2,3-dimethylmaleic anhydride (**164**) was not going to be straightforward and therefore we investigated an alternative synthetic route utilizing a novel approach.

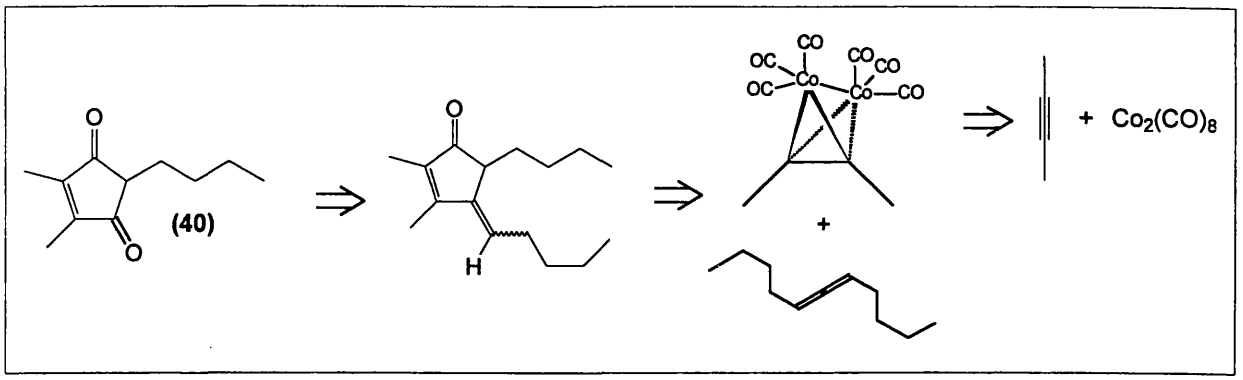
5.8 v) Pauson-Khand reaction, synthetic route to cyclopentanones

The novel synthetic route investigated involved using the Pauson-Khand reaction.[124] The Pauson-Khand reaction features an intermolecular cobalt-mediated co-cyclisation of alkynes and alkenes in the presence of carbon monoxide to produce 2-cyclopentanone derivatives. This has emerged as an important five-membered ring forming reaction. A more recent observation by Cazes has shown that allenic compounds can also participate as an 'olefinic' equivalent in the Pauson-Khand reaction.[125]

5.9 Synthetic plan to calythrone analogue (40)

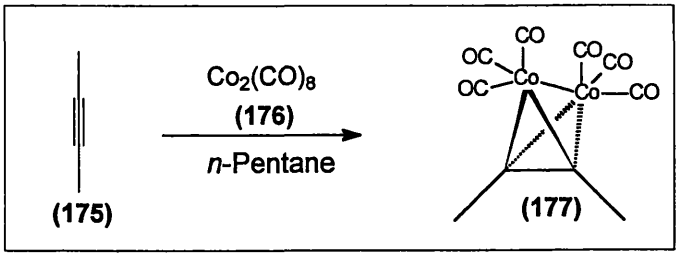
A retrosynthetic analysis of the calythrone highlighted such a synthetic route using the Pauson-Khand reaction to produce a 4-alkylidene-2-cyclopentenone from a dicobalt hexacarbonyl alkyne complex and dialkylallene. Selective olefinic cleavage would then result in the formation of the desired calythrone analogue (**40**) (Scheme **5.13**).

Retrosynthetic analysis to calythrone analogue (**40**) **Scheme 5.13**



But-2-yne (**175**) was stirred with dicobalt octacarbonyl[126] (**176**) in pentane at 0 °C to form the dicobalthexacarbonylbut-2-yne complex (**177**) in almost quantitative yield (Scheme **5.14**). It was important for the reaction to be fitted with a cold trap since the alkyne had a boiling point of 19-20 °C. The brown-orange waxy solid product (**177**) was carefully dried at 25 °C / (50 mm) and stored under argon. At a higher vacuum, decomposition of the dicobalt complex (**177**) was observed.

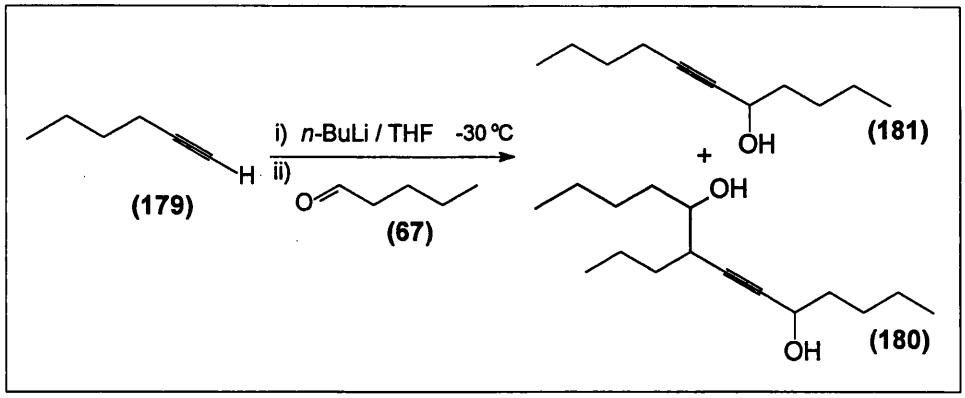
Complexation of but-2-yne (**175**) *with dicobalt carbonyl* (**176**) **Scheme 5.14**



5,6-undecadiene(**178**), required for the Pauson-Khand reaction, was synthesized *via* the alkylation of hex-1-yne (**179**) with *n*-valeraldehyde (**67**). Initially 1-hexyne (**179**) was deprotonated with *n*-butyllithium at -78 °C in tetrahydrofuran and allowed to warm to

-30 °C, however when the aldehyde (**67**) was added several products were isolated, including the diol (**180**) (Scheme **5.15**).

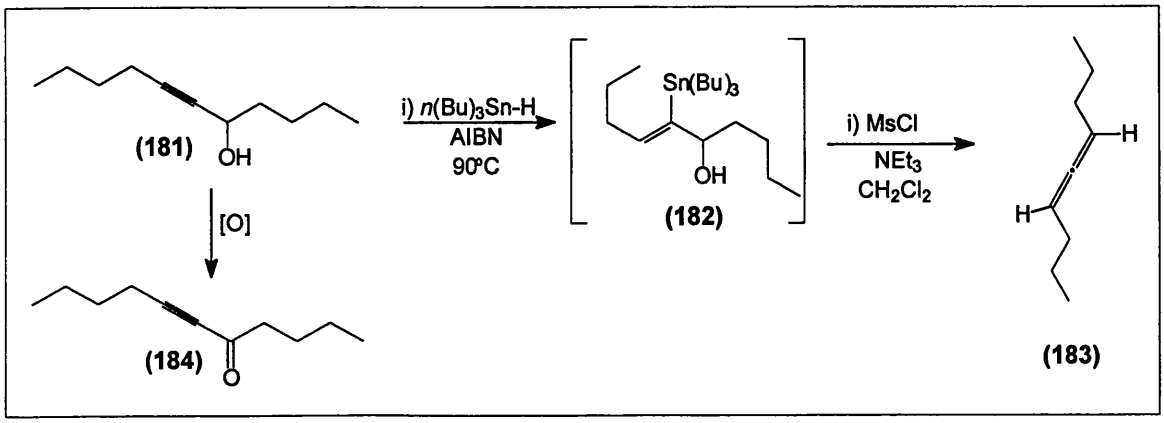
Alkylation of 1-hexyne (**179**) *with n-valeraldehyde* (**67**) **Scheme 5.15**



It was possible that the acetylenic anion generated was acting as a base for the deprotonation of propargylic protons resulting in the formation of allenes and di alkylated material. The reaction was therefore repeated at a lower temperature of -55 °C and this afforded the hydroxyalkyne (**181**) in high yield, 89 %. The hydroxy alkyne (**181**) was then heated with tributyltin hydride[127] and the free radical initiator AIBN for several hours which gave a regiospecific hydrostannylation product (**182**). The stannyl alcohol (**182**) was then converted to the mesylate, which underwent spontaneous elimination to form 5,6-undecadiene(**183**) (Scheme **5.16**).[128]

Purification of the allene (**183**) was not straightforward due to the presence of an organotin residue. This was overcome by distillation at reduced pressure to afford a colourless oil. The temperature was kept below 60 °C to ensure minimal loss of the allene (**183**) by polymerization.

Synthetic scheme to 5,6-undecadiene(**183**) **Scheme 5.16**



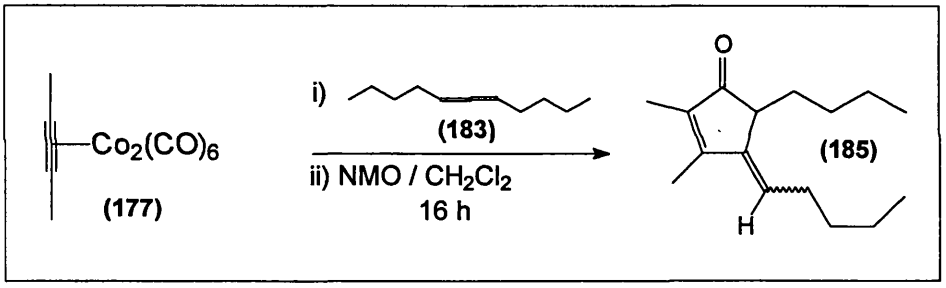
The hydroxyalkyne (**181**) was also found to undergo ariel oxidation to the corresponding ketone (**184**). This material had a pleasant pineapple odour and was sent to Bush Boake Allen for further fragrance analysis.

5.10 Cobalt-mediated co-cyclisation of 5,6-undecadiene

The Pauson-Khand reaction is usually undertaken under a carbon monoxide atmosphere, however Cazes[125] has also shown that a carbon monoxide atmosphere is not required if excess of *N*-methylmorpholine *N*-oxide is used. It is thought that carbon monoxide liberated by the dicobalt complex is sufficient for the co-cyclisation reaction (Scheme **5.17**).

The 4-alkylidene-2-cyclopentenone (**185**) was isolated in 67 % yield as a mixture of geometric isomers.

The Pauson-Khand reaction **Scheme 5.17**

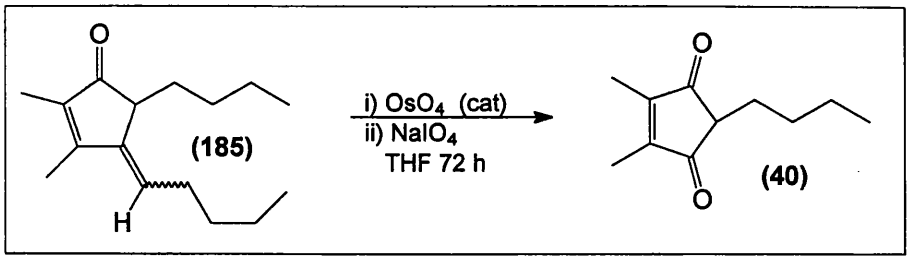


5.11 Selective oxidative cleavage of the multifunctional olefin (185)

Working upon the basis that tetrasubstituted olefins are sterically hindered along with the fact that exocyclic olefins are normally more reactive than endocyclic olefins, we anticipated high selectivity in the oxidation of the trisubstituted olefin to afford the calythrone analogue (**40**).

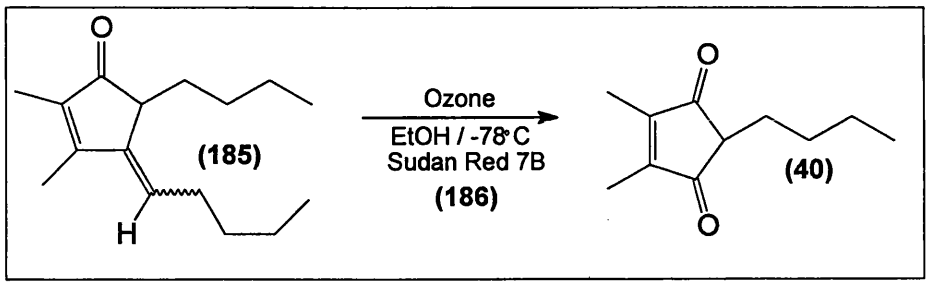
We initially tried a catalytic osmium tetraoxide / sodium periodate oxidation procedure.[129] This was performed under various conditions but only lead to selectively, the calythrone analogue (**40**) in an isolated 27 % yield. Several other side reactions were also taking place including the oxidative cleavage of the tetrasubstituted olefin (Scheme **5.18**).

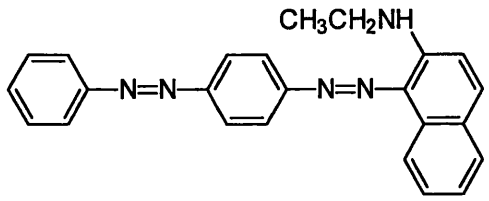
Cleavage of trisubstituted olefin with osmium tetraoxide / periodate **Scheme 5.18**



An alternative selective oxidation method was then investigated, which comprised of the use of azo-dyes with ozone. Ozonolysis of multifunctional olefins are known to proceed with a degree of chemoselectivity, especially if the alkene is connected to electron-donating / withdrawing groups. Since the two olefins present in ketone (**185**) are appreciably different, it is important to monitor the extent of the reaction. Azo-dyes[93] have been used in conjunction with ozone to serve as markers during the ozonolysis of such multifunctional olefins. The ozone reacts with the more electron rich trisubstituted olefin first before it starts oxidizing the azo-dye and then attacking the electron deficient tetrasubstituted alkene. Once the dye is oxidized it loses its conjugation and hence colour, indicating the end point of the reaction (Scheme **5.19**).

Selective ozonolysis of trisubstituted olefin (**185**) *to calythrone analogue* (**40**) **Scheme 5.19**





Sudan Red 7B (**186**)

Sudan Red 7B (**186**) (also known as solvent red 19) served as an excellent marker for the trisubstituted and tetrasubstituted olefins. The use of this oxidative

procedure gave rise to the calythrone analogue (**40**) in an isolated yield of 87 % from the multifunctional olefin (**185**).

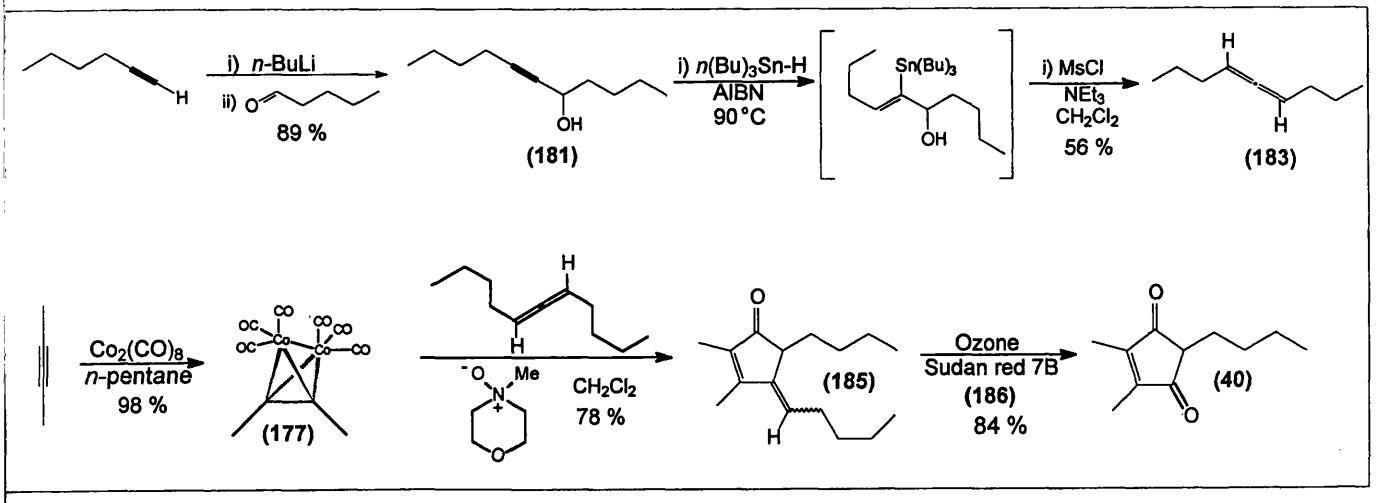
5.12 vi) Summary

Overall, we managed to improve on the first explorative route to the calythrone analogue (**40**) by optimizing several reactions. The Wittig reaction was found to give a good overall yield of the geometric isomers with only a small amount of diWittig product (**166c**) being isolated. The rearrangement was also improved by using sodium methoxide as opposed to sodium ethoxide, attributable to the more nucleophilic character of sodium methoxide.

The bi-phasic alkylation procedure offered a good alternative approach, which produced the alkylated diketone (**40**) in similar yields to the Bush Boake Allen route. Attempts to synthesise dimethylmaleic anhydride synthesis proved unfruitful. It was this that prompted investigations into a novel approach.

The Pauson-Khand reaction was utilized to construct the carbocyclic ring that underwent selective olefinic cleavage, using an azo-dye as a marker in ozonolysis. This afforded the calythrone analogue in an overall yield of 59 % over three steps. This method can also be adapted to synthesize the pentyl and hexyl diketones (**170** & **172**) by preparing the corresponding allenes using a similar procedure to that used to prepare 5,6-undecadiene (**183**) (Scheme **5.20**).

Summary of novel synthetic route to calythrone analogue (**40**) **Scheme 5.20**



Chapter Six

Experimental Section

General Procedures

^{1}H NMR spectra were recorded at 400 MHz on a Varian VXR-400 instrument or, unless stated, at 200 MHz on a Varian XL-200 instrument. ^{13}C NMR spectra were recorded at 100.6 MHz on a Varian VXR-400 instrument. Residual protic solvent was taken as internal standard, with $CDCl_3$ as solvent unless otherwise stated, stored over 4 Å molecular sieves and filtered through a pad of basic alumina prior to use.

Infra Reds were recorded as thin films on sodium chloride plates or as potassium bromide disks on a Perkin-Elmer FT-IR 1605 instrument. All peaks quoted are medium, unless otherwise stated.

Mass spectra measurements were recorded by electron impact (EI) studies with an Autospec Q, VG 7070 or VG 7070B instrument, unless fast atom bombardment (FAB) is stated, in which case a ZAB-SE instrument was used.

Optical rotations were taken with a POLAAR 2000, instrument by Optical Activity Ltd. and are given in the units 1 0^{-1}deg.CM^2.g^{-1}.Melting points were taken on a Reichert hot stage and are uncorrected.

Petrol refers to light petroleum boiling in the range 40-60°C which was distilled prior to use as a chromatography eluent. Ether refers to diethyl ether, used as received for this purpose, as were ethyl acetate, methanol and dichloromethane. For use as reaction solvents ether, tetrahydrofuran and benzene were freshly re-distilled under dry nitrogen from sodium benzophenone-ketyl and toluene from molten sodium. Dichloromethane was freshly re-distilled from phosphorous (V) oxide. Chlorobenzene and 1,2-dichloroethane were re-distilled from phosphorous (V) oxide and stored over 4 Å molecular sieves. Methanol was distilled from magnesium turnings and stored over 3 Å molecular sieves. Unless otherwise stated 'ethanol' refers to absolute ethanol (>99.7%) and was used as received. Dimethyl sulfoxide and phosphorous trichloride were distilled under reduced pressure and stored over 4 Å molecular sieves. Trimethylsilyl chloride was freshly re-distilled from calcium hydride. Triethylamine, diisopropylamine and pyridine were distilled from and stored over potassium hydroxide. Acetic anhydride was distilled under reduced pressure from magnesium powder and flushed through phosphorous (V) oxide prior to use.

Analytical thin layer chromatography was performed on pre-coated glass backed plates (Merck Kieselgel 60 F_{254}) and visualized with ultraviolet light (254nm), iodine, potassium permanganate [add 62.5g Na_2CO_3 in water (1.25 litre) to 12.5 g $KMnO_4$ in water (1.25 litre)], acidic ammonium molybdate (IV) [conc. H_2S0_4 (25 ml), ammonium molybdate tetrahydrate (10.0 g), water (250ml)], or vanillin [vanillin (2.4 g), conc. H_2SO_4 (2.5 ml), ethanol (100 ml), stored in the dark], or anisaldehyde [*p*-anisaldehyde (10.0 g) to ethanol (99.7 %, 500 ml), (conc. H_2SO_4 (10 ml), glacial acetic acid (10 ml)] as appropriate.

Preparative column chromatography was performed at low positive pressure on Merck Kieselgel 60. Enantioselectivites were determined by chiral phase HPLC using a Gilson Model M303, using dynamic mixers models M802 & M811 with a 25cm x 5 mm Chiralcel columns, using a Bischoff RI 8110 refractive detector coupled to a Hewlett Packard Integrator model HP3396A. Solvents used were HPLC grade and were degassed prior to use. Microanalysis was carried out by Alan Stone at UCL.

Reactions were carried out under a nitrogen atmosphere with freshly distilled solvents using Schlenk-line techniques and glassware (oven dried or flame dried). The Schlenk - line was served by a two-stage rotary oil pump and an on-line vacuum maintained at 0.01 and 0.05 mbar, unless otherwise noted. All solvents were reagent grade.

Commercially obtained solutions of *n*-butyllithium were quantified by direct titration with *N*-pivaloyl-*O*-toluidene before use as described:

Titration of organolithium reagents

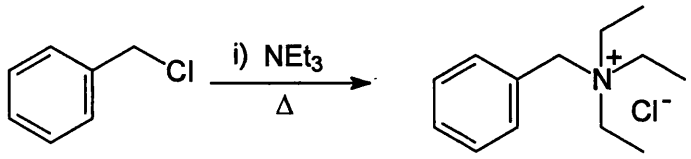
A 25 ml round bottomed flask fitted with a septum and containing a magnetic stirrer was evacuated and flushed with nitrogen. Approximately (250-380 mg) (0.9-2.0 mmol) of the *N*-pivaloyl-O-toluidine was charged into the flask. Anhydrous THF (5 ml) was added, and a white sheet of paper placed behind the flask. The organolithium solution was added from a 1 ml Hamilton gas tight syringe. The solution was rapidly stirred the end point being reached when the colourless solution turned yellow. Triplicate analyses were performed in all cases.[130]

Preparation of lithium perchlorate-diethyl ether solutions

Lithium perchlorate-diethyl ether solutions were prepared from commercial lithium perchlorate trihydrate (obtained from the Aldrich chemical company). The

reagent was dried at 150° C / 0.1 mbar for 48 hours in the presence of phosphorous pentoxide. The dried perchlorate was then added to dried diethyl ether in small portions with vigorous stirring to give the desired concentration of lithium perchlorate.[131]

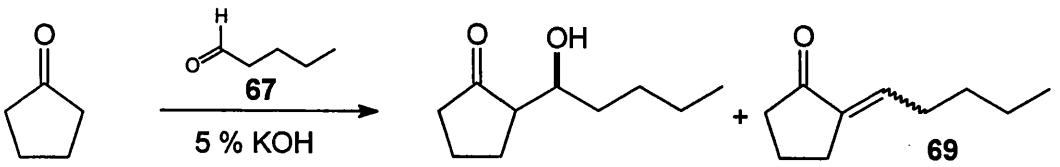
Preparation of benzyl triethylammonium chloride (BTEAC)



To freshly distilled benzyl chloride (20.0 ml, 173.6 mmol), was added triethylamine (24.2 ml, 173.6 mmol) dropwise and the reaction heated to 90°C for 18 h. A white solid formed, which was cooled to rt and washed with diethyl ether (3 x 50 ml). The resulting white solid was then dried in a vacuum at (90° C) (2mmHg) for 24 h. The title compound was isolated as a white powder (32.2 g, 81 %).

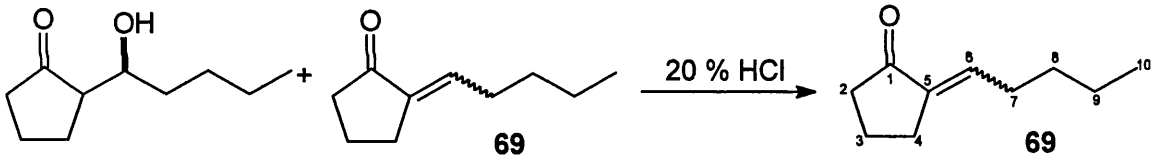
Methyl dihydrojasmonates

R1 **2-[(*E* / *Z*)pentylidene]-1-cyclopenanone (69)**



To a solution of potassium hydroxide (2.81 g, 50.1 mmol) in water (112 ml) at 0 °C was added a premixed solution of cyclopentanone (**66**) (8.41 g, 100 mmol) and *n*-valeraldehyde (**67**) (86.1 g, 100 mmol) over 40 min. The reaction was warmed to rt and stirred for a further 3 h before acetic acid (3.00 ml, 52.4 mmol) was added. The reaction mixture was extracted with ethyl acetate (3 x 40 ml), dried (Na_2SO_4) and concentrated. The mixture was taken forward to dehydration step without purification.

N.B. Spectral analysis indicated the crude material contained a mixture of aldol and aldol-condensation products.



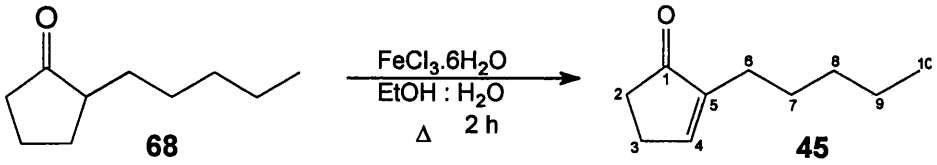
The aldol mixture (13.7 g) was added to hydrochloric acid (2.8 N, 100 ml) and the reaction heated at reflux for 3 h. The dark red reaction mixture was cooled to rt and diluted with diethyl ether (80 ml) and sodium hydrogencarbonate solution (5 %, 30 ml). The mixture was then extracted with diethyl ether (3 x 50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by reduced pressure distillation, to yield the title compound (10.9 g, 72 %) as a colourless oil.

N.B. Strong orange -fruity odour.

Bp 64-65 °C (1.0 mm); υ_{max} (NaCl; neat) / cm^{-1} 2931 (s), 2859 (s), 1710 (s), 1637 (w), 1457 (w); δ_H (400 MHz; $CDCl_3$), 0.89 (3 H, t, *J* 7.2 Hz, 10-H). 1.35 (2 H, m, 9-H), 1.43 (2 H, m, 8-H), 2.14 (2 H, m, 3-H), 2.32 (2 H, m, 2-H), 2.57 (2 H, m, 7-H), 3.86 (2 H, m, 2-H), 7.27 (1 H, m, 6-H); δ_C(100 MHz; $CDCl_3$), 13.89 (C-10), 19.83 (C-9), 22.97 (C-8), 26.74, 29.40, 30.51, 38.65, 136.40 (C-5), 137.20 (C-6), 207.31 (C-1); *m/z* (EIMS), 152

(M^+, 75 %), 137 (M^+ -CH_3, 10), 123 (M^+ -CH_2CH_3, 40), 109 (M^+ -$CH_2CH_2CH_3$, 30), 95 (M^+ -$CHCH_2CH_2CH_3$, 20); *m/z* (EIMS) Found for $C_{10}H_{16}O$ (M^+) 152.1233; Required 152.1231.

R2 **2-Pentyl-2-cyclopenten-1-one (45)**

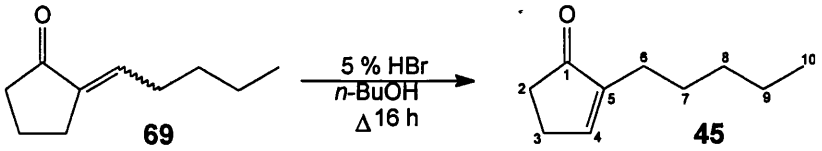


68 45

To a stirred solution of 2-pentyl-2-cyclopentanone (**68**) (10.0 g, 64.1 mmol) in ethanol (97 %,150 ml) and water (4 ml) was added iron (III) trichloride hexahydrate (52.1 g 320 mmol). The reaction was heated at reflux for 2 h. The reaction was cooled to rt and concentrated *in vacuo*. The brown sludge was then diluted with pentane (150 ml) and heated to reflux for a further 1 h. The reaction was cooled to rt and the phases separated. The aqueous layer was extracted with dichloromethane (3 x 30 ml), the combined organic layers were washed with hydrochloric acid (4 N, 100 ml) and then with sodium carbonate solution (5 %, 30 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown oil (9.52 g). The oil was subjected to flash chromatography (eluent : petroleum spirits 40-60 °C / ethyl acetate, 25 : 1). The product was isolated as a colourless oil (4.12 g), and the starting material, 2-pentyl cyclopentanone was recovered (3.52 g, 22.7 mmol). The overall yield based on consumed material was 65 %.

Bp 126 -126 °C (5 mm); υ_{max} (NaCl; neat) / cm^{-1} 2929 (s), 2859 (s), 1705 (s), 1632 (w), 1458 (w); δ_H (400 MHz; $CDCl_3$), 0.85 (3 H, t, *J* 7.0 Hz, 10-H). 1.27 (4 H, m, 9-H, 8-H), 1.44 (2 H, m, 7-H), 2.12 (2 H, m, 6-H), 2.36 (2 H, m, 3-H), 2.56 (2 H, m, 2-H), 7.27 (1 H, m, 4-H); δ_C (100 MHz; $CDCl_3$), 14.00 (C-10), 22.44 (C-9), 24.73 (C-8), 26.43 (C-7), 27.43 (C-6), 31.59 (C-3), 34.60 (C-2), 146.51 (C-4), 157.30 (C-5), 210.08 (C-1); *m/z* (EIMS), 152 (M^+, 100 %), 137 (M^+ -CH_3, 60), 123 (M^+ -CH_2CH_3, 76), 109 (M^+ -$CH_2CH_2CH_3$, 40), 96 (M^+ - $CHCH_2CH_2CH_3$, 55); *m/z* (EIMS) Found for $C_{10}H_{16}O$ (M^+) 152.1236; Required 152.1231.

R3 **2-Pentyl-2-cyclopenten-1-one (45)**

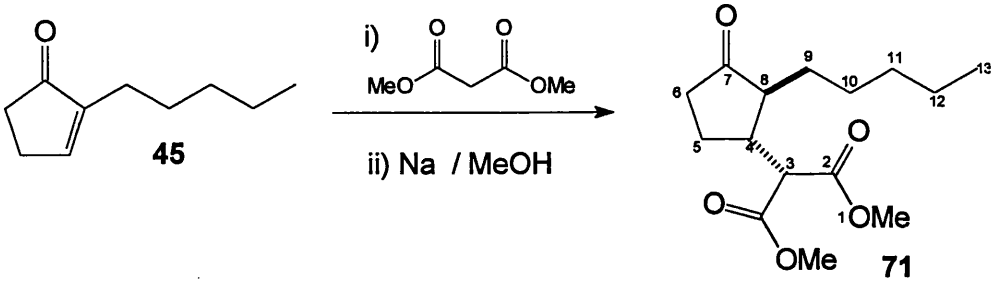


69 **45**

To a solution of cyclopentenone (**69**) (10.00 g, 65.8 mmol) in *n*-butanol (200 ml), was added hydrobromic acid (36 %, 5 ml). The reaction was heated at reflux for 16 h. The reaction was cooled to rt, neutralised by the addition of dilute sodium hydrogencarbonate (5 %, 20 ml) and diluted with brine (150 ml). The mixture was extracted with ethyl acetate (4x 50 ml). The combined organics were dried ($MgSO_4$) and reduced *in vacuo* to afford a pale yellow oil. The oil was purified by reduced pressure distillation to yield the title compound as a colourless oil (7.26g, 73 %).

Bp 126 -126 °C (5 mm); υ_{max} (NaCl; neat) / cm^{-1} 2929 (s), 2859 (s), 1705 (s), 1632 (w), 1458 (w); δ_H (400 MHz; $CDCl_3$), 0.85 (3 H, t, *J* 7.0 Hz, 10-H). 1.27 (4 H, m, 9-H, 8-H), 1.44 (2 H, m, 7-H), 2.12 (2 H, m, 6-H), 2.36 (2 H, m, 3-H), 2.56 (2 H, m, 2-H), 7.27 (1 H, m, 4-H); δ_C (100 MHz; $CDCl_3$), 14.00 (C-10), 22.44 (C-9), 24.73 (C-8), 26.43 (C-7), 27.43 (C-6), 31.59 (C-3), 34.60 (C-2), 146.51 (C-4), 157.30 (C-5), 210.08 (C-1); *m/z* (EIMS), 152 (M^+, 100 %), 137 (M^+ -CH_3, 60), 123 (M^+ -CH_2CH_3, 76), 109 (M^+ -$CH_2CH_2CH_3$, 40), 96 (M^+ - $CHCH_2CH_2CH_3$, 55), found for $C_{10}H_{16}O$ (M^+) 152.1236; Required 152.1231.

R4 **Dimethyl 2-[(1*R**,2*R**)-3-oxo-2-pentylcyclopentyl]malonate (71)**



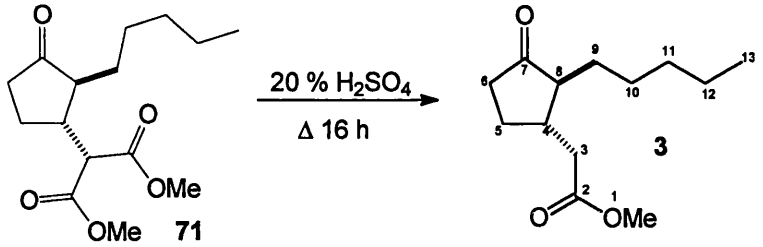
45 **71**

To a solution of dimethyl malonate (**70**) (1.04 g, 7.88 mmol), in dry methanol (3 ml) was added sodium (18 mg, 0.79 mmol). The reaction mixture was cooled to -5° C and 2-pentyl-2-cyclopenten-1-one (**45**), (1.00 g, 6.57 mmol) was added over 40 min. The reaction was then stirred for a further 1 h at -5 °C. Acetic acid (0.1 ml) was then added and the reaction warmed to rt. The reaction was diluted with water (5 ml) and the

aqueous layer extracted with ether (3x 30 ml). The combined organic extracts were washed with diluted sodium hydrogen carbonate solution (5 %, 20 ml) and then dried ($MgSO_4$). The filtrate was concentrated *in vacuo* to afford a yellow oil. The oil was purified by flash chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 15 : 1) to yield the title compound as a colourless oil (1.12 g, 65 %).

υ_{max} (NaCl; neat) / cm^{-1} 2953 (s), 2856 (m), 1738 (s); δ_H (400 MHz; $CDCl_3$), 0.85 (3 H, t, *J* 7.0 Hz, 13-H), 1.31 (6 H, m, 12-H, 11-H, 10-H), 1.56 (2 H, m, 5-H), 1.69 (1 H, m, 9-H), 2.01 (1 H, m, 4-H), 2.16 (3 H, m, 6-H, 8-H), 2.32 (1 H, m), 2.63 (1 H, m), 3.49 (1 H, d, *J* 7.4 Hz, 3-H), 3.73 (3 H, s, OCH_3), 3.74 (3 H, s, OCH_3), δ_C(100 MHz; $CDCl_3$), 13.97, 22.40, 24.41, 25.91, 28.34, 31.97, 37.21, 40.27, 52.01, 52.45, 54.44, 168.36 (CO_2CH_3), 168.70 (CO_2Me), 218.88 (C-7); *m/z* (EIMS) 284 (M^+, 1 %), 153 (M^+ -OCH_3, 1), 227 (M^+ -*n*-Bu, 1), 214 (M^+ -*n*-Pent, 9), 153 (M^+ -$HC(CO_2CH_3)$ 67), 133 ($HC(CO_2CH_3)_2$, 100), 83 (M^+ - $HC(CO_2CH_3)_2$ -*n*-Pent, 70); Found for $C_{15}H_{24}O_3$ (M^+) 284.1610; Required 284.1624.

R5 **Methyl 2-[(1*S**,2*S**)-3-oxo-2-pentylcyclopentyl]acetate (3) [Methyl dihydrojasmonate]**

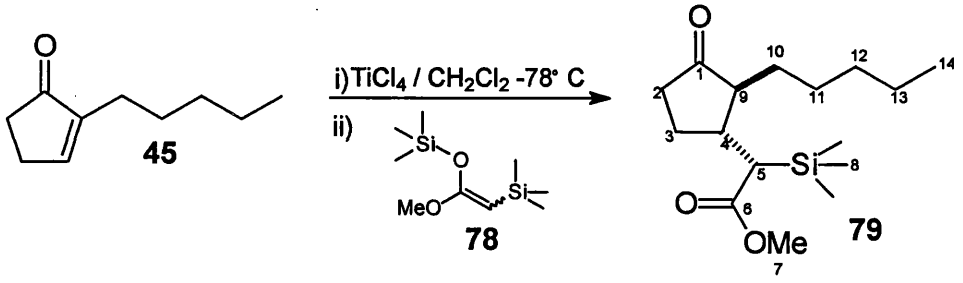


A solution of diester (**71**) (285 mg, 1.0 mmol), in sulfuric acid (20%, 30 ml) was heated at reflux and stirred for 48 h. The reaction was cooled and neutralised with dilute sodium hydrogencarbonate (50 ml) and the reaction mixture was extracted with ethyl acetate (5x 30 ml), combined, and dried ($MgSO_4$) and concentrated *in vacuo.* The crude oil was dissolved in methanol (50 ml), sulfuric acid (1 ml) was added and the reaction was heated for a further 2 h at reflux. The reaction mixture was concentrated *in vacuo* to give a colourless oil. The crude oil was purified by flash chromatography, (eluent: petroleum spirits 40-60 °C / ethyl acetate, 25:1). The title compound as a colourless oil (34 mg, 15 %).

N.B. sweet jasmine odour.

υ_{max} (NaCl; neat) / cm^{-1} 2928 (m), 2896 (s), 1725 (s), 1716 (m); δ_H (400 MHz; $CDCl_3$), 0.87 (3 H, t, *J* 7.1 Hz, 13-H), 1.26 (4 H, m, 11-H, 12-H), 1.52 (2 H, m, 10-H), 1.79 (2 H, m, 9-H), 2.22 (6 H, m, 6-H, 5-H, 4-H, 8-H *overlap*), 2.63 (2 H, m, 3-H), 3.70 (3 H, s, 1-H); δ_C (100 MHz; $CDCl_3$), 14.07 (C-13), 22.50 (C-12), 26.35 (C-11), 27.25, 27.84, 32.12, 37.73, 38.09, 39.96, 51.67, 54.24 (C-1), 172.68 (C-2), 219.73 (C-7); *m/z* (EIMS) 226 (M^+, 15 %), 195 (M^+-OCH_3, 15), 153 (M^+- CO_2Me, 45) 96 (M^+ -CO_2Me, -*n*-Bu, 100), found for $C_{13}H_{22}O_3$ (M^+) 226.1569; Required 226.1560;

R6 Methyl (2*R**)-2[(1*R**,2*R**)-3-oxo-2-pentylcyclopentyl]-2-(1,1,1-trimethylsilyl) ethanoate (79)

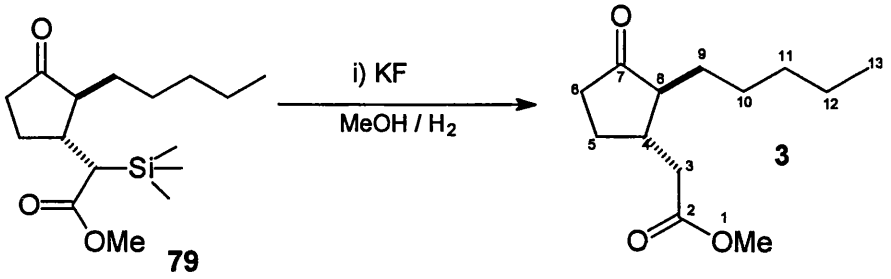


To a solution of 2-pentyl-2-cyclopenten-1-one (**45**) (500 mg, 3.3 mmol), in dichloromethane (10 ml) was added titanium tetrachloride (645 mg, 3.4 mmol) at (-78 °C). The reaction was stirred for 5 minutes and enolether (**78**) (740 mg, 3.4 mmol) was added. A dark red solution resulted, the mixture was warmed to rt and stirred for 18 h. The reaction mixture was then cooled back to (-78 °C) and quenched by the addition of aqueous potassium carbonate (1.7 M, 6 ml). The resulting mixture was stirred for 10 min at rt and extracted with ethyl acetate (3x 20 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residual oily liquid was purified by column chromatography (eluent: petroleum spirits / ethyl acetate, 20: 1) and the silane was isolated (565 mg, 80 %) as a colourless oil.

υ_{max} (NaCl; neat) / cm^{-1} 2951 (s), 2931 (s), 2254 (w), 1735 (s), 1718 (s), 1252 (s); δ_H (400 MHz; $CDCl_3$), 0.11 (9 H, s, 8-H), 0.87 (3 H, t, *J*, 7.1 Hz, 14-H), 1.24-1.34 (7 H, m *overlap* 4-H, 13-H, 12-H, 11-H), 1.44 (1 H, m, 5-H), 1.73 (1 H, m, 4-H), 2.13 (3 H, m), 2.25 (1 H, d, *J* 10 Hz), 2.35 (1 H, m), 2.56 (1 H, m, 9-H), 3.63 (3 H, s, 7-H); δ_C (100 MHz; $CDCl_3$), -1.76 (C-8), 14.04 (C-14), 22.48, 24.27, 26.19, 26.49, 32.04, 36.04,

37.92, 39.09, 51.11, 51.26 (C-7), 174.94 (C-6), 219.45 (C-1); *m/z* (EIMS) 299 (M^+ + H, 5 %), 267 (M^+ -OMe, 8), 241 (M^+ - CO_2Me, 10), 146 (M^+ -$C_{10}H_{16}O$, 40), 73 (M^+ -$C_{13}H_{20}O_3$, 100);

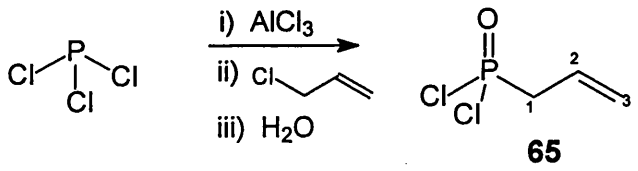
R 7 **Methyl 2-[(1*S**,2*R**)-3-oxo-2-pentylcyclopentyl]acetate (3) [Methyl dihydrojasmonate]**



To a solution of cyclopentanone (**79**) (70 mg, 0.24 mmol) in aqueous methanol (20 %, 5 ml) was added potassium fluoride (31 mg, 0.53 mmol) and the reaction mixture was stirred at rt for 4 h. The reaction was concentrated *in vacuo* and extracted with dichloromethane (3 x 20 ml). The combined extracts were dried ($MgSO_4$) and reduced *in vacuo*. The resulting oil was purified by chromatography, (eluent: petroleum spirits 40 - 60 °C / ethyl acetate, 10 :1) to afford the title compound as a colourless oil (49 mg, 96 %).

υ_{max} (NaCl; neat) / cm^{-1} 2928 (s), 2896 (s), 1745 (s), 1715 (m); δ_H (400 MHz; $CDCl_3$), 0.87 (3 H, t, *J* 7.1 Hz, 13-H), 1.26 (4 H, m, 12-H, 11-H),1.52 (2 H, 10-H), 1.79 (2 H, 5-H), 2.22 (6 H, m, 9-H, 6-H, 8-H, 4-H), 2.63 (2 H, m, 3-H), 3.70 (3 H, s,1-H); δ_C (100 MHz; $CDCl_3$), 14.07 (C-13), 22.50 (C-12), 26.35, 27.25, 27.84, 32.12, 37.73, 38.09, 39.96, 51.67, 54.24 (C-1), 172.68 (C-2), 219.73 (C-7); *m/z* (EIMS) 226 (M^+, 30 %), 195 (M^+ -OCH_3, 15), 153 (M^+ -CO_2CH_3, 45), 96 (M^+ -CO_2CH_3 -*n*-$CH_2CH_2CH_2CH_3$, 100), found for $C_{13}H_{22}O_3$ (M^+) 226.1560; Required 226.1569.

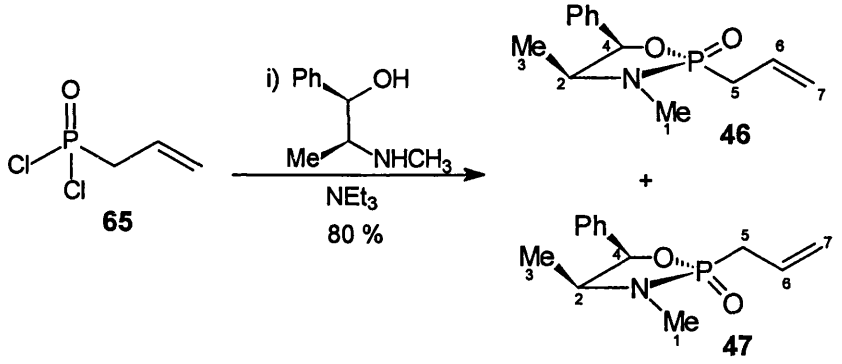
R8 **Allylphosphonic dichloride (65)**



To a freshly distilled portion of phosphorus trichloride (25.0 g, 182 mmol), purged with nitrogen was added allylchloride (3.7 ml, 45.5 mmol) at rt. Aluminium trichloride (12.1 g, 91.0 mmol) was added in five portions to the reaction mixture. A strong exotherm was noted along with a colour change (from colourless to brown / orange). The resulting mixture was then maintained at 40 °C for 30 min. The reaction mixture was then diluted with dichloromethane (100 ml) and cooled to (-40 °C). Water (144 ml, 819 mmol) was added dropwise to quench the phosphorus aluminium chloride complex, hydrogen chloride was liberated. The resulting mixture (white ppt) was filtered under reduced pressure and concentrated *in vacuo* to afford a pale orange solution. The solution was distilled under reduced pressure to afford a colourless oil (2.98 g).
N.B. Compound extremely toxic and hydroscopic therefore was used immediately.

Bp 49-50° C (2 mm); δ_H (400 MHz; $CDCl_3$), 3.40 (2 H, dd, *J* 19.0, 7.3 Hz, 1-H), 5.48 (2 H, m, 3-H), 5.67 (1 H, m, 2-H) δ_C(100 MHz; $CDCl_3$), 47.17 (C-1),124.0 (C-2),124.7 (C-3).

R9 (2*S*,4*S*,5*R*)-2-allyl-3,4-dimethyl-5-phenyl-1,3,2-λ^5-oxazaphospholan-2-one (47)
(2*R*,4*S*,5*R*)-2-allyl-3,4-dimethyl-5-phenyl-1,3,2-λ^5-oxazaphospholan-2-one (46)



To a solution of allylphosphonic dichloride (**65**) (5.20 g, 32.7 mmol) in toluene (85 ml) at (-40 ° C) was added (1*R*,2*S*)-ephedrine (5.42 g, 32.7 mmol) in one portion. The reaction was stirred for 5 min before triethylamine (9.2 ml, 65.4 mmol), added dropwise. The reaction was maintained at (-40 °C) for 1 h before being allowed to warm to rt and stirred for 12 h.

The reaction was reduced *in vacuo* to afford a solid, the solid was dissolved in petroleum spirits 40-60 °C and filtered. The filtrate was reduced *in vacuo* to afford a colourless oil. The oil was purified by flash chromatography (eluent: neat ethyl acetate).

To give phospholidinone (**46**) colourless oil, (3.41 g) and phospholidinone (**47**) white solid (3.21 g) in a combined yield of 80 %.[54]

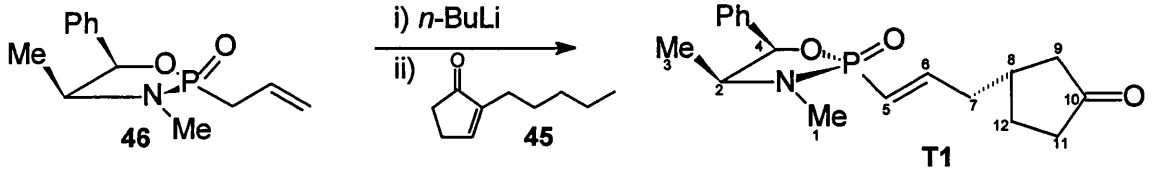
Phospholidinone (**46**)

υ_{max} (NaCl; neat) / cm^{-1} 2979 (m), 2827 (s), 1790 (s), 1641 (s); δ_H (400 MHz; $CDCl_3$), 0.78 (3 H, d, *J* 6.6 Hz, 2-H), 2.69 (3 H, d, *J* 9.8 Hz, 3-H), 2.86 (2 H, dd, *J* 12.9, 7.4 Hz, 5-H), 3.60 (1 H, m, 2-H), 5.21 (2 H, m, 7-H), 5.40 (1 H, dd, *J* 4.4, 1.8, Hz, 4-H), 5.83 (1 H, m, 6-H), 7.32 (5 H, m, Ph); δ_C(100 MHz; $CDCl_3$), 14.35, 28.60, 32.08, 33.29, 58.96, 59.05, 82.66 (C-1), 119.01, 119.77, 126.14, 128.16, 128.36 (C-6), 136.26 (C-7); *m/z* (EIMS) 251 (M^+, 8 %), 236 (M^+ -CH_3, 20), 210 (M^+ -$CH_2CH{=}CH_2$, 5), 192 (M^+ -O, -$CH_2CH{=}CH_2$, 10), 104 ($C_6H_5CH_2CH_2$, 100), found for $C_{13}H_{18}NO_2P$ (M^+) 251.1065; Required 251.1075; $[\alpha]_D^{25}$ -65.6 ° (*c*=1.03 in $CHCl_3$).

Phospholidinone (**47**)

Mp, 65-66° C, (lit 64-65° C); υ_{max} (NaCl; neat) / cm^{-1} 2979 (m), 2827 (s), 1790 (s), 1641 (s); δ_H (400 MHz; $CDCl_3$), 0.68 (3 H, d, *J* 6.7 Hz, 3-H), 2.77 (3 H, d, *J* 8.9 Hz, 1-H), 2.84 (2 H, dd, *J* 12.2, 7.5 Hz, 5-H), 3.64 (1 H, m 2-H), 5.23 (2 H, m, 7-H), 5.73 (1 H, dd, *J* 6.4 1.2 Hz, 4-H), 5.87 (1 H, m, 6-H), 7.28 (5 H, m, Ph); δ_C (100 MHz; $CDCl_3$), 14.32, 29.98, 30.05, 33.46, 34.70, 60.81, 80.02 (C-1), 119.62, 119.76, 125.59, 128.06, 128.36 (C-6), 136.07 (C-7); *m/z* (EIMS) 251 (M^+, 15 %), 236 (M^+ -CH_3, 25), 210 (M^+ -$CH_2CH{=}CH_2$, 5), 192 (M^+ -O, -$CH_2CH{=}CH_2$, 8), 104 ($C_6H_5CH_2CH_2$, 100), found for (M^+) 251.1090; Required 251.1075; $[\alpha]_D^{25}$ -54.1 ° (*c*=1.04 in $CHCl_3$).

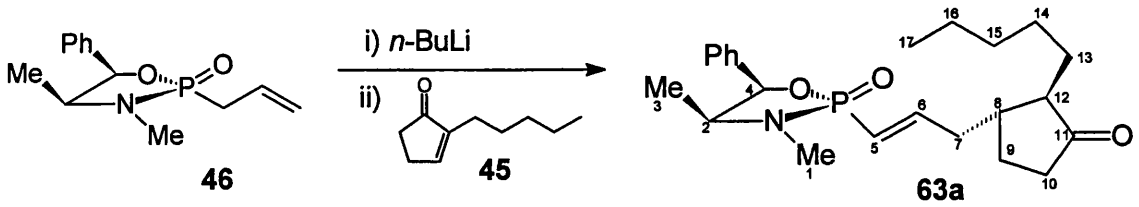
R10 (2*S*,4*S*,5*R*)-3,4-dimethyl-2-{(*E*)-3-[(1*S*)-3-oxo-cyclopentyl]-1-propenyl}-5-phenyl-1,3,2-λ^5-oxazaphospholan-2-one (T1)



To a solution of phospholidinone (**46**) (1.10 g, 4.38 mmol), in tetrahydrofuran (25 ml) at (-78 °C) was added *n*-butylithium (2.19 ml, 4.38 mmol) dropwise over 2 min and stirred for 30 min. 2-Cyclopenten-1-one (**18**) (0.37 ml, 4.38 mmol) was then added in one portion and the reaction stirred for a further 30 min. The reaction was quenched by addition of saturated ammonium chloride solution (10 ml) at (-78 °C). The reaction was warmed to rt and extracted with diethyl ether (3 x 30 ml), the combined ethereal layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a viscous oil. The oil was purified by chromatography (eluent: neat ethyl acetate), yielding a colourless oil (1.12 g, 79 %).

υ_{max} (NaCl; neat) / cm^{-1} 2980 (m), 2829 (s), 1790 (s) 1734 (s), 1641 (s); δ_H (400 MHz; $CDCl_3$), 0.85 (3 H, d, *J* 6.5 Hz, 3-H), 1.60 (1 H, m, 12'-H), 1.87 (1 H, m, 12-H) 2.25 (7 H, m, 11-H, 9-H, 8-H, 7-H *overlap*), 2.65 (3 H, d, *J* 10.1 Hz, 1-H), 3.64 (1 H, m H 2-H), 5.45 (1 H, m, 4-$H_)$), 5.79 (1 H, m, 6-H), 6.84 (1 H, m, 5-H), 7.36 (5 H, m, Ph); δ_C (100 MHz; $CDCl_3$), 14.34, 29.10, 35.88, 38.02, 39.72, 44.61, 58.85, 81.95, 119.62, 119.13, 120.97, 126.10, 128.16, 128.19, 128.29, 151.41 (C-6), 218.40 (C-11); *m/z* (FABMS) 356 (M^+ +Na, 35 %), 334 (M^+, 100 %) 310 (35) 292 (25), 218 (37); $[\alpha]_D^{25}$ -31.2 ° (*c*=0.96 in $CHCl_3$).

R11 (2*S*,4*S*,5*R*)-3,4-dimethyl-2-{(*E*)-3-[(1*S*,2*R*)-3-oxo-2-pentylcyclopentyl]-1-propenyl}-5-phenyl-1,3,2-λ^5-oxazaphospholan-2-one (63a)



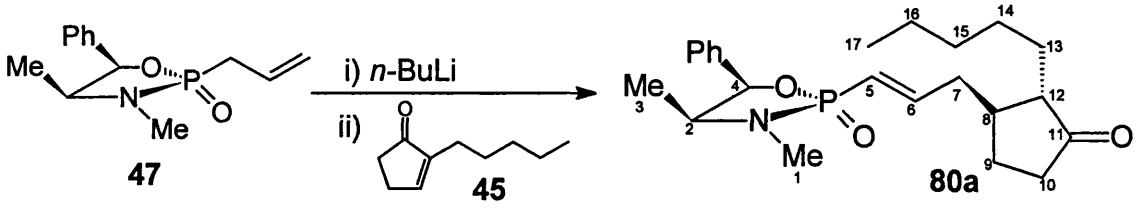
46 **45** **63a**

To a cooled solution (-78 °C) of phospholidinone (**46**), (790 mg, 3.15 mmol) in tetrahydrofuran (20 ml) was added *n*-butyllithium (3.46 mmol), the reaction was stirred for 30 min before enone (**45**) (485 mg, 3.15 mmol) was added. The reaction was stirred for a further 30 min before being quenched by addition of saturated ammonium chloride solution (5 ml). The reaction mixture was then extracted from ethyl acetate (3 x 30 ml). The combined organic layers were dried ($MgSO_4$), filtered and reduced *in vacuo* to afford a colourless syrup. The syrup was purified by column chromatography (eluent: neat ethyl acetate) to afford the title product as a colourless viscous oil (995 mg, 80 %).

(**63a**) υ_{max} (NaCl; neat) / cm^{-1} 2956 (m), 2858 (s), 2228 (s), 1736 (s), 1627 (s), 1456 (s), 1244 (s), 976; δ_H (400 MHz; $CDCl_3$), 0.80 (3 H, d, *J* 6.6 Hz, 1-H), 0.82 (3 H, t, *J* 7.0 Hz, 17-H), 1.22 (6 H, m, 16-H, 15-H, 14-H), 1.42 (3 H, m), 1.72 (1 H, m, 8-H), 2.16 (7 H, m, 7-H, 12-H, 10-H, 9-H), 2.60 (3 H, d *J* 10.3 Hz,1-H), 3.56 (1 H, m, 2-H), 5.40 (1 H, t, *J* 5.6 Hz, 6-H), 5.74 (1 H, dd, *J* 6.7, 5.6 Hz, 4-H), 6.72 (1 H, m, 5-H), 7.30 (5 H, m, Ph); δ_C (100 MHz; $CDCl_3$),14.02 (C-17), 22.46, 26.47, 27.78, 28.96, 28.39, 32.05, 37.58, 38.99, 39.20, 40.52, 54.27, 58.75, 58.85, 81.84, 119.36, 121.04, 126.13, 128.17, 128.35, 136.16 (C-5), 151.29 (C-5), 219.93 (C-11); *m/z* (FABMS) 405 (M^+, 40 %), 148 (M^+ - $C_{13}H_{21}O_3P$, 100), Found for $C_{23}H_{36}O_3NP$ (M^+) 405.2440; Required 405.2433; $[\alpha]_D^{25}$ -36.2° (*c*=0.843, $CHCl_3$).

(**63b**) minor component (non overlap peaks), δ_H (400 MHz; $CDCl_3$), 0.85 (3 H, d, *J* 6.6 Hz, 17-H) 3.01-3.12 (m), 5.28-5.38 (m, 6-H, 4-H).
Diastereoisomeric ratio of (**63a**) : (**63b**) determined by ^1H NMR to be 95 : 5 respectively.

R12 (2*R*,4*S*,5*R*)-3,4-dimethyl-2-{(*E*)-3-[(1*R*,2*S*)-3-oxo-2-pentylcyclopentyl]-1-propenyl}-5-phenyl-1,3,2-λ^5-oxazaphospholan-2-one (80a)



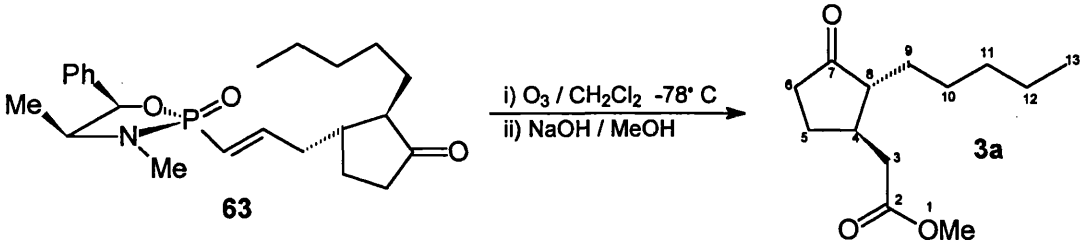
To a cooled solution (-78 ° C) of phospholidinone (**47**) (790 mg, 3.15 mmol) in THF (20 ml) was added *n*-butyllithium (3.46 mmol), the reaction was stirred for 30 min before enone (**45**) (485 mg, 3.15 mmol) was added. The reaction was stirred for a further 30 min before being quenched by addition of saturated ammonium chloride solution (5 ml). The reaction mixture was when extracted from ethyl acetate (3 x 30 ml). The combined organic layers were dried ($MgSO_4$) and reduced *in vacuo* to afford a colourless syrup. The syrup was purified by column chromatography (eluent: neat ethyl acetate) to afford the title compound a colourless viscous oil (9.96 g, 79 %).

(**80a**)υ_{max} (NaCl; neat) / cm^{-1} 2953 (m), 2859 (s), 2227 (s), 1737 (s), 1626 (s), 1454 (S), 1241 (S), 978 (s); δ_H (400 MHz; $CDCl_3$), 0.70 (3 H, d, *J* 6.6 Hz, 3-H), 0.84 (3 H, t, *J* 7.0, Hz, 17-H), 1.24 (6 H, m, 16-H, 15-H, 14-H), 1.46 (3 H, m, 9-H, 8-H), 1.75 (1 H, m, 13'-H), 2.33 (7 H, m, 7-H, 10-H, 12-H, 13'-H), 2.71 (3 H, d, 8.7 Hz, 1-H), 3.71 (1 H, m, 2-H), 5.63 (1 H, dd, *J* 6.7, 1.2 Hz, 4-H), 5.74 (1 H, dd, *J* 5.8, 1.2 Hz, 6-H), 6.93 (1 H, m, 5-H), 7.28 (5 H, m, Ph); δ_C (100 MHz; $CDCl_3$),14.03 (CH_3), 22.48, 26.56, 26.76, 26.82, 28.02, 32.06 37.59, 39.08, 39.29, 40.61, 54.31, 60.30, 60.40 (C-1), 80.38 (C-4), 120.31, 122.00, 125.68, 128.09, 128.40, 136.18 (C-6), 152.67 (C-5), 220.01 (C-11); *m/z* (FABMS) 405, (M^+, 40 %), 148 (M^+ -$C_{13}H_{21}O_3P$, 100), Found for $C_{23}H_{36}O_3NP$ (M^+) 405.2440; Required 405.2433; $[\alpha]_D^{25}$ = -18.4 ° (*c*= 0.812 in $CHCl_3$).

(**80b**) minor component (non overlap peaks), δ_H (400 MHz; $CDCl_3$), 0.89 (3 H, d, *J* 6.6 Hz, 17-H), 5.48-5.57 (m, 6-H, 4-H).

Diastereoisomeric ratio of (**80a**) : (**80b**) determined by ^1H NMR to be 93 : 7 respectively.

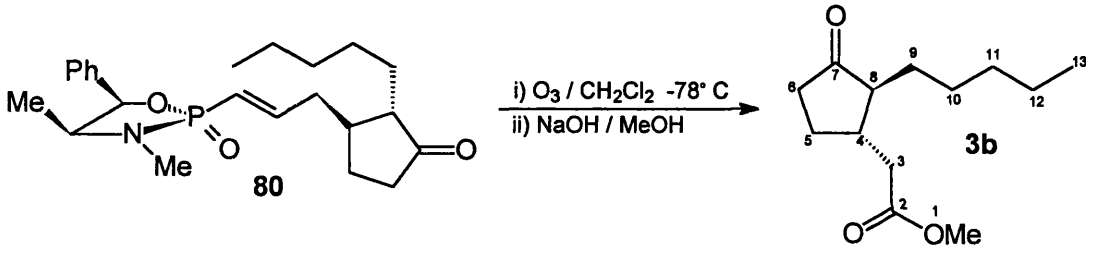
R13 **Methyl 2-[(1*R*,2*R*)-3-oxo-2-pentylcyclopentyl]acetate (3a)**
[(-)-Methyl dihydrojasmonate]



To a solution of phospholidinone (**63**) (500 mg, 1.24 mmol), in dichloromethane (30 ml) was added a solution of sodium hydroxide in methanol (2.5 M NaOH, 2.6 ml). The reaction was cooled to (-78 °C) and ozone was passed through the reaction mixture (after several min a yellow precipitate was observed), after 30 min the reaction mixture turned a pale blue colour. The flow of ozone was stopped and nitrogen was bubbled through the mixture for 30 min. The reaction was diluted with diethyl ether and extracted (4x 40 ml), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oil. The oil was purified by column chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 25 :1), the title compound was isolated as a colourless oil (160 mg, 57 %).

υ_{max} (NaCl; neat) / cm^{-1} 2928 (m), 2896 (s), 1725 (s), 1716 (m); δ_H (400 MHz; $CDCl_3$), 0.87 (3 H, t, *J* 7.1 Hz, 13-H), 1.26 (4 H, m, 11-H, 12-H), 1.52 (2 H, m, 10-H), 1.79 (2 H, m, 9-H), 2.22 (6 H, m, 6-H, 5-H, 4-H, 8-H *overlap*), 2.63 (2 H, m, 3-H), 3.70 (3 H, s, 1-H); δ_C (100 MHz; $CDCl_3$), 14.07 (C-13), 22.50 (C-12), 26.35 (C-11), 27.25, 27.84, 32.12, 37.73, 38.09, 39.96, 51.67, 54.24 (C-1) , 172.68 (C-2), 219.73 (C-7); *m/z* (EIMS) 226 (M^+, 15 %), 195 (M^+-OCH_3, 15), 153 (M^+- CO_2Me, 45), 96 (M^+ -CO_2Me, -*n*-Bu, 100), found for $C_{13}H_{22}O_3$ (M^+) 226.1569; Required 226.1560; $[\alpha]_D^{25}$ -48.2 ° (*c* =0.910 in $CHCl_3$); (92 % *ee*).

R14 **Methyl 2-[(1*S*,2*S*)-3-oxo-2-pentylcyclopentyl]acetate (3b) [(+)-Methyl dihydrojasmonate]**



To a solution of phospholidinone (**80**) (800 mg, 1.98 mmol), in dichloromethane (40 ml) was added a solution of sodium hydroxide in methanol (2.5 M NaOH, 4.1 ml). The reaction was cooled to (-78 °C) and ozone was passed through the reaction mixture (after several min a yellow precipitate was observed), after *ca* 40 min the reaction mixture turned a pale blue colour. The flow of ozone was stopped and nitrogen was bubbled through the mixture for 30 min.

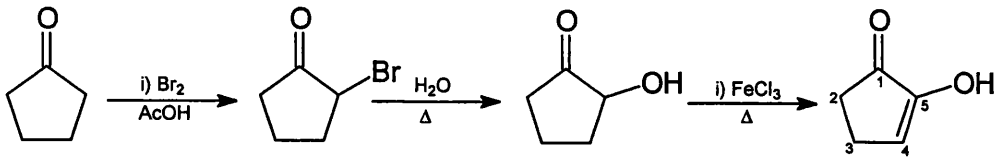
The reaction was diluted with diethyl ether and extracted (4x 50 ml), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oil. The oil was purified by column chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 25 :1), the title compound was isolated as a colourless oil (267 mg, 60 %).

υ_{max} (NaCl; neat) / cm^{-1} 2928 (m), 2896 (s), 1725 (s), 1716 (m); δ_H (400 MHz; $CDCl_3$), 0.87 (3 H, t, *J* 7.1 Hz, 13-H), 1.26 (4 H, m, 11-H, 12-H), 1.52 (2 H, m, 10-H), 1.79 (2 H, m, 9-H), 2.22 (6 H, m, 6-H, 5-H, 4-H, 8-H *overlap*), 2.63 (2 H, m, 3-H), 3.70 (3 H, s, 1-H);

δ_C (100 MHz; $CDCl_3$), 14.07 (C-13), 22.50 (C-12), 26.35 (C-11), 27.25, 27.84, 32.12, 37.73, 38.09, 39.96, 51.67, 54.24 (C-1), 172.68 (C-2), 219.73 (C-7); *m/z* (EIMS) 226 (M^+, 15 %), 195 (M^+-OCH_3, 15), 153 (M^+- CO_2Me, 45), 96 (M^+ -CO_2Me, -*n*-Bu, 100), Found for $C_{13}H_{22}O_3$ (M^+) 226.1569; Required 226.1560; $[\alpha]_D^{25}$ +38.2 ° (*c*=0.480 in $CHCl_3$); (86 % *ee*).

Methyl *trans*-jasmonates

R15 **2-Hydroxy-2-cyclopenten-1-one (116)**



116

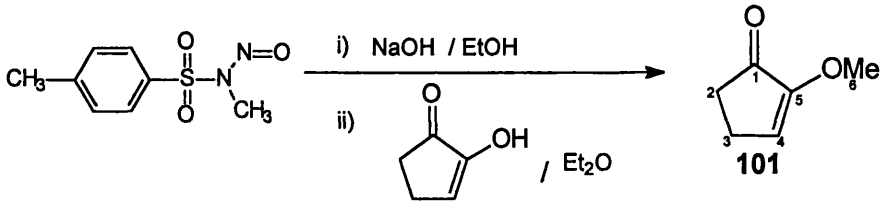
To a solution of cyclopentanone (**66**) (30 ml, 340 mmol), acetic acid (15 ml, 262 mmol), in water (65 ml) was vigorously stirred and a few drops of molecular bromine. The whole reaction was then heated to *ca* 70 °C until the bromine colour started to fade, the remaining bromine (19.5 ml, 378.4 mmol) was added *via* a dropping funnel over 15 min while maintaining the reaction temperature between 55-60 °C (achieved by external cooling using a water bath). The stirred mixture was then neutralised (congo red, pH 4-5) with solid sodium carbonate. A pale yellow oil (bromocyclopentanone) was separated below the aqueous layer. The oil was washed with water (2x 20 ml). A crude oil was separated (41.0 g), and taken forward to next step (unstable halide).

The crude bromo-ketone (41.0 g, 237.0 mmol) was stirred vigorously with water (260 ml) at 96- 98 °C until dissolution was complete (*ca* 40 min). Anhydrous ferric (III) chloride (64.3 g, 237 mmol) in hot water (80 ml) was added over 5 min with vigorous stirring. After 10 min at 98° C the mixture was cooled to 40 °C, saturated with ammonium sulfate. The resulting mixture was extracted with ethyl acetate (12x 50 ml), the ethyl acetate was dried (Na_2SO_4) and concentrated *in vacuo*. The concentrated product (brown solution) was distilled under reduced pressure to afford the title compound as a colourless oil which crystallised upon cooling to give a white crystalline solid (9.92 g, 30 %).

N.B. dione (**116**) unstable to silica gel chromatography.

Bp 80-82 °C (8 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 3362 (br) OH, 2966 (m), 2280 (m), 1720 (s), 1612 (w); δ_H (400 MHz; $CDCl_3$); 2.41 (2 H, m, 3-H), 2.49 (2 H, m, 2-H), 6.05 (1 H, s (br), -O*H*), 6.58 (1 H, t, *J* 2.5, 4-H); δ_C(100 MHz; $CDCl_3$), 21.25 (C-3), 33.63 (C-2), 126.56 (C-4), 156.98 (C-5), 201.98 (C-1); *m/z* (EIMS) 99 (M^+ + H, 20 %) 98 (M^+, 100), 83 (M^+ -O, 24); found for $C_5H_6O_2$ (M^+) 98.0366; Required 98.0368.

R16 **2-Methoxy-cyclopenten-1-one (101)**



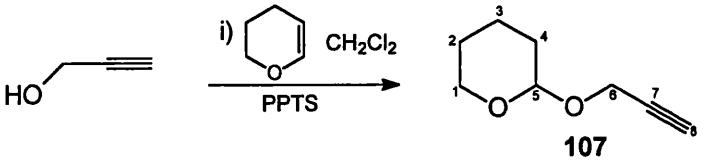
116 **101**

To a solution of Diazald® (1.76 g 8.21 mmol) in ethanol (99.7 %, 10 ml) in a ground-glass free Buchner flask, was added via a plastic syringe fitted with a plastic (polyvinylchloride) tube, a dropwise solution of sodium hydroxide (400 mg), in water (4 ml). Decomposition of diazald led to diazomethane (a yellow gas) being formed which was bubbled by a positive pressure of nitrogen into a second flask *via* the sidearm tubing of the Buchner flask containing cyclopentan-1,2-dione (**116**) distillate (500 mg, 5.1 mmol) in dry diethyl ether (25 ml). The reaction was stirred for 5 h before being quenched by bubbling nitrogen over a period of 2 h, the organics were concentrated *in vacuo*. The oil was purified by kugelrohr distillation, to afford the title compound as a colourless oil (310 mg).

N.B. this material is unstable to column chromatography.

Bp 110-115 °C (12 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 2966 (s), 2280 (m), 1720 (s), 1611 (w); δ_H (400 MHz; $CDCl_3$); 2.42 (2 H, m, 3-H) 2.51 (2 H, m, 2-H), 3.72 (3 H, s, 6-H), 6.38 (1 H, t, *J* 2.9 Hz, 4-H); δ_C(100 MHz; $CDCl_3$), 21.85 (C-3), 33.21 (C-2), 57.10 (C-6), 127.00 (C-4), 157.60 (C-5), 202.46 (C-1); *m/z* (EIMS), 113 (M^+ +H, 87 %), 83 (M^+ -OCH_3, 68), found for $C_6H_9O_2$ (M^+ +H) 113.0615; Required 113.0603.

R17 **2-(2-Propynyloxy)tetrahydro-2*H*-pyran (107)**

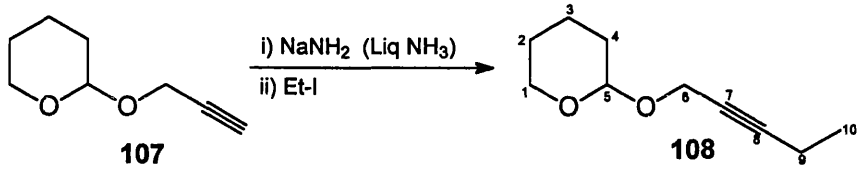


107

To a stirred solution of freshly distilled propargyl alcohol (**105**) (8.21 g, 147 mmol) in dry dichloromethane (240 ml) was added 2,3-dihydropyran (21.12 g, 235.2 mmol) and pyridinium *para*-toluene sulfonate (360 mg, 1.5 mmol). The mixture was stirred at rt for 5 h before being concentrated *in vacuo* to afford a colourless liquid. The material was distilled under reduced pressure, to afford the title compound as a colourless oil (19.55 g, 95 %).

Bp 82 °C (50-49 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 3290 (m), 2940 (s), 2871 (s) 2363 (m), 2229 (m), 1447 (m); δ_H (400 MHz; $CDCl_3$), 1.43-1.87 (6 H, m, 2-H, 3-H, 4-H), 2.38 (1 H, t, *J* 2.5 Hz, 8-H), 3.50 (1 H, m, 1'-H), 3.72 (1 H, m, 1'-H), 4.22 (2 H, d *J* 2.5 Hz, 6-H), 4.78 (1 H, t, *J* 3.4 Hz, 5-H), δ_C(100 MHz; $CDCl_3$), 19.97 (C-3), 25.31 (C-2), 30.18 (C-4), 53.9 (C-1), 61.96 (C-6), 74.00 (C-6), 79.74 (C-7), 96.80 (C-5); *m/z* (EIMS), 140 (M^+, 44 %), 83 (M^+ - $C_5H_{10}O$, 100).

R18 **2-(2-Pentynyloxy)tetrahydro-2*H*-pyran (108)**

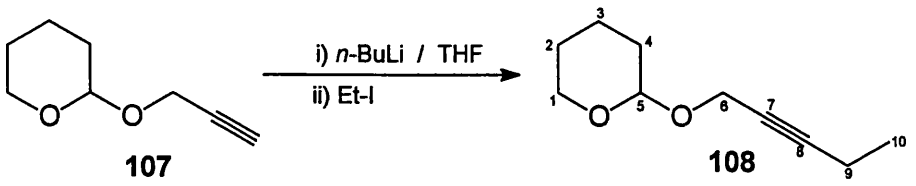


107 **108**

To a 2-litre 3-necked flask purged with nitrogen was fitted a cold finger trap was condensed 500 ml of liquid ammonia (cooled by acetone dry ice bath to -50 °C). Sodium (13.2 g, 575.2 mmol) washed in petroleum spirits 40-60 °C was added in small portions to the ammonia solution. A dark blue precipitate resulted. The pyran ether (**107**) was (67.1 g, 479.2 mmol) was added over 10 min and reaction stirred for 1 h. Bromoethane (47.1 ml, 575.1 mmol) was added over 10 min. The reaction was stirred for further 3 h before the reaction was allowed to warm up to rt. The ammonia was allowed to evaporate. The resulting white slurry was dissolved in water (50 ml) and extracted with diethyl ether (4 x 50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by reduced pressure distillation to give the title compound (62.6 g, 80 %).

Bp 85-88 °C (9-10 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 2940 (s), 2872 (s), 2361 (w), 2251 (w), 1024 (s); δ_H(400 MHz; $CDCl_3$), 1.14 (3 H, t, *J* 7.5 Hz, 10-H), 1.58 (4 H, m, 3-H, 2-H), 1.78 (2 H, m, 4-H), 2.23 (2 H, m, 9-H), 3.53 (1 H, m, 1'-H), 3.82 (1 H, m, 1'-H), 4.24 (2 H, dd *J* 11.0, 1.8 Hz 6-H), 5.30 (1 H, t, *J* 1.8 Hz, 5-H); δ_C(100 MHz; $CDCl_3$), 12.54 (C-10), 13.80, 19.13, 24.42, 30.32, 54.68 (C-1), 61.98 (C-6), 75.10 (C-7), 88.03 (C-8), 96.70 (C-5); *m/z* (EIMS), 168 (M^+, 12 %), 140 (M^+ -CH_2CH_3, 24), 83 (M^+ - $C_5H_{10}O$, 100).

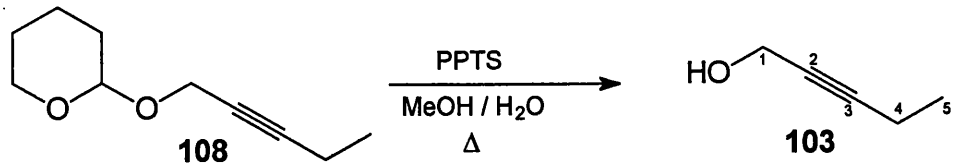
R20 **2-(2-Pentynyloxy)tetrahydro-2*H*-pyran (108)**



To a cooled solution of 2-propynyl 2-tetrahydropyranyl ether (**107**) (18.00 g, 128.6 mmol) in dry toluene (250 ml) at -78° C was added a dropwise solution of *n*-butyllithium (128.6 mmol). After 40 min of stirring at -78 °C, ethyl iodide (23.12 g, 128.6 mmol) was added in one portion and the reaction allowed to warm to rt over 4 h and then stirred for a further 48 h at rt. The reaction was quenched by addition of saturated ammonium chloride solution. The organics were extracted with diethyl ether (3x 60 ml), the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a brown oil. The oil was purified by flash chromatography, (eluent: petroleum spirits / ethyl acetate, 25:1). The title compound was isolated in 42 % yield.

Bp 85-88 °C (9-10 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 2940 (s), 2872 (s), 2361 (w), 2251 (w), 1024 (s); δ_H(400 MHz; $CDCl_3$), 1.14 (3 H, t, *J* 7.5 Hz, 10-H), 1.58 (4 H, m, 3-H, 2-H), 1.78 (2 H, m, 4-H), 2.23 (2 H, m, 9-H), 3.53 (1 H, m, 1'-H), 3.82 (1 H, m, 1'-H), 4.24 (2 H, dd *J* 11.0, 1.8 Hz 6-H), 5.30 (1 H, t, *J* 1.8 Hz, 5-H); δ_C(100 MHz; $CDCl_3$), 12.54 (C-10), 13.80, 19.13, 24.42, 30.32, 54.68 (C-1), 61.98 (C-6), 75.10 (C-7), 88.03 (C-8), 96.70 (C-5); *m/z* (EIMS), 168 (M^+, 12 %), 140 (M^+ -CH_2CH_3, 24), 83 (M^+ - $C_5H_{10}O$, 100).

R21 **2-Pentyn-1-ol (103)**

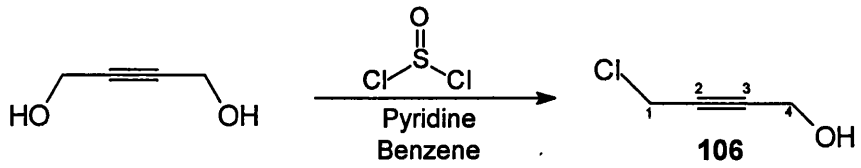


To a solution of 2-pentynyl 2-tetrahydropyranyl ether (**108**) (1.51 g, 9.0 mmol) in methanol (60 ml) was added pyridinium *p*-toluenesulfonate (255 mg, 1.0 mmol). The reaction warmed to 55° C for 3 h, cooled to rt and concentrated *in vacuo* (low bath temperature due to volatility of product). The oil was purified by reduced

pressure distillation. The title compound was isolated as a colourless oil (620 mg, 85 %).

Bp. 85 °C (55 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 3363 (br) (OH), 2976 (m), 2934 (s) 2876 (s) 2290 (m), 2229 (m); δ_H(400 MHz; $CDCl_3$), 1.13 (3 H, t, *J* 7.5 Hz, 5-H), 2.00 (1 H, s (br), O*H*), 2.21 (2 H, m, 4-H), 4.23 (2 H, dd, *J* 4.1, 1.9 Hz, 1-H); δ_C(100 MHz; $CDCl_3$), 12.42 (C-5), 13.78 (C-4), 51.30 (C-1), 77.69 (C-2), 87.81 (C-3); *m/z* (EIMS) 83 (M^+ - H, 74), 65 (M^+ -CH_3, 65), 55 (M^+ -CH_2CH_3, 85).

R22 **4-Chloro-2-butyn-1-ol (106)**



106

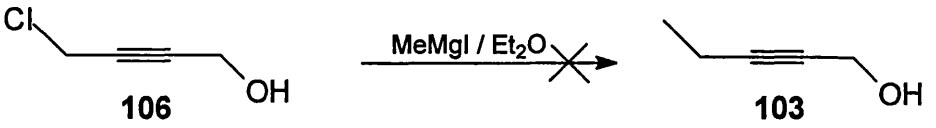
1,4-But-2-yn-diol (17.01 g, 196 mmol) in benzene (200 ml) was heated to reflux, using a Dean and Stark apparatus, 1.5 ml of water was collected. The reaction then cooled down (N.B., 1-4 but-2-yne diol did not dissolve in benzene). The reaction was then cooled to 0 °C and purged with nitrogen was added pyridine (17.02 g, 1.1 e.q). The reaction was then stirred for 5 min before thionyl chloride (11.12 g. 1.1e.q) was added over 6 h (using a syringe pump). The temperature of the reaction mixture was maintained at 10 °C and then after the addition was allowed to warm to rt and stirred for 14 h.

The reaction mixture was then poured into crushed ice (400 g). The benzene layer was separated and the aqueous was extracted with diethyl ether (4x 50 ml), the combine organic layers were was with saturated sodium hydrogen carbonate solution (50 ml), then with ice cold water (30 ml). The organics were then dried (Na_2SO_4) and concentrated *in vacuo* to afford a colourless liquid. The crude liquid was purified by reduced pressure distillation. The title compound was isolated as a colourless oil (10.71 g, 54 %).

N.B. Powerful skin irritant

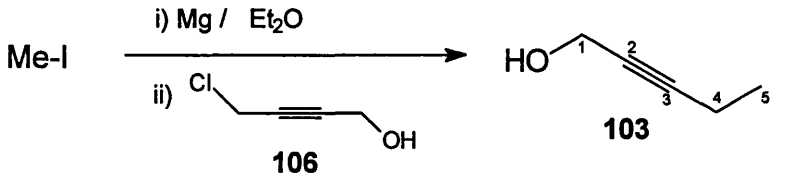
Bp 55-58 °C (0.5 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 2974 (br), 2932 (s) 2876 (s); δ_H (400 MHz; $CDCl_3$); 2.61 (1 H, s (br), O*H*), 4.17 (2 H, t, *J* 2.0 Hz, 1-H), 4.30 (2 H, t, *J* 2.0 Hz, 4-H), δ_C(100 MHz; $CDCl_3$), 30.33 (C-1), 50.80 (C-4), 80.35 (C-2), 84.56 (C-3).

R23 **2-Pentyn-1-ol (103)**



To a solution of 4-chlorobut-2-yn-1-ol (**106**) (1.01 g, 9.6 mmol) in ether (20 ml) was added magnesium turnings (258 mg, 10.63 mmol). The reaction was warmed to 30° C and 1,2-dibromoethane (180 mg, 0.96 mmol) was added, after continual heating for 5 h of the Grignard failed to form. The reaction was cooled and filtered. The starting material, 4-chlorobut-2-yn-1-ol was recovered in almost quantitative yield.

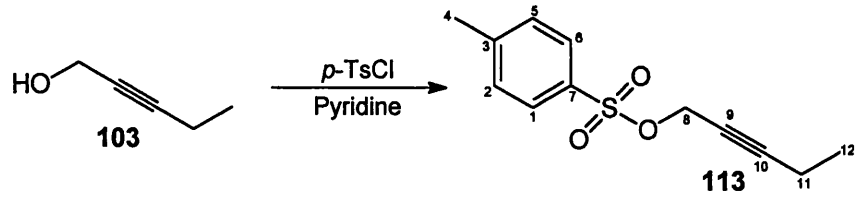
R24 **2-Pentyn-1-ol (103)**



To a solution of methyl iodide (2.97 g, 20.9 mmol) in diethyl ether (2 ml), tetrahydrofuran (10 ml) was added magnesium turnings (500 mg, 20.9 mmol), after about 10 min of heating the reaction started to reflux under its own exotherm. The heat was removed and the reaction stirred until all the magnesium had dissolved. After 1 h the reaction was cooled to 0 °C and 4-chloro-2-butyn-1-ol (**106**) (1.03 g, 9.6 mmol) was added dropwise (a large exotherm resulted). The reaction was heated to reflux for 3 h, cooled to rt and stirred for a further 12 h. The reaction was then cooled to 0° C and saturated ammonium chloride solution (20 ml) added. A large exotherm was noted. The mixture was extracted with diethyl ether (4x 30 ml) dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow oil purified by Kugel Rohr distillation to give the title compound as a colourless oil (450 mg, 60 %).

Bp. 85 °C (55 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 3363 (br) (OH), 2976 (m), 2934 (s) 2876 (s) 2290 (m), 2229 (m); δ_H(400 MHz; $CDCl_3$), 1.13 (3 H, t, *J* 7.5 Hz, 5-H), 2.00 (1 H, s (br), O*H*), 2.21 (2 H, m, 4-H), 4.23 (2 H, dd, *J* 4.1, 1.9 Hz, 1-H); δ_C(100 MHz; $CDCl_3$), 12.42 (C-5), 13.78 (C-4), 51.30 (C-1), 77.69 (C-2), 87.81 (C-3); *m/z* (EIMS) 83 (M^+ - H, 74), 65 (M^+ -CH_3, 65), 55 (M^+ -CH_2CH_3, 85).

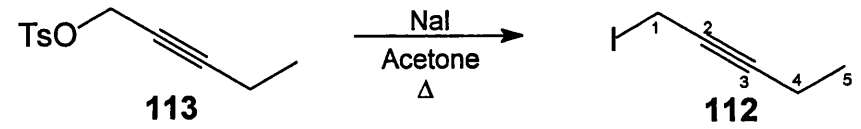
R25 **2-Pentynyl-4-methyl-1-benzenesulphonate (113)**



To 2-pentyn-1-ol (**103**) (250 mg, 3 mmol) was added tosyl chloride (630 mg, 1.1 e.q) in pyridine (3 ml). The reaction was sealed and placed in a freezer (-19° C) for 16 h. A white solid was observed and was carefully removed by filtering though filter paper. The reaction mixture was then extracted with diethyl ether (4x10 ml), the combined organics were washed with hydrochloric acid (1 N, 5 ml) and then several times with saturated copper sulfate solution (until copper sulfate colour persisted). The ethereal layer was then dried (Na_2SO_4) and concentrated *in vacuo* (low bath temperature) to afford a pale yellow liquid. The liquid was taken through crude to next step.

υ_{max} (NaCl; neat) / cm^{-1} 2987 (s), 2136 (w), 812 (s); δ_H (400 MHz; $CDCl_3$); 1.13 (3 H, t, *J* 7.5 Hz, 12-H), 2.10 (3 H, s, 4-H), 2.28 (2 H, qt, *J* 7.5, 2.2 Hz, 11-H), 3.95 (2 H, t, *J* 2.2 Hz, 8-H), 7.38 (2 H, d, *J* 7.8 Hz, 5-H, 2-H), 8.01 (2 H, d, *J* 7.8 Hz, 2-H, 6-H), δ_C (100 MHz; $CDCl_3$), 12.70, 12.52, 15.77, 21.46, 74.65 (C-9), 89.46 (C-10) 140.36 (C-3), 141.75 x2 (Ph), 141.89 x2 (Ph); *m/z* (EIMS) 238 (M^+, 8 %), 224 (M^+ -CH_3, 32), 210 (M^+ -CH_2CH_3, 12), 83 (M^+ -$C_7H_7SO_2$, 88);

R26 **1-Iodo-2-pentyne (112)**

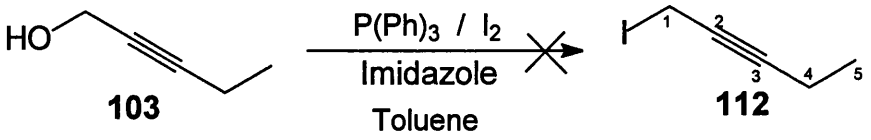


To a solution of tosylate (**113**) (180 mg, 0.75 mmol) in acetone (20 ml) was added sodium iodide (1.50 g, 10.4 mmol). The reaction was heated to reflux for 3 h before being allowed to cool to rt and filtered. The filtrate was concentrated *in vacuo* to afford a yellow oil. The oil was purified by flash chromatography (eluent: petroleum spirits 30-40 °C / diethyl ether, 40 : 1). The title compound was isolated as a colourless liquid (78 mg, 55 %).

N.B. strong antiseptic odour.

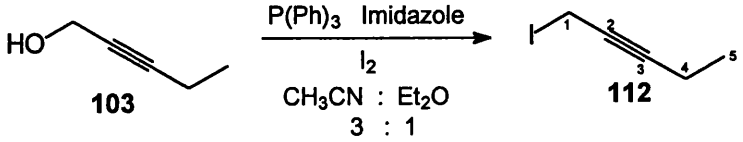
υ_{max} (NaCl; neat) / cm^{-1} 2976 (m) , 2934 (s) 2876 (s), 2290 (w), 2229 (w); δ_H(400 MHz; $CDCl_3$); 1.12 (3 H, t, *J* 7.5, 5-H), 2.21 (2 H, m, 4-H), 3.71 (3 H, t, *J* 2.3, 2-H); δ_C(100 MHz; $CDCl_3$), 13.48 (C-5), 21.23 (C-4), 76.41 (C-2), 87.93 (C-3), 231.93 (C-1); (EIMS) *m/z* 194 (M^++ H, 87 %), 179 (M^+ - CH_3, 40).

R27 **1-Iodo-2-pentyne (112)**



To a solution of 2-pentyn-1-ol (**103**) (250 mg, 3 mmol), triphenylphosphine (3.21 g, 12.0 e.q), imidazole (825 mg, 12 mmol) in benzene (10 ml) was added molecular iodine (2.28 g, 9.0 mmol), the reaction was stirred at rt. However after 30 min of stirring the material polymerised, a brown tar formed. The reaction was diluted with saturated sodium hydrogen carbonate (30 ml) and the organics extracted with ethyl acetate (3 x 20 ml), the combined organics were washed with metabisulfite solution and then washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown – tar, (the material had polymerised).

R28 **1-Iodo-2-pentyne (112)**

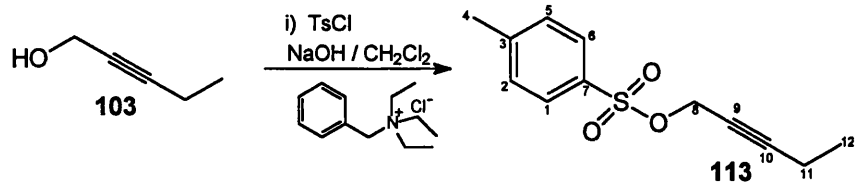


To solution of 2-pentyn-1-ol (**103**) (250 mg, 3 mmol), triphenylphosphine (1.18 g, 4.5 mmol), imidazole (310 mg, 4.5 mmol) in acetonitrile / diethyl ether (25 ml, 3:1), was added molecular iodine (1.15 g, 4.5 mmol) in small portions over 2 min the reaction turned brown. After 40 min of stirring the reaction was quenched by addition of saturated sodium hydrogen carbonate solution (25 ml). The reaction mixture was then extracted with diethyl ether (3 x 25 ml), the combined organic extracts were washed with sodium metabisulfite solution (5 % 20 ml), the ethereal layers was dried (Na_2SO_4) and concentrated *in vacuo* (low bath temperature 10 °C). The oil was then purified by flash chromatography (eluent: petroleum spirits 30-40 °C / diethyl ether, 25:1), to afford a colourless liquid (171 mg) in 29 % yield.

N.B. Strong antiseptic odour.

υ_{max} (NaCl; neat) / cm^{-1} 2976 (m) , 2934 (s) 2876 (s), 2290 (w), 2229 (w); δ_H(400 MHz; $CDCl_3$); 1.12 (3 H, t, *J* 7.5, 5-H), 2.21 (2 H, m, 4-H), 3.71 (3 H, t, *J* 2.3, 2-H); δ_C(100 MHz; $CDCl_3$), 13.48 (C-5), 21.23 (C-4), 76.41 (C-2), 87.93 (C-3), 231.93 (C-1); (EIMS) *m/z* 194 (M^++ H, 87 %), 179 (M^+ - CH_3, 40).

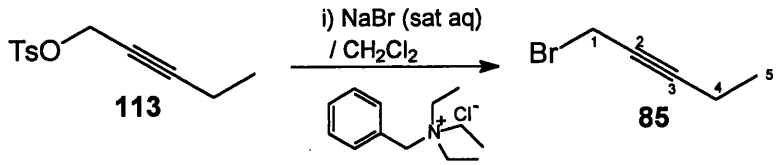
R29 **2-Pentynyl-4-methyl-1-benzenesulphonate (113)**



To a vigorously stirred solution of sodium hydroxide (50 %, 25 ml) was added a dropwise solution of *para*-toluensulfonyl chloride (6.67 g, 35.0 mmol), benzyl triethyl ammonium chloride (182 mg, 0.80 mmol), 2-pentyne-1ol (**103**) (2.10 g, 25.0 mmol) in dichloromethane (25 ml). The reaction was stirred for 25 min before being diluted with diethyl ether (20 ml) and extracted with diethyl ether (3x 50 ml) dried, ($MgSO_4$) and concentrated *in vacuo.* To afford the title compound as a colourless liquid (8.10 g, 99 %).

υ_{max} (NaCl; neat) / cm^{-1} 2987 (s), 2136 (w), 812 (s); δ_H (400 MHz; $CDCl_3$); 1.13 (3 H, t, *J* 7.5 Hz, 12-H), 2.10 (3 H, s, 4-H), 2.28 (2 H, qt, *J* 7.5, 2.2 Hz, 11-H), 3.95 (2 H, t, *J* 2.2 Hz, 8-H), 7.38 (2 H, d, *J* 7.8 Hz, 5-H, 2-H), 8.01 (2 H, d, *J* 7.8 Hz, 2-H, 6-H), δ_C (100 MHz; $CDCl_3$), 12.70, 12.52, 15.77, 21.46, 74.65 (C-9), 89.46 (C-10) 140.36 (C-3), 141.75 x2 (Ph), 141.89 x2 (Ph); *m/z* (EIMS) 238 (M^+, 8 %), 224 (M^+ -CH_3, 32), 210 (M^+ -CH_2CH_3, 12), 83 (M^+ -$C_7H_7SO_2$, 88);

R30 **1-Bromo-2-pentyne (85)**

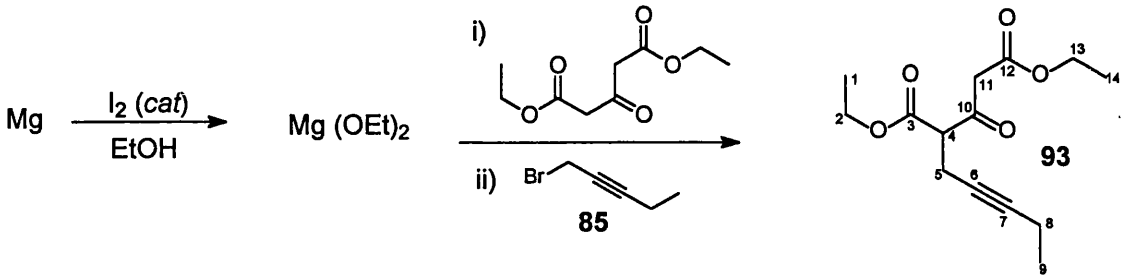


To a vigorously stirred solution of tosylate (**113**) (35 mmol) in dichloromethane (115 ml) was added a solution of sodium bromide (23.71 g, 230.1 mmol) and benzyl triethylammonium chloride (1.05 g, 4.6 mmol) in water (29 ml). The reaction was stirred for 18 h and then diluted with water (30 ml) an extracted with dichloromethane (3 x 50 ml). The combined extracts were dried (Na_2SO_4) and

concentrated *in vacuo.* The pale yellow liquid was purified by reduced pressure distillation to afford the title compound as a colourless liquid, (3.29 g, 81 %).
N.B. Strong antiseptic odour.

Bp (71-72 °C) (40 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 2987 (s), 2136 (w), 812 (s); δ_H (400 MHz; $CDCl_3$); 1.14 (3 H, t, *J* 7.5 Hz, 5-H), 2.26 (2 H, qt, *J* 7.5, 2.2, 4-H), 3.95 (2 H, t, *J* 2.2 Hz 1-H); δ_C(100 MHz; $CDCl_3$), 12.52 (C-5), 12.70 (C-4),15.77 (C-1), 74.65, (C-2), 89.46 (C-3); *m/z* (EIMS), 147 (M^+, 6 %), 67 (M^+ -Br, 72), 57 (100).

R31 **Diethyl 3-oxo-2-(2-pentynyl)pentandioate (93)**



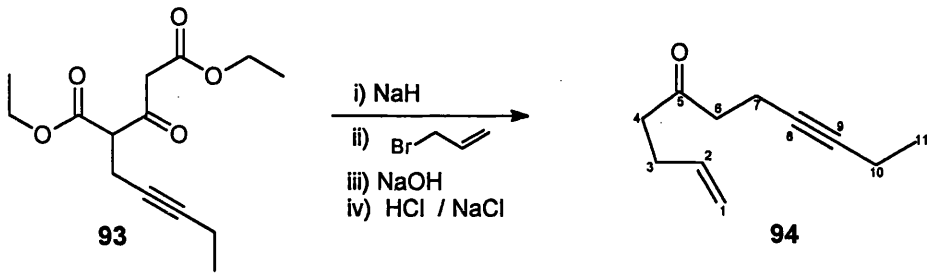
A mixture of absolute alcohol (55 ml), magnesium turnings (1.80 g, 75 mmol) and molecular iodine (0.1 g, 0.4 mmol) was refluxed with stirring until all the magnesium had disappeared (*ca* 24 h). To the solution was added ethyl 3-oxoglutarate (10.11 g, 50 mmol). After refluxing for 1 h, 1-bromo-2-pentyne (**85**) (8.12 g, 55 mmol) was added *via* a syringe pump over 30 min.

The reaction mixture was heated for a further 10 h before being cooled to rt and then the solvent was removed under reduced pressure. The residual brown liquid was acidified with hydrochloric acid (2 N, 40 ml), and extracted with diethyl ether (3 x 40 ml), the combined organic extracts were further washed with sodium bicarbonate solution (5 %, 30 ml) and then with brine (30 ml), dried ($MgSO_4$) and evaporated *in vacuo.* The residue was distilled to give the title compound as a colourless oil (3.40 g, 25 % yield).

Bp 120-123 °C (0.9 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 1740 (s), 1720 (s), 1370 (s); δ_H (400 MHz; $CDCl_3$) 1.08 (3 H, t, *J* 7.5 Hz, 9-H), 1.28 (6 H, t, *J* 6.8 Hz 14-H, 1-H), 2.19 (2 H, tq, *J* 7.5, 2.3 Hz, 8-H), 2.71 (2 H, m, 11-H), 3.64 (2 H, dt, *J* 7.2, 2.3 Hz, 5-H), 3.83 (1 H, t, *J* 7.2 Hz, 4-H), 4.20 (4 H, q, *J* 6.8.Hz, 13-H, 2-H); δ_C (100 MHz; $CDCl_3$), 12.35, 14.02, 14.09, 17.90, 48.76, 51.23, 61.56 (C-13), 61.91 (C-2), 74.90 (C-6), 84.19 (C-7), 166.45 (C-3), 167.85 (C-12), 196.54 (C-10); *m/z* (EIMS) 268 (M^+, 2 %),

222 (M^+ -OEt, 15), 207 (M^+ -CO_2Et, 45) 188 (M^+ - 2x (OEt), 23), 146 (M^+ -2x (CO_2Et), 100).

R32 **1-Undecen-8-yn-5-one(94)**



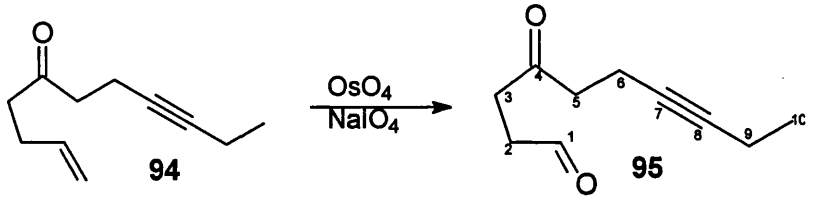
93 **94**

A solution of diester (**93**) (2.91 g, 10.8 mmol) in dry 1,2 dimethoxyethane (5 ml) was added dropwise to a stirred solution of sodium hydride (430 mg, 10.8 mmol) in dry dimethoxyethane (8 ml) at rt under nitrogen. The mixture was allowed to stir for 1 h. Allyl bromide (1.62 g, 13.2 mmol) and finely divided powdered sodium iodide (1.62 g, 10.8 mmol) was then added to the mixture and refluxed with stirring for 15 h

The reaction mixture was then cooled to rt and the solvent was removed *in vacuo.* Sodium hydroxide solution (20 %, 30 ml) was added to the residue and heated for 18 h. The reaction mixture was acidified with hydrochloric acid (14 N, 5 ml), saturated with brine, and extracted with diethyl ether (3 x 30 ml). The ether solution was washed with brine (20 ml), dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was purified by column chromatography (eluent, petroleum spirits 40-60 °C / ethyl acetate, 20 : 1). The title compound was isolated as a colourless oil (320 mg, 19 %).

υ_{max} (NaCl; neat) / cm^{-1} 3078 (w), 2976 (s), 2919 (s), 2289 (w), 2234 (w), 1711 (s), 1641 (m); δ_H (400 MHz; $CDCl_3$), 1.08 (3 H, t, *J* 7.5 Hz, 11-H), 2.13 (2 H, tq, *J* 7.5, 2.4 Hz, 10-H), 2.33 (2 H, dd, *J* 6.8, 2.4 Hz, 7-H), 2.38 (2 H, m, 3-H), 2.53 (2 H, t, *J* 7.5 Hz, 4-H), 2.60 (2 H, t, *J* 7.5 Hz); 5.00 (2 H, m, 1-H), 5.80 (1 H, m, 2-H); δ_C (100 MHz; $CDCl_3$), 12.38, 13.43, 14.21, 27.68, 41.90, 42.13, 77.79 (C-7), 82.26 (C-10), 115.28 (C-1), 137.02 (C-2), 208.47 (C-5); *m/z* (EIMS) 164 (M^+, 4 %), 149 (M^+ -CH_2, 18), 135 (M^+ -$CH{=}CH_2$, 35), 122 (96), 109 (M^+ -$C{\equiv}CCH_2CH_3$, 100), 81 (M^+ -$CH{=}CH_2$, -$C{\equiv}CCH_2CH_3$, 55), 79 (48), found for $C_{11}H_{16}O$ (M^+) 168.1209; Required 168.1201.

R34 **4-oxo-7-decynal (95)**

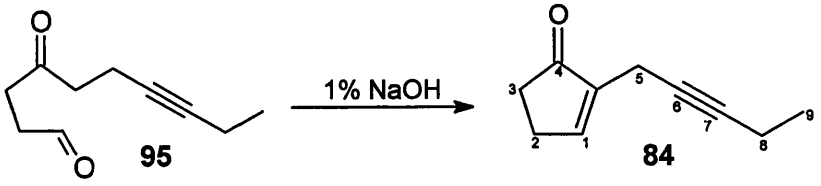


A solution of osmium tetroxide (25 mg) in water (1 ml) was added dropwise to a stirred solution of 5-oxo-8-undecyn-1-ene (**94**) (150 mg, 1 mmol) in tetrahydrofuran (5 ml). After 10 min at 0° C, finely divided sodium periodate (660 mg, 3.1 mmol) was added to it over 20 min and the stirring continued for 1 h at rt. A white solid precipitated during the reaction and was filtered and washed with diethyl ether.

The reaction mixture was further extracted with diethyl ether (4 x 30 ml), the combined organic extracts were washed with saturated $NaHCO_3$ (20 ml) and then brine (20 ml), dried ($NaSO_4$) and concentrated *in vacuo* to give a yellow oil. The oil was purified by column chromatography (eluent: petroleum spirits 30-40° C / diethyl ether, 5:1). The title compound was isolated as a colourless oil (84 mg, 55 %).

υ_{max} (NaCl; neat) / cm^{-1} 2731 (s), 1735 (s), 1710 (s), 1412 (s); δ_H (400 MHz; $CDCl_3$), 1.08 (3 H, t, *J* 7.4 Hz, 10-H), 2.13 (2 H, tq, *J* 7.4, 2.4 Hz, 9-H), 2.33 (2 H, t, *J* 6.8 Hz, 5-H), 2.38 (2 H, m, 6-H), 2.52 (2 H, t, *J* 7.5 Hz, 3-H), 2.61 (2 H, t, *J* 7.5 Hz, 2-H), 9.66 (1 H, s, 1-H);

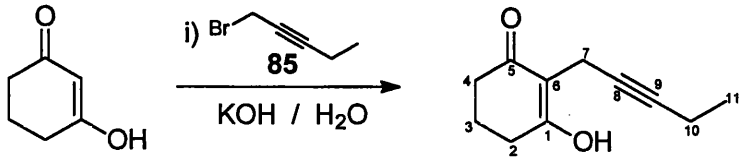
R35 **2-(2-pentynyl)-2-cyclopenten-1-one (84)**



4-Oxo-7-decyn-1-al (40 mg, 0.24 mmol) was treated with aqueous sodium hydroxide solution (1%, 5 ml) for 1 h at 70 °C, the reaction was cooled to rt and extracted with diethyl ether (3x 20 ml) the combined organic extracted were dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown oil the oil was purified by column chromatography (eluent: petroleum spirits 40-60 °C / diethyl ether, 15 : 1). The title compound was isolated as a colourless oil (21 mg, 61 %).

υ_{max} (NaCl; neat) / cm^{-1} 2975 (s), 2920 (s), 2236 (w), 1698 (s), 1638(m), 1442 (s), 1362 (s); δ_H (400 MHz; $CDCl_3$), 1.08 (3 H, t, *J* 7.5 Hz, 9-H), 2.13 (2 H, tq, *J* 7.5, 2.4, 8-H), 2.42 (2 H, m, 2-H), 2.58 (2 H, t, *J* 4.9, 3-H), 3.00 (2 H, dd, *J* 4.6, 2.4, 5-H), 7.57 (1 H, m, 1-H); δ_C (100 MHz; $CDCl_3$), 12.41 (C-9), 14.16 (C-8), 15.62, 26.38, 34.93, 23.79, 84.05,142.57 (C-1), 159.13, 208.27 (C-4); *m/z* (EIMS) 148 (M^+, 100 %), 133 (M^+ -H -CH_3, 95), 105 (M^+ -CH_2CH_3, 25), 84 (M^+ - $CH_2C{\equiv}CCH_2CH_3$, 78), found for $C_{10}H_{12}O$ (M^+) 148.0880; Required 148.0888.

R36 **2-(2-Pentynyl)-1,3-cyclohexanedione (89)**



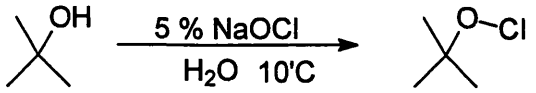
89

1-Bromo-2-pentyne (**85**) (6.70 g, 45.8 mmol) was added to an ice cooled solution of cyclohexan-1-3-dione (**88**) (6.30 g, 53.8 mmol) in potassium hydroxide (3.78 g, 67.3 mmol) and water (14 ml). The reaction mixture was stirred at rt for 15 h before being heated to 50 °C for 2 h.

The mixture was then cooled to rt and poured into sodium hydroxide solution (4 N, 35 ml). The solution was then extracted with diethyl ether (2x 30 ml) to remove any neutral organic compounds. The aqueous layer was then neutralised with hydrochloric acid (14 N, 27 ml) in crushed ice (≈27 g). A white precipitate formed which was filtered and washed with dilute sodium carbonate solution (5 %, 20 ml) and then with water (20 ml), dried and then recrystallised from methanol to afford the title compound as colourless crystals (5.61 g, 65 %).[73]

Mp 179-181° C; υ_{max} (KBr) / cm^{-1} 3330 (s), 1620 (w), 1575 (s) 1215 (s), 1012 (s); δ_H (400 MHz; $CDCl_3$), 1.14 (3 H, t, *J* 7.5 Hz, 11-H), 1.96 (2 H, m, 3-H), 2.21 (2 H, tq, *J* 7.5, 2.6, 10-H), 2.42 (4 H, m, 2-H, 4-H), 3.26 (2 H, d, *J* 2.6 Hz, 7-H), 8.37 (1 H, s, O*H*); δ_C(100 MHz; $CDCl_3$) 12.63 (C-11), 13.22 (C-10), 24.41, 32.23, 36.80, 68.01, 73.42 (C-8), 85.61 (C-9), 125.47 (C-6), 144.16 (C-1), 200.75 (C-5); *m/z* (EIMS) 178 (M^+, 46 %), 163 (M^+ -CH_3, 100), 149 (M^+ -H, -CH_2CH_3, 19), 122 (M^+ -O, -CH_2CH_3, 22), 107 (M^+ -O, $C{\equiv}CCH_2CH_3$, 31), found for $C_{11}H_{14}O_2$ (M^+)178.1000; Required 178.0994.

R37 ***tert*-Butyl hypochlorite (90)**

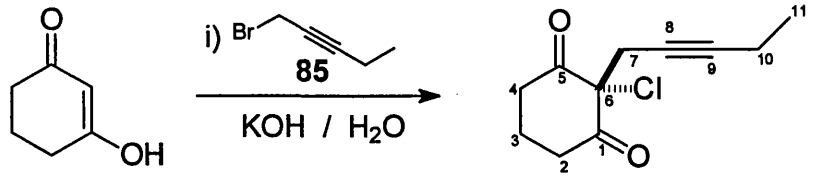


90

In a I litre conical flask, was placed commercial household bleach (500 ml) containing sodium hydrochlorite (5 %). The solution was cooled to 10 °C, and a solution of *t*-butyl alcohol (37 ml, 0.39 mol) in glacial acetic acid (24.5 ml, 0.43 mol) was added in one portion to the bleach solution with rapid stirring, (light in the vicinity of the apparatus was turned off). The reaction mixture was stirred for 5 min before being poured into a separating funnel. The lower aqueous layer was discarded and the oily yellow organic layer was washed with sodium carbonate solution (10 %, 50 ml) and then water (50 ml). The product was dried ($CaCl_2$) and filtered, to afford the title compound (30.12 g, 76 %).

υ_{max} (NaCl; neat) / cm^{-1} 2983 (s), 2936 (s), 1458(s), 1390(s), 1367(s), 1247 (s); δ_H (300 MHz; $CDCl_3$), 1.35 (9 H, s).

R38 **2-Chloro-2-(2-pentynyl)-1,3-cyclohexanedione (87)**



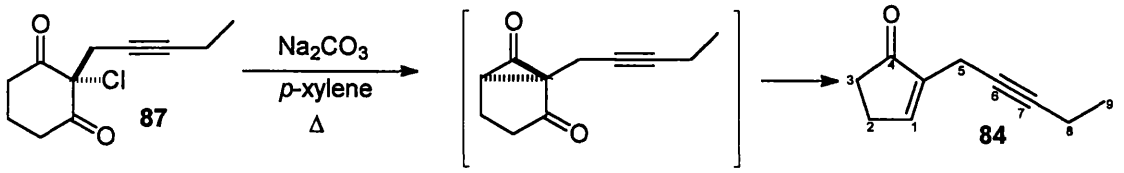
89

t-Butyl hypochlorite (**90**) (3.41 g, 30.9 mmol) was added under nitrogen atmosphere over a 2 h period to a suspension of 2-(2-Pentynyl)-1,3-cyclohexanedione (**89**) (5.52 g, 30.9 mmol) in dry chloroform (45 ml) at -20 °C. After addition was complete the reaction mixture was allowed to warm up to rt over 2 h. The chloroform was removed *in vacuo* to afford a brown oil which was purified by column chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 10:1). The title compound was isolated as a colourless oil, (6.22 g, 93 %).[73]

υ_{max} (NaCl; neat) / cm^{-1} 2976 (s), 2937 (s), 2878 (s), 2234 (w), 1743 (s), 1719 (s), 1414 (s), 1320 (s); δ_H (400 MHz; $CDCl_3$), 1.04 (3 H, t, *J* 7.5 Hz, 11-H), 1.83 (1 H, m 3'-H), 2.07 (2 H, tq, *J* 7.5, 2.4,10-H), 2.19 (1 H, m, 3-H), 2.63 (2 H, m, 4'-H, 2'-H, *overlap*), 3.00 (2 H, t, *J* 2.4 Hz, 7-H), 3.07 (2 H, m, 4'-H, 2'-H *overlap*); δ_C(100 MHz; $CDCl_3$), 12.36 (C-11), 13.92 (C-10), 17.09, 23.79, 36.80, 68.01 (C-6), 73.61 (C-8),

85.61(C-9), 199.76 (C-5, C-1); *m/z* (EIMS) 180 (M^+ -H, 3 %), 151 (M^+ -CH_2CH_3, 45), 80 (34), 77 (100), found for $C_{11}H_{13}O_2Cl$ (M^+) 212.0620; Required 212.0604;

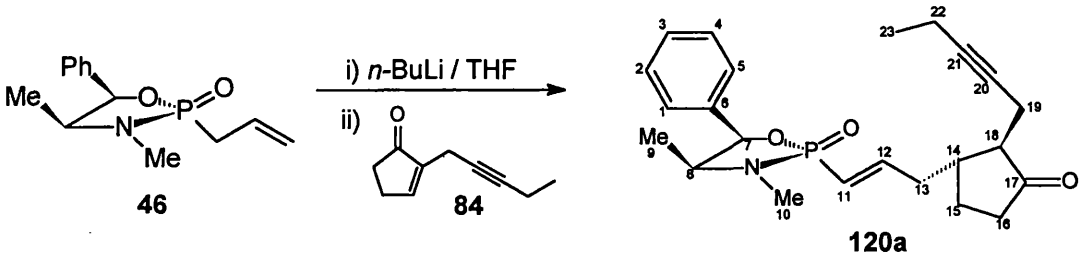
R39 2-(2-Pentynyl)-2-cyclopenten-1-one (84)



1-Chloro-1-(2-pentynl)-2,6-cyclohexanedione (**87**) (6.02 g, 28.2 mol) in dry *p*-xylene (55 ml) was allowed to reflux in the presence of anhydrous sodium carbonate (3.01 g, 23.3 mmol) until gas evolution had ceased (*ca* 18 h). The reaction mixture was cooled and diluted with petroleum spirits 40-60 °C before being filtered. The filtrate was concentrated *in vacuo* to a pale brown oil. The oil was purified by flash chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 20 :1) to afford the title compound as a colourless oil (1.92 g, 48 %).[73]

υ_{max} (NaCl; neat) / cm^{-1} 2975 (s), 2920 (s), 2236 (w), 1698 (s), 1638(m), 1442 (s), 1362 (s); δ_H (400 MHz; $CDCl_3$), 1.08 (3 H, t, *J* 7.5 Hz, 9-H), 2.13 (2 H, tq, *J* 7.5, 2.4, 8-H), 2.42 (2 H, m, 2-H), 2.58 (2 H, t, *J* 4.9, 3-H), 3.00 (2 H, dd, *J* 4.6, 2.4, 5-H), 7.57 (1 H, m, 1-H); δ_C (100 MHz; $CDCl_3$), 12.41 (C-9), 14.16 (C-8), 15.62, 26.38, 34.93, 23.79, 84.05,142.57 (C-1), 159.13, 208.27 (C-4); *m/z* (EIMS) 148 (M^+, 100 %), 133 (M^+ -H -CH_3, 95), 105 (M^+ -CH_2CH_3, 25), 84 (M^+ - $CH_2C{\equiv}CCH_2CH_3$, 78), found for $C_{10}H_{12}O$ (M^+) 148.0880; Required 148.0888.

R40 (2*S*,4*S*,5*R*)-3,4-dimethyl-2-{(*E*)-3-[(1*S*,2*R*)-3-oxo-2-(2-pentynyl)cyclopentyl]-1-propenyl}-5-phenyl-1,3,2-λ^5-oxazaphospholan-2-one (120a)



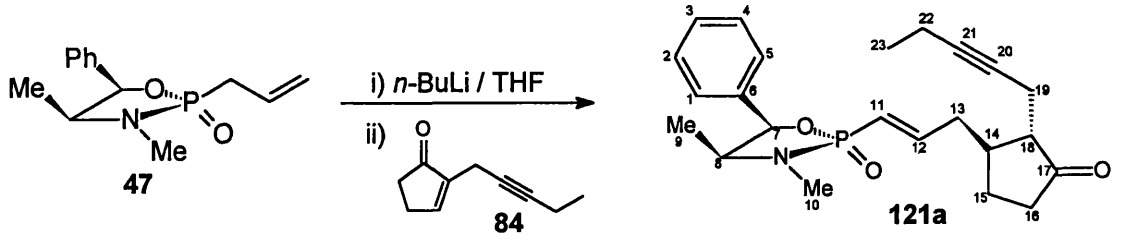
To a cooled solution (-78 °C) of phospholidinone (**46**), (1.70 g, 6.76 mmol) in tetrahydrofuran (20 ml) was added *n*-butyllithium in *n*-hexanes (2.7 ml, 6.76 mmol),

the reaction was stirred for 30 min before enone (**84**) (1.01 g, 6.76 mmol) was added. The reaction was stirred for a further 30 min before being quenched by addition of saturated ammonium chloride solution (5 ml). The reaction mixture was when extracted from ethyl acetate (3x 30 ml). The combined organic layers were dried ($MgSO_4$) and reduced *in vacuo* to afford a colourless syrup. The syrup was purified by column chromatography (eluent: neat ethyl acetate) to afford the title compound as a colourless viscous oil (2.05 g, 76 %).

(**120a**) υ_{max} (NaCl; neat) / cm^{-1} 2973 (s), 2934 (s), 2228 (w), 1741 (s), 1627 (m); δ_H (400 MHz; $CDCl_3$), 0.84 (3 H, d, *J* 6.5 Hz, 9-H), 1.06 (3 H, t, *J* 7.5 Hz, 23-H), 1.17 (1 H, m), 1.48 (1 H, m,), 1.85 (1 H, m,), 2.15 (6 H, m, 13-H, 15-H, 16-H), 2.49 (2 H, dtq, *J* 7.3, 4.6, 2.2 Hz, 22-H) 2.64 (3 H, d, *J* 10.1 Hz, 10-H), 2.72 (1 H, m), 3.60 (1 H, m 8-H), 5.44 (1 H, dd, *J* 4.6, 1.3 Hz, 7-H), 5.81 (1 H, dd, *J* 5.6, 1.4 Hz, 12-H), 6.94 (1 H, m, 11-H), 7.36 (5 H, m, Ph); δ_C (100 MHz; $CDCl_3$), 12.26 (C-23), 14.22 (C-22), 17.45, 26.79, 28.41, 37.67, 38.72, 38.93, 40.14, 52.97, 58.81, 75.66 (C19), 81.77 (C-7), 83.71 (C-21), 119.36, 121.01, 126.07 (C-2, C-4)), 128.11 (C-11), 128.30 (x2,), 151.07 (12-H), 217.78 (C-17); *m/z* (FABMS), 399 (M^+, 6 %), 384 (M^+ -CH_3, 6), 370 (M^+ -CH_2CH_3, 1), 342 (M^+ -$C{\equiv}CCH_2CH_3$, 1), 278 (15), 194 (35), 148 (30), 104 (36), 91 (42 %), 58 (100 %); found for $C_{23}H_{31}O_3PN$ (M^+ +H) 400.2030; Required 400.2040; $[\alpha]_D^{25}$ = -66.9 ° (*c*=1.25 in EtOH).

(**120b**) minor component, (non overlap signals); δ_H (400 MHz; $CDCl_3$), 0.85 (3 H, d, *J* 6.6 Hz, 9-H), 3.55 (1 H, m, 7- H), 5.37-5.44 (2 H, m, 7-H, 12-H, overlap).
Diastereoisomeric ratio of (**120a**) : (**120b**) determined by ^{1}H NMR to be 94 : 6 respectively.

R41 (2*R*,4*S*,5*R*)-3,4-dimethyl-2-{(*E*)-3-[(1*R*,2*S*)-3-oxo-2-(2-pentynyl)cyclopentyl]-1-propenyl}-5-phenyl-1,3,2-λ^5-oxazaphospholan-2-one (121a)



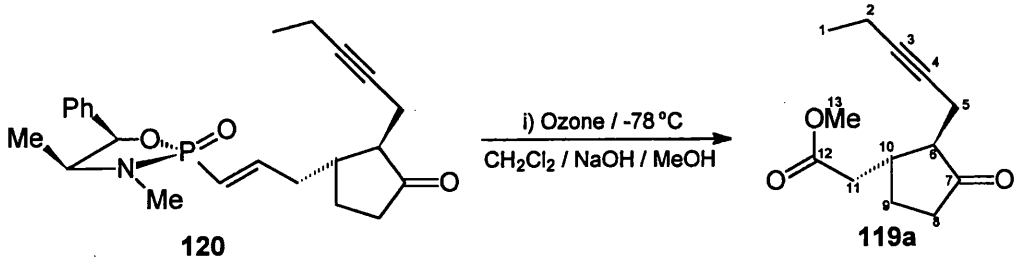
To a cooled solution (-78 °C) of phospholidinone (**47**) (1.70 g, 6.76 mmol) in tetrahydrofuran (20 ml) was added *n*-butyllithium in *n*-hexane (2.7 ml, 6.76 mmol),

the reaction was stirred for 30 min before enone (**84**) (1.00 g, 6.76 mmol) was added. The reaction was stirred for a further 30 min before being quenched by addition of saturated ammonium chloride solution (5 ml). The reaction mixture was when extracted from ethyl acetate (3 x 30 ml). The combined organic layers were dried ($MgSO_4$) and reduced *in vacuo* to afford a colourless syrup. The syrup was purified by column chromatography (eluent: neat ethyl acetate) to afford the title compound as a a colourless viscous oil (2.23 g, 83 %).

(**121a**) υ_{max} (NaCl; neat) / cm^{-1} 2973 (s), 2934 (s), 2614 (m), 2228 (w), 1741 (s), 1627 (s), 1454; δ_H (400 MHz; $CDCl_3$), 0.72 (3 H, d, *J* 6.7, 9-H), 1.08 (3 H, t, *J* 7.5, 23-H), 1.50 (1 H, m) 1.88 (1 H, m), 2.17 (7 H, m), 2.51 (2 H, dtq, *J* 6.9, 5.1, 2.4, 22-H), 2.73 (3 H, d, *J* 9.6, 10-H), 2.78 (1 H, m, 13'-H), 3.74 (1 H, m, 7-H), 5.71 (2 H, m, 9-H, 12-H), 7.07 (1 H, m, 11-H), 7.32 (5 H, m, Ph); δ_C (100 MHz; $CDCl_3$),12.30 (C-23), 14.01, 14.18 17.50, 26.78, 37.73, 38.79, 39.00, 39.97, 52.95, 60.35, 75.69 (C-20), 80.34, 83.76 (C-21), 120.34, 122.64, 125.65 (C-12), 128.69 (x2), 128.36 (x2), 151.52 (C-11), 217.79 (C-17); *m/z* (FABMS), 400 (M^+ +H, 8 %), 384 (M^+ -CH_3, 4), 370 (M^+ -CH_2CH_3, 2), 342 (M^+ -$C{\equiv}CCH_2CH_3$, 1), 307 (M^+ -CH_3, -C_6H_5, 5), 278 (15), 194 (30), 148 (30), 104 (80), 91 (40), 58 (100), found for $C_{23}H_{30}O_3PN$ (M^+) 399.1950; Required 399.1963; $[\alpha]_D^{25}$ = -14.2 ° (*c*=1.25 in EtOH).

(**121b**) minor component, (non overlap signals); δ_H (400 MHz; $CDCl_3$), 0.79 (3 H, d, *J* 6.3 Hz, 9-H), 3.65 (1 H, m, 7- H), 5.40-5.56 (2 H, m).
Diastereoisomeric ratio of (**121a**) : (**121b**) determined by ^1H NMR to be 92 : 8 respectively.

R42 Methyl 2-[1*R*,2*R*)-3-oxo-2-(2-pentynyl)cyclopentyl] acetate (119a) [(-)-Methyl dehydrojasmonate]



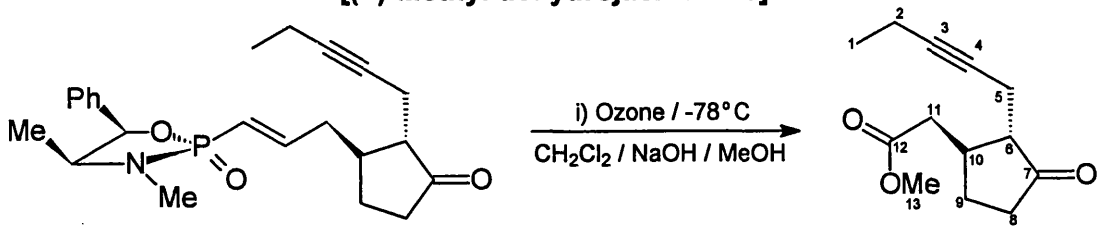
120 **119a**

To a cooled solution of alkyne (**120**) (2.00 g, 5.1 mmol) in anhydrous dichloromethane (150 ml) at -78 °C was bubbled molecular oxygen for 5 min, before ozone was allowed to pass. The reaction was monitored by tlc analysis and after 1.5 h the reaction mixture had turned a pale yellow colour. Tlc analysis showed

formation of a new compound, (R_f 0.3, petroleum spirits 40-60°C – ethyl acetate, 4: 1) The reaction bubbled with nitrogen and then allowed to warm to rt. The mixture was diluted with water (20 ml). The organic layer was separated and the aqueous layer extracted from diethyl ether (3 x 30 ml), the combined organics were dried ($MgSO_4$) and reduced *in vacuo* to afford a brown oil. The product was obtained after flash chromatography (eluent: petroleum spirits / ethyl acetate, 20:1). The title compound was isolated as a colourless oil (360 mg, 35 %). (Starting material (510 mg) was also recovered, leading to an overall yield of 45 % based on consumed material).

υ_{max} (NaCl; neat) / cm^{-1} 2934 (s), 2953 (s), 2937 (s), 1742 (s),1740 (s); δ_H (400 MHz; $CDCl_3$), 1.08 (3 H, t, *J*, 7.6 Hz, 1-H), 1.51 (1 H, m), 1.93 (1 H, m), 2.11 (2 H, tq, *J* 4.7, 1.7 Hz, 2-H), 2.29 (1 H, m), 2.41 (2 H, m), 2.48 (2 H, m), 2.54 (1 H, m, 11'-H), 2.84 (1 H, dd, *J* 15.3, 4.6 Hz, 11'-H), 3.71 (3 H, s, 13-H); δ_C (100 MHz; $CDCl_3$), 12.32, 14.11, 17.45, 27.15, 37.67, 37.88, 38.55, 51.60 (C-11), 52.87 (C-5), 75.76 (C-3), 88.68 (C-4), 172.52 (C-12), 217.50 (C-7); *m/z* (EIMS) 223 (M^+ + H, 20%), 193 (M^+ - OMe, 32), 149 (M^+ - CH_2CO_2Me, 29), found for $C_{13}H_{18}O_3$ (M^+) 222.1259; Required 222.1256; $[\alpha]_D^{25}$ = -75.5 ° (*c*=0.675 in MeOH).

R43 Methyl 2-[1*S*,2*S*)-3-oxo-2-(2-pentynyl)cyclopentyl] acetate (119b) [(+)-Methyl dehydrojasmonate]



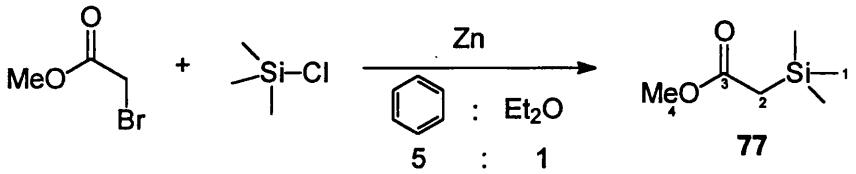
121 **119b**

To a cooled solution of alkyne (**121**) (2.01 g, 5.1 mmol) in anhydrous dichloromethane (150 ml) at -78 °C was bubbled molecular oxygen for 5 min, before ozone was allowed to pass. The reaction was monitored by tlc analysis and after 40 min the reaction mixture had turned a pale yellow colour. (New spot R_f 0.3 petroleum spirits 40 -60° C / ethyl acetate, 4 :1). The reaction was bubbled with nitrogen and then allowed to warm to rt. The mixture was diluted with water (20 ml). The organic layer was separated and the aqueous layer extracted from ethyl diethyl ether (3 x 30 ml), the combined organics were dried ($MgSO_4$) and reduced *in vacuo* to afford a brown oil. The product was obtained after flash chromatography (eluent: petroleum

spirits 40 -60° C / ethyl acetate, 20:1), as a colourless oil (373 mg, 36 %). (Starting material (**121**) was also recovered (610 mg) leading to an overall yield of 55 % based on consumed material).

υ_{max} (NaCl; neat) / cm^{-1} 2934 (s), 2953 (s), 2937 (s), 1742 (s),1740 (s); δ_H (400 MHz; $CDCl_3$), 1.08 (3 H, t, *J*, 7.6 Hz, 1-H), 1.51 (1 H, m), 1.93 (1 H, m), 2.11 (2 H, tq, *J* 4.7, 1.7 Hz, 2-H), 2.29 (1 H, m), 2.41 (2 H, m), 2.48 (2 H, m), 2.54 (1 H, m, 11'-H), 2.84 (1 H, dd, *J* 15.3, 4.6 Hz, 11'-H), 3.71 (3 H, s, 13-H); δ_C (100 MHz; $CDCl_3$), 12.32, 14.11, 17.45, 27.15, 37.67, 37.88, 38.55, 51.60 (C-11), 52.87 (C-5), 75.76 (C-3), 88.68 (C-4), 172.52 (C-12), 217.50 (C-7); *m/z* (EIMS) 223 (M^+ + H, 20%), 193 (M^+ - OMe, 32), 149 (M^+ - CH_2CO_2Me, 29), found for $C_{13}H_{18}O_3$ (M^+) 222.1259; Required 222.1256; $[\alpha]_D^{25}$ = +61.5 ° (*c*=0.750 in MeOH).

R44 **Methyl 2-(1,1,1 trimethylsilyl) acetate (77)**

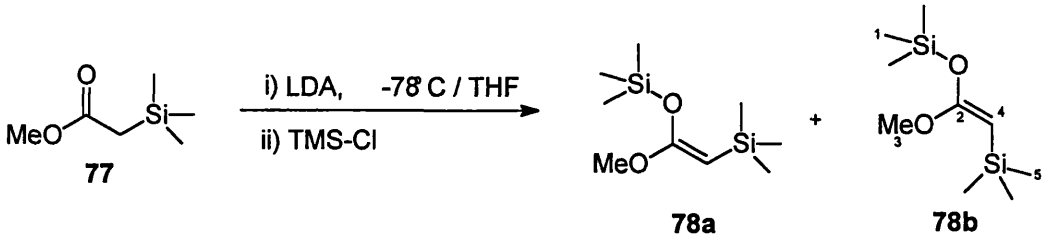


77

A solution of zinc (6.12 g, 97 mmol) in benzene (100 ml) was gently warmed to 50° C and a premixed solution of methyl bromoacetate (9.5 ml, 100 mmol), trimethyl silyl chloride (10.2 ml, 80 mmol), benzene (20 ml) and diethyl ether (20 ml) was added over 30 min. After the addition was complete the reaction was stirred until all the zinc had dissolved (ca 1.5 h). The reaction was then cooled to 0° C. and diluted with hydrochloric acid (1 N, 80 ml) over 15 min. The reaction was stirred for a further 5 min before the organics were separated. The aqueous layer was extracted with diethyl ether (2x 30 ml). The combined organics were washed with dilute hydrochloric acid (1 N, 20 ml) and then treated with saturated bicarbonate (20 ml). The organic lacer was then dried ($MgSO_4$) and reduced *in vacuo* to afford a pale yellow oil. The crude material was distilled under reduced pressure to give the title compound as a colourless oil (5.82 g, 49 %).

Bp 38-39° C (13 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 2413 (m), 1728 (s); δ_H (400 MHz; $CDCl_3$), 0.12 (9 H, s, H_3CSi), 1.79 (2 H, s, CH_2), 3.52 (3 H, s, CH_3O); δ_C (100 MHz; $CDCl_3$), -1.72 ($Si(CH_3)_2$), 26.42 ($C(O)CH_2Si$) , 51.72 (OCH_3), 173.81 (CO_2Me); *m/z* (EIMS) 146 (M^+, 2 %), 131 (M^+ - CH_3, 20 %), 101 (M^+ -OCH_3, 26 %).

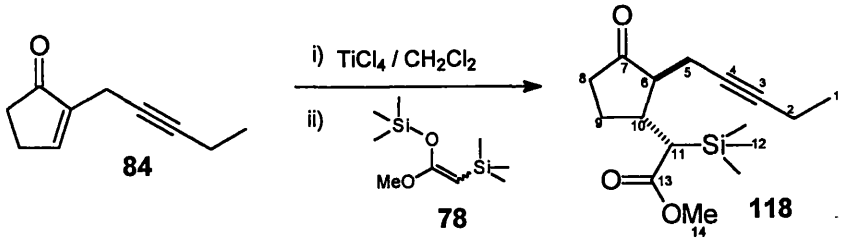
R45 {[(*Z*)-1-methoxy-2-(1,1,1-trimethylsilyl)-1-etheny]oxy}(trimethyl)silane (78a)
{[(*E*)-1-methoxy-2-(1,1,1-trimethylsilyl)-1-etheny]oxy}(trimethyl)silane (78b)



To a tetrahydrofuran solution (26 ml) of lithium diisopropylamide generated from *n*-butyllithium (21.8 mmol,) and diisopropylamine (2.24 g, 22.2 mmol) was added methyl (trimethylsilyl) acetate (**77**) (2.31 g, 15.7 mmol) at -78 °C. After being stirred for 3.5 h at -78 °C, the reaction mixture was quenched with an excess of chlorotrimethylsilane (2.81 g, 26.1 mmol) at the same temperature. The mixture was stirred for a further 1.5 h at rt and concentrated under reduced pressure. Distillation of the residual liquid afforded the title compounds as a colourless liquid (2.81 g, 81 %). (Mixture of geometric isomers).

Bp 40-41° C (0.5 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 1612 (w), 1252 (s) ($SiCH_3$); δ_H (400 MHz; $CDCl_3$), *major isomer* -0.01 (9 H, s, 1-H), 0.25 (9 H, s, 5-H), 2.78 (1 H, s, 4-H), 3.46 (3 H, s, 3-H); *minor isomer* 0.01 (9 H, s, 1-H), 0.19 (9 H, s, 5-H), 2.86 (1 H, s, 4-H), 3.51 (3 H, s, H_3CO); *m/z* (EIMS) 217 (M^+ -H, 30 %), 129 (M^+ -$OSi(CH_3)_3$, 23), 73 ($Si(CH_3)_3$, 100).

R46 Methyl (2*R)-2-[(1*R**,2*R**)-3-oxo-2-(2-pentynyl)cyclopentyl]-2-(1,1,1- trimethylsilyl)ethanoate (118)**

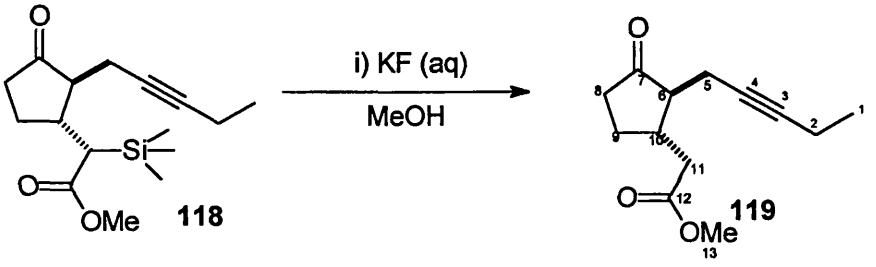


To a solution of 2-pentynyl-2-cyclopenten-1-one (**84**) (250 mg, 1.84 mmol), in dichloromethane (5 ml) was added titanium tetrachloride (360 mg, 1.9 mmol) at -78 °C, the reaction was stirred for 5 min before enolether (**78**) (410 mg, 1.9 mmol) was added. A dark red solution resulted, the mixture was warmed up to rt and stirred for 18 h. The reaction mixture was then cooled back to -78 °C and quenched by addition of aqueous potassium carbonate (1.7 M, 3 ml). The resulting mixture was stirred for 10 min at rt and extracted ethyl acetate (3x 20 ml). The combined extracts

were dried ($MgSO_4$) and concentrated *in vacuo*. The residual oily liquid was purified by column chromatography (eluent: petroleum spirits / ethyl acetate, 20: 1). The title compound was isolated as a colourless oil (255mg, 52 %).

υ_{max} (NaCl; neat) / cm^{-1} 2974 (s), 2223 (w), 1741 (s), 1725 (s); δ_H (400 MHz; $CDCl_3$), 0.18 (9 H, s, 12-H), 1.08 (3 H, t, *J* 7.4 Hz, 1-H), 2.04 (1 H, m), 2.10 (2 H, qt, *J* 4.2, 2.3 Hz, 2-H), 2.22 (1 H, m), 2.36-2.49 (6 H, m,8-H, 5-H), 2.56 (1 H, d, *J* 3.4, 11-H), 3.64 (3 H, s, 14-H); δ_C (100 MHz; $CDCl_3$), -1.40 (C-12), 12.32, 14.20, 17.03, 24.05, 37.47, 38.86, 39.74, 50.80, 51.43 (14-H), 75.66 (C-4), 83.78 (C-3), 174.22 (C-13), 217.89, (C-7); *m/z* (EIMS) 295 (M^+ + H, 5 %), 265 (M^+ + H, - OCH_3, 20), 149 (M^+ - MeO_2C-$CHSi(CH_3)_3$, 30), found for $C_{16}H_{26}O_3Si$ (M^+) 294.1650; Required 299.1651.

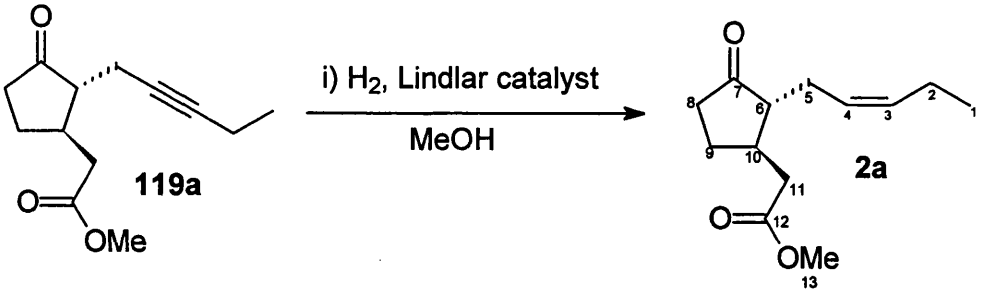
R47 Methyl 2-{(1*S**, 2*S**)-3-oxo-2-(2-pentynyl)cyclopentyl}acetate (119) [Methyl dehydrojasmonate]



To a solution of cyclopentan-1-one (**118**) (200 mg, 0.68 mmol) in aqueous methanol (20 %, 6 ml) was added potassium fluoride (200 mg, 3.5 mmol) and stirred at rt for 4 h. The reaction was worked up by reducing *in vacuo* and extracted with dichloromethane (3 x 30 ml), the combined extracts were dried ($MgSO_4$) and reduced *in vacuo*. The resulting oil was purified by chromatography, (eluent : petroleum spirits 40 -60 °C / ethyl acetate, 15 :1) at afford the title compound as a colourless oil (125 mg, 83 %).

υ_{max} (NaCl; neat) / cm^{-1} 2934 (s), 2953 (s), 2937 (s), 1742 (s),1740 (s); δ_H (400 MHz; $CDCl_3$), 1.08 (3 H, t, *J*, 7.6 Hz, 1-H), 1.51 (1 H, m), 1.93 (1 H, m), 2.11 (2 H, tq, *J* 4.7, 1.7 Hz, 2-H), 2.29 (1 H, m), 2.41 (2 H, m), 2.48 (2 H, m), 2.54 (1 H, m, 11'-H), 2.84 (1 H, dd, *J* 15.3, 4.6 Hz, 11'-H), 3.71 (3 H, s, 13-H); δ_C (100 MHz; $CDCl_3$), 12.32, 14.11, 17.45, 27.15, 37.67, 37.88, 38.55, 51.60 (C-11), 52.87 (C-5), 75.76 (C-3), 88.68 (C-4), 172.52 (C-12), 217.50 (C-7); *m/z* (EIMS) 223 (M^+ + H, 20%), 193 (M^+ - OMe, 32), 149 (M^+ - CH_2CO_2Me, 29), found for $C_{13}H_{18}O_3$ (M^+) 222.1259; Required 222.1256.

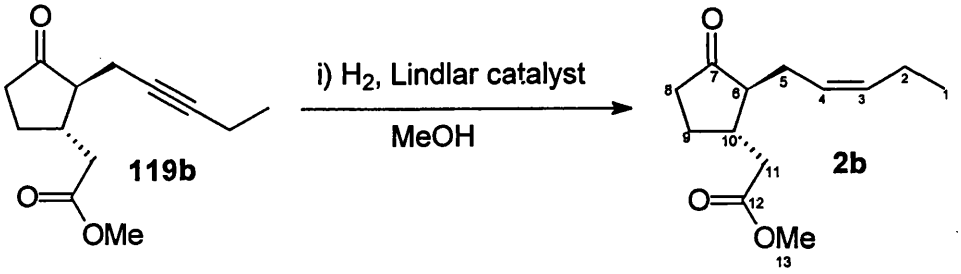
R48 Methyl 2-{(1*R*,2*R*)-3-oxo-2-[(*Z*)-2-pentenyl]cyclopentyl} acetate (2a) [(-)-Methyl jasmonate]



A stirred solution of Lindlar catalyst (Pd-C, containing 5 % calcium carbonate) (20 mg) in methanol (10 ml) was prehydrogenated for 10 min before (-)-(1*R*,2*R*) methyl dehydrojasmonate (**119a**) (120 mg, 0.54 mmol) was added in methanol (2 ml). Hydrogen (13.5 cm^3) was absorbed when uptake was complete, (*ca* 1.5 h). The reaction mixture was filtered through celite and concentrated *in vacuo*. The resulting oil was purified by chromatography (eluent: petroleum spirits / ethyl acetate, 10: 1) to afford the title compound as a colourless oil (110 mg, 88 % yield).

υ_{max} (NaCl; neat) / cm^{-1} 3007 (w), 2962 (s), 2874 (s), 1740 (s), 1654 (w); δ_H (400 MHz; $CDCl_3$), 0.96 (3 H, t, *J* 7.6 Hz, 1-H), 1.49 (1 H, m), 1.89 (1 H, m, 9'-H), 2.06 (2 H, m, 5'-H, 9'-H *overlap*), 2.13 (1 H, m, 5'-H), 2.21-2.40 (6 H, m, 11'-H), 2.67 (1 H, m, 11'-H), 3.70 (3 H, s, 13-H), 5.26 (1 H, m, 4-H), 5.46 (1 H, m, 3-H); δ_C (100 MHz; $CDCl_3$), 14.07 (C-1), 20.57, 25.45, 27.19, 37.71, 37.98, 38.78, 51.58, 53.97 (C-11), 124.89 (C-4), 134.06 (C-3) , 172.51 (C-12), 218.92 (C-7); *m/z* (EIMS) 224 (M^+, 25 %), 194 (M^+ - OCH_3, 27), 151 (M^+ - CH_2CO_2Me, 35), 83 (M^+ -CH_2CO_2Me - C_5H_9, 100), found for $C_{13}H_{20}O_3$ (M^+) 224.1408; Required 224.1412;$[\alpha]_D^{20}$ = -85.5° (*c*=1.54 in MeOH). (Lit $[\alpha]_D^{20}$ = -90.4 ° (*c*= 0.31, MeOH).[13]

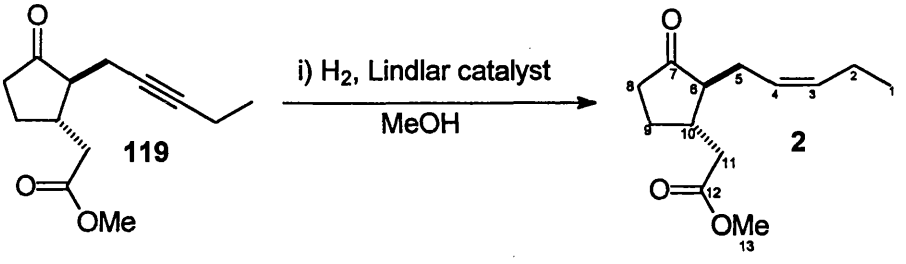
R49 Methyl 2-{(1*S*,2*S*)-3-oxo-2-[(*Z*)-2-pentenyl]cyclopentyl} acetate (2b) [(+)-Methyl jasmonate]



A stirred solution of Lindlar catalyst (Pd-C, containing 5 % calcium carbonate) (20 mg) in methanol (10 ml) was prehydrogenated for 10 min before (+)-(1*S*, 2*S*) methyl dehydrojasmonate (**119b**) (120 mg, 0.54 mmol) was added in methanol (2ml). Hydrogen (13.5 cm^3) was absorbed when uptake was complete, (after 1.5 h). The reaction mixture was filtered through celite and then concentrated *in vacuo*. The resulting oil was purified by chromatography (eluent: petroleum spirits / ethyl acetate, 10: 1) to afford a colourless oil (97 mg) in 82 % yield.

υ_{max} (NaCl; neat) / cm^{-1} 3007 (w), 2962 (s), 2874 (s), 1740 (s), 1654 (w); δ_H (400 MHz; $CDCl_3$), 0.96 (3 H, t, *J* 7.6 Hz, 1-H), 1.49 (1 H, m), 1.89 (1 H, m, 9'-H), 2.06 (2 H, m, 5'-H, 9'-H *overlap*), 2.13 (1 H, m, 5'-H), 2.21-2.40 (6 H, m, 11'-H), 2.67 (1 H, m, 11'-H), 3.70 (3 H, s, 13-H), 5.26 (1 H, m, 4-H), 5.46 (1 H, m, 3-H); δ_C (100 MHz; $CDCl_3$), 14.07 (C-1), 20.57, 25.45, 27.19, 37.71, 37.98, 38.78, 51.58, 53.97 (C-11), 124.89 (C-4), 134.06 (C-3) , 172.51 (C-12), 218.92 (C-7); *m/z* (EIMS) 224 (M^+, 25 %), 194 (M^+ - OCH_3, 27), 151 (M^+ - CH_2CO_2Me, 35), 83 (M^+ -CH_2CO_2Me - C_5H_9, 100), found for $C_{13}H_{20}O_3$ (M^+) 224.1408; Required 224.1412; $[\alpha]_D^{20}$= -80.5° (*c*=1.07 in MeOH), (Lit $[\alpha]_D^{20}$ = +90.4 ° (*c*= 0.33 in MeOH).[13]

R50 Methyl 2-{(1*S,2*S**)-3-oxo-2-[(*Z*)-2-pentenyl]cyclopentyl} acetate (2) [Methyl jasmonate]**

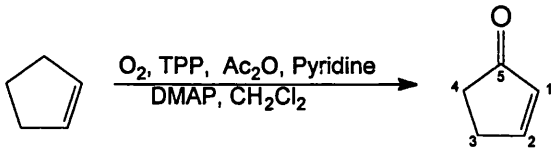


A stirred solution of Lindlar catalyst (Pd-C, containing 5 % calcium carbonate) (20 mg) in methanol (10 ml) was prehydrogenated for 10 min before methyl dehydrojasmonate (**119**) (120 mg, 0.54 mmol) was added in methanol (2 ml). Hydrogen (13.5 cm^3) was absorbed when uptake was complete, (after 1.5 h). The reaction mixture was filtered through celite and then concentrated *in vacuo*. The resulting oil was purified by chromatography (eluent: petroleum spirits / ethyl acetate, 10: 1) to afford the title compound as a colourless oil (105 mg, 87 %).

υ_{max} (NaCl; neat) / cm^{-1} 3007 (w), 2962 (s), 2874 (s), 1740 (s), 1654 (w); δ_H (400 MHz; $CDCl_3$), 0.96 (3 H, t, *J* 7.6 Hz, 1-H), 1.49 (1 H, m), 1.89 (1 H, m, 9'-H), 2.06 (2 H, m, 5'-H, 9'-H *overlap*), 2.13 (1 H, m, 5'-H), 2.21-2.40 (6 H, m, 11'-H), 2.67 (1 H, m, 11'-H), 3.70 (3 H, s, 13-H), 5.26 (1 H, m, 4-H), 5.46 (1 H, m, 3-H); δ_C (100 MHz; $CDCl_3$), 14.07 (C-1), 20.57, 25.45, 27.19, 37.71, 37.98, 38.78, 51.58, 53.97 (C-11), 124.89 (C-4), 134.06 (C-3) , 172.51 (C-12), 218.92 (C-7); *m/z* (EIMS) 224 (M^+, 25 %), 194 (M^+ - OCH_3, 27), 151 (M^+ - CH_2CO_2Me, 35), 83 (M^+ -CH_2CO_2Me - C_5H_9, 100), found for $C_{13}H_{20}O_3$ (M^+) 224.1408; Required 224.1412;

Methyl *epi*-jasmonates

R51 **2-Cyclopenten-1-one (18)**



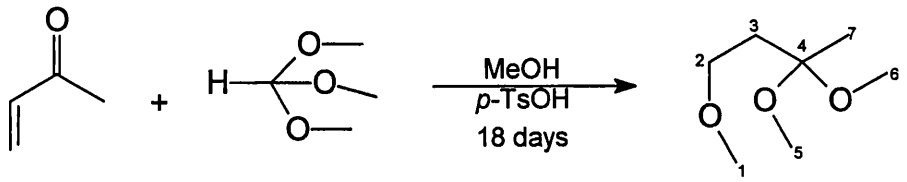
18

To an immersion-well reactor (500 ml capacity) was added a solution of cyclopentene (20.00 g, 294 mmol), acetic anhydride (29.1 ml, 303 mmol), tetraphenylporphin[74] (21 mg, 0.034 mmol), pyridine (11.9 ml, 147 mmol), dimethyl-aminopyridine (716 mg, 6.0 mmol) in dichloromethane (270 ml). (The immersion-well jacket was cooled by circulating cold water), while a gentle stream of oxygen gas was bubbled through. After 10 min the sodium lamp was switched on.

After 2.5 h, the reaction was diluted with dichloromethane (100 ml) and addition of saturated sodium bicarbonate solution (3 x 30 ml). The organic layer was further washed with hydrochloric acid (2 M, 2 x 50 ml). The (lime green) organic layer was treated with saturated copper sulfate solution (30 ml), and then dried ($MgSO_4$) and reduced *in vacuo* to give (22.52 g) crude product. The product was purified by reduced pressure distillation, to give the title compound as a colourless oil (17.12 g, 71 %).

Bp 62-64 °C (30 mmHg);[97] υ_{max} (NaCl; neat) / cm^{-1} 2925 (s), 1709 (s) (C=O), 1588 (w); δ_H (400 MHz; $CDCl_3$), 2.35 (2 H, m, 3-H), 2.67 (2 H, dt, *J* 2.4, 2.3 Hz, 4-H), 6.17 (1 H, m, 2-H), 7.70 (1 H, m, 1-H); δ_C(100 MHz; $CDCl_3$), 28.98 (C-3), 34.01 (C-4), 134.52 (C-2), 164.96 (C-1), 210.64 (C-5); *m/z* (EIMS), 82 (M^+, 45 %), 55 (15);

R52 **1,3,3-Trimethoxybutane (134)**



134

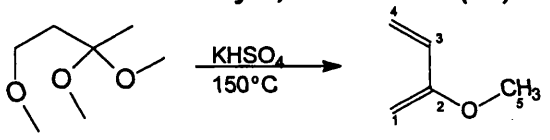
To a solution of methyl vinyl ketone (163 ml, 1.96 mol), trimethyl orthoformate (357 ml, 3.27 mol) in dry methanol (238 ml) was added *p*-toluenesulfonic acid

monohydrate (80.7 mg, 0.43 mmol). An initial exotherm was observed and the reaction mixture turned a dark green colour over a period of 1 h. The reaction mixture was allowed to stand for 12 days.

Potassium carbonate (5.22 g, 37.7 mmol) was added and the reaction stirred for a further 3 days. The reaction was worked up by filtering the reaction mixture. The filtrate was distilled at atmospheric pressure to remove solvent (fraction boiling at 46-64 °C, 276 g), the remaining liquid was distilled under reduced pressure to give the title compound as a colourless oil (211 g, 73 %). [101]

Bp 50-51 °C (15 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 2947 (s), 2889 (s), 2830 (s), 1174 (s), 1117 (s), 1055 (s); δ_H (400 MHz; $CDCl_3$), 1.23 (3 H, s, 7-H), 1.94 (2 H, t, *J* 7.2 Hz, 3-H), 3.17 (6 H, s, 5-H, 6-H), 3.33 (3 H, s, 1-H), 3.43 (2 H, t, *J* 7.2 Hz, 2-H); δ_C (100 MHz; $CDCl_3$), 21.42, 36.17, 47.34, 58.44, 68.74, 100.33, 114.22; *m/z* (EIMS) 149 (M^+, 100%) 117 (M^+ -OMe, 6).

R53 **2-Methoxy-1,3-butadiene (23)**



134 **23**

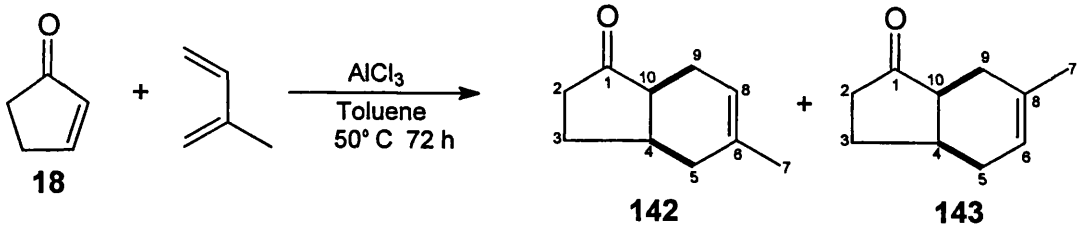
To a 2-necked round bottomed flask (250 ml) fitted with a dropping funnel, 6' Vigreux column and a thermometer, was added 1,3,3 trimethoxybutane (**134**) (8.02 g, 54.1 mmol), potassium hydrogen sulfate (5.8 mg, 0.043 mmol) and hydroquinone (5 mg, 0.043 mmol). The distillation apparatus was purged with nitrogen and the pot flask immersed in a pre-heated oil bath at 145-150 °C. The remaining 1,3,3-trimethoxybutane was added to the pot at a steady rate to maintain a constant amount of material in the pot flask. The distillate was cooled in a flask immersed in an acetone / dry-ice bath. The distillation head temperature remained constant at 60 °C.

The clear distillate was warmed to rt, washed with water (20 ml) and the mixture poured back and forth in separating funnel (not shaken). This was repeated until the organic layer remained a constant volume (*ca x* 4). The organic layer (29.1 g) was then filtered through a fluted filter paper to remove excess water and stored in a fridge over activated 4 Å molecular sieves overnight.

The colourless liquid was re-distilled under atmospheric pressure through a 6' Vigreux column. The title compound was isolated as a colourless oil (11.93 g, 54 %). Fraction boiling 80-94 °C (760 mm) afforded 2.35 g of a mixture containing semi-pyrolysed products.[101]

Bp 75-76 °C (760 mm); υ_{max} (NaCl; neat) / cm^{-1} 3102 (s), 2994 (s), 2942 (s), 2851 (s), 1654 (m), 1582 (m); δ_H (400 MHz; $CDCl_3$), 3.65 (3 H, s, 5-H), 4.16 (2 H, d, *J* 11.0 Hz, 4-H), 5.35 (2 H, m, 1-H), 6.17 (1 H, dd, *J* 11.0, 6.5 Hz, 3-H); δ_C (100 MHz; $CDCl_3$), 54.64 (C-5), 86.40 (C-3), 114.08 (C-4), 133.12 (C-1), 159.85 (C-2); *m/z* (EIMS) 84 (M^+, 75 %), 69 (M^+ -CH_3, 25).

R54 **(3a*R**,3a*S**)-5-Methyl-2,3,3a,4,7,7a-hexahydro-1*H*-1-indenone (142)**
(3a*R,3a*S**)-6-Methyl-2,3,3a,4,7,7a-hexahydro-1*H*-1-indenone (143)**



18 **142** **143**

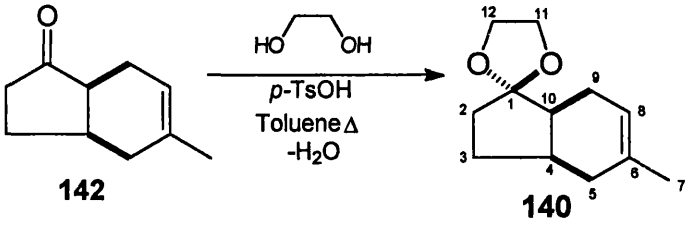
To aluminium trichloride (81 mg, 0.609 mmol), was added a solution of 2-cyclopenten-1-one (**18**) (250 mg, 3.05 mmol) in dry toluene (6 ml) at 10 °C. The reaction mixture was heated to 70 °C for 15 min (complexation period). The reaction was cooled to 50 °C and a solution of isoprene (3.11 g, 45.73 mmol), in dry toluene (29.5 ml) added, under a nitrogen atmosphere and stirred at 50 °C for 72 h.

The reaction was cooled and diluted with water (30 ml) and the mixture was extracted with ether (3 x 60 ml). The combined organic layers were washed with sodium bicarbonate solution (10 %, 20 ml) and dried (Na_2SO_4) and reduced *in vacuo* to give a pale yellow oil. The crude oil was purified by flash chromatography (eluent: with petroleum spirit 40-60 °C / ethyl acetate 20:1). The title compound was isolated as a colourless oil (207 mg, 43 %), (a significant amount of regioisomer from the Diels-Alder cycloadduct was also detected by ^1H NMR).[99]

N.B. mixture of regio isomers, major (**132**) and minor (**133**) components.

υ_{max} (NaCl; neat) / cm^{-1}, 2924 (s), 1734 (s), 1684 (s); δ_H (400 MHz; $CDCl_3$), 1.63 (3 H, s, C-7), 2.03 (2 H, m), 1.77 (2 H, m), 2.27 (6 H, m), 2.52 (1 H, m,10-H), 5.33 (1 H, s x2 (br), 8-H, 6-H); δ_{Ca} (100 MHz; $CDCl_3$ (**142**), 21.69. 23.87, 26.45, 30.80, 32.81, 34.17, 46.53, 118.71 (C-6), 132.22 (C-8), 201.12 (C-1) δ_{Cb} (100 MHz; $CDCl_3$ (**143**), 23.53, 24.81, 27.79, 37.31, 37.71, 39.37, 51.14, 120.23 (C-6), 134.33 (C-6), 202.31 (C-1); *m/z* (EIMS), 150 (M^+,30 %), 135 (M^+ -CH_3, 25), found for $C_{10}H_{14}O$ (M^+) 150.1045; Required 150.1041.

R55 1,4-Dioxaspiro-6-bicyclo-9-methyl[4.4.0]non-8-ene (140)



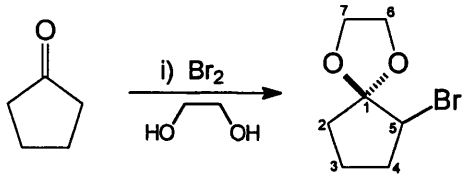
142 **140**

To a solution of ketone (**142**) (351 mg, 2.34 mmol) and *p*-toluenesulfonic acid (51 mg, 0.268 mmol) in dry toluene (20 ml) was added ethylene glycol (freshly distilled) (12.2 ml, 196 mmol). The mixture was heated to reflux, and stirred for 5 h. The reaction was quenched by diluting with water and extracting with ether (3 x 30 ml). The organic layer was washed with sodium bicarbonate solution (5 %, 20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless liquid. The product was purified by flash chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 10 : 1). The title compound was isolated as a colourless oil (238 mg, 53 %).[103]

N.B. A fresh-jasmine like odour.

υ_{max} (NaCl; neat) / cm^{-1} 2879 (s), 2827 (s), 1684 (s), 1663 (w), 1172 (s), 1128 (s); δ_H (400 MHz; $CDCl_3$), 1.25 (1 H, m), 1.54 (1 H, m), 1.63 (3 H, s, 7-H), 1.88 (8 H, m, 2-H, 3-H, 5-H, 9-H), 3.87 (4 H, m, 12-H, 11-H), 5.37 (1 H, s, 8-H); δ_C (100 MHz; $CDCl_3$), 23.44, 24.28, 28.64, 36.60, 37.42, 39.04, 48.59, 64.67, 64.71, 117.04, 120.57, 133.61; *m/z* (EIMS) 194 (M^+, 2%), 150 (M^+ -OCH_2CH_2, 25 %), 135 (M^+ - OCH_2CH_2OH, 15 %), 105 (M^+-$OCH_2CH_2OCCH_2$, 100), found for $C_{12}H_{18}O_2$ (M^+) 194.1314; Required 194.1307.

R56 **6-Bromo-1,4-dioxaspiro[4,4]nonane (139)**

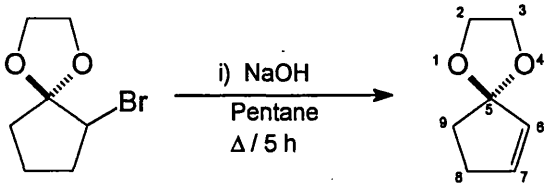


139

To a solution of cyclopentanone (**66**) (1.01 g, 11.9 mmol), in ethylene glycol (15 ml), at rt was added a dropwise molecular bromine (1.91 g, 11.9 mmol). After a short period the uptake of bromine was complete (decolourisation) and the remainder of the bromine was added gradually, at rate as to maintain a faint orange colouration, at a temperature of 14-17 °C. After 1 equivalent of bromine a faint colouration persisted. The reaction was poured into anhydrous sodium carbonate (3.02 g, 28.3 mmol) and pentane (12 ml). After 5 min of stirring, the reaction was diluted with water (15 ml) and the reaction mixture was then extracted with pentane (3x 30 ml). The combined pentane extracts were dried (Na_2SO_4) and concentrated *in vacuo* (low bath temperature). The colourless oil was purified by flash chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 30:1). The title compound was isolated as a colourless oil (1.25 g, 51 %).

υ_{max} (NaCl; neat) / cm^{-1} 2959 (s), 2888 (s), 1471 (m), 1109 (s), 948 (s); δ_H (400 MHz; $CDCl_3$), 1.72 (1 H, m, 3'-H), 1.90 (2 H, m, 3'-H, 2'-H), 2.09 (2 H, m 4'-H, 2'H), 2.31 (1 H, m, 4'-H), 4.03 (5 H, m, 7-H, 6-H, 5-H *overlap*); δ_C(100 MHz; $CDCl_3$), 19.69, 32.18, 33.88, 55.04 (C-5), 65.18 (C-2), 65.53 (C-7), 116.33 (C-1); *m/z* (EIMS) 206 (M^+, 85%), 125 (M^+ -Br, 60), found for $C_7H_{11}O_2Br$ (M^+) 205.9950; Required 205.9942. [104]

R56 **1,4-Dioxaspiro[4.4]non-6-ene (138)**



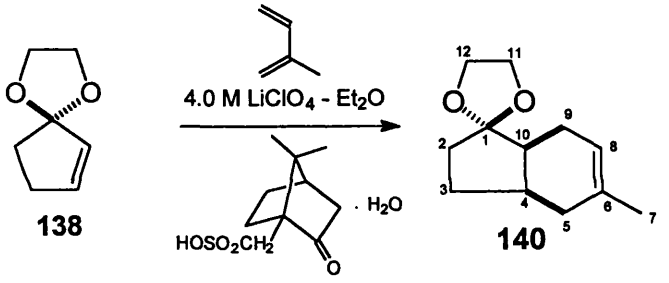
139 **138**

To a solution of 6-bromo-1,4-dioxaspiro[4,4]nonane (**139**) (1.00 g, 4.9 mmol), in methanol (6 ml), was added sodium hydroxide (1.42 g, 35.0 mmol). The reaction mixture was heated to reflux for 5 h. The reaction was allowed to cool to rt and then poured into

saturated brine (11 ml). The product was extracted with pentane (3 x 30 ml) and the combined organics dried (Na_2SO_4) and reduced *in vacuo* (low bath temperature as product, volatile). The title compound was isolated by reduced pressure distillation to give the title compound as a colourless oil (375 mg, 61 %).[104]

Bp 58-60 °C (20 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 3057 (s), 2926 (s), 1619 (m); δ_H (400 MHz; $CDCl_3$), 1.76 (2 H, m, 8-H), 2.24 (2 H, m, 9-H), 3.85 (4 H, m, 2-H, 3-H *overlap*), 5.59 (1 H, m, 7-H), 5.95 (1 H, m, 6-H); δ_C(100 MHz; $CDCl_3$), 29.64 (C-8), 34.30 (C-9), 64.72 (C-2, C3), 120.41 (C-5), 130.31 (C-7), 137.32 (C-6); *m/z* (EIMS) 126 (M^+, 45 %), 83 (M^+ -Br, 100), found for $C_7H_{10}O$ (M^+) 126.0690; Required 126.0681.

R57 1,4-Dioxaspiro-6-bicyclo-9-methyl[4.4.0]non-8-ene (140)



138 **140**

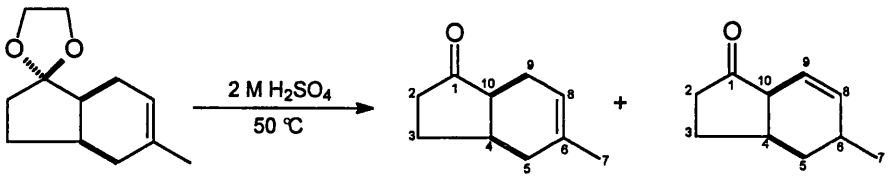
To a solution of 2-cyclopenten-1-one ethylene ketal (**138**) (1.26 g, 10 mmol) in lithium perchlorate- diethyl ether (4.0 M, 40 ml, 160 mmol) was added isoprene (4.0 ml, 40 mmol) and camphor sulfonic acid in tetrahydrofuran (0.5 M, 46 µl, 1 mol %). After 20 minutes a yellow colouration was observed. After 40 minutes, triethylamine (25 µl, 0.18 mmol) was added. (Reaction mixture then turned colourless) the mixture was diluted with water (20 ml) and extracted with diethyl ether (4x 30 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The oil was purified by column chromatography eluent : petroleum spirits 40- 60 C / ethyl acetate, 25 :1) yielding the title compound as a colourless oil (1.65 g, 85 %). [103]

N.B. fruity-jasmine like odour.

υ_{max} (NaCl; neat) / cm^{-1} 2879 (s), 2827 (s), 1684 (s), 1663 (w), 1172 (s), 1128 (s); δ_H (400 MHz; $CDCl_3$), 1.25 (1 H, m), 1.54 (1 H, m), 1.63 (3 H, s, 7-H), 1.88 (8 H, m, 2-H, 3-H, 5-H, 9-H), 3.87 (4 H, m, 12-H, 11-H), 5.37 (1 H, s, 8-H); δ_C (100 MHz; $CDCl_3$), 23.44,

24.28, 28.64, 36.60, 37.42, 39.04, 48.59, 64.67, 64.71, 117.04, 120.57, 133.61; *m/z* (EIMS) 194 (M^+, 2%), 150 (M^+ -OCH_2CH_2, 25 %), 135 (M^+ - OCH_2CH_2OH, 15 %), 105 (M^+-$OCH_2CH_2OCCH_2$, 100), found for $C_{12}H_{18}O_2$ (M^+) 194.1314; Required 194.1307.

R58 **(3a*R**,3a*S**)-5-Methyl-2,3,3a,4,7,7a-hexahydro-1*H*-1-indenone (142)**
(3a*R,3a*S**)-5-Methyl-2,3,3a,5,7,7a-hexahydro-1*H*-1-indenone (144)**

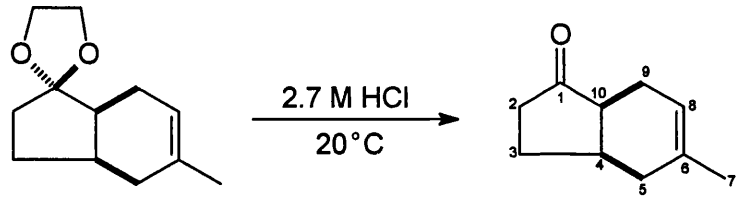


140 **142** **144**

To a solution of spiro ketal (**140**) (194 mg, 1.0 mmol) in water (5 ml) at rt was added dilute sulfuric acid (2.0 M, 1 ml). The reaction mixture was heated to 50° C for 2 h then poured into saturated sodium hydrogencarbonate solution (10 ml) and extracted with petroleum spirits 30-40° C (3 x 20 ml). The combined organic extracts were dried, ($MgSO_4$) and concentrated. The crude oil was purified by column chromatography (eluent: petroleum spirits / diethyl ether, 15:1) yielding a mixture of ketones (**142**, **144**) in combined yield (120 mg, 62 %, 4: 1).
N.B. Approximately 4 : 1 mixture.

υ_{max} (NaCl; neat) / cm^{-1} 2924 (s), 2920 (s), 1734 (s), 1684 (w); δ_H (400 MHz; $CDCl_3$), 1.62 (3 H, s, 7-H),1.74-1.81 (2 H, m), 1.97-2.10 (2 H, m), 2.23-2.40 (6 H, m, 2-H, 3-H, 5-H *overlap*), 2.47-2.53 (1 H, m), 5.31 (1 H, s, 8-H); 5.45-5.37 (2 H, s, 9-H, 8-H (**144**); δ_C (100 MHz; $CDCl_3$), 21.69, 23.87, 26.45, 30.79, 32.81, 34.16, 46.53, 118.71, 132.22, 219.71 (C-1); *m/z* (EIMS), 150 (M^+, 30 %), 135(M^+ -CH_3, 25 %), found for $C_{10}H_{14}O$ (M^+) 150.1042; Required 150.1041.

R59 **Bicyclo-5-methyl[4.3.0]non-4-en-1-one (142)**

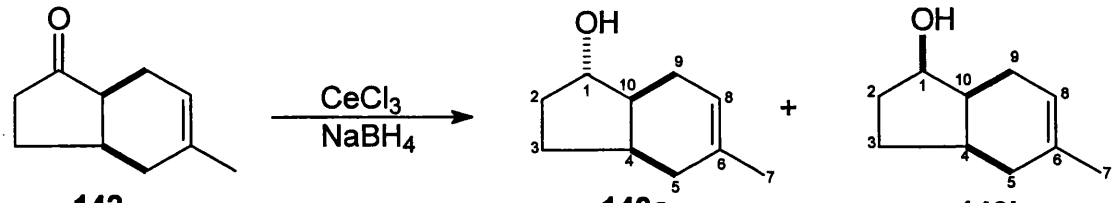


140 **142**

To a solution of spiroketal (**140**) (194 mg, 1.0 mmol) in methanol (5 ml) at 0 °C was added slowly (over 5 minutes) a solution of Hydrochloric acid (2.7 M, 310 μl). After 2 h the reaction was poured into saturated sodium hydrogencarbonate solution (10 ml) and extracted with petroleum spirits 30-40 °C (3x 20 ml). The combined organic extracts were dried, ($MgSO_4$) and concentrated. The crude oil was purified by column chromatography (eluent: petroleum spirits / diethyl ether, 15: 1) yielding the title ketone as a colourless oil (130 mg, 87 %).

υ_{max} (NaCl; neat) / cm^{-1} 2924 (s), 2920 (s), 1734 (s), 1684 (w);δ_H (400 MHz; $CDCl_3$), 1.62 (3 H, s, 7-H),1.77-1.81 (2 H, 3-H), 1.97-2.10 (2 H, m), 2.23-2.40 (6 H, m, 2-H, 9-H, 5-H *overlap*), 2.47-2.53 (1 H, m, 10-H), 5.31 (1 H, s, 8-H); δ_C (100 MHz; $CDCl_3$), 21.69, 23.87, 26.45, 30.79, 32.81, 34.16, 46.53, 118.71 (C-6), 132.22 (C-8), 219.71 (C-1); *m/z* (EIMS), 150 (M^+, 30 %), 135 (M^+ -CH_3, 25), found for $C_{10}H_{14}O$ (M^+)150.1045; Required 150.1041.

R60 **(1*R**,3a*R**,7a*S**)-5-methyl-2,3,3a,4,7,7a-hexahydro-1H-1-indenol (143a)**
(1*R,3a*R**,7a*S**)-5-methyl-2,3,3a,4,7,7a-hexahydro-1H-1-indenol (143b)**



142 **143a** **143b**

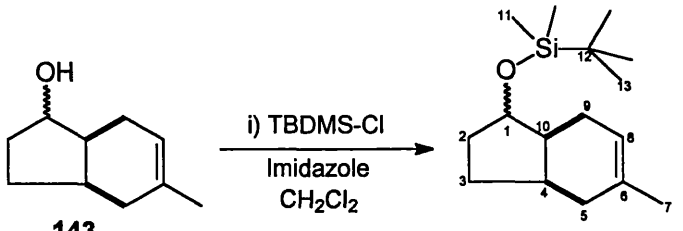
To a solution of ketone (**142**) (1.75 g, 11.6 mmol), in methanol (100 ml) was added cerium (III) chloride heptahydrate (4.47 g, 12.0 mmol). The reaction mixture was cooled to 0° C and sodium borohydride (460 mg, 12.0 mmol) was added in one portion. The reaction was stirred for 1 h and then diluted with brine (20 ml). The mixture was concentrated *in vacuo* (removal of methanol) and then diluted with diethyl ether (50 ml)

and extracted with diethyl ether (5 x 30 ml). The organic layer was dried ($MgSO_4$) and concentrated. The crude alcohol was purified by column chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 10 : 1) yielding the title alcohols as colourless viscous oil (1.61 g, 89 % yield). [105]

N.B. Mixture of diastereoisomers (**143a / 143b**),10: 1).

υ_{max} (NaCl; neat) / cm^{-1} 3324 (s br), 2955 (s), 2940 (s), 2883 (s), 14.38 (m); δ_H (400 MHz; $CDCl_3$), 1.50-1.54 (1 H, m), 1.54-1.64 (2 H, m, *overlap*), 1.66 (3 H, s, 7-H), 1.67-190 (3 H, m, *overlap*), 1.95-2.16 (5 H, m), 4.25 (1 H, m, 1-H), 5.47-5.58 (1 H, m, 8-H); δ_C (100 MHz; $CDCl_3$), 21.57, 23.89, 28.88, 31.91, 32.73, 34.72, 39.94, 76.51 (C-1), 119.60 (C-6), 133.48 (C-8); *m/z* (EIMS) 152 (M^+, 15 %), 136 (M^+ -CH_3, 17), 84 (M^+ - C_5H_8,100), found for $C_{10}H_{16}O$ (M^+) 152.1060; Required 152.1061.

R61 {[1*S,3a*R**,7a*S*)-5-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-1-indenyl]-oxy}(*tert* butyl)dimethylsilane (145)**



143 **145**

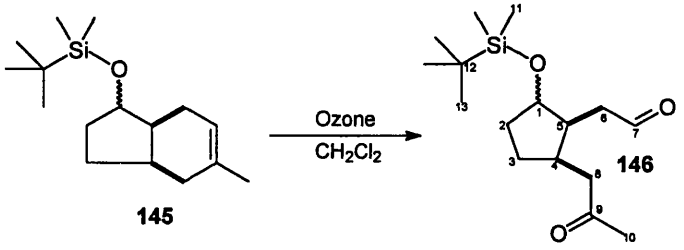
A solution of alcohol (**143**) (1.80 g, 11.8 mmol) imidazole (1.21 g, 17.8 mmol) and *t*-butyl dimethyl silyl chloride (2.68 g, 17.8 mmol) in dichloromethane (25 ml) was stirred at rt for 18 h. The reaction mixture was diluted with dichloromethane (30 ml) and water (30 ml). The organic layer was extracted with dichloromethane (3 x 30 ml) and dried ($MgSO_4$) and concentrated *in vacuo*. The crude silyl ether was purified by column chromatography (eluent: petroleum spirits 30-40 °C / diethyl ether, 20 : 1) yielding the title compound a colourless oil as a mixture of diastereoisomers (2.55 g, 81 %).

N.B. Inseparable diastereoisomers.

υ_{max} (NaCl; neat) / cm^{-1} 2961 (s), 2956 (s), 1638 (w); δ_H (400 MHz; $CDCl_3$), 0.03 (6 H, s, 11-H), 0.87 (9 H, s, 13-H), 1.49-1.51 (2 H, m), 1.56-1.63 (2 H, m), 1.65 (3 H, s, 7-H), 1.73-1.78 (2 H, m), 1.86-1.92 (2 H, m), 1.92-2.08 (2 H, m), 4.23 (1 H, dt, *J* 6.4 5.6 Hz, 1-H), 5.41 (1 H, s, 8-H); δ_C (100 MHz; $CDCl_3$), -4.94 (C-11'), -4.72(C-11'), 18.07, 21.53,

23.87, 25.83 x 3, 25.99, 28.14, 32.01, 32.78, 34.73, 40.11, 76.49, 119.34, 131.92 (C-1); *m/z* (EIMS) 266 (M^+, 5 %), 209 (M^+ -$C(CH_3)_3$, 40), 133 (M^+ -$OSi(CH_3)_2C(CH_3)_3$, 50), 75 ($OSi(CH_3)_2$, 100).

R62 2-(1*R, 2*R**, 5*S**)-2-{1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-5-(2-oxopropyl) cyclopentyl]acetaldehyde (146)**



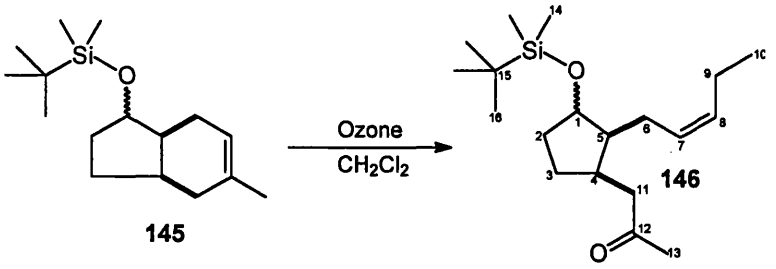
145 146

To a stirred solution of the silylether (**145**) (1.00 g, 3.7 mmol) in dichloromethane (20 ml) at -78 °C was bubbled molecular oxygen. After 5 min ozone was bubbled through the reaction mixture until a faint blue colouration persisted (*ca* 30 min). (Presence of excess ozone in solution). Nitrogen was then bubbled through the mixture until the faint blue colouration had disappeared. Dimethyl sulfide (2 ml, 21.1 mmol) was added at -78 °C and the mixture stirred for 3 h, allowing gently warming back up to rt. The mixture was the concentrated *in vacuo* and the crude viscous oil used without purification.

N.B. Inseparable diastereoisomers

υ_{max} (NaCl; neat) / cm^{-1} 2979 (s), 2955 (s), 2890 (s), 1734 (s), 1718 (m); δ_H (400 MHz; $CDCl_3$), 0.02-0.04 (6 H, s, 11-H), 0.87-0.89 (9 H, s, 13-H), 1.25-1.28 (1 H, m), 1.44-1.89 (1 H, m), 1.53-1.61 (1 H, m), 1.64-1.89 (2 H, m), 2.12 (3 H, s, 10-H), 2.13-2.20 (1 H, m), 2.21-2.35 (1 H, m), 2.48-2.63 (2 H, m), 4.24-4.25 (1 H, m, 1-H), 7.27-7.77 (1 H, m, 7-H); δ_C (100 MHz; $CDCl_3$), -4.94 (C-11'), -4.73 (C-11'), 17.98, 25.83, 28.83, 29.25, 30.25, 30.21, 33.45, 34.85, 43.55, 46.24, 74.96, 75.06, 132.08 (C-7), 243.36 (C-9); *m/z* (EIMS) 296 (M^+, 1 %), 277 (10), 183 (M^+ -$Si(CH_3)_2C(CH_3)_3$, 20), 137 (M^+ -$OSi(CH_3)_2C(CH_3)_3$, 10), 75 ($OSi(CH_3)_2$, 100);

R63 1-{1*S, 2*R**, 3*R**)-3-{1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-2-[(*Z*)-pentenyl]cyclopentyl}acetone (148a)**

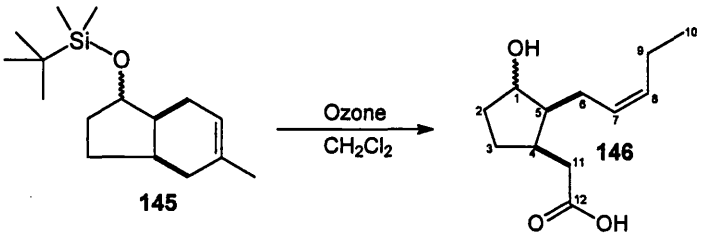


To a solution of sodium *bis*(trimethylsilyl)amide(1.0 M, 2.4 ml, 2.4 mmol) in tetrahydrofuran (10 ml), was added propyl triphenylphosphium bromide (925 mg, 2.4 mmol), the reaction mixture turned deep orange. The reaction mixture was cooled to -30 °C and a solution of the aldehyde (**146**) (600 mg) in tetrahydrofuran (2 ml) was added dropwise over 10 min. The reaction mixture was maintained at -30 °C for a further 2 h before it was allowed to warmed to rt. After a further 1 h of stirring the reaction mixture was diluted with methanol (1 ml) ad brine (5 ml). The reaction mixture was extracted with ether (3 x 20 ml) and dried over ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by column chromatography (eluent : petroleum spirits 40-60 °C / ethyl acetate, 20 : 1) yielding the methyl ketone (**148a**) in 67 % yield.

N.B. Inseparable diastereoisomers

υ_{max} (NaCl; neat) / cm^{-1} 2997 (s), 2956 (s), 2891 (s), 1714 (s), 1711 (m); δ_H (400 MHz; $CDCl_3$), -0.03-0.06 (6 H, s, 14-H), 0.87-0.90 (9 H, s, 16-H), 0.96 (3 H, t, *J* 6.3 Hz,10-H), 1.38-1.45 (1 H, m), 1.56-1.63 (2 H, m), 1.68-1.94 (6 H, m), 2.00-2.08 (1 H, m), 2.10 (3 H, s, 13-H), 2.12-2.18 (1 H, m), 2.43-2.56 (1 H, m), 4.09-4.14 (1 H, m, 1-H), 5.31-5.38 (2 H, m,7-H, 8-H); δ_C (100 MHz; $CDCl_3$), -5.08 (C-14'), -4.45 (C-14'), 20.75, 23.33, 25.86 (C-15), 29.61, 30.40, 34.87, 45.16, 46.52, 48.52, 75.32 (C-1), 128.31(C-6),, 131.93 (C-7), 209.73 (C-12); *m/z* (EIMS) 324 (M^+, 2 %), 282 (M^+ -$CHCH_2CH_3$, 5 %), 268 (M^+ -$CH_2C(O)CH_3$, 25), 200 (M^+ -$SiC(CH_3)_2C(CH_3)_3$, 6), found for $C_{18}H_{35}O_3Si$ (M^++H) 327.2340; Required 327.2355.

R64 1-{1*S, 2*R**, 3*R**)-3-hydroxy-2-[(*Z*)-2-pentenyl]cyclopentyl}acetic acid (149) [(+/-)-*Epi*-cucubric acid]**



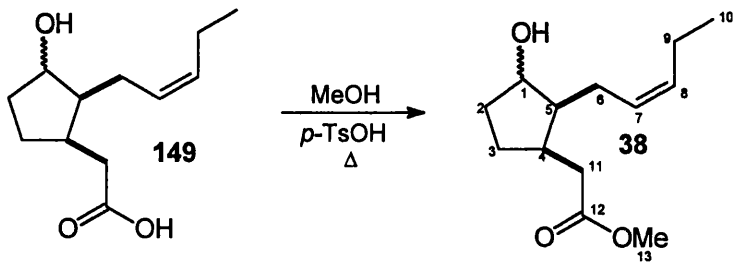
145 146

A stirred solution of sodium hypobromite was prepared by addition of molecular bromine (0.50 g, 3.1 mmol) to aqueous sodium hydroxide solution (3.1 M, 4 ml). The colourless solution was then added dropwise to methyl ketone (**148a**) (193 mg, 0.597 mmol) in dioxane (3 ml), and left to stand overnight at rt.

A solution of sodium sulfite (130 mg, 1.03 mmol) in water (1 ml) was added. The dioxane was removed *in vacuo.* The crude mixture was then extracted with diethyl ether (1 x 30 ml). The aqueous phase was then acidified with sulfuric acid (25 %, 3 ml), (pH 2-3). The colourless solution was extracted with diethyl ether (3 x 30 ml). The extracts were dried ($MgSO_4$) and concentrated *in vacuo.* The acid was purified by column chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 10:1) to afford the title compound as a colourless oil (112 mg, 61 %).

υ_{max} (NaCl; neat) / cm^{-1} 3623-3422 (br) (O-H), 2956 (s), 2942 (s), 2899 (s), 1712 (s) (C=O), 1651 (w) (C=C); δ_H (400 MHz; $CDCl_3$), 0.97 (3 H, t, *J* 6.6 Hz, 10-H), 1.41-1.49 (1 H, m), 1.60-1.68 (2 H, m), 1.73-1.99 (7 H, m, *overlap*), 2.06-2.21 (1 H, m), 2.35-2.41 (1 H, m), 2.42-2.48 (1 H, m), 4.08-4.22 (1 H, m, 1-H), 5.29-5.35 (2 H, m, 7-H, 8-H) 8.12-9.45 (1 H, s Br, COO*H*); δ_C (100 MHz; $CDCl_3$), 20.49, 24.73, 31.92, 36.56, 37.92, 39.10, 45.34, 48.24, 57.22 (C-1),126.33 (C-7), 133.74 (C-8), 161.23 (C-12), found for $C_{12}H_{20}O_3$ (M^+) 212.1408; Required 212.1412.

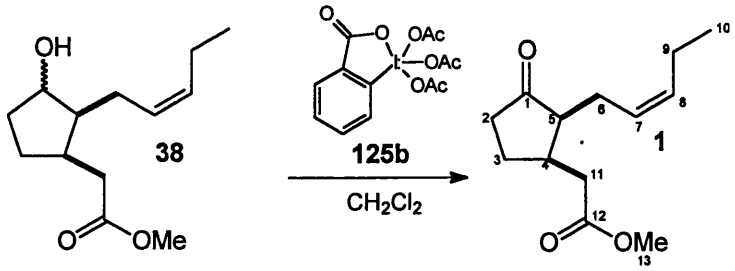
R65 Methyl 2-{1*S, 2*R**, 3*R**)-3-hydroxy-2-[(*Z*)-2-pentenyl]cyclopentyl}acetate (38)**
[(+/-)-Methyl-*epi*-cucubrate]



To a stirred solution of cucuburic acid (**149**) (120 mg, 0.567 mmol) in methanol (10 ml) was added sulfuric acid (14 M, 0.5 ml) and heated for 12h at reflux. The reaction was allowed to cool to rt. and then diluted with diethyl ether (30 ml) and brine (10 ml). The reaction mixture was extracted with diethyl ether (3 x 20 ml). The combined organics were dried over ($MgSO_4$) and reduced *in vacuo*. The crude oil was purified by chromatography (eluent: petroleum spirits 40-60°C / ethyl acetate, 10: 1), to afford the title compound as a colourless oil (109 mg, 92 %).

υ_{max} (NaCl; neat) / cm^{-1} 3418 (br) (O-H), 2956 (s), 2874 (s), 1732 (s) (C=O), 1641 (w) (C=C); δ_H (400 MHz; $CDCl_3$), 0.98 (3 H, t, *J* 7.2 Hz, 10-H), 1.42-1.46 (1 H, m), 1.59-1.65 (2 H, m), 2.07-2.32 (9 H, m, 2-H, 3-H, O*H*, 6-H, 9-H, *overlap*), 2.32-2.39 (1 H, m), 2.41-2.44 (1 H, m), 4.11-4.19 (1 H, m, 1-H), 5.27-5.39 (2 H, m, 7-H, 8-H); δ_C (100 MHz; $CDCl_3$), 22.45, 25.73, 32.14, 35.46, 38.72, 45.31, 45.23, 48.67, 57.45 (C-1), 61.34 (C-12),127.34 (C-7), 132.81 (C-8), 161.23 (C-12); found for $C_{13}H_{23}O_3$ (M^++H) 227.1660; Required 227.1647.

R66 Methyl 2-{1*S, 2*R**, 3*R**)-3-hydroxy-2-[(*Z*)-2-pentenyl]]cyclopentyl}acetate (38)**
[(+/-)-Methyl *epi*-jasmonate]

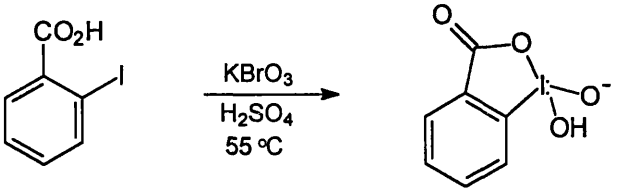


To a stirred solution of methyl *epi*-cucubrate (**38**) (150 mg, 0.694 mmol) in dichloromethane (5 ml) was added 1,1,1,-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-1*H*-one (400 mg, 0.942 mmol) in one portion. The reaction was stirred for 30 minutes before a white precipitate formed which. The solid was filtered and the filtrate was concentrated *in vacuo* to give a pale yellow oil. The oil was purified by chromatography (eluent: petroleum sprints 40-60 °C / ethyl acetate, 10:1), to afford the title compound as a colourless oil (141 mg, 94 %).

N.B. Strong-sweet jasmine smell.

υ_{max} (NaCl; neat) / cm^{-1} δ_H (400 MHz; $CDCl_3$), 0.98 (3 H, t, *J* 7.4 Hz, 10-H), 1.49 (1 H, m), 1.90 (1 H, m), 2.07 (2 H, m), 2.14 (1 H, m), 2.20-2.42 (5 H, m, *overlap*), 2.71 (1 H, m), 2.82 (1 H, m), 3.65 (3 H, s, 13-H), 5.25 (1 H, m, 7-H), 5.45 (1 H, m, 8-H); δ_C (100 MHz; $CDCl_3$), 14.08, 20.60, 25.48, 27.34, 37.88, 37.96, 38.78, 51.45 (C-5), 53.96 (C-11), 124.88 (C-8), 134.07 (C-7), 172.49 (C-12), 218.93 (C-1); *m/z* (EIMS) 224 (M^+, 25 %), 194 (M^+ - OCH_3, 22), 151 (M^+ -CH_2CO_2Me, 40), 83 (M^+ -CH_2CO_2Me - C_5H_9, 100), found for $C_{13}H_{20}O_3$ (M^+) 224.1408; Required 224.1412.

R67 **1-Hydroxy-1,2-benziodoxol-3-1*H*-one (125a)**

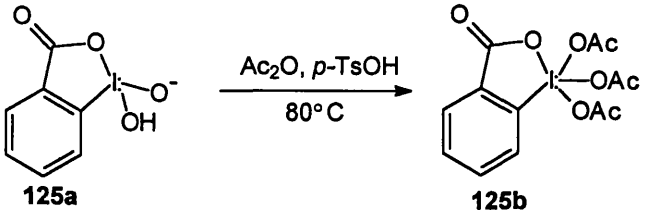


125a

Potassium bromate (7.60 g, 45 mmol) was added over 30 min to a vigorously stirred mixture of 2-iodobenzoic acid (8.52 g, 34 mmol) in sulfuric acid (73 ml, 0.73 M). During the addition the reaction temperature was kept below 55 °C. The mixture was warmed to 65 °C and stirred for further 4 h. The reaction mixture was then cooled to 0 °C and filtered. The off white solid was washed with water (100 ml) followed by ethanol (2 x 50 ml) and then diethyl ether (3 x 30 ml) to afford a white solid (8.90 g, 32 mmol, 93 %). [45a]

N.B. This material has been reported to be explosive under excess heating (>140°C) and impact sensitive therefore it was taken through crude to next step.

R68 1,1,1,-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3-1*H*-one (125b)

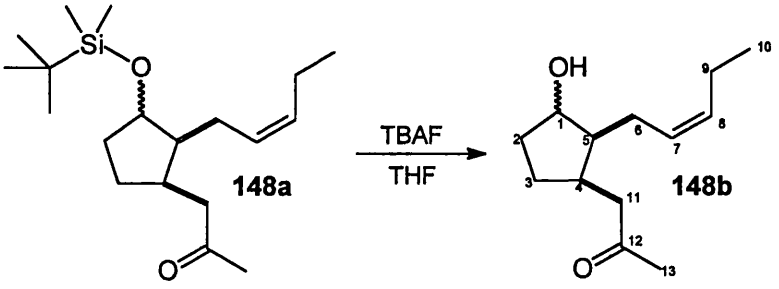


125a **125b**

1-Hydroxy-1,2-benziodoxol-3-1*H*-one (**125a**) (7.50 g, 26.9 mmol) was added slowly to a stirred solution of acetic anhydride (30 ml), *para*-toluenesulfonic acid monohydrate (40 mg). The mixture was heated to 80 °C for 2 h and then cooled in an ice water bath. The cold mixture was filtered and washed with diethyl ether (5 x 15 ml). To give the title compound as a crystalline white solid (10.0 g, 90 %), The solid was quickly transferred to an argon flushed amber glass bottle and stored in a freezer.[45b]

Mp 124-125 °C (lit 133-134 °C);[45c] δ_H (400 MHz; $CDCl_3$), 1.99 (6 H, s, OAc x2), 2.32 (3 H, s, OAc), 7.91 (1 H, t, *J* 8.1 Hz), 8.09 (1 H, t, *J* 8.1 Hz), 8.28-8.31 (2 H, m *overlap*); δ_C (100 MHz; $CDCl_3$), 20.21, 20.43, 129.95, 126.52, 131.76, 133.82, 135.84, 142.21, 166.10, 174.04, 175.73;

R70 2-(2-Pentylidene)-3-(propan-2-one)cyclopentan-1-ol (148b)



148a **148b**

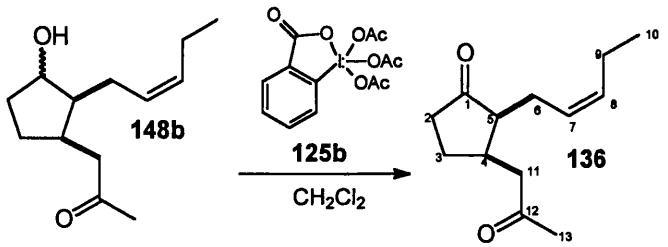
To a stirred solution of silylether (**148a**) (65 mg, 0.20 mmol) in tetrahydrofuran (1 ml) was added a solution of tetra *n*-butylammonium fluoride in tetrahydrofuran (1 M, 0.4 ml). The reaction was stirred for 2 hours and then diluted with diethyl ether (10 ml) and brine (2 ml). The reaction mixture was extracted with diethyl ether (3 x 10 ml). The combined organics were dried over ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by chromatography (eluent: petroleum spirits 40-60 °C / diethyl ether, 8 : 1). The title compound was isolated as a colourless oil (24 mg, 68 %).

N.B. Mixture of diastereoisomers.

υ_{max} (NaCl; neat) / cm^{-1} 3612 (br) (O-H), 2986 (s), 2936 (s), 2896 (s), 1714 (s) (C=O), 1645 (w) (C=C); δ_H (400 MHz; $CDCl_3$), 0.98 (3 H, t, *J* 6.5 Hz, 10-H), 1.35-1.48 (1 H, m), 1.59-1.67 (2 H, m, 3-H), 1.72-1.99 (7 H, m, 2-H, 6-H, 9-H, 5-H, *overlap*), 2.08-2.19 (1 H, m), 2.21 (3 H, s, 13-H), 2.31-2.39 (1 H, m), 2.43-2.58 (1 H, m), 4.12-4.36 (1 H, m, 1-H), 5.34-5.39 (2 H, m, 7-H, 8-H); δ_C (100 MHz; $CDCl_3$), 21.45, 23.78, 31.70, 34.33, 37.71, 38.71, 39.72, 46.67, 48.54, 58.23 (C-1), 127.43 (C-8), 132.87 (C-7), 210.23 (C-12), found for $C_{13}H_{21}O_2$ (M^+-H) 209.1557; Required 209.1541.

R71 (2*S, 3*R**)-3-(2-oxo-propyl)-2[(*Z*)-2-pentenyl]cyclopentan-1-one (136)**

[*Epi* magnolia ketone]

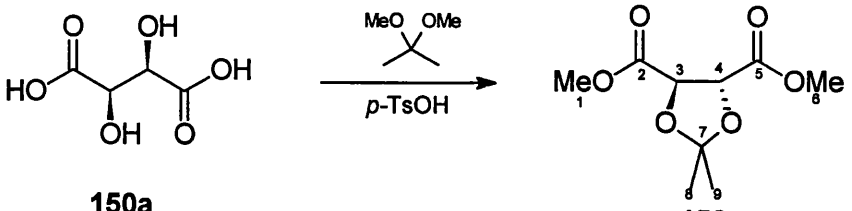


To a stirred solution of methyl-*epi*-cucburate (**148b**) (35 mg, 0.162 mmol) in dichloromethane (2 ml) was added 1,1,1,-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-1*H*-one (**125b**) (100 mg, 0.236 mmol) in one portion. The reaction was stirred for 30 minutes before a white precipitate formed which. The solid was filtered and the filtrate concentrated *in vacuo*. The crude material was purified by chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 10:1). The title compound was isolated as a colourless oil (24 mg, 68 %).

N.B. Pleasant floral odour

υ_{max} (NaCl; neat) / cm^{-1} 2984 (s), 2937 (s), 2894 (s), 1743 (s) (C=O), 1717 (s) (C=O), 1641 (w) (C=C); δ_H (400 MHz; $CDCl_3$), 0.99 (3 H, t, *J* 7.2 Hz, 10-H), 1.32-1.48 (1 H, m), 1.60-1.68 (2 H, m), 2.06-2.20 (8 H, m, O*H*, 2-H, 6-H, 9-H, 4-H *overlap*), 2.21 (3 H, s, 13-H), 2.33-2.40 (1 H, m, 11'-H), 2.44-2.61 (1 H, m, 11'-H), 5.25 (1 H, m, 7-H), 5.45 (1 H, m, 8-H); δ_C (100 MHz; $CDCl_3$), 14.23, 20.34, 24.83, 34.75, 37.71, 38.71, 39.72, 44.98, 46.34, 124.13 (C-8), 133.90 (C-7), 210.23 (C-12), 218.92 (C-1), found for $C_{13}H_{20}O_2$ (M^+) 208.1460, Required 208.1463.

R72 Dimethyl (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4-5-dicarboxylate (150a)

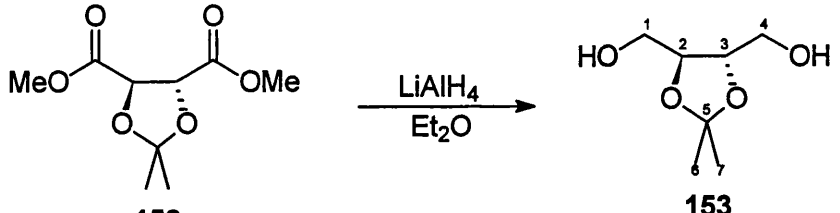


150a **152**

To a mixture of (L)-tartaric acid (**150a**) (10.10 g, 67.3 mmol), 2,2-dimethoxypropane (16.05 g, 154 mmol), in dry methanol (4 ml) was added *para*-toluenesulfonic acid monohydrate (40 mg, 0.25 mmol). The mixture was warmed to 90 °C for 1.5 h. To the dark red homogenous solution was added an additional portion of 2,2-dimethoxypropane (7.95 g, 76.4 mmol), and cyclohexane (45 ml), the resulting mixture was heated to reflux, the azeotropes were slowly removed by distillation. After 18 h, 60 ml of distillate was collected. Additional 2,2-dimethoxypropane (1.00 g, 9.4 mmol) was added and allowed to react for a further 15 min. the mixture was then cooled to rt. Anhydrous potassium carbonate (100 mg) was added to neutralise the acid. The solvent and unreacted 2,2-dimethoxypropane were removed under reduced pressure. The crude oil was purified under reduced to give the title compound as a colourless oil (14.08 g, 96 %).

Bp 119-121 °C (1 mmHg); υ_{max} (NaCl; neat) / cm^{-1} 2993 (s), 2957 (s), 1761 (s), 1761 (s), 1112 (s); δ_H (400 MHz; $CDCl_3$), 1.44 (6 H, s, 8-H, 9-H), 3.78 (6 H, s, 1-H, 6-H), 4.76 (2 H, s, 3-H, 4-H); δ_C (100 MHz; $CDCl_3$), 26.23, 52.77 (C-1, C-6), 76.90 (C-3, C-4), 113.79 (C-7), 170.00 (C-2, C-5); $[\alpha]_D^{25}$-51.1° (neat liquid), (lit $[\alpha]_D^{25}$ -53.1 ° neat).[132]

R75 [(4*S*,5*S*)-5-(Hydroxymethyl)-2,2,-dimethyl-1,3-dioxolan-4-yl]methanol (153)



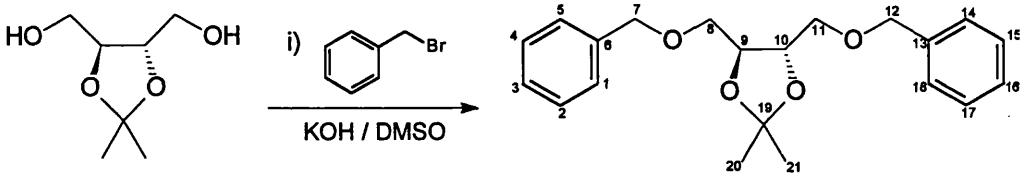
152 **153**

A suspension of lithium aluminium hydride (10.50 g, 275 mmol) in diethyl ether (110 ml) was refluxed for 30 min with vigorous stirring. A solution of dimethyl

2,3,-isopropylidene-(L)-tartrate (**152**) (30.05 g, 138 mmol) in diethyl ether (150 ml) was added dropwise without heating over a period of 3 h, the heat of reaction causing gentle reflux. After additional heating for 3 h. Ethyl acetate (40 ml) was carefully added and the reaction mixture cooled to 0 °C and water (10 ml) was added dropwise followed by sodium hydroxide solution (4 N, 10 ml) and then water (33 ml). An inorganic precipitate formed which was washed thoroughly with ethyl acetate (*ca* 5 x 200 ml). The combined organics were dried (Na_2SO_4) and the reduced *in vacuo*. The crude oil was distilled under reduced pressure, to afford the title compound as a colourless oil (17.83 g, 82 %).

Bp 101-105 °C (1 mmHg);[133] υ_{max} (NaCl; neat) / cm^{-1} 2340 (br), 2987 (s), 2935 (s), 2879 (s), 1051 (s); δ_H (400 MHz; $CDCl_3$), 1.42 (6 H, s, 6-H, 7-H), 2.26-2.41 (2 H, s (br), O*H*), 3.72 (4 H, m, 1-H, 4-H, *overlap*), 4.97 (2 H, td, *J* 11.8, 3.5 Hz, 2H, 3-H); δ_C (100 MHz; $CDCl_3$), 27.00 (C-6,C-7), 61.96 (C-1, C-4), 77.97 (C-2, C-3), 109.25 (C-5); *m/z* (EIMS) 150 (M^+ +2H, -CH_3, 35 %), 131 (M^+ - 2CH_3, 20); $[\alpha]_D^{25}$ +3.3 ° (*c*=1.17, in $CHCl_3$).

R76 (4*S*,5*S*)-4-[(Benzyloxy)methyl]-5-[(2,4-cyclohexadienylmethoxy)methyl]-2,2-dimethy-1,3-dioxolane (154)

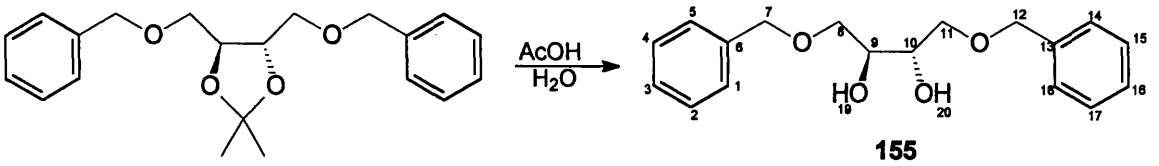


To a stirred solution of diol (**153**) (1.65 g, 10 mmol), in DMSO (10 ml) at rt was added finely powdered potassium hydroxide (4.48 g, 80 mmol). After addition the reaction turned a light brown colour. Benzyl bromide (3.42 g, 20.0 mmol) was added over 30 minutes. The reaction was stirred for further 4 h and then quenched by addition of methanol. The mixture was then extracted with diethyl ether (3 x 30 ml), the ethereal layer was dried ($MgSO_4$) and then reduced *in vacuo*. The crude oil was purified by chromatography (eluent: petroleum spirits / ethyl acetate 25:1), to afford the title compound as a colourless oil (2.94 g, 86 %).

υ_{max} (NaCl; neat) / cm^{-1} 2989 (s), 2935 (s), 2880 (s); δ_H (400 MHz; $CDCl_3$), 1.44 (6 H, s, 20-H, 21-H), 3.62 (4 H, m, 7-H, 12-H, *overlap*), 4.05 (2 H, m, 9-H, 10-H *overlap*), 4.58 (4

H, s, 8-H, 11-H), 7.30 (10 H, m, Ph); δ_C (100 MHz; $CDCl_3$), 27.00 (C-20, C-21), 70.64, 73.49, 77.46, 109.66 (C-19), 127.61, 128.34, 137.93, *m/z* (EIMS) 321 (M^++H, -CH_3, 22 %), 254 (29), 205 (40), 89 ($C_6H_5CH_2$, 100); $[\alpha]_D^{25}$ -6.7 ° (*c* =1.47, in $CHCl_3$).

R77 (2*S*,3*S*)-1-(Benzyloxy)-4-(2,4-cyclohexadienylmethoxy)butane-2,3-diol

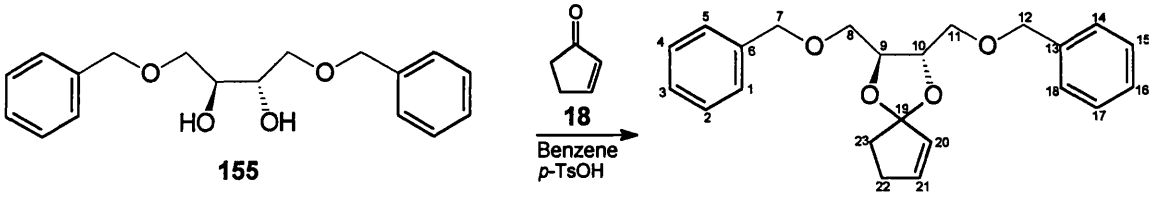


154 **155**

Dibenzyl 2,3-isopropylidene-(L)-threitol (**154**) (1.00 g, 2.92 mmol) was dissolved in acetic acid (glacial, 2.5 ml, 39.6 mmol) and water (2.5 ml), the mixture was heated to 60 °C for 3 h and then cooled to rt. The acetic acid was neutralised with sodium hydroxide (1.58 g, 2.92 mmol) and mixture extracted with ethyl acetate (5 x 30 ml). The combined organics were dried (Na_2SO_4) and reduced *in vacuo* to afford the title compound as a white solid (820 mg, 92 %).

Mp 54-56 °C, (lit 55-57 °C); υ_{max} (NaCl; neat) 3275 (br), 3030 (m), 2864 (s) 1634 (s), 1092 (s) / cm^{-1} δ_H (400 MHz; $CDCl_3$), 3.10 (2 H, s (br), O*H*), 3.61 (4 H, ddd, *J* 5.7, 4.7, 1.8, 8-H,12-H), 3.89 (2 H, td, *J* 3.7, 4.7 Hz, 9-H, 10-H), 4.56 (4 H, dd, *J* 11.8, 4.7 Hz, 7-H, 12-H), 7.33 (10 H, m, Ph); δ_C (100 MHz; $CDCl_3$), 70.50, 71.88, 73.50, 127.73, 127.78, 128.41, 137.65; *m/z* (EIMS) 298 (M^+ -4 H, 36 %), 192 (11), 89 ($C_6H_5CH_2$, 100), found for $C_{18}H_{22}O_4$ (M^+) 302.3701; Required 302.3703; $[\alpha]_D^{25}$ -6.9 ° (*c*=1.10 in $CHCl_3$), [lit $[\alpha]_D^{20}$ -6.0° (*c*= 5.00, in $CHCl_3$).

R78 (2*S*,3*S*)-2-[(benzyloxy)methyl]-3-[2,4-cyclohexadienylmethoxy)methyl]-1,4-dioxaspiro[4.4]nonane (151)



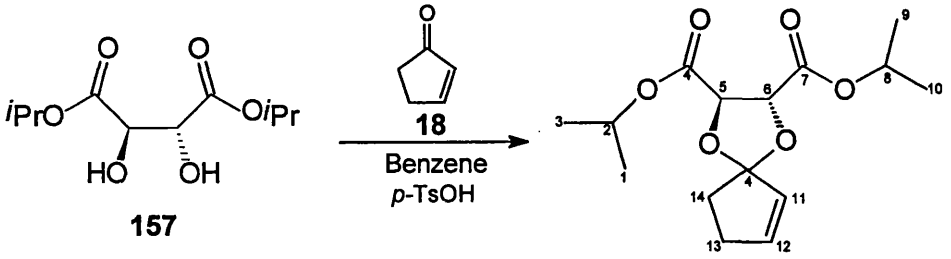
155 **151**

A 500 ml round bottomed flask was charged with 2-cyclopenten-1-one (**18**) (9.73 g, 118 mmol), 1,4-di-*O*-benzyl-(L)-threitol (**155**) (11.91 g, 39 mmol), PPTS (2.45 g, 9.56

mmol) and dry benzene (350 ml). The flask was then fitted with a soxhlet extractor, an extraction thimble containing calcium carbide (*ca* ≈ 3 g), and a reflux condenser. The magnetically stirred reaction mixture was heated to reflux for 96 h. After cooling the mixture was diluted with dichloromethane (500 ml) and washed with water (100 ml), saturated bicarbonate solution (100 ml), dried ($MgSO_4$) and concentrated. The crude oil was purified by column chromatography (eluent : hexane / ethyl acetate, 9 : 1) to yield the title compound as a pale yellow oil (8.25 g, 57 %).

υ_{max} (NaCl; neat) / cm^{-1} 2876 (m), 2864 (s), 1615 (w) (C=C), 1082 (s) (C-O) / cm^{-1} δ_H (400 MHz; $CDCl_3$), 2.11 (2 H, m, 22-H), 2.38 (2 H, m, 20-H), 3.60 (4 H, m, 7-H, 12-H), 4.05 (2 H, m, 9-H, 10-H), 4.55 (4 H, s, 8-H, 11-H), 5.72 (1 H, m, 21-H), 6.05 (1 H, m, 20-H), 7.29 (10 H, m, Ph); δ_C (100 MHz; $CDCl_3$), 29.63, 35.20, 70.51, 73.47, 77.42, 77.89, 121.40 (C-19), 127.63 , 128.35, 131.23, 137.16, 137.93 (C-20); *m/z* (EIMS) 366 (M^+ -H, 19 %),192 (11 %), 89 ($C_6H_5CH_2$, 100 %), found for $C_{18}H_{22}O_4$ (M^+) 366.1830; Required 366.1831; $[\alpha]_D^{25}$ -3.1 ° (*c*=0.82 in $CHCl_3$).

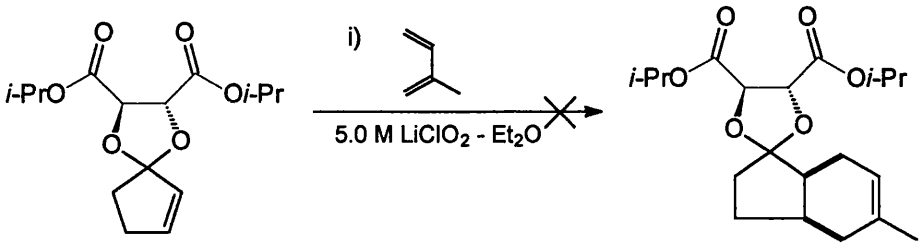
R79 **2-Cyclopenten-1-one 1,4-di-O-isopropyl-(L)-threitol ketal (158)**



A 500 ml round bottomed flask was charged with 2-cyclopenten-1-one (**18**) (9.73 g, 118 mmol), diisopropyltartrate (**157**) (9.12 g, 39 mmol), PPTS (2.45 g, 9.56 mmol) and dry benzene (350 ml). The flask was then fitted with a soxhlet extractor, an extraction thimble containing calcium carbide (*ca* ≈ 3 g), and a reflux condenser. The magnetically stirred reaction mixture was heated to reflux for 120 h. After cooling the mixture was diluted with dichloromethane (500 ml) and washed with water (100 ml), saturated bicarbonate solution (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The Crude oil was purified by column chromatography (eluent: hexane / ethyl acetate, 9 : 1) to yield the title ketal as a pale yellow oil (349 mg, 3 %). (Unreacted starting materials recovered).

υ_{max} (NaCl; neat) / cm^{-1} 2879 (s), 2884 (s), 1720 (s) (C=O), 1612 (w), 1082 (s) (C-O); δ_H (400 MHz; $CDCl_3$), 1.33 (12 H, d, *J* 6.2 Hz, 3-H, 1-H, 9-H, 10-H), 2.16 (2 H, m, 13-H), 2.35 (2 H, m, 14-H), 4.71 (2 H, s, 5-H, 6-H), 5.13 (2 H, sept, *J* 6.2 Hz, 2-H, 8-H) 5.78 (1 H, m, 12-H), 6.15 (1 H, m, 11-H); δ_C (100 MHz; $CDCl_3$), 21.71, 29.71, 34.73, 69.72, 73.39, 77.51, 125.23 (C-4), 130.34 (C-12), 138.65 (C-11), 169.20 (C-4, C-7); *m/z* (FABMS) 296 (M^+ -2H, 4 %), found for $C_{15}H_{22}O_6$ (M^+) 298.1419; Required 298.1416; $[\alpha]_D^{25}$ -2.1 ° (*c*=2.32, in $CHCl_3$).

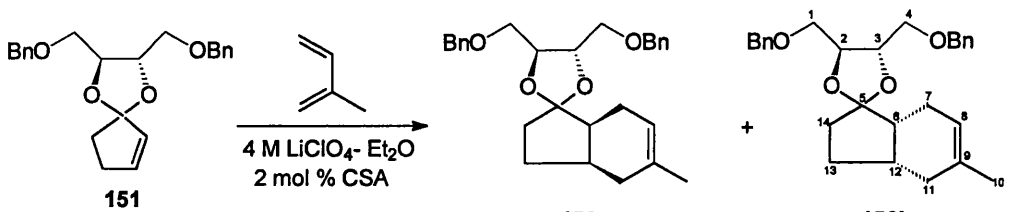
R80 {[1,4-di-*O*-isopropyl-(L)-threitol ketal] (3a*R,7a*S**)-5-methyl-2,3,3a,4,7,7a-hexahydro-1H-1-indenone**



158

To a solution of 2-cyclopenten-1-one diethyl-(L)-tartrate ketal (**158**) (2.70 g, 10 mmol) in lithium perchlorate- diethyl ether (4.0 M, 40 ml, 160 mmol) was added isoprene (4.0 ml, 40 mmol). The reaction was stirred for 24 h at rt. The mixture was diluted with water 20 ml and extracted with diethyl ether (4x 30 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The starting ketal (**158**) was recovered in almost quantitative yield.

R81 1,4-Dioxaspiro-[2*R*, 3*R*,dibenzyl]-6-bicyclo-9-methyl-[4.4.0]-non-8-ene (156a & 156b)



151 **156a** **156b**

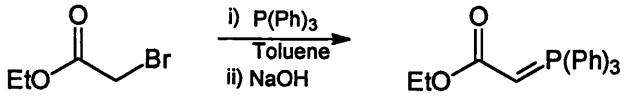
To a solution of dibenzyl-(L)-threitol ketal (**151**) (3.00 g, 10 mmol) in lithium perchlorate- diethyl ether (4.0 M, 40 ml, 160 mmol) was added isoprene (4.0 ml, 40 mmol) and camphorsulfonic acid in tetrahydrofuran (0.5 M,138 µl, 3 mol %). After 20 minutes a yellow colouration was observed. After 40 minutes, triethylamine (75 µl, 0.54 mmol) was added. The reaction mixture then turned colourless and was then diluted with water 20 ml and extracted with diethyl ether (4x 30 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The oil was purified by column chromatography (eluent: petroleum spirits 40- 60 °C / ethyl acetate, 20 :1) yielding the title compounds as a colourless oil (3.35 g, 91 %).

N.B. Inseparable diastereoisomeric mixture (1: 1).

υ_{max} (NaCl; neat) / cm^{-1} 2876 (s), 2847 (s), 1684 (s), 1643 (w), 1172 (s), 1128 (s) (C-O); δ_H (400 MHz; $CDCl_3$), 1.45 (1 H, m, 13'-H), 1.66 (3 H, s, 10-H), 1.82-2.32 (7 H, m, 13'-H, 14-H, 12-H, 11-H, 7'-H *overlap*), 2.35 (1 H, m, 7-H), 3.59 (4 H, m,OCH_2Ph), 3.97 (2 H, m, 2-H, 3-H), 4.58 (4 H, m, 1-H, 4-H), 5.36 (1 H, s (br), 8-H), 7.30 (10 H, m, 2x Ph); δ_C (100 MHz; $CDCl_3$), 23.87, 23.91, 26.49, 26.90, 31.73, 31.83, 34.56, 34.88, 34.93, 35.00, 35.05, 42.29, 42.76, 70.68, 70.80, 71.02, 73.43, 73.51, 76.97, 77.14, 77.26, 77.69, 77.89, 77.94, 118.95, 119.10, 120.70, 120.86, 127.65, 128.39, 131.92, 131,97, 138.07, 138.05; *m/z* (FABMS) 433 (M^+, 34 %), 339 (M^+ -CH_2Ph, 40), 181 (100), 154 (M^+ -$(OCHCH_2OBn)_2$, 50), found for $C_{28}H_{35}O_4$ (M^++H) 435.2520; Required 435.2535; $[\alpha]_D^{25}$ 0.0 ° (*c*=0.82, $CHCl_3$).

Calythrone analogues

R82 Carbethoxyethylidene triphenylphosporane (165)

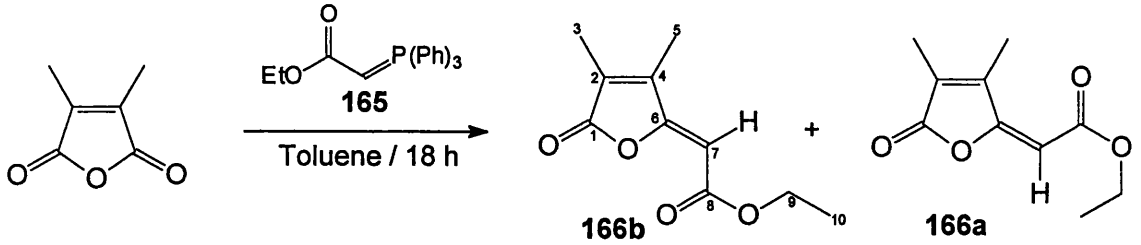


165

To a solution of ethyl bromoacetate (4.8 ml, 43.3 mmol) in toluene (160 ml) was added triphenylphosphine (15.40 g, 43.3 mmol) and stirred for 18 h. The white precipitate that formed was filtered to afford a white salt (19.21 g). The salt was dissolved in tetrahydrofuran (80 ml), sodium hydroxide solution (10 %, 200 ml). The mixture was extracted with ethyl acetate (4 x 60 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The off white solid was recrystallised from ethyl acetate / petroleum spirits 40-60 °C to afford the title phosphorane as a white crystalline solid (13.82 g, 89 %).

Mp 128-129 °C (Ethyl Acetate), (lit 128-131° C)[134]; υ_{max} (KBr) / cm^{-1} δ_H (400 MHz; $CDCl_3$), 1.10 (3 H, t, *J* 7.0 Hz, CH_3), 2.89 (1 H, s, br, $(Ph)_3P=CH$), 3.99 (2 H, q, *J* 7.0 Hz, CH_2), 7.23- 7.53 (15 H, m, Ph);

R83 Ethyl 2-{3,4-dimethyl-5-oxo-2,5-dihydro-2-[(*E*)-furanyliden)} acetate (166a)
Ethyl 2-{3,4-dimethyl-5-oxo-2,5-dihydro-2-[(*Z*)-furanyliden)} acetate (166b)



To a solution of 2,3-dimethylmaleic anhydride (**164**) (3.50 g, 27.7 mmol), in dry toluene (140 ml), was added phosphorane (**165**) (8.88 g, 25.5 mmol) in one portion and the mixture was stirred for 18 h at rt. The reaction was reduced *in vacuo* to afford a white solid. The crude material was dissolved in petroleum spirit 40-60 °C (50 ml) and the white solid, (triphenylphosphinoxide) filtered off. The filtrate was reduced in *vacuo* to give a pale yellow oil. The crude oil was subjected to flash chromatography (eluent: petroleum spirit 40-60 °C / ethyl acetate (20:1→ 5:1). The two products (*Z*) (**166b**) (2.02 g) and (*E*) (**166a**) (2.12 g), were isolated in a combined yield 76 %, approximately 1:1). (R_f 0.75 (*Z*), 0.45 (*E*), 7:1 petroleum spirits / ethyl acetate).

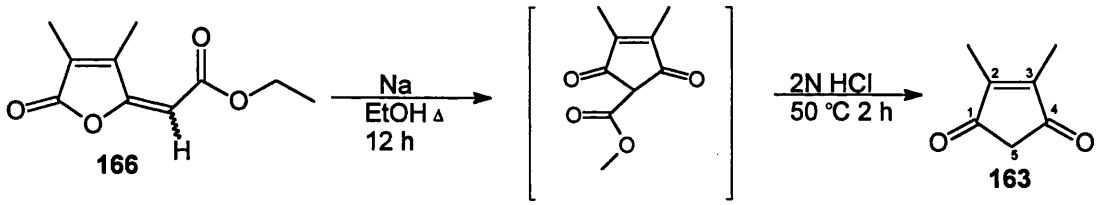
Ethyl 2-{3,4-dimethyl-5-oxo-2,5-dihydro-2-[(*E*)-furanyliden)} acetate (166a)

υ_{max} (NaCl; neat) / cm^{-1} 3085 (s), 2981 (s), 1786 (s), 1720 (s), 1654 (m); δ_H (400 MHz; $CDCl_3$), 1.30 (3 H, t, *J* 7.1 Hz, 10-H), 1.96 (3 H, s, 5-H), 2.05 (3 H, s, 3-H), 4.24 (2 H, q, *J* 7.1 Hz, 9-H), 5.40 (1 H, s, 7-H); δ_C(100 MHz; $CDCl_3$), 9.08, 9.86, 14.17, 60.84, 96.72 (C-4), 128.99 (C-2), 147.37 (C-7), 157.63 (C-6), 163.54 (C-8),169.14 (C-6); *m/z* (EIMS) 196 (M^+, 15 %), 151 (M^+ -OEt, 59), 127 (M^+ -$OCOCHCH_3$, 100).

Ethyl 2-{3,4-dimethyl-5-oxo-2,5-dihydro-2-[(*Z*)-furanyliden)} acetate (166b)

Mp 45-46 °C; υ_{max} (KBr) / cm^{-1} 2985 (s), 2938 (s), 1787 (s), 1723 (s), 1649 (s); δ_H (400 MHz; $CDCl_3$) 1.29 (3 H, t, *J* 7.1 Hz, 10-H), 1.95 (3 H, s, 5-H), 2.31 (3 H, s, 3-H), 4.18 (2 H, q, *J* 7.1 Hz, 9-H), 5.91 (1 H, s, 7-H); δ_C(100 MHz; $CDCl_3$), 9.02, 13.44, 14.07, 60.93, 102.86, 131.74, 146.46 (C-7), 158.82 (C-6), 164.44 (C-8), 168.76 (C-1); *m/z* (EIMS) 196 (M^+, 16 %), 151 (M^+ -OEt, 60), 127 (M^+ -$OCOCHCH_3$, 100).

R84 **4,5-Dimethyl-4-cyclopentene-1,3-dione (163)**



166 **163**

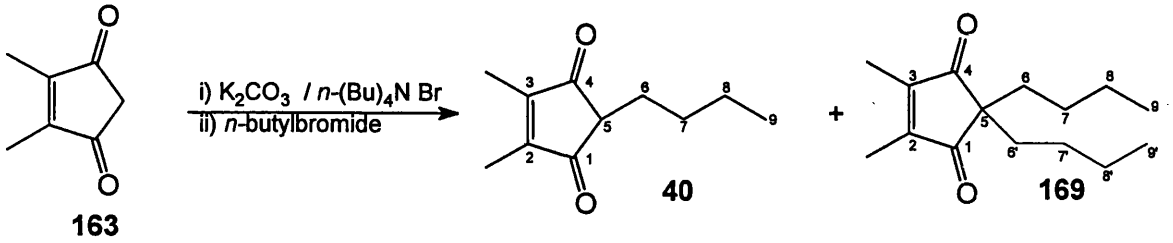
To a stirred solution of γ-lactone (**166**) (482 mg, 2.46 mmol), in ethanol (100 %, 15 ml), was added sodium (75 mg, 3.26 mmol). The reaction was heated to reflux and stirred for 12 h, (a bright orange precipitate formed). The orange precipitate was filtered and washed with ethanol (2 x 20 ml). The orange solid was then dissolved in hydrochloric acid (2 N, 30 ml) and stirred for 2 h at 50 °C.

The reaction was worked up by extraction with ethyl acetate (3 x 40 ml). The combined organics were washed with sodium hydrogen carbonate saturated (30 ml), dried ($MgSO_4$) and reduced *in vacuo* to afford a brown oil. The oil was dissolved in petroleum spirits 40-60 °C (35 ml) and ethyl acetate (5 ml) and filtered through a small plug of silica gel to remove the insoluble material. The pale yellow filtrate was concentrated *in vacuo* to give the title compound as a pale yellow waxy solid, (196 mg, 71 %).

N.B. Strong butter-like smell.

υ_{max} (NaCl; neat) / cm^{-1} 2912 (s), 2887 (s), 1698 (s), 1640 (m); δ_H (400 MHz; $CDCl_3$), 1.99 (6 H, s, $(CH_3)_2$), 2.83 (2 H, s, 5-H); δ_C (100 MHz; $CDCl_3$), 9.28 (C-5), 40.81 (CH_3), 156.41 (C-2, C-3), 200.47 (C-1, C-4); (Found: C, 67.73; H, 6.54 $C_7H_8O_2$, calculated C, 67.71; H, 6.50); *m/z* (EIMS) 124 (M^+, 100 %), 108 (M^+ -O, 25), 96 (M^+ -C=O, 90), 54 (M^+ -O=C-O-C=O, 85).

R85 **2-Butyl-4,5-dimethyl-4-cyclopentene-1,3-dione (40)**
2,2-Dibutyl-4,5-dimethyl-4-cyclopentene-1,3-dione (169)



To a stirred solution of diketone (**163**) (124 mg, 1.00 mmol) in toluene (3 ml), was added anhydrous potassium carbonate (617 mg, 4.46 mmol) and a catalytic amount of tetra *n*-butylammonium bromide (4 mg, 0.01 mmol). The reaction mixture was heated to reflux for 2 h before being allowed to cool to rt. *n*-Butylbromide (164 mg, 1.2 mmol) was added in one portion and the reaction stirred for 24 h. The reaction mixture was filtered through a pad of celite using *n*-hexane. The filtrate was concentrated *in vacuo* to afford a brown oil which was purified by flash chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 25 : 1), to yield 2,3-dimethyl-5-butyl-cyclopent-2-en-1,4-dione (**40**) as a pale yellow oil (36 mg, 20 %) and 2,3-dimethyl-5,5'-dibutyl-cyclopent-2-en-1,4-dione (**169**) also as a yellow oil (9 mg, 4 %). (Unreacted starting diketone (**163**) also recovered (46 mg, 38 %).

N.B. (**40**) sweet jasmine odour; (**169**) weak fatty-jasmine odour.

2-Butyl-4,5-dimethyl-4-cyclopentene-1,3-dione (40)

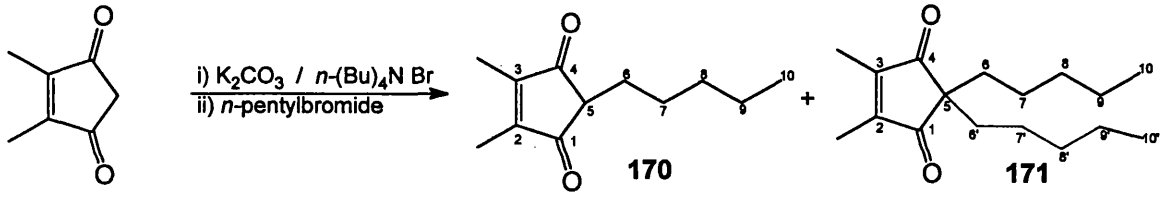
υ_{max} (NaCl; neat) / cm^{-1} 2929 (s), 2859 (s), 1701 (s), 1647 (m); δ_H (400 MHz; $CDCl_3$), 0.86 (3 H, t, *J* 7.9 Hz, 9-H), 1.34 (4 H, m, 7-H, 8-H), 1.75 (2 H, m, 6-H), 2.02 (6 H, s, 2'-

H, 3'-H), 2.60 (1 H, t, *J* 6.1 Hz, 5-H); δ_C(100 MHz; $CDCl_3$), 9.26 (C-9), 13.78, 22.73, 26.67, 28.25, 48.84 (C-5), 155.30 (C-2, C-3), 204.16 (C-1, C-4); *m/z* (EIMS) Found for $C_{11}H_{16}O_2$ (M^+) 180.1145; Required 180.1150.

2,2-Dibutyl-4,5-dimethyl-4-cyclopentene-1,3-dione (169)

υ_{max} (NaCl; neat) / cm^{-1} 2931 (s), 2862 (s), 1706 (s), 1649 (m); δ_H (400 MHz; $CDCl_3$), 0.75 (6 H, t, *J* 7.4 Hz, (9-H, 9'-H), 0.86 (4 H, m, (8-H, 8'-H), 1.13 (4 H, pent, *J* 7.4 Hz, 8-H, 8'-H), 1.58 (4 H, m, 7-H, 7'-H), 1.91 (6 H, s, 2'-H, 3'-H); δ_C(100 MHz; $CDCl_3$), 9.08 (C-9), 13.68, 22.99, 26.75, 34.38, 53.77, 155.42 (C-2, C-3), 207.85 (C-1, C-4); *m/z* (EIMS) Found for $C_{15}H_{24}O_2$ (M^+) 236.1770; Required 236.1776.

R86 **4,5-Dimethyl-2-pentyl-4-cyclopentene-1,3-dione (170)**
4,5-Dimethyl-2,2-dipentyl-4-cyclopentene-1,3-dione (171)



163 **170** **171**

To a stirred solution of diketone (**163**) (124 mg, 1.00 mmol) in toluene (3 ml), was added anhydrous potassium carbonate (617 mg, 4.46 mmol) and a catalytic amount of tetra *n*-butylammonium bromide (4 mg, 0.01 mmol). The reaction mixture was heated to reflux for 2 h before being allowed to cool to rt. *n*-Pentylbromide (175 mg, 1.2 mmol) was added in one portion and the reaction stirred for 24 h. The reaction mixture was filtered through a pad of celite using *n*-hexane. The filtrate was concentrated *in vacuo* to afford a brown oil which was purified by flash chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 25 : 1), to yield 2,3-dimethyl-5pentyl-cyclopent-2-en-1,4-dione (**170**) as a pale yellow oil (37 mg, 19 %) and 2,3-dimethyl-5,5'-dipentyl-cyclopent-2-en-1,4-dione (**171**) also as a yellow oil (7 mg, 4 %). (Unreacted starting diketone also recovered (48 mg, 38 %).

N.B. (**170**) weak jasmine odour; (**169**) odourless.

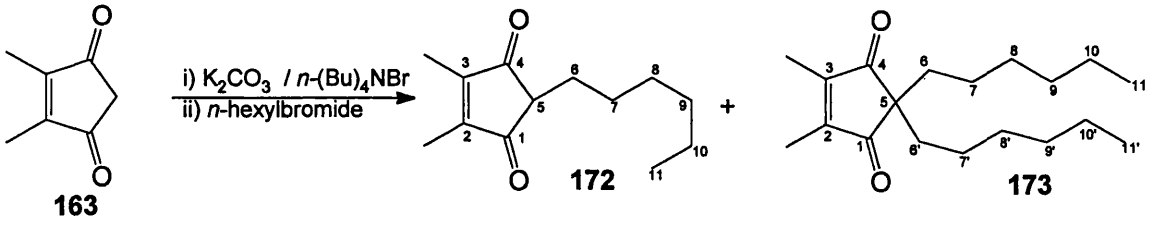
4,5-Dimethyl-2-pentyl-4-cyclopentene-1,3-dione (170)

υ_{max} (NaCl; neat) / cm^{-1} 2930 (s), 2856 (s), 1701 (s), 1643 (m), 1413 (m); δ_H (400 MHz; $CDCl_3$), 0.85 (3 H, t, *J* 7.1 Hz, 10-H), 1.27 (4 H, m, 8-H, 9-H), 1.73 (2 H, m, 6-H), 2.00 (6 H, s, 2'-H, 3'H), 2.60 (1 H, t, *J* 6.1 Hz, 5-H); δ_C(100 MHz; $CDCl_3$), 9.26 (C-10), 14.00, 22.33, 25.80, 26.89, 31.79, 48.86 (C-5), 155.27 (C-2, C-3), 204.13 (C-1, C-4), *m/z* (EIMS) Found for $C_{12}H_{18}O_2$ (M^+), 194.1302; Required 194.1307.

4,5-Dimethyl-2,2-dipentyl-4-cyclopentene-1,3-dione (171)

υ_{max} (NaCl; neat) / cm^{-1} 2931 (s), 2851 (s), 1697 (s), 1639 (m), 1412 (w); δ_H (400 MHz; $CDCl_3$), 0.79 (6 H, t, *J* 7.5 Hz, 10-H, 10'-H), 0.92 (4 H, m, 9-H, 9'-H), 1.19 (8 H, m, 7-H, 7'-H, 9-H, 8'-H), 1.60 (4 H, m, 6-H, 6'-H), 2.03 (6 H, s, 2'-H, 3'-H); δ_C(100 MHz; $CDCl_3$), 9.32, 13.96, 19.14, 22.8, 26.83, 34.45, 53.84, 155.35 (C-2,C-3), 204.6 (C-1, C-4); *m/z* (EIMS) Found for $C_{17}H_{28}O_2$ (M^+) 264.0156; Required 264.0161.

R87 **2-Hexyl-4,5-dimethyl-4-cyclopentene-1,3-dione (172)**
2,2-Dihexyl-4,5-dimethyl-4-cyclopentene-1,3-dione (173)



To a stirred solution of diketone (**163**) (124 mg, 1.00 mmol) in toluene (3 ml), was added anhydrous potassium carbonate (617 mg, 4.46 mmol) and a catalytic amount of tetra *n*-butylammonium bromide (4 mg, 0.01 mmol). The reaction mixture was heated to reflux for 2 h before being allowed to cool to rt. *n*-Hexylbromide (198 mg, 1.2 mmol) was added in one portion and the reaction stirred for 24 h. The reaction mixture filtered through a pad of celite using hexane. The filtrate was concentrated *in vacuo* to afford a brown oil which was purified by flash chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 25:1), to yield 2,3-dimethyl-5-hexyl-cyclopent-2-en-1,4-dione (**172**) as a pale yellow oil (32 mg, 11 %) and 2,3-dimethyl-5,5'-dihexyl-cyclopent-2-en-1,4-dione (**173**) also as a yellow oil (9 mg, 3 %). (Unreacted starting diketone also recovered (51 mg, 42 %).

N.B. (**170**) odourless; (**169**) odourless.

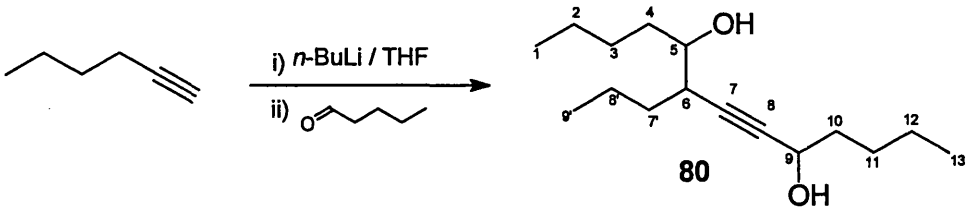
2-Hexyl-4,5-dimethyl-4-cyclopentene-1,3-dione (172)

υ_{max} (NaCl; neat) / cm^{-1} 2929 (s), 2860 (s), 1699 (s), 1641 (w), 1420 (w); δ_H (400 MHz; $CDCl_3$), 0.85 (3 H, t, *J* 6.6 Hz, 11-H), 1.27 (8 H, m, 7- H, 8-H, 9-H, 10-H), 1.74 (2 H, m, 6-H), 2.01 (6 H, s, 2'-H, 3'-H), 2.59 (1 H, t, *J* 6.0 Hz, 5-H); δ_C(100 MHz; $CDCl_3$), 9.26 (C-11), 14.05, 22.56, 26.95, 29.28, 29.69, 31.49, 48.86 (C-5),155.28 (C-2, C-3), 204.15 (C-1, C-4); *m/z* (EIMS) Found for $C_{13}H_{20}O_2$ (M^+) 208.1458; Required 208.1453.

2,2-Dihexyl-4,5-dimethyl-4-cyclopentene-1,3-dione (173)

υ_{max} (NaCl; neat) / cm^{-1} 2927 (s), 2856 (s), 1696 (s), 1648 (w), 1423 (w); δ_H (400 MHz; $CDCl_3$), 0.83 (6 H, t, *J* 7.2 Hz, (11-H, 11'-H), 0.90 (4 H, m, 10-H, 10'-H), 1.19 (12 H, m, 7-H, 8-H, 9-H,7'-H, 8'-H, 9'-H), 1.65 (4 H, m, 6-H, 6'-H), 2.02 (6 H, s, 2'-H, 3'-H), δ_C(100 MHz; $CDCl_3$), 8.99 (C-11, C-11'), 13.48, 19.24, 20.39, 22.95, 26.63, 34.43, 53.82, 155.43 (C-2, C-3), 204.10 (C-1, C-4); *m/z* (EIMS) Found for $C_{19}H_{32}O_2$ (M^+) 292.1658; Required 292.1653.

R88 **(5S*,9S*)-8-Propyl-6-tridecyne-5,9-diol (180)**

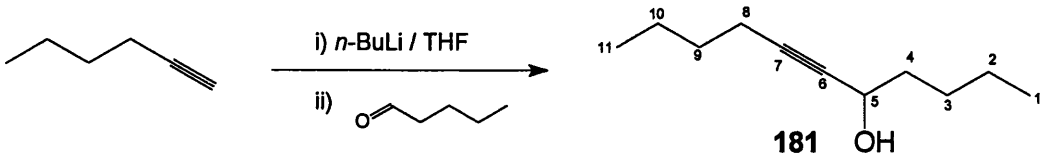


80

To a solution of hex-1-yne (1.4 ml, 12.2 mmol) at -78 °C in dry tetrahydrofuran was added *n*-butyllithium (2.0 M, 6.1 ml, 12.2 mmol) dropwise over a period of 5 min. The reaction was warmed to -20 ° C over 40 min and then cooled down to -78 °C and *n*-valeraldehyde (1.3 ml, 12.2 mmol) was added to the reaction mixture over 2 min. The reaction mixture was then stirred for a further 3 h, warming to 0 °C and was quenched by the addition of saturated ammonium chloride solution (30 ml). The reaction mixture was extracted with ethyl acetate (3 x 30 ml). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil. The oil was purified by flash column chromatography (eluent: petroleum spirits 40-60° C / ethyl acetate, 25 :1 → 10:1) to afford the title compound as the major component (597 mg, 19 %) .

υ_{max} (NaCl; neat) / cm^{-1} 3346 (br), 2957 (s), 2873 (m) 1742 (w), 1726 (w); δ_H (400 MHz; $CDCl_3$), 0.91-0.99 (9 H, m, 1-H, 9'-H, 13-H overlap), 1.40-1.56 (16 H, m, 2-H, 3-H, 4-H, 7'-H, 8'-H, 10-H, 11-H, 12-H), 2.88 (2 H, S (br), (O*H*)$_2$), 3.77 (3 H, m, 5-H, 6-H, 9-H overlap); δ_C(100 MHz; $CDCl_3$), 14.11, 14.39, 20.43, 20.89, 22.78, 28.59, 30.92, 32.90, 35.36, 43.98, 64.14 (C-9), 64.87 (C-5), 75.54 (C-8), 75.94 (C-7).

R89 **(5S*)-6-Undecyn-5-ol (181)**

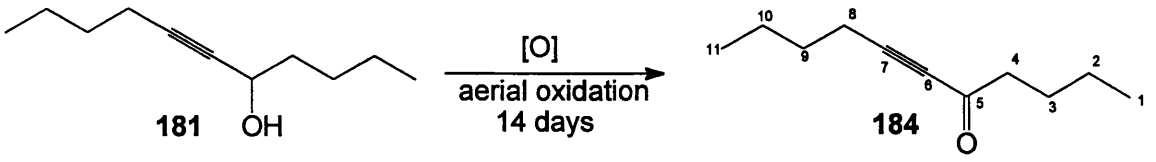


181

To a solution of 1-hexyne (5.6 ml, 48.8 mmol) at -78 °C in dry tetrahydrofuran was added *n*-butyllithium (48.8 mmol) dropwise over a period of 1 min. The reaction was warmed to -55 °C over 20 min and then cooled down to -78 °C. *n*-Valeraldehyde (5.2 ml, 48.8 mmol) was added to reaction mixture over 2 min, the reaction mixture was stirred for a further 2 h, warming to 0 °C. The reaction was quenched by addition of saturated ammonium chloride solution (30 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. The oil was purified by flash column chromatography (eluent: petroleum spirits 40-60° C / ethyl acetate, 10 : 1) to give the title compound as a colourless oil (7.12 g, 89 %).

υ_{max} (NaCl; neat) / cm^{-1} 3346 (OH, br), 2953 (s), 2939 (s) 1741 (w), 1727 (w); δ_H (400 MHz; $CDCl_3$), 0.89 (6 H, m, 1-H, 11-H *overlap*), 1.40 (8 H, m, 2-H, 3-H, 10-H, 9-H), 1.66 (2 H, m, 4-H, 1.97 (1 H, s, OH), 2.19 (2 H, td, *J* 5.1, 2.0 Hz, 8-H), 4.33 (1 H, tt, *J* 2.8,1.9 5-H); δ_C(100 MHz; $CDCl_3$), 13.59 (C-1), 14.04 (C-11), 18.37, 21.93, 22.41, 27.41, 30.77, 37.92, 62.73 (C-5), 81.38 (C-6), 85.40 (C-7); *m/z* (EIMS) Found for $C_{11}H_{20}O$ (M^+) 168.1510; Required 168.1514.

R90 **6-Undecyn-5-one (184)**

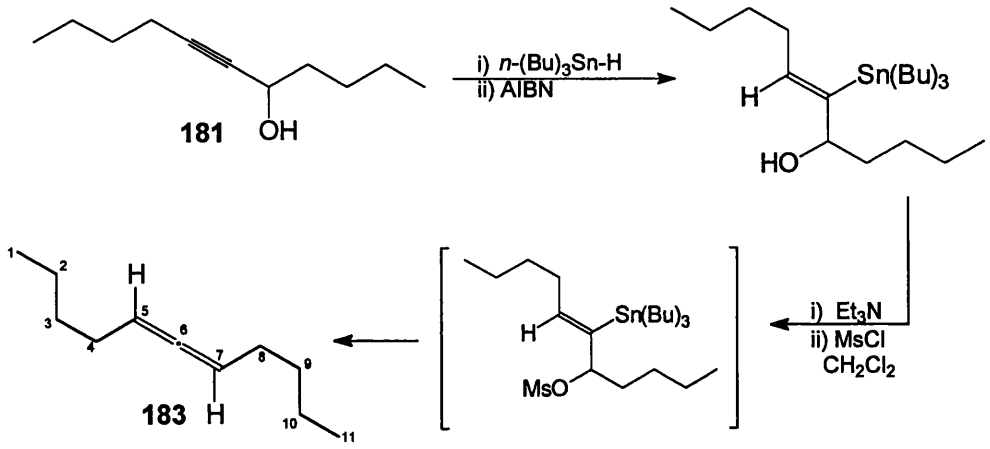


A sample of (**181**) was left in the presence of air for 14 days at rt. The sample oxidised to the corresponding ketone (**184**). The ketone was purified by flash chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 20 : 1).

N.B. Sweet pineapple odour.

υ_{max} (NaCl; neat) / cm^{-1} 2960 (s), 2872 (s), 2214 (s), 1672 (s); δ_H (400 MHz; $CDCl_3$), 0.91 (3 H, t, *J* 7.3 Hz, 11-H), 0.91 (3 H, t, *J* 7.3 Hz, 1-H), 1.38 (4 H, m, 2-H, 10-H), 1.58 (4 H, m, 9-H, 3-H), 2.35 (2 H, t, *J* 7.3 Hz, 4-H), 2.50 (2 H, t, *J* 7.3 Hz, 8-H); δ_C(100 MHz; $CDCl_3$), 13.44 (C-11), 13.75 (C-1), 18.58, 21.90, 22.08, 26.18, 29.70, 45.21 (C-4), 80.84 (C-7), 94.15 (C-6), 188.52 (C-5); *m/z* (EIMS) 166 (M^+ -O, 30 %), 137(M^+ -CH_2CH_3, 35), 123 (M^+ -*n*-Pr, 100).

R91 **(5R*)-6-Undecadiene (183)**



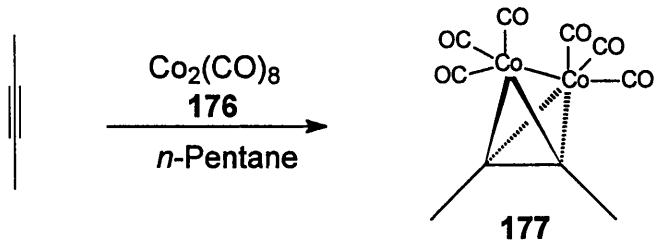
To a mixture of alcohol (**181**) (1.71 g, 10.0 mmol) and *n*-tributyltin hydride (2.9 ml, 11 mmol), was added a catalytic amount of free radical initiator AIBN (≈ 5 mg). The mixture was heated (in the absence of solvent) at 90 °C for 4 h. The reaction was cooled to rt and diluted with dichloromethane (20 ml). Triethylamine (2.8 ml, 20 mmol) was added dropwise. The reaction was further cooled to 0 °C and methanesulfonyl chloride

(1.7.1 g, 15.1 mmol) added cautiously (effervescence noted) and allowed to warm up to rt over 30 min. Pouring into dilute hydrochloric acid (2 N, 20 ml) quenched the reaction.

The aqueous solution was extracted with ethyl acetate (3x 30 ml). The combined organic washing were further washed with dilute sodium bicarbonate solution (5 %, 20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil. The oil was purified by flash chromatography, (eluent: *n*-hexane) and then distilled under reduced pressure using a Vigreux column to afford the title compound as a colourless liquid (1.19 g, 56 %).

υ_{max} (NaCl; neat) / cm^{-1} 2874 (s), 2953 (s) 1926 (w), 1963 (w) 1458 (w); δ_H (400 MHz; $CDCl_3$), 0.89 (3 H, t, *J* 7.0 Hz, 1-H, 11-H), 3.71 (8 H, m, 2-H, 3-H, 9-H, 10-H), 1.91 (4 H, m, 4-H, 8-H), 5.06 (2 H, m (5-H, 7-H); δ_C(100 MHz; $CDCl_3$), 13.93 (C-1, C-11), 22.19, 28.74, 31.42, 90.87 (C-5, C-7), 203.83 (C-6); *m/z* (EIMS) Found for $C_{11}H_{20}$ (M^+) 152.1560; Required 152.1565.

R92 **Dicobalt hexacarbonyl-but-2-yne (177)**



177

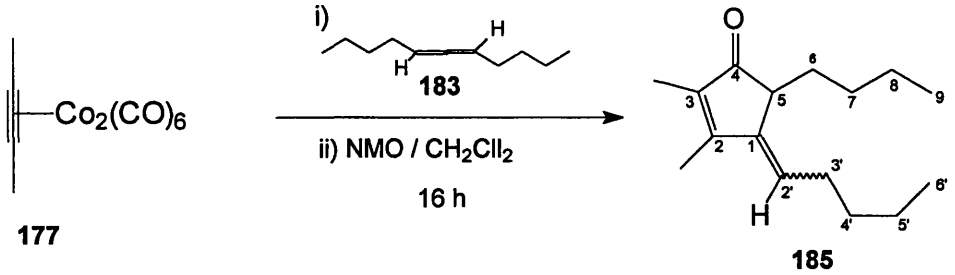
To a stirred solution of dicobalt octacarbonyl (**176**) (2.51 g, 7.31 mmol) in dry pentane under argon was added *n*-but-2-yne (0.65 ml, 8.2 mmol) at 0 °C (straight from the fridge, using a pre-cooled syringe). Effervescence was noted, after 3 h the reaction was concentrated *in vacuo* to give a brown / orange solid. The solid was purified by chromatography (eluent : neat *n*-pentane) to afford the title compound as a brown waxy solid (2.81 g, 98 %).

N.B. Unstable to heat.

υ_{max} (KBr) / cm^{-1} 3428 (br), 2905 (w) 2678 (w), 2300 (w), 2044 (s); δ_H (400 MHz; $CDCl_3$), 2.12 (6 H, s, CH_3); *m/z* (EIMS) 340 (M^+, 10 %), 312 (M^+, -C=O, 63), 284 (M^+, -$(C=O)_2$,

21) 256 (M^+, -$(C=O)_3$, 17), 228 (M^+, -$(C=O)_4$, 35), 200 (M^+, -$(C=O)_5$, 100), 172 (M^+, -$(C=O)_6$, 52).

R93 5-Butyl-2,3-dimethyl-4-[(*E*/*Z*)pentylidene]-2-cyclopenten-1-one(185)

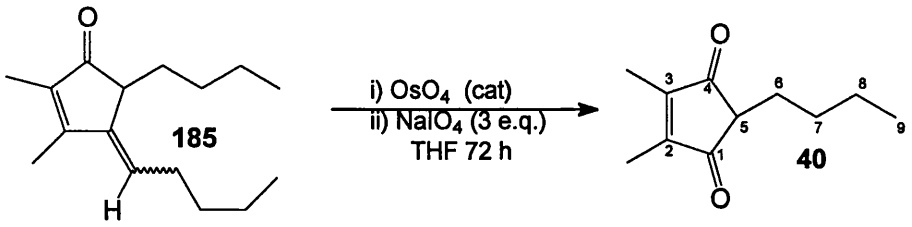


177 185

To a stirred solution of dicobolt octacarbonyl but-2-yne complex (**177**) (2.72 g, 8.0 mmol) and dibutylallene (**183**) (1.88 g, 12.2 mmol) in dry dichloromethane (80 ml) at 0 °C was added *N*-methyl morpholine oxide gradually over 2 min. The reaction was then allowed to warm to rt and stirred for 16 h. A purple precipitate formed (cobalt salt). The reaction was filtered through a pad of silica gel. The brown filtrate was concentrated *in vacuo* to afford a dark brown oil. The oil was purified by flash chromatography, (eluent: neat petroleum spirits 40-60° C, petroleum spirits / ethyl acetate 20 :1 product). The product was isolated as a colourless oil (1.49 g) in 78 % yield, (yield based on cobalt complex).

υ_{max} (NaCl; neat) / cm^{-1} 2928 (s), 2856 (s), 1667 (s), 1643 (m), 1616 (s); δ_H (400 MHz; $CDCl_3$), 0.87 (6 H, m, 6'-H, 9-H *overlap*), 1.20 (6 H, m, 7-H, 8-H, 5'-H), 1.65 (2 H, m, 6-H), 1.78 (3 H, s, 2"-H), 1.93 (2 H, m 4'-H), 2.04 (3 H, s, 3"-H), 2.56 (2 H, m 3-H), 2.90 (1 H, t, *J* 4.5 Hz, 5-H), 5.67 (1 H, t, *J* 7.7 Hz, 2'-H); δ_C(100 MHz; $CDCl_3$),13.92 (C-9), 13.98 (C-6'), 22.50, 22.95, 26.61, 29.11, 29.36, 29.65, 30.12, 31.74, 46.29, 124.68 (C-2'), 137.43 (C-1), 141.20 (C-3), 163.28 (C-2), 208.50 (C-4); *m/z* (EIMS) 234 (M^+, 14%), 178 (M^+ - *n*-Bu, 40), 136 (M^+ -*n*-Bu - *n*-Pr, 100), found for $C_{16}H_{26}O$ (M^+) 234.1978; Required 234.1984.

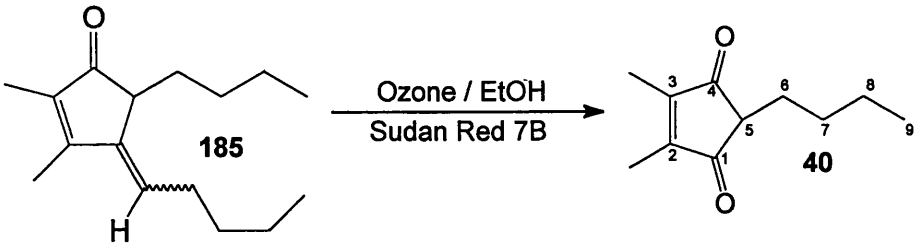
R94 **2-Butyl-4,5-dimethyl-4-cyclopentene-1,3-dione (40)**



To a solution of tetrahydrofuran (3 ml) and osmium tetraoxide (0.2 ml of 0.04 M solution), at 0 °C was added the functionalized enone (**185**) (102 mg, 4.42 mmol) and stirred for 10 min. Sodium periodate (307 mg, 13.26 mmol) was added gradually over 20 min, the reaction was sealed and stirred for 72 h at rt. The reaction was filtered though a pad of celite and concentrated the filtrate *in vacuo*. The crude oil was purified by flash chromatography, (eluent: petroleum spirits 40-60 °C / ethyl acetate, 30 : 1) to give the target compound as a yellow oil (51 mg, 56 %).

υ_{max} (NaCl; neat) / cm^{-1} 2929 (s), 2859 (s), 1701 (s), 1647 (m); δ_H (400 MHz; $CDCl_3$), 0.86 (3 H, t, *J* 7.9 Hz, 9-H), 1.34 (4 H, m, 7-H, 8-H), 1.75 (2 H, m, 6-H), 2.02 (6 H, s, 2'-H, 3'-H), 2.60 (1 H, t, *J* 6.1 Hz, 5-H); δ_C(100 MHz; $CDCl_3$), 9.26 (C-9), 13.78, 22.73, 26.67, 28.25, 48.84 (C-5), 155.30 (C-2, C-3), 204.16 (C-1, C-4); *m/z* (EIMS) Found for $C_{11}H_{16}O_2$ (M^+) 180.1145; Required 180.1150.

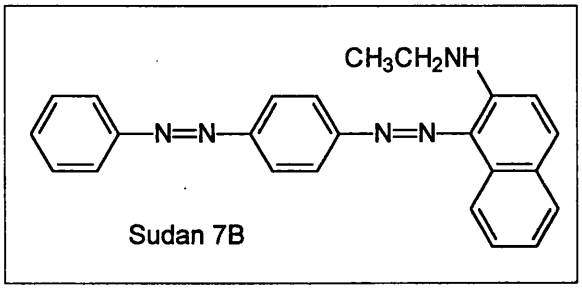
R95 **2-Butyl-4,5-dimethyl-4-cyclopentene-1,3-dione (40)**



To a solution of enone (**185**) (0.50 g, 2.14 mmol) in ethanol (30 ml), was added Sudan 7B (1 ml of a saturated solution of Sudan Red 7B in ethanol), the reaction mixture was cooled to -78 °C and ozone was bubbled through. After 40 min the red colour had almost disappeared, and the reaction was stopped and bubbled with

nitrogen. The mixture was warmed to room temperature and concentrated *in vacuo*. The yellow oil was purified by chromatography (eluent: petroleum spirits 40-60 °C / ethyl acetate, 30 : 1) to afford the target compound (325 mg, 84 %).

υ_{max} (NaCl; neat) / cm^{-1} 2929 (s), 2859 (s), 1701 (s), 1647 (m); δ_H (400 MHz; $CDCl_3$), 0.86 (3 H, t, *J* 7.9 Hz, 9-H), 1.34 (4 H, m, 7-H, 8-H), 1.75 (2 H, m, 6-H), 2.02 (6 H, s, 2'-H, 3'-H), 2.60 (1 H, t, *J* 6.1 Hz, 5-H); δ_C(100 MHz; $CDCl_3$), 9.26 (C-9), 13.78, 22.73, 26.67, 28.25, 48.84 (C-5), 155.30 (C-2, C-3), 204.16 (C-1, C-4); *m/z* (EIMS) Found for $C_{11}H_{16}O_2$ (M^+) 180.1145; Required 180.1150.



Sudan 7B

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