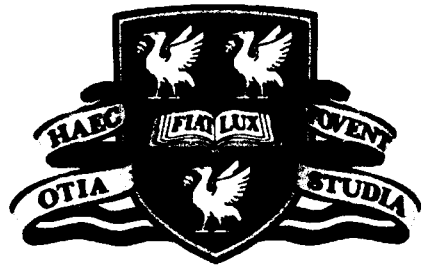


THE UNIVERSITY
of LIVERPOOL

The Robert Robinson Laboratories

The Synthesis and Biological Evaluation of Natural and Unnatural Cyclopentenone Prostanoids

Thesis submitted by

Timothy J. Snape

In accordance with the requirements of

The University of Liverpool for the degree of

Doctor of Philosophy

In the Faculty of Science

2003

I certify that all material in this thesis which is not my own work has been identified and no material is included for which a degree has previously been conferred upon me.

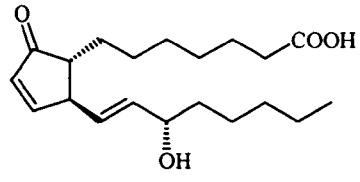
To my wife and family

Where observation is
concerned, chance favours
only the prepared mind.

Louis Pasteur; 1900

Abstract

Research into the synthesis and biological properties of the cyclopentenone prostaglandins has become the focus of many research groups over the past few years. The ability for cyclopentenone prostaglandins, for example prostaglandin A_1, to reduce virus yields and inflammation, both *in vitro* and *in vivo*, and to act as anti-cancer agents *in vitro* has made them important biological targets.



prostaglandin A_1

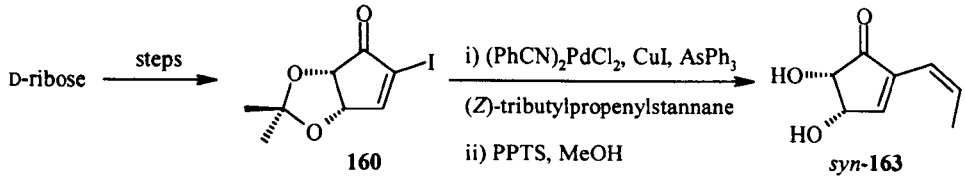
In view of this, a great deal of work is currently being undertaken towards the preparation of cyclopentenone prostaglandin analogues, in the hope of harnessing the innate biological activity of this system.

Part of the ongoing research into the cyclopentenone prostaglandins is the work currently being undertaken at The University of Liverpool, and this Ph.D. thesis is part of the contribution made by the Roberts' group.

This thesis begins with an introductory section, Chapter 1, outlining the background and biological properties of the natural prostaglandins, along with examples of their chemical syntheses and some of the work carried out on other, related cyclopentenone-based natural products. Chapter 2 goes on to elaborate upon the

biological results obtained during the course of this Ph.D., the synthesis of various prostaglandin analogues and the discussion of these results. The latter part of Chapter 2 describes the synthesis and ultimately the revision of stereochemistry of a natural product isolated from ascomycete strain A23-98.

It has been shown that α-iodo-cyclopentenone **160**, generated in 7 steps from D-ribose, can undergo a palladium-catalysed Stille reaction, followed by deprotection of the masked diol, to reveal the natural product *syn*-**163**.



Following the synthesis it was subsequently discovered that the geometry of the side-chain is *cis*, as shown in *syn*-**163**, and not *trans* as proposed by NMR studies and correlation to similar natural products.

Finally, Chapter 3 describes the experimental details associated with the compounds prepared throughout this thesis, followed by a reference section giving relevant citations in the chemical literature.

Table of Contents

Acknowledgements

There are so many people who contributed to this Ph.D. that I am afraid one or two pages would not be enough to include everyone.....

First, and most importantly, I would like to thank Professor Stanley M. Roberts for giving me the opportunity to work within his research group. I would especially like to thank him for his encouragement and support over the past three years, I truly found this opportunity both mentally stimulating and a great learning experience. I would also like to thank him for securing financial support, for reviewing this manuscript and providing me with helpful suggestions throughout my Ph.D.

I would also like to thank Charterhouse Therapeutics Limited for providing the financial support and allowing me to work as a part of their team during the years of this Ph.D. Thank you to all the people involved with Charterhouse Therapeutics Limited; the management team, for all their hard work and commitment; the chemists here in Liverpool, and all the excellent and speedy work of the biologists in Rome.

There are also many very talented chemists who contributed to this work, and a special thank you must go to Dr. Paul Evans who gave me invaluable help and encouragement, and allowed me to develop both my practical and theoretical skills enormously through listening and contributing to my never-ending questions.

I would certainly never have been able to get through this Ph.D. without the constant and helpful support of my friends and colleagues in Liverpool. Thank you to Alan,

Hervé, Jérôme, John, Jon, Nicolette, Paul, Roger, Vasu and everyone from the SMR group both past and present, there are so many more to thank.....

Thank you also to the technical staff in the chemistry department for their invaluable work, especially Alan and Moya (Mass Spec.), Paul and Sandra (NMR) and Steve (Microanalysis), without whose hard work I would not have been able to complete the experimental details of this work.

Last of all, but certainly not least, I would like to extend my greatest thanks and affection to my mum and dad, Lynda and Alan, and my brother Ben, whose love and support has meant everything to me. Thank you also to my wife and best friend, Lucy, for your amazing patience, for your love, support and confidence in me. Only you really know what this Ph.D. has meant to me.

Abbreviations

Ac	acetate
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
BINAL	2,2'-dihydroxy-1,1'-binaphthylaluminium hydride
br. s	broad singlet
Bu	butyl
Bz	benzoate
ca.	approximately
cat.	catalytic
cf.	compared with
CI	chemical ionisation
COX	cyclooxygenase
CSA	10-camphorsulfonic acid
cy	cyclopentenone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DHP	3,4-dihydro-2*H*-pyran
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide

DNA	deoxyribonucleic acid
ee	enantiomeric excess
EI	electron ionisation
ent	enantiomer
epi	epimer
eq.	equivalent
ES	electrospray
Et	ethyl
FVP	flash vacuum pyrolysis
FVT	flash vacuum thermolysis
GC	gas chromatography
gem	geminal
HIV	human immunodeficiency virus
HSE	heat shock elements
HSF	heat shock factors
HSP	heat shock proteins
HSV	human simplex virus
Hz	hertz
ID_{50}	concentration of test compound necessary to reduce virus load by 50%
IL	interleukin
LDA	lithium diisopropylamide
lit.	literature
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl

m.p.	melting point
Ms	methanesulfonyl
NaHMDS	sodium hexamethyldisilazide
NCE	new chemical entity
NF-κB	nuclear factor *kappa* B
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NSAID	non-steroidal anti-inflammatory drug
Nuc	nucleophile
$^1O_2$	singlet oxygen
$^3O_2$	triplet oxygen
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	prostaglandin
Ph	phenyl
Piv	pivaloylate
PLE	pig liver *esterase*
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
pyr.	pyridine
rac	racemic
rt	room temperature
SAR	structure activity relationship
SEAP	secreted alkaline phosphatase
S_N	nucleophilic substitution

TBS	*tert*-butyldimethylsilyl
TD_{100}	concentration of test compound necessary to kill 100% of the virus
TEA	triethylamine
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
t_r	retention time
Ts (tosyl)	4-toluenesulfonyl
W	Watt
wt.	weight

Chapter 1:

Introduction

1 Introduction

1.1 Historical background of medicinal chemistry

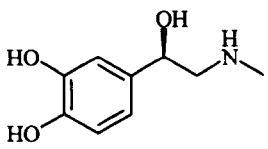
Medicinal chemistry is the science that deals with the discovery or design of new therapeutic chemicals and their development into useful medicines. In its crudest sense medicinal chemistry has been practiced for several thousand years, whereby man has searched for cures of illnesses by chewing herbs, berries, roots and barks.[1] Therefore, in centuries gone by medicinal chemistry comprised of herbal elixirs and potions based upon the folklore known at the time. Although a few of these herbal remedies had an effect on various illnesses and diseases (for example the root *Dichroa febrifuga*, which was prescribed for fevers and contains alkaloids which are used in the treatment of malaria today) the eradication of the effects of the disease was extremely slow.[2] In recent years, particularly over the last century, medicinal chemistry has undergone a revolutionary change. Rapid advances in the biological sciences has resulted in a much better understanding of how the body functions at the cellular and molecular levels.[2]

If the approach to drug design had continued at the rate it did thousands of years ago, few diseases would be treatable today.[2] Natural products do, however, make up a small percentage of drugs on the current market, but more importantly, their molecular scaffold is exploited and chemically modified in order to improve their pharmacological properties. With the advances made in chemical synthesis and biochemical techniques since the 1940s a more rational approach to drug discovery has been developed basing the emphasis on the element of molecular structural design.[2]

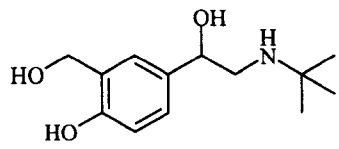
As a consequence of this greater understanding, harnessing the innate biological activity of our planet's flora and fauna has been the goal of medicinal chemists for some time. Despite this, improving upon the natural level of activity exhibited by the active ingredients found in certain species has become a major challenge. The amount of research that has been directed towards this area is huge and medicinal chemists have now made it possible to exploit the core structure of a naturally occurring compound by way of manipulation of its periphery. This advance ultimately leads to drug candidates for the clinic with a better biological profile than the natural products themselves.

1.1.1 The Salbutamol story

One such example of this relatively new approach to medicinal chemistry, whereby "Nature's agonists" are used as the starting point to a clinically useful drug, is the use of the body's natural bronchodilator adrenaline as the lead compound that led to Salbutamol, the anti-asthmatic drug.[3]



adrenaline



Salbutamol

It is easy to see the relationship between adrenaline and Salbutamol, the only differences being the alkyl group on nitrogen and the extension of the phenolic alcohol to a methyl alcohol. In spite of the close similarities, an enormous number of compounds had to be prepared and tested before Salbutamol was finally discovered.[3] Such subtle changes away from the structure of adrenaline are, however, essential

since they diminish the effects on the heart, a property exhibited by adrenaline, resulting in a drug that acts exclusively on the receptors in the lungs. Thus, Salbutamol acts as an agonist on the β_2-receptor sub-type of the lungs, whereas adrenaline also behaves as a β_1-agonist on the heart, a difference caused by the changes in the chemical structure of the two compounds.[3] It was also essential to extend one of the phenol groups to a hydroxy-methyl group to prevent the drug being rendered inactive by the action of *catechol-O-methyl transferase*.

The use of natural products as lead compounds exemplifies the enormous potential of using rational drug design by synthetic chemists to prepare remedies for various disease states.

One such class of natural product that has received a great deal of attention for the possibility of encapsulating their biological activity is the eicosanoid class, a C_{20} fatty acid derived set of natural compounds which appear in both marine and terrestrial life and possess potent biological properties.[4]

Arguably the most famous group of natural products from the eicosanoid class are the prostaglandins. The diverse and potent biological actions of the prostaglandins, on almost all organs in the body, has stimulated a great deal of research on these fascinating molecules since their discovery; the area continues to interest chemists and biologists today.

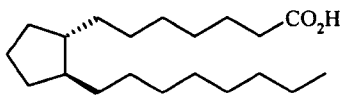
1.2 Historical background of the prostaglandins

The prostaglandins were first discovered in 1933-34 when Goldblatt[5,6] and *von* Euler[7] independently demonstrated the presence of vasodepressor and smooth muscle stimulating material in human seminal plasma extracts and in the vesicular glands of sheep. *von* Euler's research also showed that the biological activity of this material was due to its lipid solubility and acidic properties, and, mistakenly assuming it to be solely produced in the prostate gland, named the material prostaglandin.[8-11]

Much later, a continuation of this study led, in 1957, to Bergström and Sjövall[12-14] isolating two biologically active compounds also from the vesicular glands of sheep. They named these compounds prostaglandin E_1 (PGE_1, since it was soluble in Ether) and prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$, since it was soluble in Fosfate (Swedish spelling) buffer).

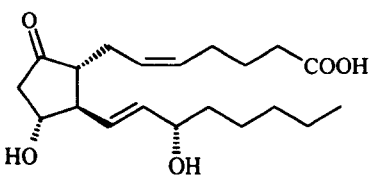
Their research found that PGE_1 was a very potent vasodepressor and smooth muscle stimulant whereas $PGF_{1\alpha}$, interestingly, only possessed smooth muscle stimulating activity. Later, additional compounds were isolated from the same tissue and were named PGE_2 and PGE_3.[15] Further investigation showed that the prostaglandins were more widely distributed in animal tissues than first thought and, in fact, prostaglandins were found to be widely dispersed throughout both various tissue types and animal species.

The prostaglandins, belonging to the eicosanoid (*eico*, Greek for 20) class of compounds, contain twenty carbon atoms and a terminal carboxylic acid residue and their core structure is based on the prostanoic acid skeleton.

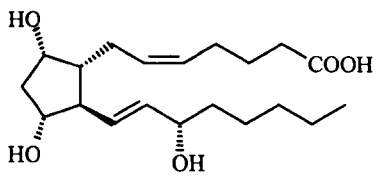


prostanoic acid

The prostaglandins, although discovered in the 1930's, had their structures elucidated only in the 1960's.[16] Since then there has been considerable interest from chemists attempting to synthesise the natural prostaglandins, especially the PGEs and PGFs, as well as unnatural prostaglandin analogues (prostanoids).[17-21] Not only was this undertaken to gain insight into their biological activities but at the time such a highly functionalised chiral molecule posed a significant synthetic challenge to organic chemists. As such, over a period of about a decade a tremendous amount of research was undertaken on the synthesis and biological activity of these primary prostaglandins.



PGE_2



$PGF_{2\alpha}$

The initial surge of prostaglandin based research in the sixties and seventies saw the prostaglandins become a 'hot' topic once again and the focus of attention for many chemists, biochemists and pharmachologists. Their molecular identity and role as regulators of numerous physiological and pathological processes suggested it should be possible to use them to treat a range of conditions and diseases. Thus, by utilising the core prostanoic acid skeleton as a molecular scaffold, the preparation of various

analogues ensued with the aim of improving upon the biological properties of the natural compounds.

1.3 Chemical synthesis of the prostaglandins

The prostaglandins have a wide ranging and very important role in the well being of mammals and since their discovery have been the focus of a vast amount of research in an attempt to try and understand their biology more thoroughly. Unfortunately, the miniscule amounts available from nature make this task very difficult. A solution to this problem came about with the elucidation of their chemical structure and thus subsequent chemical synthesis.

The vast amount of research directed at the synthesis of the prostaglandins was finally rewarded with the outstanding achievement of E. J. Corey[22-26] for his "pioneering" bicyclic lactone approach to PGE_2 and $PGF_{2\alpha}$ and R. Noyori[27-29] for his elegant 3-component coupling approach to prostaglandins of the E-series.

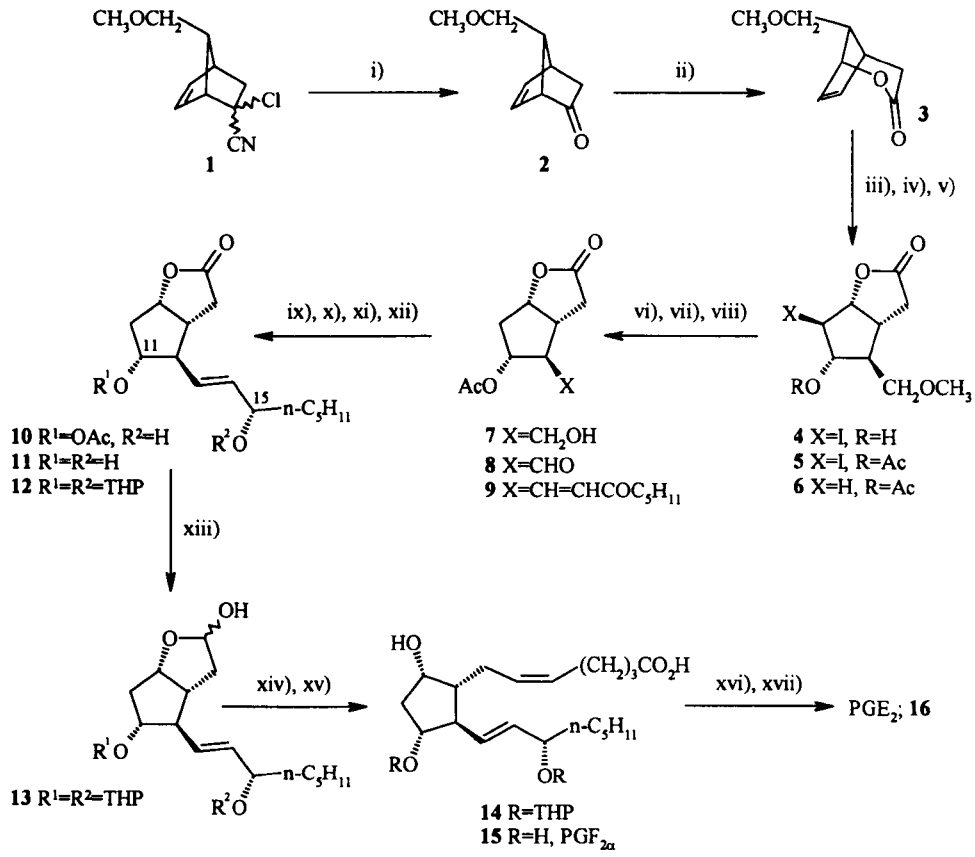
1.3.1 Corey's asymmetric synthesis of the prostaglandins

Back in the 1960's it was E. J. Corey who completed the first total asymmetric synthesis of the prostaglandins.[22] In doing so he developed the so called "Corey lactone" approach, which provided a general synthetic route into both PGE_2 and $PGF_{2\alpha}$ prostaglandins, in an enantiopure form from a common starting material, Scheme 1.3.1.

The synthesis begins with a Diels-Alder reaction between 5-methoxymethyl-cyclopenta-1,3-diene and 2-chloroacrylonitrile to provide the racemic, bicyclic

compound **1**. Treatment of **1** with potassium hydroxide then resulted in the racemic bicyclic ketone **2**.

Entry into the five-membered ring system of the prostaglandins was successfully achieved *via* a regioselective Baeyer-Villiger oxidation of ketone **2** with *m*-CPBA. Base induced saponification, followed by resolution with (+)-amphetamine provided the enantiomerically pure hydroxy acid.



Scheme 1.3.1: *Corey's asymmetric synthesis of the prostaglandins - Reagents*: i) KOH, ii) *m*-CPBA, $NaHCO_3$, iii) aq. NaOH, KI, I_2, iv) Ac_2O, pyr., v) Bu_3SnH, AIBN, vi) BBr_3, vii) CrO_3, pyr., viii) dimethyl 2-oxoheptyl-phosphonate, ix) $Zn(BH_4)_2$, x) separation of diastereomers using prep. TLC, xi) K_2CO_3, MeOH, xii) DHP, H^+, xiii) DIBAL, xiv) $Ph_3P{=}CH(CH_2)_3CO_2^-$, xv) AcOH, H_2O, xvi) $H_2Cr_2O_7$, xvii) AcOH, H_2O.

Subsequent iodolactonisation, by treatment of the hydroxy acid with potassium triiodide, resulted in the iodo-lactone **4**. Esterification of the secondary hydroxyl group in **4** was undertaken before deiodination with tributyl tin hydride and 2,2'-azobisisobutyronitrile (AIBN) finally revealed **6**, the now famous Corey-lactone. Demethylation followed by oxidation of the resulting alcohol with Collins' reagent (CrO_3-pyridine) yielded the β-acetoxy aldehyde **8**. A Horner-Wadsworth-Emmons reaction on the crude aldehyde installed the lower side-chain to furnish (*E*)-enone **9**. Subsequent zinc borohydride reduction of **9** afforded the allylic alcohol as a mixture of epimers (1:1) at C-15. Isolation of the desired isomer from the mixture followed by deacetylation gave the diol **11**, which was converted to the *bis*-tetrahydropyranyl derivative **12**. Reduction of this compound with diisobutylaluminium hydride yielded the lactol **13** which underwent a Wittig reaction to install the upper side-chain of $PGF_{2\alpha}$ as its *bis*-tetrahydropyranyl derivative **14**. Hydrolysis of this compound, under acidic conditions, afforded $PGF_{2\alpha}$, **15**, whereas oxidation of **14** and subsequent removal of the tetrahydropyran protecting groups afforded PGE_2, **16**.

It is advantageous that 15-*epi*-**10**, the undesired epimer, could be converted to the desired compound through simple functional group interconversions. Thus, oxidation of the alcohol with manganese dioxide or dichlorodicyano-*p*-benzoquinone provided the precursor **9** which, when followed by a second reduction step, would give a mixture of alcohols again, ready to carry forward in a similar manner. This process could be repeated as many times as necessary.

Due to its importance as an industrial process and because of the interest by academic scientists, this synthesis has undergone a lot of modifications and improvements. For

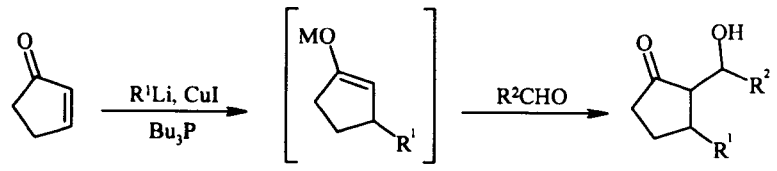
example, the stereoselective reduction of **9** to provide the desired epimer **10** was accomplished using the chiral reducing agent (*S*)-BINAL-H.[30] Improvements by Corey himself have also led to several asymmetric Diels-Alder reactions to provide the bicyclic lactone in a highly enantioenriched form.[31] There have also been attempts to make the bicyclic lactone *via* palladium chemistry (Larock[32]) and radical cyclisations (Stork[33]).

In addition to this classical prostaglandin synthesis developed by Corey an elegant 3-component coupling approach was developed by Noyori,[27-29] Scheme 1.3.2.3.

1.3.2 Noyori's synthesis of PGE_1

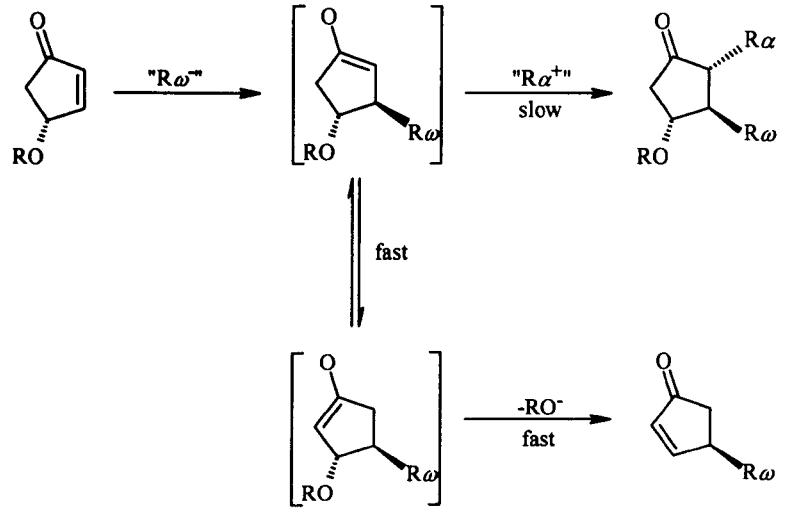
Whilst other syntheses of the prostaglandins cleverly solved the main problems associated with their synthesis, *i.e.* the creation of four or five asymmetric centres, the stereospecific formation of carbon-carbon double bonds, as well as overcoming the inherent instability of the β-hydroxy ketone functionality, Noyori's highly convergent 3-component coupling approach is much more desirable since it dramatically reduces the number of linear synthetic steps.

Noyori's synthesis hinges on the successful addition of the ω- and α-side-chains *via* a double vicinal carbon-carbon bond forming reaction. Therefore, addition of the lower ω-side-chain by way of an organocopper species with consecutive enolate trapping using an electrophilic equivalent of the upper α-side-chain would provide the C_{20} backbone in one-pot; such as the reaction seen in Scheme 1.3.2.1.



Scheme 1.3.2.1

At the time of Noyori's development of this protocol the existing procedures for the consecutive addition of two side-chains into 4-oxygenated-2-cyclopentenones were totally unsatisfactory. The main problem was the efficient trapping of the organometallic-generated enolate with the electrophilic equivalent of the α-side-chain, without loss of the oxygen functionality at C-4, due to the fast equilibration of the enolate, Scheme 1.3.2.2.

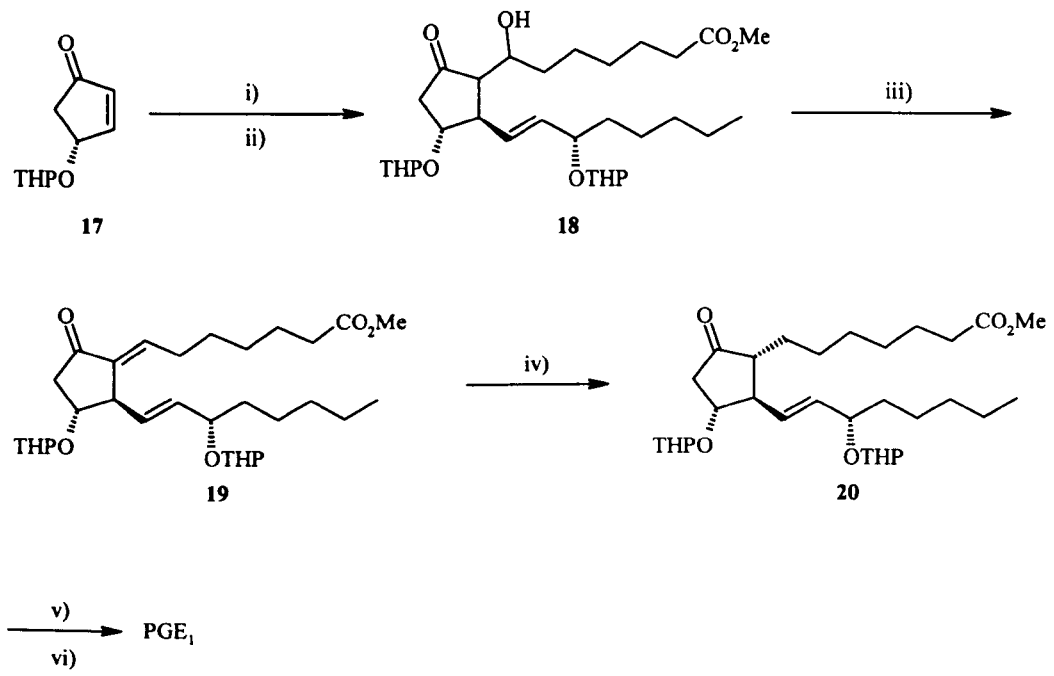


Scheme 1.3.2.2

Simple conjugate additions are usually carried out with an excess of the organocopper reagent to ensure respectable yields. However, since only one group is transferred when cuprates of the type R_2CuLi (Gilman reagents) are used, the protocol is wasteful

and expensive when complex R-groups are used. An excess of the organometallic ω-side-chain also disturbs the reaction between the generated enolate and the electrophilic α-side-chain. Since excess nucleophiles would be present, this results in complex mixtures. Thus, Noyori concluded that if only one equivalent of the organocopper species was present then the enolate generated would be the only nucleophile present to react with the electrophilic α-side-chain. In view of this, Noyori reinvestigated the existing procedure and found that, using equimolar amounts of copper(I) iodide and the organolithium compound along with 2-3 equivalents of tri-*n*-butylphosphine, good yields of the conjugated adduct were obtained.

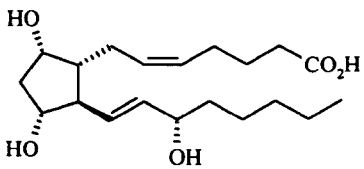
Consequently, having secured an efficient approach to the prostaglandin skeleton, Noyori applied this methodology to the synthesis of PGE_1 in a most elegant manner, Scheme 1.3.2.3.



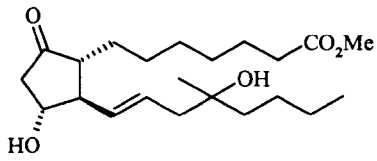
Scheme 1.3.2.3: *Noyori's synthesis of PGE_1* - *Reagents*: i) RωLi, CuI, Bu_3P, ii) RαCHO, iii) MsCl, DMAP, iv) Zn, AcOH, v) H^+, vi) PLE.

In the event, addition of the lower side-chain of PGE_1, as an organocuprate, to the α,β-unsaturated ketone of **17** resulted in the corresponding Li-enolate. Trapping of the transiently formed enolate with the electrophilic equivalent of the upper side-chain resulted in **18** as a diastereomeric mixture in 83% yield. Dehydration utilising methanesulfonyl chloride and 4-dimethylaminopyridine provided **19** in 92% yield, resulting in the simplification of the number of diastereomers. Reduction of the newly formed double bond, with zinc dust in acetic acid, resulted in the *trans*-ketone **20** in 84% yield. Removal of the tetrahydropyranyl groups, followed by *porcine liver esterase* (PLE) catalysed saponification, completed Noyori's synthesis of PGE_1.

Unfortunately, despite this new flurry of research and the elegant syntheses developed by Corey and Noyori, the prostaglandin-based therapies that followed were not considered to be practical due to their multiple side effects on the body. Such side effects were a decrease in blood pressure as well as inflammatory and immune responses. Despite this, some prostaglandins have been used clinically, for example $PGF_{2\alpha}$ (Dinoprost) for the induction of labour and Misoprostol as an anti-ulcer remedy.



$PGF_{2\alpha}$ (Dinoprost)

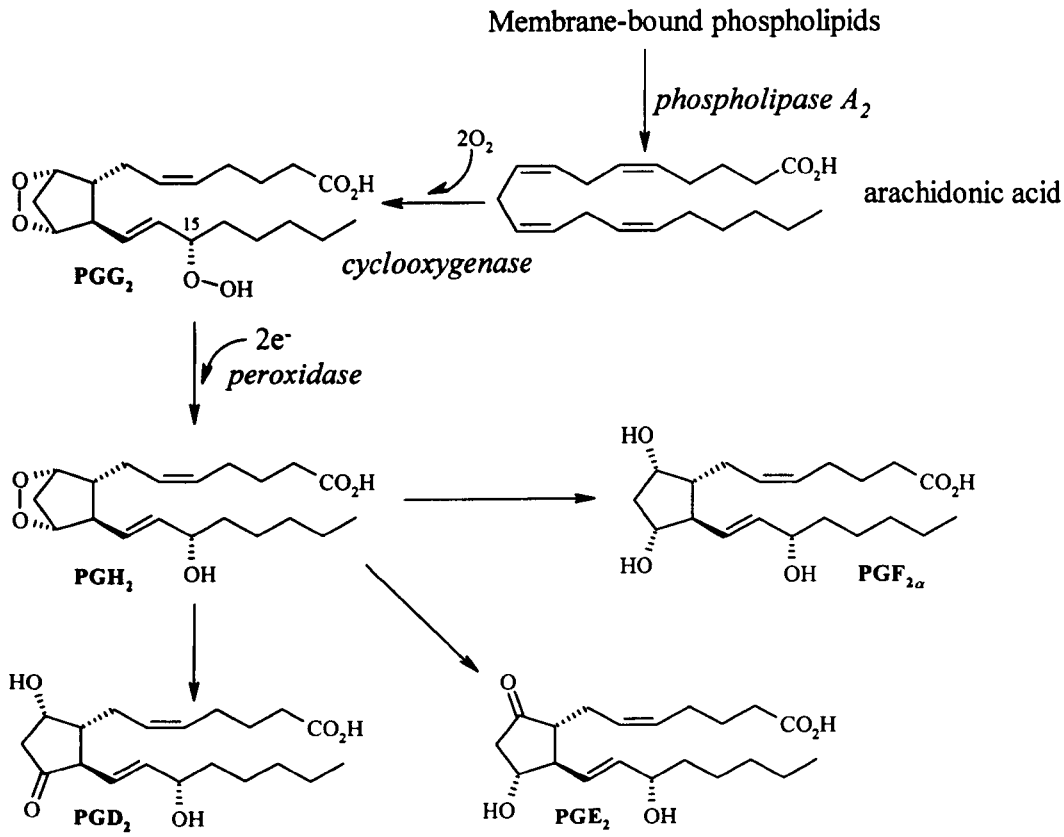


Misoprostol

1.4 Biosynthesis of the natural prostaglandins

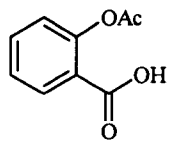
The prostaglandins are continuously being produced in mammals within most nucleated cells; the general pathway is illustrated in Scheme 1.4.1.

The biosynthesis begins with intracellular release of arachidonic acid, from membrane-bound phospholipids, utilising *phospholipase* A_2. Arachidonic acid is converted to the pivotal prostaglandin precursor PGH_2 utilising the enzyme *PGH synthase*. This enzyme catalyses the *cyclooxygenase* oxidation of arachidonic acid to form the endoperoxide cyclopentane ring of PGG_2 followed by *peroxidase* reduction, of the peroxide bond at C-15 in PGG_2, to form the prostaglandin precursor PGH_2.



Scheme 1.4.1: Biosynthesis of the prostaglandins

Inhibition of the *cyclooxygenase* catalysed oxidation step is very important in the fight against pain and inflammation. The enzyme *cyclooxygenase* (COX) is the target for aspirin, the pain relief remedy.



aspirin

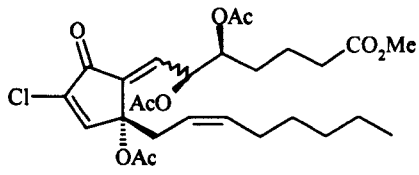
As seen, Scheme 1.4.1, the prostaglandins are synthesised *via* the prostaglandin precursor PGH_2, which is generated from the oxidation of arachidonic acid by the two isoforms of the enzyme *cyclooxygenase*, COX-1 and COX-2. Traditional non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, inhibit COX-1 and COX-2 by docking at their active site. This prevents oxidation of arachidonic acid to PGG_2 and subsequently prevents the downstream synthesis of the pro-inflammatory prostaglandin PGE_2. Thus, aspirin is used to relieve headache, decrease fever and reduce inflammation.[34]

Returning to the biosynthesis of the prostaglandins sees all the natural products prepared directly from PGH_2 *via* their specific prostaglandin synthase enzymes, for example, *PGE_2 synthase*, *PGD_2 synthase* etc. The cyclopentenone prostaglandins PGA_2, PGA_1 and PGJ_2 are formed by dehydration of the cyclopentane ring of PGE_2, PGE_1 and PGD_2 respectively, yielding the α,β-unsaturated cyclic ketone.

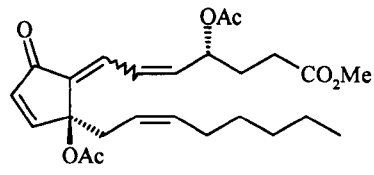
1.5 The punaglandins, clavulones and chlorovulones

Despite all the interest directed at the synthesis of the prostaglandins, especially the PGEs and PGFs, it is unfortunate that, in general, their chemical instability and biological side effects prevented the vast majority of them, or their analogues, from advancing to the clinic.

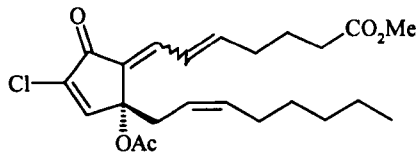
Harnessing the great potential of the prostaglandins, however, had not been totally exhausted since the isolation and structural elucidation of three new series of natural products, the punaglandins,[35] the clavulones[36-39] and the chlorovulones[40-42] generated a marked elevation of interest into cyclopentenone based natural products.



punaglandins



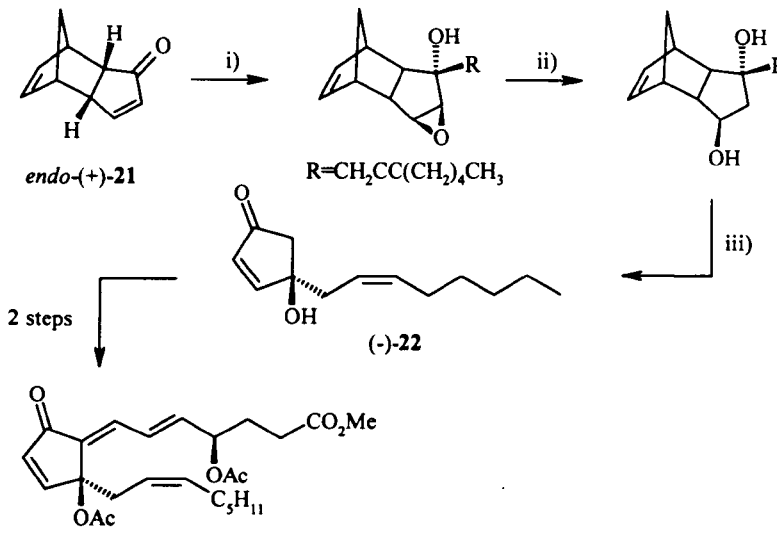
clavulones



chlorovulones

1.5.1 Zwanenburg's synthesis of clavulone II

Isolated in 1982 from the Stolonifer *Clavularia viridis* Quoy and Gaimard, clavulone II has been the target for a number of research groups. In particular, Zwanenburg has described an enantioselective synthesis of clavulone II and analogues starting from the key intermediate γ-hydroxycyclopentenone (-)-**22**, Scheme 1.5.1.[43]



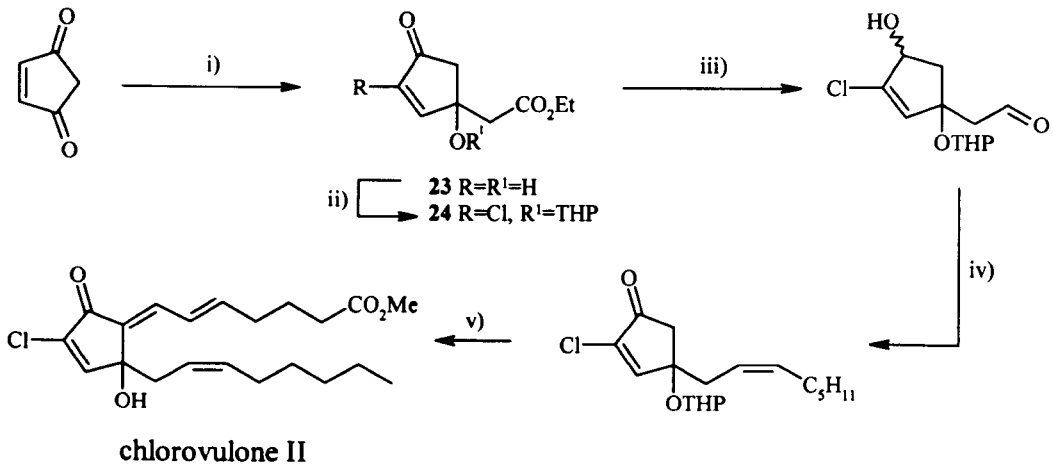
clavulone II

Scheme 1.5.1: *Zwanenburg's synthesis of clavulone II - Reagents*: i) H_2O_2, aq. NaOH, 30 min then $BrZnCH_2CC(CH_2)_4CH_3$, 12 h, ii) $LiAlH_4$, THF, 3 d, iii) FVT, 3 × 10^{-2} mbar, 550 °C then PCC, CH_2Cl_2, 4 h followed by H_2, Lindlar cat., toluene.

The synthesis of **22** can in turn be derived from enantiopure *endo*-tricyclo[5.2.1.0]decadienone (+)-**21**.[43] Completion of the synthesis of clavulone II then proceeds *via* acetylation and aldol condensation with the desired side-chain.

1.5.2 Ciufolini's synthesis of (±)-chlorovulone II

While the punaglandins and clavulones have attracted much interest from synthetic organic chemists and biologists alike,[35-39] it is the halogen-containing chlorovulones that might prove therapeutically most useful, showing pronounced anti-tumour activity. (±)-Chlorovulone II, one of the most active members of this class of compound, has been synthesised in nine steps from simple precursors by Ciufolini.[44] The synthesis begins with the aldol addition of the enolate of ethyl acetate to cyclopent-4-ene-1,3-dione giving the key intermediate **23** in 86% yield. Introduction of the chlorine atom into compound **23** proceeded uneventfully, and the resultant chloroenone **24** was transformed into chlorovulone II, as shown in Scheme 1.5.2.

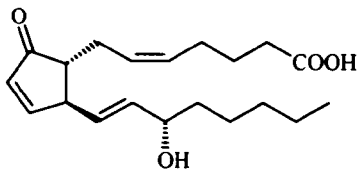


chlorovulone II

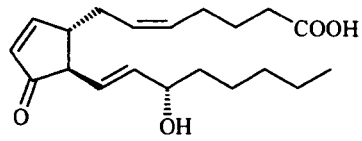
Scheme 1.5.2: *Ciufolini's synthesis of (±)-chlorovulone II - Reagents*: i) Ethyl acetate, LDA, THF, -78 °C, ii) Cl_2 gas, Et_3N then DHP, CSA, CH_2Cl_2, iii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C then DIBAL, THF, -78 °C, iv) $Ph_3PCH_2(CH_2)_4CH_3Br$, BuLi, THF, DMPU, -40 °C then PDC, DMF, v) LDA, THF then $MeO_2C(CH_2)_3CH{=}CHCHO$ followed by TsOH, MeOH.

The marked level of activity of these cross-conjugated compounds, compared to the cyclopentanone prostaglandins, has contributed to the renewal of interest into cyclopentenone based natural products and in particular the cyclopentenone prostaglandins. As such, the synthesis of these biologically interesting molecules has been of great interest in recent years.

At about the same time as the discovery of the clavulones, a serendipitous discovery by Professor Santoro, at the University of Rome, revealed that one group of prostaglandins, the cyclopentenone species, appear to confer protection on cells, a response that the cyclopentane prostaglandins of the E- and F-series do not accommodate.[45-49] It was this discovery that led to a more recent interest in the cyclopentenone prostaglandins and their analogues, thus, moving research away from such prostaglandins as the PGEs and PGFs, and directing it towards prostaglandins of the A- and J-series.



PGA_2

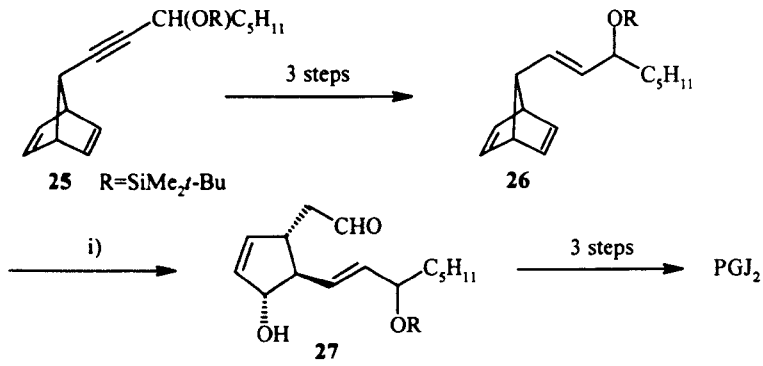


PGJ_2

This area has now become attractive to synthetic organic chemists and biologists alike, since efficient pathways to cyclopentenone prostaglandins and analogues are required to define further the therapeutic potential of these fascinating materials in a host of disease areas.

1.5.3 Roberts' versatile synthesis of the cyclopentenone prostaglandins

One such synthesis of the cyclopentenone prostaglandins is the short, versatile route developed by Roberts, Scheme 1.5.3.[50] Reaction of an appropriate alkyne Grignard reagent with 7-chloronorbornadiene furnishes the bicyclic alkyne **25**. Deprotection of the silicon group, followed by selective reduction of the alkyne and reprotection then provides (*E*)-alkene **26**, which, following a two-step oxidation-hydrolysis sequence affords hydroxyaldehyde **27**. Hydroxyaldehyde **27** can then be transformed in three simple steps to PGJ_2. It is worthy of note that hydroxyaldehyde **27** is also an intermediate in the Roberts synthesis of PGE_2 and $PGF_{2\alpha}$, and thus the synthesis is an extremely versatile route to a whole host of natural prostaglandins and prostaglandin analogues.[50]



Scheme 1.5.3: *Roberts' versatile synthesis of the cyclopentenone prostaglandins - Reagents*: i) CH_3CO_3H, CH_3CO_2H, CH_3CO_2Na, CH_2Cl_2, then HCl, CH_2Cl_2, 61%.

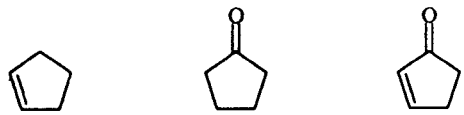
1.6 Biological activity of cyclopentenone prostaglandins

1.6.1 Background

The cyclopentenone prostaglandins of the A- and J-type display anti-inflammatory and anti-viral behaviour in contrast to the other non-cyclopentenone prostaglandins which do not. The reason for this biological distinction is due to the difference in the process by which the prostaglandins elicit a response from cells. Cyclopentenone prostaglandins elicit their response by interacting with signalling molecules and transcription factors[46] whereas the other prostaglandins elicit a response by binding to trans-membrane glyco-protein coupled receptors.[4]

Recently, Santoro reported potent anti-viral activities for prostaglandins-A_1, -A_2 and -J_2.[45-49] The wide-ranging anti-viral activity of the natural cyclopentenone prostaglandins was attributed to two factors. Firstly, prostaglandins of the A- and J-series induce the synthesis of cytoprotective heat-shock proteins *via* activation of the heat shock transcription factor (HSF) type 1. Secondly, the same compounds down-regulate the transcription factor Nuclear Factor-kappa B (NF-κB), known to be involved in the transcription of viral DNA. It was believed that the protection of cells by such cyclopentenone prostaglandins could be conferred by just one small part of

the molecule, *viz.* the cyclopentenone ring. The other prostaglandins that do not contain such a functional group do not, therefore, possess the same portfolio of biological activities, nor do the simple molecules cyclopentene **28** or cyclopentanone **29**, while cyclopentenone itself, **30**, does exhibit analogous activity, albeit to a small extent.[51]



28 **29** **30**

The mechanism of the cyclopentenone anti-viral activity is distinct from that of any other known anti-viral agent, owing its unique activity to the α,β-unsaturated carbonyl group in the ring.

1.6.2 Mode of action of the cyclopentenone prostaglandins

The mechanism for anti-viral behaviour involves the prostaglandins inhibiting viral replication by turning on an intracellular defence response. This involves the control of NF-κB activators and the induction of cytoprotective heat shock proteins (HSP).

1.6.2.1 NF-κB inhibition

NF-κB is a crucial regulator of an immediate pathogen response and is also an activator of the immune system. It normally exists as part of an inactive complex bound to a protein of the IκB family and is activated in response to pathogenic stimuli, for example viruses or bacteria. Stimulation triggers a rapid process which liberates NF-κB and translocates it to the cell nucleus. There it binds to DNA and rapidly induces a variety of signaling proteins, Figure 1.6.2.1.

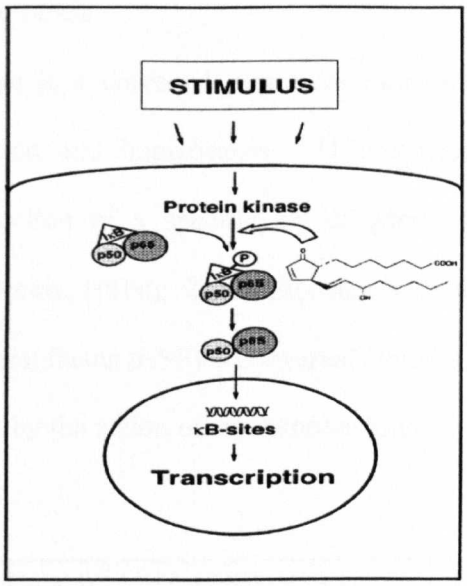


Figure 1.6.2.1: *NF-κB inhibition*: NF-κB normally exists as an inactive heterodimer of p50 and p65 subunits bound to the inhibitory protein IκBα. Activation by stimuli such as viruses and bacteria triggers the phosphorylation and subsequent degradation of IκBα resulting in the translocation of NF-κB into the nucleus where it binds to DNA at κB-sites. Cyclopentenone prostaglandins act by inhibiting IκBα phosphorylation and subsequent degradation.

NF-κB is involved in many pathological events, including inflammation and the proliferation of viruses, including HIV. Consequently, it is an attractive target for novel anti-inflammatory, anti-viral and cytoprotective therapies.[49]

The cyclopentenone prostaglandins have been shown to inhibit NF-κB activation by preventing the degradation of the IκBα protein, thereby inhibiting the liberation of NF-κB. Therefore, cyclopentenone prostaglandins and analogues could provide a lead into a new class of drug molecule.

Interestingly, in human cells, inhibition of NF-κB by cyclopentenone prostaglandins is closely associated with the induction of the heat shock response.

1.6.2.2 The heat shock response

The heat shock response is a universal protective mechanism that cells utilise to conserve cellular function and homeostasis. This complex defence mechanism involves the rapid induction of a specific set of genes encoding cytoprotective proteins (heat shock proteins, HSPs). Upon exposure to heat shock or other stimuli the heat shock transcription factor (HSF) is converted from its non-DNA binding form to its DNA binding form by the action of an unknown kinase.

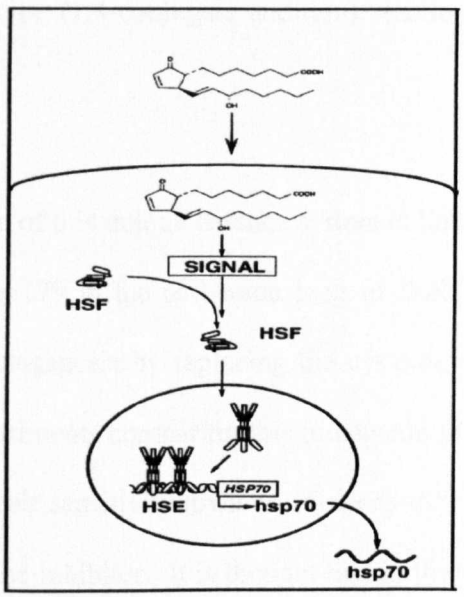


Figure 1.6.2.2: *The heat shock response*: The synthesis of cytoprotective heat shock proteins (HSP) are induced by cyclopentenone prostaglandins *via* the activation of heat shock transcription factors (HSFs). Heat shock transcription factors convert from a monomeric non-DNA binding form to an oligomeric form that translocates into the nucleus and binds to specific promoter elements (HSE) located upstream of heat shock genes.

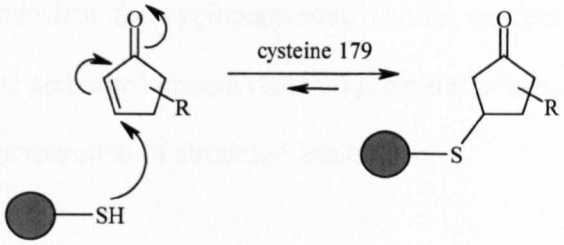
These factors then translocate to the nucleus where they regulate the transcription of heat shock proteins (in particular HSP70). Once in the cell, these proteins express their cytoprotective activity by protecting the cell against the external stimulus, thereby restoring the cell to its previous equilibrium.[49] Figure 1.6.2.2.

Thus, cyclopentenone prostaglandins potentially constitute a new class of anti-viral and anti-inflammatory agents and as a result have invoked a new surge of research into these compounds in the hope of optimising this innate biological activity.

1.6.3 Mechanism of action of the cyclopentenone prostaglandins

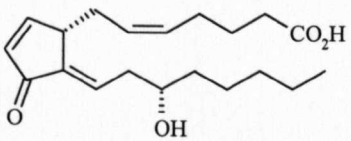
The biochemical mechanism of anti-viral activity stems from the fact that the enone moiety in such cyclopentenone prostaglandins of the A- and J-series contains an electrophilic carbon centre. This functionality, therefore, makes these compounds susceptible to Michael-type (1,4-conjugate addition) reactions with suitable cellular nucleophiles.

The mechanism of action of this unique defence system is linked directly to the amino acid cysteine at position 179 in the activation loop of IKK.[46] This was confirmed through site-directed mutagenesis by replacing the cysteine at position 179 with an alanine unit. Thus, experiments comparing this mutagenic IKKβ alongside the wild-type IKKβ, measuring their sensitivity towards 15-deoxy-$\Delta^{12,14}$-PGJ_2 showed that the mutant was resistant to the inhibitor. It is thought that in the wild-type case, cysteine acts as a nucleophile in a 1,4-conjugate addition reaction with the cyclopentenone nucleus of the prostaglandins. The consequences of this are a reduction in virus replication as well as a reduction in inflammation. Such a mechanism is obviously not available for the mutant which lacks nucleophilic properties at position 179.

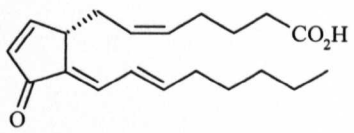


1.6.4 Reaction of cyclopentenone prostaglandins with glutathione

Glutathione is a ubiquitous molecule found within cells and it is employed as a biological transport agent to remove xenobiotic molecules from the cell. However, formation of a glutathione adduct with the cyclopentenone prostaglandins is reversible.[52,53] In a review by Glass, it is reported that Δ^{12}-PGJ_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2, react with glutathione to furnish conjugate addition products that are less stable than their single enone counterparts *i.e.* PGJ_2.[53]



Δ^{12}-PGJ_2



15-deoxy-$\Delta^{12,14}$-PGJ_2

The consequence of this means that the relative amount of free enone versus the conjugated compound in the cell is predicted to be higher for the cross-conjugated adduct than the enone compounds. This might in part account for the higher activity of the cross-conjugated compounds compared with the enone compounds in certain assays.[52] Once formed, the adducts are eliminated from the cell and are therefore no longer biologically active, again increasing the concentration of the cross-conjugate compound in the cell.

Based upon this precedent for cyclopentenone natural products to possess potent biological activity we embarked upon a research programme in an attempt to optimise this activity *via* the preparation of structural analogues.

Chapter 2:

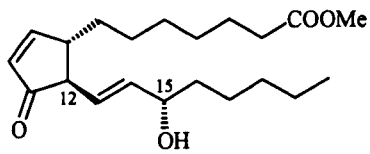
Results and Discussion

2 Results and Discussion

2.1 Project aims

The interesting biological activity exhibited by α,β-unsaturated and cross-conjugated cyclopentenones, for example the punaglandins, clavulones and chlorovulones, and especially the novel mode of action of the cyclopentenone prostaglandins (*vide supra*), has encouraged a research collaboration between Professor Roberts and Professor Santoro. It was hoped that such a collaboration would allow us to harness the activity shown by these cross-conjugated compounds, and hopefully develop new therapies for anti-viral and anti-inflammatory diseases.

Initially, the types of compounds prepared were confined to analogues closely related to the natural prostaglandins. For example, it has been shown by Roberts *et al.*, that PGJ_1 methyl ester shows potent activity *in vitro* against the Sendai virus.[45]



PGJ_1 methyl ester

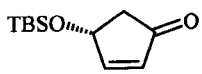
Following on from this, a research programme was embarked upon in the hope of preparing new classes of compounds that would allow us access to more biologically active chemical entities. It was envisaged that this might occur by the diversification away from the structures of the natural prostaglandins and towards structurally more simple compounds. Not only would this provide a greater chance of finding biological activity but it may also lead to compounds possessing the desired target-selectivity, a feature which the natural products do not satisfy.[48] Also, novel

structures would circumvent the minefield of patent literature that had built up over the past twenty years.

The activity of our compounds, with respect to heat shock factor activation and NF-κB inhibition, was determined using electrophoretic mobility-shift assays. Our compounds were also tested for anti-viral activity based on their ability to inhibit the proliferation of the Sendai virus, and it is the viral assay which is used throughout this thesis to depict activity. The compounds are reported for their ability to inhibit virus proliferation (ID_{50}) as well as the dose that causes total death of the virus (TD_{100}). A secondary screen was also developed to determine the compounds' activity against psoriasis; however these biological data are not shown. Finally, a tertiary screen was developed to investigate the compounds ability to reduce virus yields and inflammation *in vivo*. For details of the individual tests see Appendix III.

2.1.1 Derivatisation of the core cyclopentenone nucleus of 31

The lead compound was 4-(*tert*-butyldimethylsilanyloxy)-cyclopent-2-enone **31**, a compound which has also been utilised by Noyori in his landmark asymmetric 3-component coupling synthesis of the prostaglandins, *vide supra*.[27-29]



(+)-31

(*R*)-(*tert*-butyldimethylsilanyloxy)-cyclopent-2-enone

It was envisaged that modification of **31** would involve preparing cross-conjugated analogues, reminiscent of the cross-conjugated prostaglandins of the A- and J-series

and exemplified by **32**, as well as the preparation of analogues bearing alkyl groups at C-5 (**31** numbering, Figure 2.1.1) exemplified by **33**. It was also mooted that varying the group at C-4 would affect biological activity.

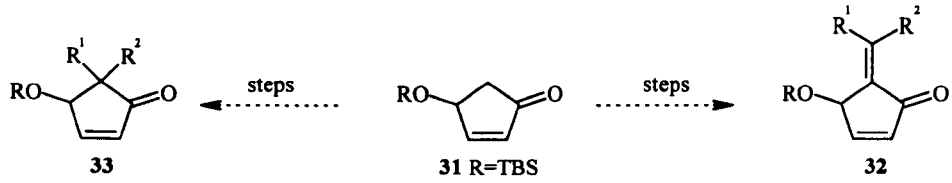


Figure 2.1.1

2.1.2 Strategy for the synthesis of cyclopentenone prostanoids

Our quest to capture the natural tendency of the cyclopentenone prostaglandins to inhibit NF-κB and confer protection on cells *via* the induction of heat shock proteins (shown by their ability to inhibit proliferation of the Sendai virus) we focussed our research on a target-oriented approach towards the inhibition of the enzyme IKK. It was also necessary, when preparing compounds for commercial application, that we would need to circumscribe the molecular architecture for potent biological activity, provide novel chemical structures for patent protection as well as to design compounds with optimum physical properties, such as chemical stability and log P etc.

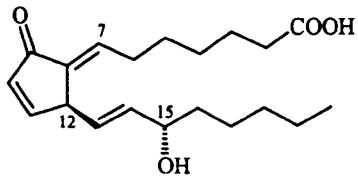
Unfortunately, since the target enzyme IKK is only isolable in minute quantities, its crystal structure has proved very elusive. As such, conformational information that we could extract from an X-ray crystal structure is unavailable. This means that information on the size and shape of the active site and the molecular interactions necessary for a good substrate-active site fit is not available to us. This has therefore resulted in a classical hit-to-lead drug design strategy being adopted.

Such a strategy has meant that the compounds depicted in this thesis have been prepared by derivatisation of other active compounds in the appropriate series. This was achieved by utilising pharmacophores that appeared interesting in the biological screens, both from my own research and of others in the group. It was hoped this would then lead to a structure-activity relationship (SAR) becoming apparent which might enable a rough map of the binding site to be formulated. This approach to drug design is in contrast to *in silico* methods where compounds are prepared based on information gathered from computational studies on the X-ray crystal structure of the biological target, an approach unfortunately not readily available to us.

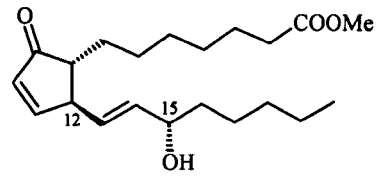
2.2 Background to cyclopentenone prostaglandin research

2.2.1 Reaction of prostaglandin-A_1 analogues with thiols

Noyori and co-workers have described in detail the reactions of Δ^7-PGA_1 and analogues with thiols.[52]



Δ^7-PGA_1



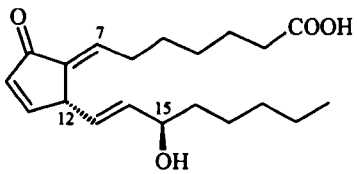
PGA_1 methyl ester

In this work, Noyori demonstrates that prostaglandins that possess a cross-conjugated dienone moiety exhibit anti-tumour and anti-viral behaviour. It is also reported that these prostaglandins react with thiol nucleophiles, such as glutathione, at the *endo*-cyclic carbon-carbon double bond selectively. The reaction is believed to be reversible in solution, with considerable amounts of free thiol and prostaglandin being

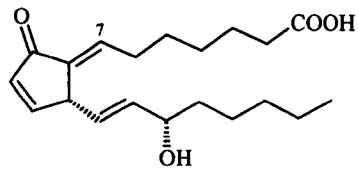
present. However, when Sepharose-bound thiols are used, being regarded as models for protein-containing thiols, the reaction is irreversible. On the other hand, the adducts of PGA_1 methyl ester, which lacks the carbon-carbon double bond at C-7, are substantially more stable than those of the cross-conjugated prostaglandins.

This result, therefore, gives rise to the increased biological activity of cross-conjugated prostaglandins since glutathione-prostaglandin adducts themselves have no antiproliferative activity against cancerous cells.

In a subsequent piece of work Noyori used molecular design to overcome the metabolic instability of Δ^7-PGA_1 while maintaining its anti-tumour activity.[54] Δ^7-PGA_1 methyl ester and the corresponding acid are rapidly metabolised in rat serum by the action of prostaglandin isomerases. Therefore, it is evident that it is necessary to overcome this biological instability if viable therapeutic agents are to be prepared. It was envisaged that since the isomerases recognise the proton at C-12 for abstraction, epimerisation at this position might lead to biological stability.



ent-Δ^7-PGA_1



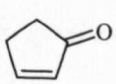
12-*iso*-Δ^7-PGA_1

In the event, synthesis of the enantiomer and C-12-epimer of Δ^7-PGA_1 (*ent*-Δ^7-PGA_1 and 12-*iso*-Δ^7-PGA_1 respectively) resulted in stable, biologically active prostaglandins

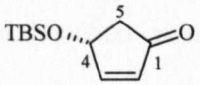
with considerably longer half-lives in serum; this difference in stability is believed to be due to the difference in the rate of transformations catalysed by the isomerases.

2.2.2 Previous cyclopentenone prostanoid work within the Roberts group

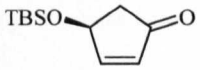
As already mentioned, the first, structurally more simple prostanoids, synthesised by the group, which possessed considerable biological activity were the enantiomers of 4-(*tert*-butyldimethylsilanyloxy)-cyclopent-2-enone, (+)-**31** and (-)-**31**, (entries 3 and 4, Table 2.2.2).[55]



30



(+)-**31**



(-)-**31**

Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	0.5	-	**PG-J_1 methyl ester**[a]
2	90	500	**30**
3	1	50	(-)-**31**
4	2	50	(+)-**31**

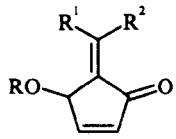
Table 2.2.2 Biological evaluation of (+)- and (-)-**31** against the Sendai virus. [a] Reported in reference 45.

The extraordinary increase in activity, compared to cyclopentenone **30** (entry 2), sees an increase in the selectivity index (TD_{100}/ID_{50}) from ~5 to 50. This increase, it seems, can only be attributed to the silicon-protected alcohol at C-4, and was the first indication as to how dramatic ring substituents could influence biological activity.

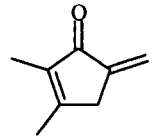
2.3 Natural and unnatural cross-conjugated cyclopentenones

A number of marine and terrestrial natural products with biological activity have been isolated that are known to incorporate the cross-conjugated cyclopentenone moiety

seen in target series **32**. As well as the naturally occurring cross-conjugated prostaglandins already mentioned, the structurally more simple, terrestrial natural product methyleneomycin B contains the cross-conjugated cyclopentenone pharmacophore and possesses antibiotic activity.[43]



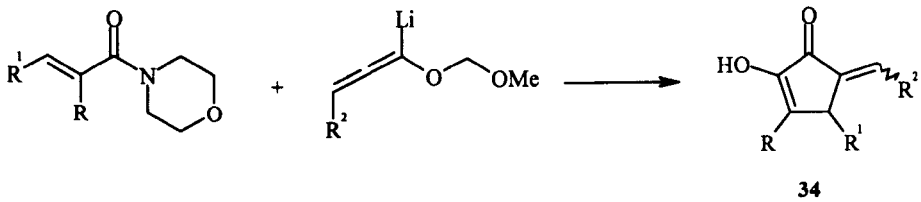
32



metheleneomycin B

2.3.1 Tius' synthesis of biologically potent cross-conjugated cyclopentenones

Based on the knowledge that cross-conjugated cyclopentenone compounds exhibit potent biological activity Tius *et al.* embarked upon a research programme with the aim of preparing a library of cross-conjugated cyclopentenones based on the general structure **34**. In doing so they hoped of finding a lead compound for anti-cancer, anti-fungal or anti-bacterial therapies.[56, 57]



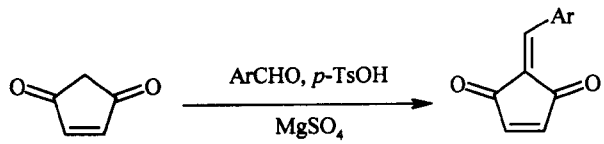
34

R= Ph, F, Me, EtO, Br or alkyl
R^1= Ar, H or alkyl
R^2= H, Me or C_2H_5O

Promising leads were subsequently discovered from this research, possibly due to the inclusion of the cyclopentenone pharmacophore, and it has since provided an indication of the structural features required for biological activity.

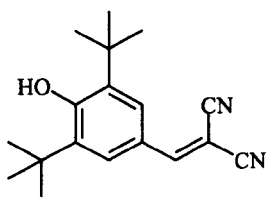
2.3.2 Hori's synthesis of protein tyrosine kinase inhibitors

Yet another research group probing the biological activity of cross-conjugated cyclopentenones is that led by Hori.[58] Research within this group investigated the preparation of compounds exemplified by structure **35**.

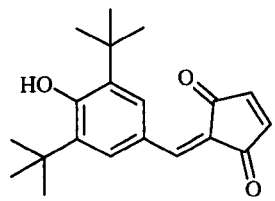


35

The research towards the development of such cross-conjugated enediones was directed at finding compounds that displayed protein tyrosine kinase inhibition and possessed structures similar to the known active compound **36**, but with lower mitochondrial toxicity.



36



37

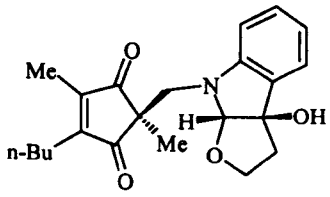
Having prepared a range of 2-hydroxyarylidene-4-cyclopentene-1,3-diones, the results showed that **37** was indeed more potent than **36** and also showed the desired lower mitochondrial toxicity.

2.4 Naturally occurring 5,5-dialkyl cyclopentenone species

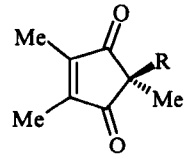
2.4.1 van Vranken's synthesis of the madindolines

There are examples of 5,5-dialkyl ring systems that also possess biological activity. For example, the work of *van* Vranken has been targeted at preparing a series of model compounds of the naturally occurring madindolines.[59]

The madindolines are thought to inhibit cytokine signalling through Interleukin-6 (IL-6) and IL-11 *via* modification of the gp130 receptor. The extracellular domain of gp130 has two free cysteines that are believed to form a disulfide linkage during cytokine activation, and so the presence of the enone ring system in the madindolines, which is known to react with thiols, is a key feature of these compounds.[59]



madindoline A



R= H, Me

model system

Interestingly, it was found that for R=H, the model compound (above) formed a thiol adduct with *N*-acetylcysteamine whereas the more complete model (R=Me), failed to form thiol adducts under the conditions investigated. Thus, the alkyl substituents on madindoline conspire to inhibit non-specific Michael addition by thiols. Therefore, it

is possible that the preparation of simple analogues, such as **33**, may also allow only specific thiol addition, as needed in our target system.

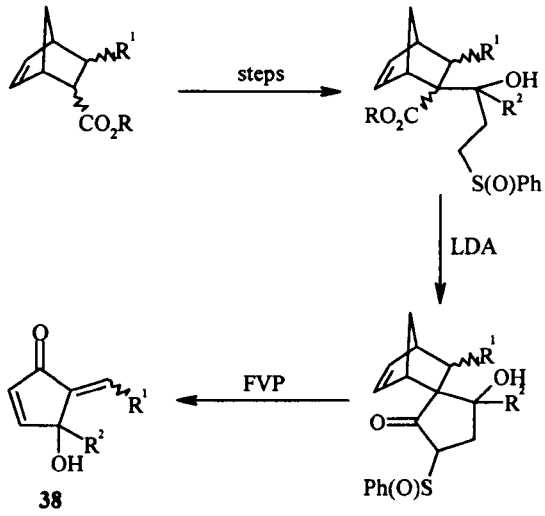
With such examples of biologically active cyclopentenones in the literature, we were confident of finding success in our search for novel anti-viral compounds based on the cross-conjugated series exemplified by **32** and the dialkyl series exemplified by **33**. We also hoped that probing the effect of derivatisation of the C-4 hydroxy group (**31** numbering) would guide us to interesting biological molecules with a unique structural make-up.

2.5 Synthesis of cross-conjugated cyclopentenones

The 4-hydroxy-5-alkylidene-cyclopent-2-enone skeleton is known in the literature and has been synthesised elegantly by Pohmakotr[60] and Thebtaranonth,[61] both methods of which utilise a retro Diels-Alder reaction as the key step to unmask the *exo*-cyclic carbon-carbon double bond.

2.5.1 Pohmakotr's synthesis of the 4-hydroxy-5-alkylidene-cyclopent-2-enone skeleton

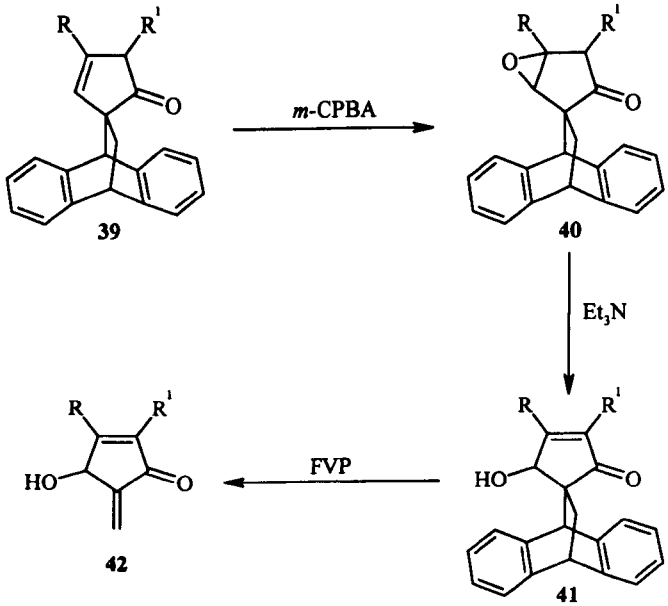
Pohmakotr's synthesis commences from simple bicyclic esters and accesses the desired 4-hydroxy cross-conjugated enone system in 4 steps, Scheme 2.5.1.[60] The final step being the flash vacuum pyrolysis of the tricyclic system to reveal **38** in modest overall yields (14-40%).



Scheme 2.5.1

2.5.2 Thebtaranonth's synthesis of the 4-hydroxy-5-alkylidene-cyclopent-2-enone skeleton

Again, utilising flash vacuum pyrolysis to perform the retro Diels-Alder reaction, Thebtaranonth's approach relies upon the elimination of anthracene to generate the *exo*-cyclic enone of **42**, Scheme 2.5.2.

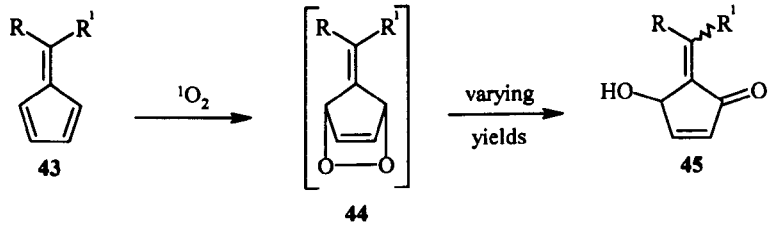


Scheme 2.5.2

Thus, readily available spirocyclopentenone **39**[62] is oxidised with *m*-chloroperbenzoic acid, followed by treatment of the crude mixture with triethylamine to effect a clean conversion to the spiro-ketol **41** albeit in modest yields (26-65%). Flash vacuum pyrolysis of **41** then yields the desired 4-hydroxy cross-conjugated enone **42**, in near quantitative yields.

2.5.3 Uda and Ohloff's synthesis of the 4-hydroxy-5-alkylidene-cyclopent-2-enone skeleton

Despite this literature precedent for other routes, our synthetic work began by following the synthesis developed, independently, by Uda[63-65] and Ohloff.[66] Uda and Ohloff's work utilises the fact that singlet oxygen can behave as a dienophile, in a [4+2] cycloaddition reaction with dienes, in a hetero Diels-Alder reaction. Thus, dye-sensitised, photochemical oxidation of fulvenes, such as **43**, can establish the desired 4-hydroxy cross-conjugated cyclopentenone ring as seen in **45**, following degradation of the *endo*-peroxide intermediate **44**, in one step.



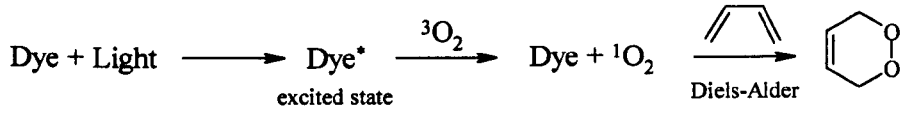
43 **44** **45**

This approach is particularly appealing since by varying the side-chains of fulvene **43**, a whole range of products can be produced containing the desired core-functionality of **45**. Mixtures of (*E*)- and (*Z*)-isomers are produced during the photochemical oxidation step, which gives rise, following separation, to two compounds for biological evaluation.

2.6 Photochemical synthesis of cross-conjugated cyclopentenones

2.6.1 Singlet oxygen

The route employed to synthesise the target compounds utilises a photochemical step as the key transformation.[63-66]

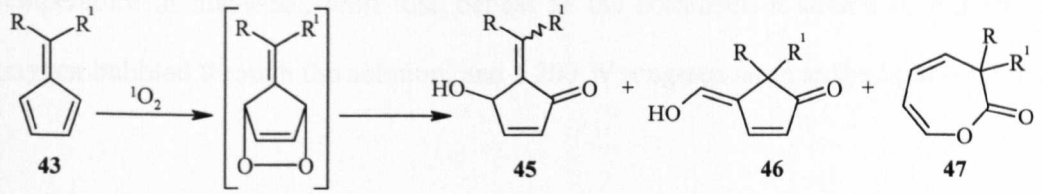


Molecular oxygen exists naturally in the triplet ground state ($^3O_2$), but can be excited to its singlet state ($^1O_2$) by, amongst other methods, photosensitisation. Photosensitisation involves the use of a dye, for example rose bengal, and a source of radiation that matches the absorbing wavelength of the dye. Energy transfer from the excited-dye to ground state triplet oxygen then produces singlet oxygen.[67]

The final step in the reaction can be thought of as a [4+2] process, analogous to the Diels-Alder reaction. Only when oxygen is in its singlet-excited state can it possess dienophile-like properties and then undergo the cycloaddition reaction.

2.6.2 Photooxidation products of fulvenes

The *endo*-peroxides formed upon reaction with fulvenes are believed to rearrange, *via* various degradation pathways, to amongst other compounds, 4-hydroxy-5-alkylidene-cyclopent-2-enones **45**, 5-alkyl-4-hydroxymethylene-cyclopent-2-enones **46** and oxepinone **47**, depending on the reaction conditions.[63]



In their work, Uda and co-workers have shown that the product distribution varies significantly depending on the choice of solvent, dye and reaction temperature employed. Thus, they have shown that the photochemical oxidation of 6,6-dimethyl fulvene (R=R^1=Me in **43**) gives rise to mixtures of **45**, **46** and **47**-type compounds. At first they studied the effect of solvent and found that no considerable difference in the yield of oxepinone **47** was observed in carbon disulfide, chloroform, acetone or benzene. However, a striking difference was observed when the oxidation was carried out in methanol, with rose bengal as sensitiser. Table 2.6.2.[63]

Solvent	Irradiation time (h)	Yield of 47 (%)	Yield of 45 (%)
Benzene	6	27	4
Carbon Disulfide	2	25	4
Chloroform	4	30	4
Acetone	2	29	0
Methanol	2	4.5	50

Table 2.6.2 The effect of methanol on the photochemical oxidation of fulvenes

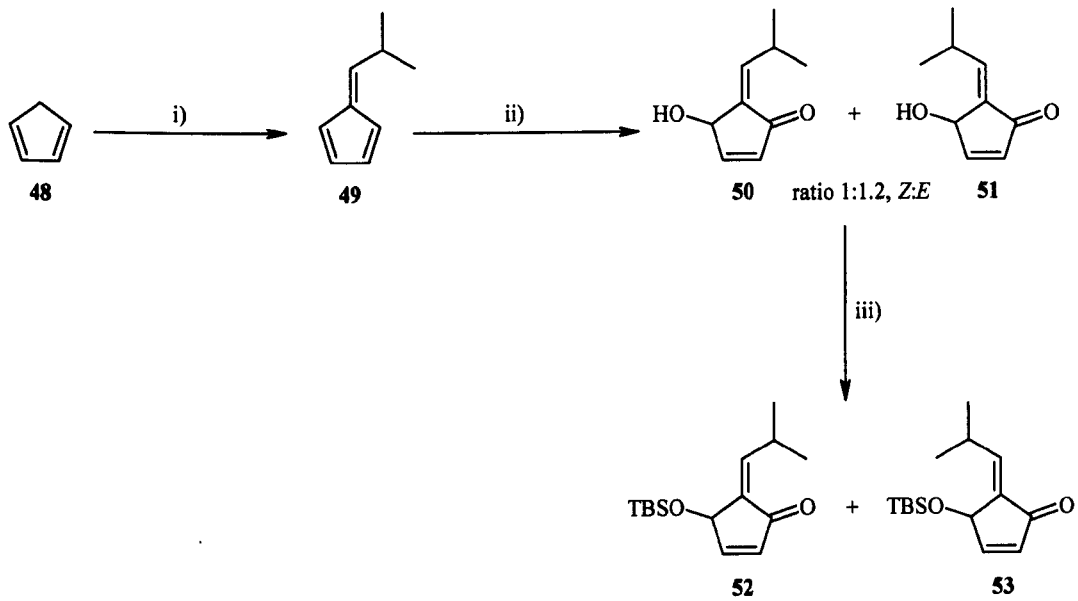
In methanol, the 4-hydroxy cross-conjugated enone **45** was obtained as the major product in 50% yield and the oxepinone in 4.5% yield.

Subsequent studies, then led to the development of optimum conditions for the formation of **45**.[64] It was found that a 50% yield of the 4-hydroxy cross-conjugated enone system of **45** could be achieved by carrying out the reaction at room

temperature in methanol, with rose bengal as the sensitiser, a stream of molecular oxygen bubbled through the solution, and a 200 W tungsten lamp as the light source.

2.6.3 Synthesis of 4-hydroxy-5-alkylidene-cyclopent-2-enones

Our first synthesis, Scheme 2.6.3.1, utilised 5-isobutylidene-cyclopenta-1,3-diene **49**, obtained from the condensation of freshly cracked cyclopentadiene **48** and isobutyraldehyde.[68]



Scheme 2.6.3.1: *Photochemical synthesis of cross-conjugated cyclopentenones* - *Reagents*: i) isobutyraldehyde, pyrrolidine, MeOH, 100%, ii) *hv*, O_2, rose bengal, MeOH, ~25% iii) TBSCl, TEA, DMAP, DCM, 39%.

The reaction was initially carried out using a 125 W medium pressure mercury Hanovia lamp and hydroquinone in pyridine, following the work of Ohloff,[66] at room temperature as well as at -25 °C. Later, we found that similar results could be obtained using a 250 W or 500 W halogen spot light, in methanol as solvent, without the need for specialist glassware, following more closely the conditions developed by Uda.[63-65]

Reaction of fulvene **49** with singlet oxygen, in methanol at room temperature gave an inseparable mixture of the desired 4-hydroxy cross-conjugated enones **50** and **51** (1.2:1, *E*:*Z*), albeit in the modest yield of ~25%. Due to the broad range of photochemical oxidation products possible, it is likely that the low yield is due to the formation of other oxidation products. However, these by-products were not isolated or characterised. Classical protection of the secondary hydroxyl group using *tert*-butyldimethylsilyl chloride, triethylamine and 4-dimethylaminopyridine in dichloromethane[69,70] gave a separable mixture of the geometric isomers **52** and **53**. The geometry of the side-chain in **53** was first assigned using nOe experiments (Figure 2.6.3) and was later confirmed by X-ray crystallography of the homochiral compound (Figure 2.13.2). A possible explanation for the low yield (overall 39%) encountered for the protection step was the base sensitivity of 4-hydroxy cyclopentenone compounds, and the propensity for molecules of this structural type to polymerise under basic conditions (*vide infra*). However, it is noteworthy to point out that no effort was made to optimise yields during the synthesis of these compounds since only ~5 mg of each compound was required for biological evaluation.

With the synthetic route to compounds of the type exemplified by **52** and **53** now established, we were in a position to prepare various analogues. Initial efforts were concerned with the preparation of compounds bearing alkylidene side-chains (R^1 and R^2=alkyl in **32**, particularly compounds possessing side-chains more closely resembling the natural prostanoids, for example **54** and **55**); to allow for faster throughput of test compounds the study of compounds possessing aromatic side-chains was left to my collegues.[71]

Straight away a very important discovery was made. Compound **53** (entry 3, Table 2.6.3), containing the short (*E*)-isopropyl side-chain was shown to be an order of magnitude more active than the natural prostaglandin Δ^{12}-PGJ_2 (entry 1), suggesting that chain-length is important and that perhaps shorter chains are preferable in this system.

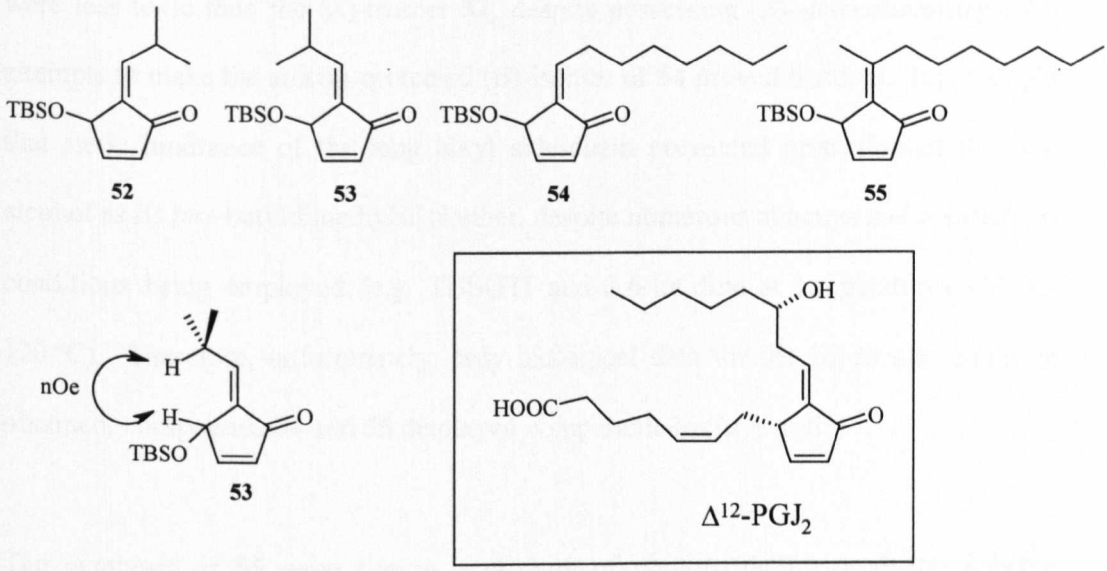


Figure 2.6.3

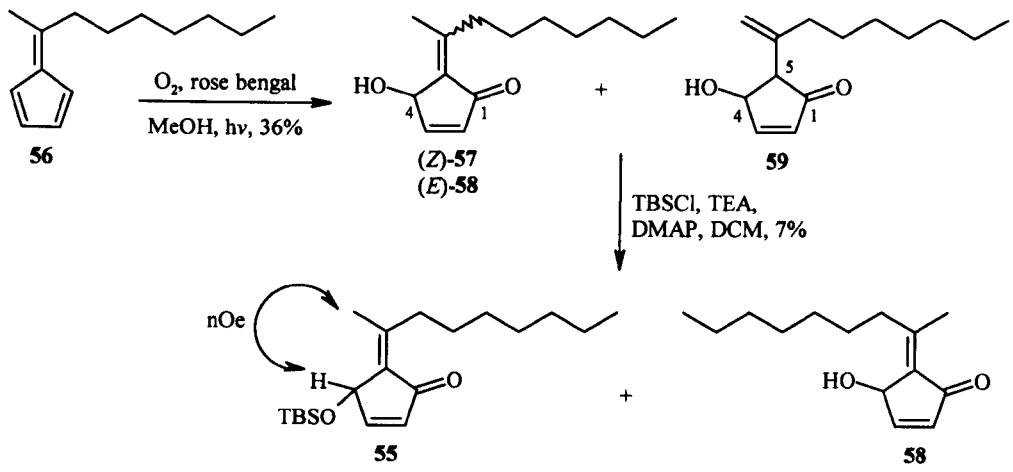
Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	3	50	**Δ^{12}-PGJ_2**
2	0.7	TOXIC	**52**
3	0.4	50	**53**
4	3	50	**54**
5	4	50	**55**

Table 2.6.3 Biological evaluation of Δ^{12}-PGJ_2 analogues against the Sendai virus

Interestingly, **52** (entry 2, Table 2.6.3), the double bond isomer of **53** (entry 3) is toxic at all doses in the same assay.

The synthesis of **54** proceeded smoothly and the (*Z*)-isomer was shown to have an activity less than that of the shorter isobutylidene compounds **52** and **53** (entry 4, Table 2.6.3), confirming our belief that the shorter side-chains are preferable. Interestingly, the activity of **54** and **55**, with a longer carbon side-chain more reminiscent of the natural prostaglandins, actually saw the activity drop to that of the natural compounds (entries 1, 4 and 5, Table 2.6.3). However, compounds **54** and **55** were less toxic than the (*Z*)-isomer **52**, despite possessing (*Z*)-stereochemistry. All attempts to make the silicon-protected (*E*)-isomer of **54** proved fruitless. It is thought that steric hindrance of the long alkyl side-chain prevented protection of the (*E*)-alcohol as its *tert*-butyldimethylsilyl ether, despite numerous attempts and a variety of conditions being employed (e.g. TBSOTf and 2,6-lutidine at temperatures -78 °C-120 °C). Therefore, unfortunately, only biological data for the (*Z*)-isomer could be obtained; compounds **54** and **55** displayed comparable toxicity to **53**.

The synthesis of **55** gave rise to a mixture of photooxidation products, Scheme 2.6.3.2. It seems that upon photochemical oxidation of fulvenes such as **56**, a mixture of the 4-hydroxy cross-conjugated isomers, **57** and **58**, as well as an isomer resulting from the migration of the *exo*-cyclic double bond out of conjugation such as **59**, are formed.[63]



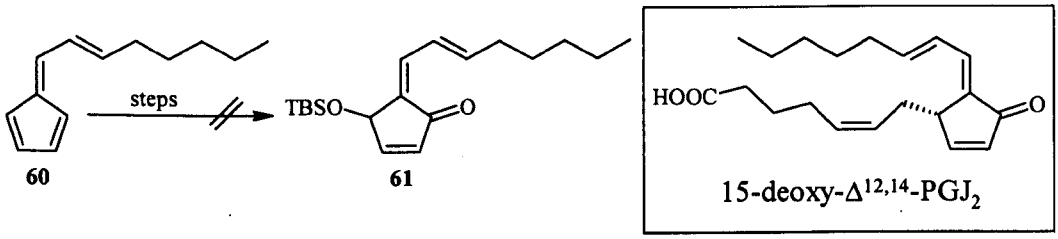
Scheme 2.6.3.2

The ^{1}H NMR data for the isomers showed signals at δ_H 4.97 (1H, m, C(4)H), 6.29 (1H, d, *J* 6.0, C(2)H) and 7.31 (1H, dd, *J* 2.5 and 6.0, C(3)H) corresponding to the major cross-conjugated isomer and δ_H 3.30 (1H, d, *J* 6.5, C(5)H), 4.97 (1H, m, C(4)H), 4.73 (1H, s, -C=C*H*H), 5.18 (1H, s, -C=CH*H*), 6.33 (1H, d, *J* 5.8, C(2)H) and 7.63 (1H, dd, *J* 2.3 and 5.8, C(3)H) corresponding to isomer **59**.

However, treatment of the mixture of isomers **57**, **58** and **59** with *tert*-butyldimethylsilyl chloride, triethylamine and 4-dimethylaminopyridine in dichloromethane resulted in the desired (*Z*)-protected isomer **55** (7%) plus the unprotected (*E*)-isomer **58**, 20%. It seems that upon treatment with base, the "out-of-conjugation" product **59** isomerises back into conjugation, resulting in a mixture of (*Z*)-**57** and (*E*)-**58**; only the less sterically hindered (*Z*)-isomer can be protected, giving rise to **55**, the stereochemistry of which was determined by nOe experiments.[63]

Unfortunately, compound **61**, possessing the full 15-deoxy-$\Delta^{12,14}$-PGJ_2 side-chain, also resisted synthesis *via* this route, since the highly conjugated system is susceptible

to Diels-Alder reactions. Fulvene **60**, or the product of oxidation, could react in this way, resulting in complex mixtures of products being obtained after attempted alcohol protection.



60 **61**

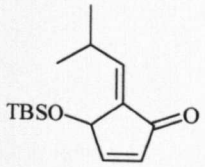
2.7 Synthesis of cross-conjugated cyclopentenone analogues of 53

2.7.1 Closely related analogues of 53

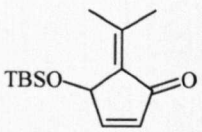
In addition to the few examples of cross-conjugated cyclopentenones mentioned above, we envisaged that more subtle changes in the alkylidene side-chain might affect the activity. Thus, various analogues were synthesised, concentrating on smaller side-chains related to the less toxic analogue **53**, since it has already been shown that the longer, more prostaglandin-like side-chains, have a negative effect on activity.

It was envisaged that the synthesis of the dimethyl **62**, diethyl **63** and (*E*)-methyl-isopropyl **64** (the stereochemistry of which was determined by ^{1}H NMR and comparison with **53**) analogues would create a more hindered *exo*-cyclic carbon-carbon double bond, and as a result, alter the compound's biological profile. Increasing the steric bulk of these compounds would possibly make them more selective for their target. In the event, these compounds were synthesised according to the developed method, shown in Scheme 2.6.3.1. Unfortunately, the results show (Table 2.7.1) an equivalent activity, within experimental error, to the isopropyl

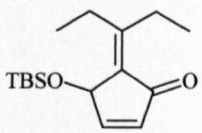
analogue **53**, along with a slight increase in toxicity. Thus, an increase in the selectivity had not been achieved.



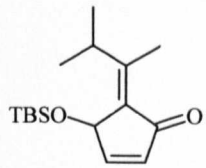
53



62



63



64

Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	0.4	50	**53**
2	0.3	10	**62**
3	0.2	10	**63**
4	0.1	10	**64**

Table 2.7.1 Biological evaluation of cross-conjugated cyclopentenone analogues of **53** against the Sendai virus

Such similar activities suggest that sterically crowding the *exo*-cyclic double bond is not hugely detrimental to activity. This lack of difference in activity may be due to the fact that our proposed target enzyme IKK (see Section 1.6) possesses an open active site where such subtle changes in substrate structure cannot influence activity. Nevertheless, the carbon-carbon *exo*-cyclic double bond is an aid to potency, because it allows an increase in the availability of the compound in the cell (refer to Section 2.2.1 *vide supra*).[52, 53]

The photochemical synthesis of **62** and **64** again resulted in the isomerisation, "out-of-conjugation", of the *exo*-cyclic carbon-carbon double bond along with the desired cross-conjugated isomer. These isomers were characterised by the ^{1}H NMR signals at δ_H 2.09 (3H, s, CH_3), 2.32 (3H, s, CH_3), 6.32 (1H, m, C(2)H), 7.33 (1H, dd, *J* 2.5 and 6.0, C(3)H) corresponding to the cross-conjugated isomer and the "out-of-

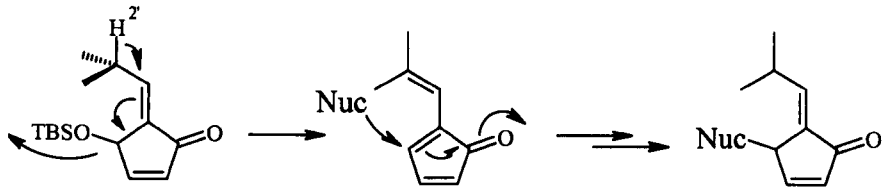
conjugation" product identified by the ^{1}H NMR signals at δ_H 1.80 (3H, m, CH_3), 3.30 (1H, d, *J* 6.6, C(5)H), 4.81 (1H, m, -C=C*H*H), 5.18 (1H, m, -C=CH*H*), 6.32 (1H, m, C(2)H), 7.64 (1H, dd, *J* 2.5 and 5.9, C(3)H) for **62** and δ_H 3.16 (1H, m, C(4)H), 4.40 (1H, m, C(4)H), 6.28-6.33 (2H, 2 × dd, 2 × C(2)H), 7.29-7.33 (2H, 2 × d, 2 × C(3)H) corresponding to the cross-conjugated isomers ((*E*) and (*Z*)), and the "out-of-conjugation" isomer identified by the ^{1}H NMR signals at δ_H 3.35 (1H, d, *J* 6.5, C(5)H), 4.59 (1H, s, -C=C*H*H), 5.22 (1H, s, -C=CH*H*) for **64**.

Although no "out-of-conjugation" isomer was seen during the synthesis of **63**, the extremely poor yield (1%), suggests that the oxidation was more difficult; had the oxidation mixture been taken on without purification of the cross-conjugated isomer, a better yield may have resulted. Nevertheless, protection of the secondary alcohol of the mixture of isomers with *tert*-butyldimethylsilyl chloride, triethylamine and 4-dimethylaminopyridine in dichloromethane resulted in the formation of **62** and **64** (after the base induced isomerisation of the double bond back into conjugation) and subsequent silylation allowing the isolation of the desired isomer, albeit in a poor yield (10% and 34% respectively for the silylation).[63]

2.7.2 Proposed toxicity mechanism

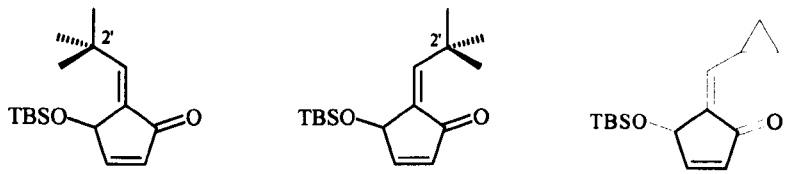
Despite the increased activity of these cross-conjugated compounds, over the natural prostaglandins-A and -J, our "Achilles heel" proved to be the associated toxicities. The high toxicity of these compounds, we postulated, may stem from the relatively acidic allylic proton at C-2'. Elimination the 4-silanyloxy group, would then give rise to a very reactive intermediate which could react further with cellular nucleophiles, and possibly be the source of toxicity. Such high energy and consequently reactive

anti-aromatic molecules would be alkylating agents, possibly alkylating a whole host of physiological nucleophiles in a non-selective manner.



53 anti-aromatic **65**

In an attempt to prevent this proposed elimination, the synthesis of the *tert*-butyl analogues **66** and **67**, lacking any such C-2' proton, was undertaken hopefully to determine the source of the toxicity of these compounds.



66 **67** **68**

Following the chemistry outlined in Scheme 2.6.3.1, the preparation of **66** and **67** utilises pivalaldehyde as the source of the side-chain. In a similar vein, we attempted to prepare the cyclopropyl analogue **68**, a compound which is also incapable of eliminating the 4-silanyloxy group. Unfortunately, such a compound resisted synthesis *via* our photochemical method. To our chagrin, the *tert*-butyl analogues **66** and **67** proved to be very toxic (Table 2.7.2) indicating that the hypothesised mechanism was not directly responsible for the observed toxicity of these compounds.

Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	0.4	50	**53**
2	0.5	10	**66**
3	0.6	10	**67**

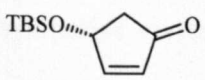
Table 2.7.2 Biological evaluation of *tert*-butyl analogues **66** and **67** against the Sendai virus

Having prepared a small number of alkylidene compounds, all of which elicit a biological response that is an order of magnitude greater than the natural compounds, we were unable to improve upon sub-micromolar activities without a detrimental affect on the toxicity. As a result, we turned our attention to the protecting group on the hydroxyl group at C-4, in an attempt at improving the selectivity index.

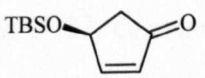
2.8 Structure activity relationships regarding the C-4 hydroxyl group

2.8.1 Effect of different groups on biological activity

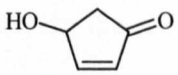
The first non-prostaglandin like compounds prepared by the group were the enantiomers of **31**.



(+)-**31**

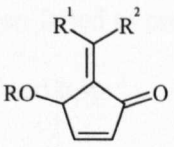


(-)-**31**



69

Preliminary results showed that the silicon group was the entity of choice for modifying alcohols that were to be sent for biological evaluation. In general, it had been observed that the free hydroxyl group (as seen in **69**) was not as potent as the derivatised analogue. Such a lack of activity associated with the unprotected alcohol (Table 2.8.1) may be due to the transport mechanism involved, since the more polar alcohol may not pass into the cell as readily as the more lipophilic, protected alcohol.



32

Entry	R in 32	R^1 in 32	R^2 in 32	ID_{50} (μM)	TD_{100} (μM)	Compound
1	H	*i*-Pr	H	2	10	(-)-**51**
2	-OTBS	H	*i*-Pr	0.7	TOXIC	**52**
3	-OTBS	*i*-Pr	H	0.4	50	**53**
4	-OTBS	*i*-Pr	H	0.3	10	(-)-**53**
5	-OTBS	*i*-Pr	H	4	50	(+)-**53**

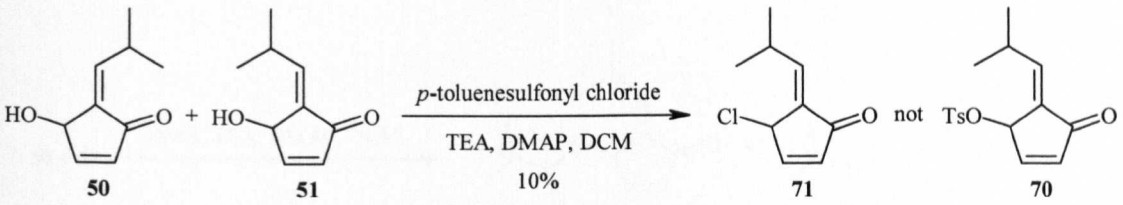
Table 2.8.1 Biological evaluation of structural analogues of **53** against the Sendai virus

2.8.2 Changes in the C-4 hydroxyl group

It was found, through early studies in the *gem*-dimethyl series (*vide infra*), that a *p*-toluenesulfonyl (tosyl) protecting group resulted in a compound that was selective for inhibiting NF-κB, whereas an acetate protecting group resulted in a compound that was selective for activating HSF. Interestingly, an analogous compound possessing a *tert*-butyldimethylsilyl ether protecting group was non-selective. Therefore, we set out to synthesise various analogues of **32**, concentrating on varying the unit on the hydroxyl group.

We speculated that the 4-tosylate analogue of **32**, such as **70** may also exhibit similar activity towards the inhibition of NF-κB. Unfortunately, in the event, derivatisation using *p*-toluenesulfonyl chloride in dichloromethane failed to produce the desired product. It was believed that during the reaction, the transiently formed tosylate **70**, was displaced by the chloride counter ion resulting in the 4-chloro analogue **71**. Using diethyl ether as solvent (in the hope that the triethylamine hydrochloride salt

would precipitate out of solution) also failed to produce the tosylate **70**. However, the 4-chloro compound **71** was isolated and tested.



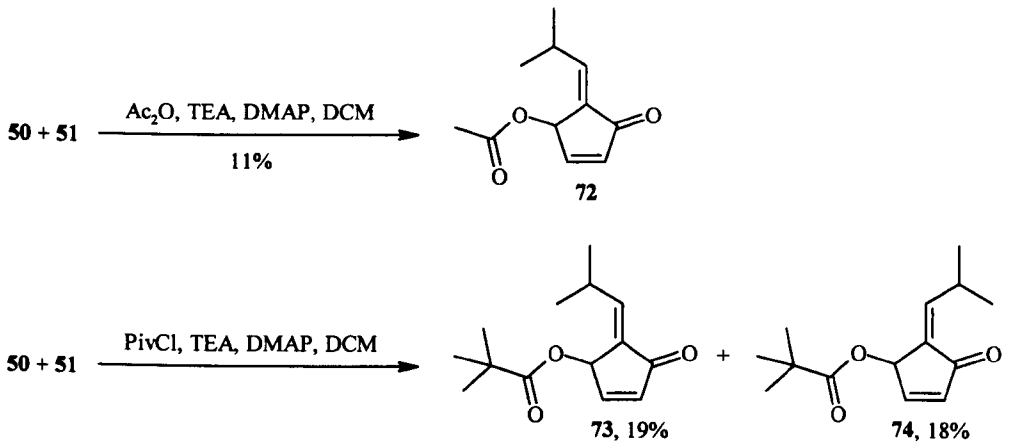
50 **51** **71** **70**

It showed activity similar to that of the, now standard, 4-silanyloxy analogue **53**, however, this was accompanied by a slight increase in toxicity (entries 1 and 2, Table 2.8.2).

Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	0.4	50	**53**
2	0.4	10	**71**
3	1	10	**72**
4	0.6	10	**73**
5	0.4	10	**74**

Table 2.8.2 Biological evaluation of *O*-alkyl analogues of **53** against the Sendai virus

Other groups that could be coupled directly to the hydroxy enone nucleus of the mixture of alcohols **50** and **51** were prepared. Unfortunately, the number of these was limited due to the lability of the 4-hydroxy cross-conjugated enone system under basic reaction conditions (the use of milder trichloroacetimidates was not attempted). As such, acetate **72**, and pivaloylates **73** and **74**, (entries 3-5, Table 2.8.2) could be prepared and were chosen as representatives of compounds with differing stereochemical parameters.

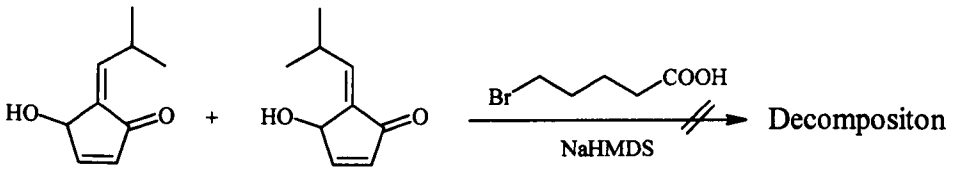


Disappointingly, the preparation of **72** resulted in the complete consumption of the starting material; one spot was observed by TLC, with the formation of base-line material, and only the *E*-compound was formed as indicated by ^{1}H NMR (250 MHz) of the crude reaction mixture. In contrast both (*E*)- and (*Z*)-isomers were isolated for the pivaloylate analogue! The stereochemistry of the carbon-carbon double bond for compounds **72** to **74** was determined by comparison of the chemical shifts in the ^{1}H NMR spectra to **53**. The biological results, Table 2.8.2, showed that the more bulky and lipophilic pivaloylate analogues **73** and **74** displayed the greatest activity. Interestingly, even the (*Z*)-isomer **74** was active (unlike **52** which was toxic at all doses). In fact, the trend of an increase in lipophilicity at C-4, accompanying an increase in activity, was beginning to become clear, suggesting that these compounds may be best used as topically applied treatments, since systemic bioavailability would be expected to be very poor with these lipophilic compounds.

2.9 Synthesis of O-alkyl analogues of 53

2.9.1 Base sensitivity of the 4-hydroxy-5-alkylidene-cyclopent-2-enone ring system

In an attempt to prepare compounds that were alkylated at the hydroxyl oxygen, an alternative synthetic route was required. Since the hydroxy enone nucleus of **50** and **51** is very base sensitive, any formal deprotonation leads instantly to polymerisation. This was exemplified by our attempts to prepare oxaprostaglandin analogues[72-75] *via* the derivatisation of the mixture of alcohols **50** and **51**, using 6-bromohexanoic acid. Unfortunately, the reaction yielded only decomposition products.

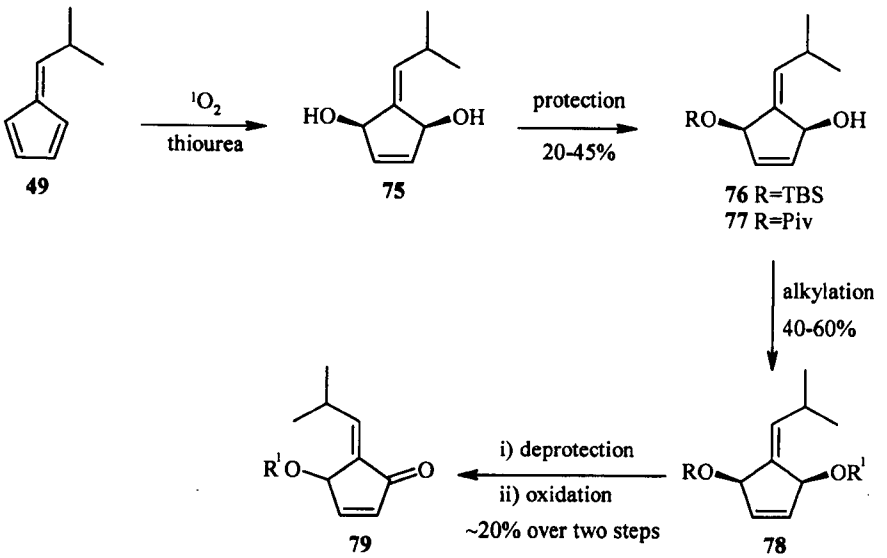


50 **51**

As a result of this problem, we resolved to remove the electrophilic enone moiety and replace it temporarily with a second hydroxyl function.

2.9.2 Redressing the synthesis of 32

The synthesis of *syn*-diol **75** began with the photosensitised oxidation of fulvene **49**. Employing thiourea in the oxidation reaction cleaves the *endo*-peroxide intermediate, generating *syn*-diol **75**, Scheme 2.9.2.[76]

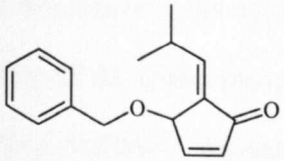


49 75 76 R=TBS 77 R=Piv 78 79

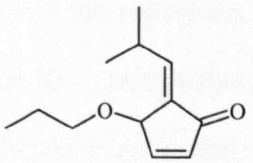
Scheme 2.9.2

Taking advantage of the different steric environment of the hydroxyl groups, due to the alkylidene substituent, mono-protection was achieved with either *tert*-butyldimethylsilyl chloride or pivaloyl chloride, in modest yields. Subsequent alkylation of the desired hydroxyl group using sodium hexamethyldisilazide and the appropriate alkyl halide in tetrahydrofuran at 0 °C resulted in **78** functionalised in the desired manner (40-60%). Removal of the silyl or pivaloyl group, using *tert*-butylammonium fluoride or diisobutylaluminium hydride respectively, followed by oxidation of the crude product, utilising Dess-Martin periodinane or pyridinium dichromate, resulted in molecules of the type exemplified by **79**, the *O*-alkylated analogues of **53**, albeit in a poor overall yield (2-5% from **75**).

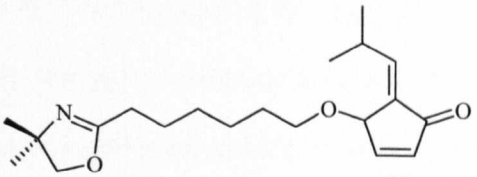
Three analogues were chosen to ascertain the biological activities of this *O*-alkyl system, **80**, **81** and **82**.



80



81



82

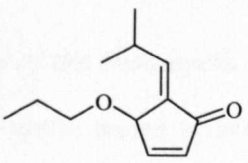
The benzyl analogue **80** was chosen because of its lipophilicity, hoping this would increase activity, as we had seen before, and also because of its potential to π-stack, a feature that may well cause it to bind to the active site of IKK more tightly.

Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	0.4	50	**53**
2	0.5	10	**80**
3	0.3	10	**81**
4	0.3	10	**82**
5	0.3	10	**83**

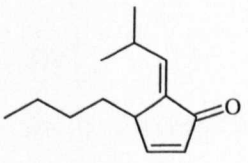
Table 2.9.2 Biological evaluation of *O*-alkyl analogues of **53** against the Sendai virus

Unfortunately, the activity of the benzyl analogue **80** (entry 2, Table 2.9.2) did not differ considerably from the 4-silanyloxy analogue **53** (entry 1) and was more toxic.

Compound **81** was prepared as a direct oxygen analogue of **83**, a compound developed by one of my colleagues which had shown excellent biological activity in our assays, (entries 3 and 5, Table 2.9.2).



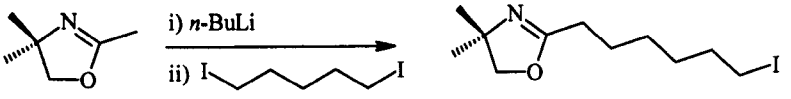
81



83

Unfortunately, the activity of the oxa-analogue **81** did not significantly improve upon that of the carba-analogue **83**. Disappointingly, the poor selectivity index proved to be a problem. We had hoped initially that the oxygen-based series would be a step away from a highly patented area. Finally, the oxazoline derivative **82** was prepared both for its ability to be cleaved to the corresponding acid (or ester/amide) and its more prostaglandin-like nature.

The oxazoline derivative **82** was prepared from the corresponding silyl ether derivative **76** using an iodo-derivative of the side-chain, prepared by one of my colleagues using the method shown below.[77]



Unfortunately, none of the *O*-alkylated analogues produced interesting activity to warrant further testing or analogue preparation.

As a result of the lack of improvement in selectivity index, efforts on modifying this core skeleton were terminated. It is relevant to note at this point that a nitrogen atom at the 4-position greatly enhances the activity of the compound, but since this work is not my own, it will be reported elsewhere.

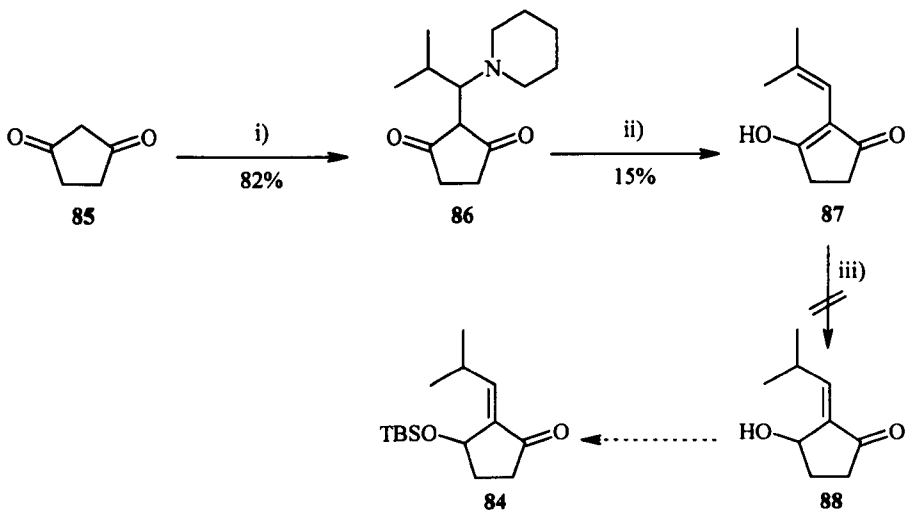
2.10 Removal of the endo-cyclic enone system of 53

Since the *endo*-cyclic enone system is more reactive to nucleophiles than the *exo*-cyclic one,[78] we sought to remove the *endo*-cyclic enone unit and reveal a softer

Michael-acceptor in the guise of the *exo*-cyclic enone. This would also allow us to determine if the *endo*-cyclic enone was crucial in maintaining biological activity. Removing the *endo*-cyclic enone would also hopefully render the compound less toxic.

2.10.1 Initial attempts at a reduced analogue of **53**

Initial attempts to prepare compound **84**, whilst maintaining the stereochemical integrity of the *exo*-carbon-carbon double bond proved unsuccessful, Scheme 2.10.1. Starting with cyclopentane-1,3-dione **85** and subjecting this to a Knoevanagel-type reaction with isobutyraldehyde and piperidine in dichloromethane yielded **86** in excellent yield (82%).[79] However, elimination of the piperidine ring in an acidic medium provided the enolised form of the desired compound **87** in low yield (15%) as the sole isolable product.

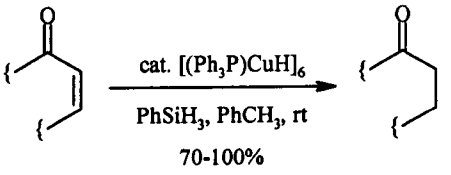


Scheme 2.10.1 *Reagents and conditions*: i) isobutyraldehyde, piperidine, DCM, rt, ii) H^+, iii) $NaBH_4$ reduction.

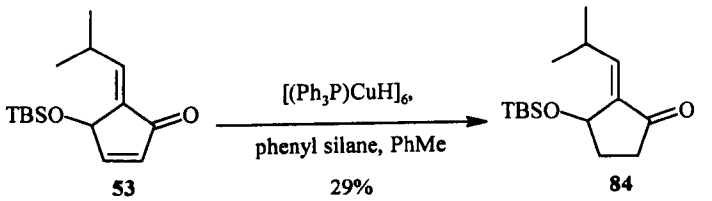
Partial reductions using Lüche[80] conditions or modified Lüche conditions, $NaBH(OMe)_3/CeCl_3.7H_2O$, failed to produce the target alcohol **88**, after which silylation would have provided compound **84**.

2.10.2 Stryker reduction of 53

It was decided to investigate selective reduction of **53** to compound **84**. It is known, through the work of Lipshutz, that catalytic quantities of Cu(I) can aid in the efficient 1,4-reduction of conjugated ketones.[81]



Therefore, based on this strategy, a sample of the racemic **53** underwent a 1,4-hydride reduction, using Stryker's reagent ($[(Ph_3P)CuH]_6$),[82] in a modest 29% yield. Pleasingly, this gave the target compound **84**, thus allowing us to determine if we had improved selectivity.



53 **84**

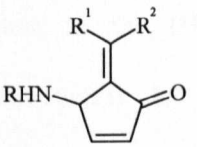
Although marginal activity was observed (suggesting that Michael addition can occur at the remaining *exo*-cyclic enone) the compound was less active, by as much as an

order of magnitude than the parent compound **53**, whilst the toxicity remained approximately unchanged, Table 2.10.2. This suggests that the *exo*-cyclic enone system enhances the activity of the *endo*-cyclic enone by allowing the compound to exist in the cell longer before being excreted, or that it helps to bind the compound in the active site.[53] Unfortunately, the innate toxicity still remains.

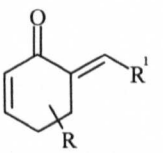
Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	0.4	50	**53**
2	4	50	**84**

Table 2.10.2 Biological evaluation of the reduced analogue of **53** against the Sendai virus

Work in the area of cross-conjugated enone systems still continues in the group with a great deal of effort being applied to the synthesis of nitrogen analogues of **53**, exemplified by **88**, as well as six-membered ring analogues, for example **89**.



88



89

2.11 In vivo biological data for 53

The biological activities mentioned in the previous section, which refer to the cross-conjugated compounds, were initially determined from *in vitro* tests on the Sendai virus, courtesy of Santoro *et al.* in Rome (see Appendix III for information on the biological tests).

Compound **53** was found to be the most potent member of this series and since such remarkable activity was seen *in vitro* we expanded its biological profile, and set out to determine its activity *in vivo*. The *in vivo* studies carried out by our collaborators began with a murine human simplex virus (HSV)-1 infection model.[83] Having been formulated into a topical cream it was administered at a range of concentrations from 0.04 μM to 4 mM, and the preliminary results were very promising. The vehicle (cream in which **53** was dissolved) alone was mildly inflammatory, however, in uninfected mice, **53** appeared to be anti-inflammatory and reduced the swelling produced by the vehicle alone in a dose dependant manner. In infected mice preliminary evidence suggested that **53** produced an anti-viral effect, as evidenced by a reduction in ear swelling and infectious virus titres in the skin. Thus **53** may be one of the first synergistic anti-viral/anti-inflammatory compounds of this type.

Further *in vivo* studies carried out by our collaborators, examined the anti-inflammatory effect of **53** in the murine carrageenan air pouch model, as a complementary test to the (HSV)-1 model, as well as to confirm the anti-inflammatory result seen in that model.[84] It was found that in this system, when the compound was injected directly into the air pouch, inflammation was reduced in a dose dependant manner. This was comparable to the non-steroidal anti-inflammatory drug (NSAID) indomethacin in the same test system, but **53** was found to be a better anti-inflammatory compound than the natural cyclopentenone prostaglandin 15-deoxy-$\Delta^{12,14}$-PGJ_2. When tested against inflammation in the IL-1 driven monoarticular arthritis model in the rat, **53** seemed to be ineffective at controlling joint swelling at a dose of 30 μg, accompanied by a change in behaviour of the administered rats. However, in a topical application of the same compound there

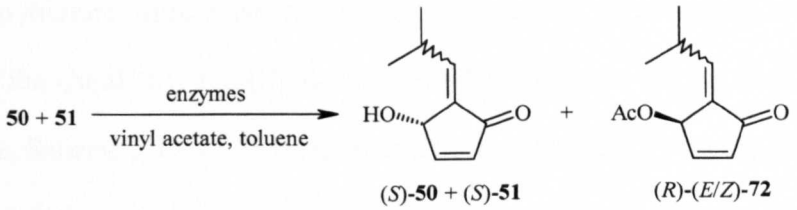
seemed to be a small trend towards reducing the effect of the IL-1β on glycosaminoglycan loss, though this was not significant. During a two-day trial, administering the compound twice a day, no acute or chronic adverse drug reactions were noted. The preparation was well tolerated and it is therefore possible that elevating the dose of the topically applied compound may be of some benefit.

With such promising biological data *in vivo*, supporting our *in vitro* data, we set about resolving racemic **53** into its enantiomers. The discovery of the greater potency of **53**, over and above the other analogues initially prepared, encouraged us to believe that one enantiomer would have a better biological profile than the other. This is often widely seen in medicinal chemistry, for example thalidomide, the morning sickness remedy. In this case one enantiomer is a potent anti-emetic cure whilst the other enantiomer causes terrible birth defects.[85] It was hoped that structural information on the active site could be inferred if the absolute stereochemistry of the carbon bearing the silanyloxy group in **53** was known.

2.12 Enantiomerically enriched synthesis of 53

2.12.1 Enzymatic resolution of 53

A mixture of the (*Z*)- and (*E*)-alcohols **50** and **51** were subjected to a screen of 25 enzymes, Table 2.12.1.[86] The results of this screen revealed *Pseudomonas cepacia* lipase as one of the most suitable enzymes for the resolution of this system (entry 2, Table 2.12.1), thus the remainder of the mixture of geometric isomers were subjected to acylation by this enzyme, up to a gram scale.

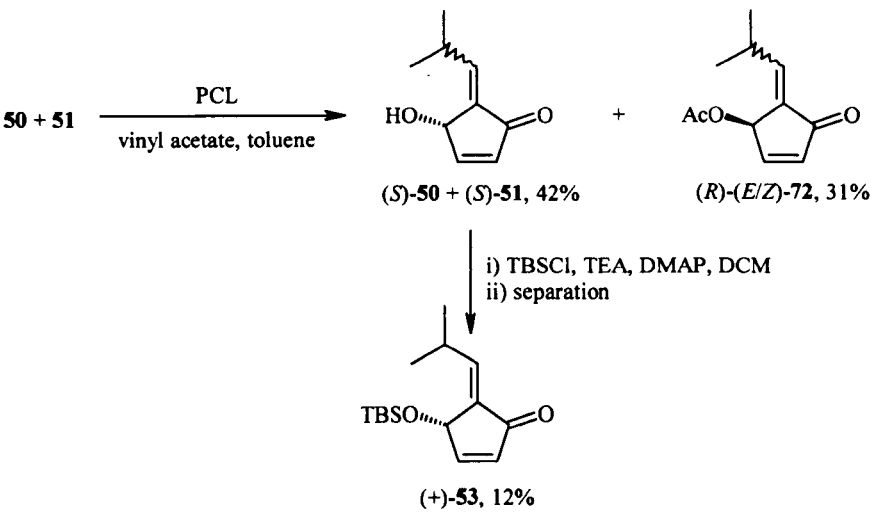


Entry	Enzyme	Substrate for enzyme
1	Pig Liver Esterase	Y
2	*Pseudomonas cepacia* Lipase	Y
3	Porcine Pancreatic Lipase	N
4	*Candida rugosa* Lipase	Y
5	alpha-Chymotrypsin	N
6	*Aspergillus niger* Lipase	N
7	*Rhizomucor miehei* Lipase	Y
8	*Candida antarctica* "A" Lipase	Y
9	*Candida lypolytica* Lipase	N
10	*Candida antarctica* "B" Lipase	Y
11	*Thermomyces lanuginosus* Lipase	Y
12	*Bacillus stearothermophilus* Protease	N
13	ChiroCLEC-CR (dry) (*Candida rugosa* Lipase)	Y
14	ChiroCLEC-BL (dry) (Subtilisin Carlsberg)	Y
15	ChiroCLEC-PC (dry) (*Burkholderia cepacia* Lipase)	Y
16	*Rhizopus delemar* Lipase	N
17	*Rhizopus oryzae* Lipase	N
18	*Alcaligenes species* Lipase	Y
19	*Mucor javanicus* Lipase	N
20	*Aspergillus oryzae* Protease	N
21	*Candida rugosa* Esterase	Y
22	*Bacillus lentus* Protease	N
23	*Bacillus lentus* Protease	N
24	*Thermomyces lanuginosus* Lipase	Y
25	*Penicillium roqueforti* Lipase	Y

Table 2.12.1 Enzyme screen.

The transesterification with *Pseudomonas cepacia* lipase using vinyl acetate in toluene at room temperature was left to progress to ~50% (^{1}H NMR). Purification of

the reaction mixture, using flash column chromatography, permitted the isolation of a mixture of the chiral (*E*)- and (*Z*)-alcohols, (*S*)-**50** and (*S*)-**51** (42%), unacetylated by the enzyme, Scheme 2.12.1. These compounds were silylated (*tert*-butyldimethylsilyl chloride, triethylamine, 4-dimethylaminopyridine in dichloromethane) and the pair of isomers separated, yielding the desired optically pure (*E*)-isomer (12%).

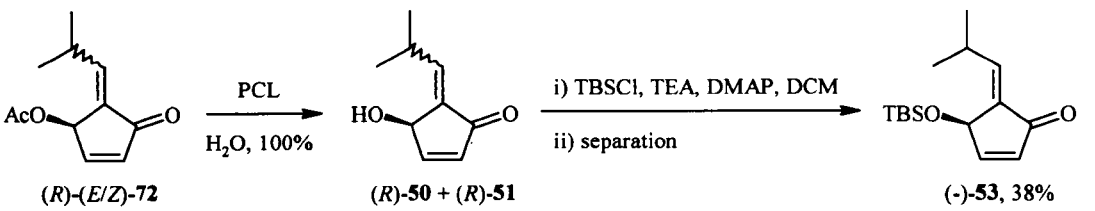


Scheme 2.12.1

The protected (*E*)-isomer, (+)-**53**, was isolated with an enantiomeric excess (ee) of >99% as determined by chiral gas chromatography (CHIRASIL-DEX CB, WCOT fused silica, 25 M × 0.25 mm, DF=0.25; retention time (t_r)=20.71 min. at 140 °C isotherm).

Access to its enantiomer, (-)-**53**, *via* hydrolysis of acetates (*R*)-(*E*/*Z*)-**72** acquired from the enzyme resolution, using potassium carbonate in methanol/water, proved fruitless, with only polymerised product resulting. However, hydrolysis in water, again utilising *Pseudomonas cepacia* lipase, provided the mixture of optically pure alcohols

(*R*)-**50** and (*R*)-**51**, which upon silylation and separation resulted in the isolation of (-)-**53**, Scheme 2.12.2. Again the enantiomeric excess was >99% by chiral gas chromatography (CHIRASIL-DEX CB, WCOT fused silica, 25 M × 0.25 mm, DF=0.25; retention time (t_r)=20.22 min. at 140 °C isotherm).



Scheme 2.12.2

The desired (*E*)-isomer being silylated less quickly than the (*Z*)-isomer, resulted in the isolation of unreacted starting material enriched in the (*E*)-alcohol (*R*)-(-)-**51** (contaminated with ca. 5% of the (*Z*)-alcohol, by ^{1}H NMR), see Table 2.8.1.

Shown below, Figure 2.12.2, is an example of the gas chromatography trace of (+)-**53**. On the left is the trace of the racemic material, and on the right is the (+)-enantiomer (the slower of the two enantiomers to elute from the column) showing an enantiomeric excess of >99%.

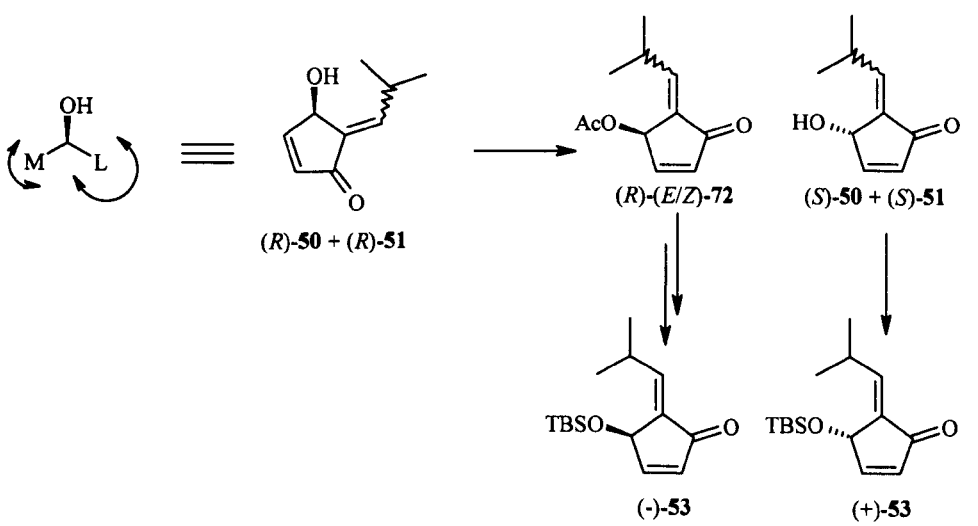
Figure 2.12.2: (±)-**53** (left) and (+)-**53** (right).

2.13 Determination of the absolute stereochemistry of (+)- and (-)-53

2.13.1 Kaslauskas' lipase model

Despite the excellent resolution obtained by *Pseudomonas cepacia* lipase, the absolute stereochemistry of the enantiomers was unknown. Kazlauskas has recently developed a model for the prediction of lipase-catalysed resolutions as a tool to determine the outcome of enzyme catalysed transesterification reactions.[87]

In this lipase model, it is suggested that the alcohol, which becomes esterified fastest, can be determined based on the size (or hydrophobicity) of the substituents at the stereogenic centre, Scheme 2.13.1.



Scheme 2.13.1: Exemplification of Kazlauskas' model applied to **50** and **51** (enantiomer shown reacts fastest).

The model works by distinguishing between large and small groups adjacent to the stereogenic centre. Acetylation of the β-hydroxy group occurs for the enantiomers with the largest group flanking the stereogenic centre on the right-hand side, and the alcohol at the top. Secondary alcohols, which have substituents that differ

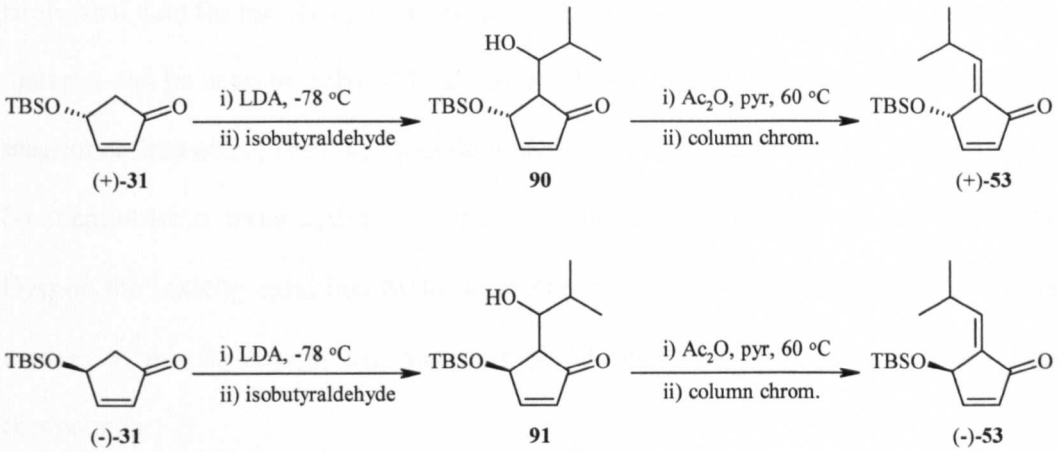
significantly in size, are more efficiently resolved than those whose substituents are sterically similar. Therefore, applied to our substrate, which has a large isobutylidene group on one side and a small proton on the other side of the stereogenic centre, this should allow an excellent prediction on the outcome of the resolution. For *Pseudomonas cepacia* lipase, this model correctly predicts the enantiomeric outcome of 63 out of 64 (98%) substrates, and in fact, the model correctly predicts the result for our substrate, see Scheme 2.13.1.

The major advantage of this model is its simplicity, and that it can be applied to a wide range of substrates. However, the rule cannot allow for the subtleties in the selectivity of enzymes since large conformational changes are needed before the substrate can bind to the active site in lipases, and the model does not account for this flexibility of the active site.[87]

2.13.2 Proof of absolute stereochemistry of **53**

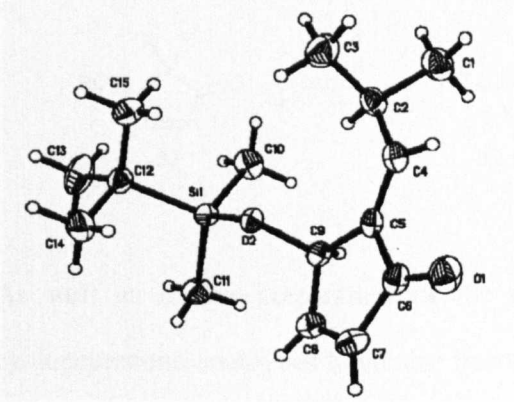
In addition to this model, we were able to determine the absolute stereochemistry unequivocally, *via* an alternative synthetic route, using a commercially available chiral starting material of a known absolute stereochemistry.

The asymmetric route begins with an aldol condensation of the commercially available[88] (*R*)- or (*S*)-(*tert*-butyldimethylsilanyloxy)-cyclopent-2-enone, (+)-**31** or (-)-**31** and isobutyraldehyde. Subsequent dehydration using acetic anhydride in pyridine followed by purification, resulted in the desired (*E*)-isomer of (+)- and (-)-**53**.



Scheme 2.13.2 Asymmetric synthesis of homochiral (+)-**53** and (-)-**53**.

Despite a poor yield (~5%), their respective spectroscopic and analytical data were sufficient to prove the stereochemistry, Scheme 2.13.2. The sign of the optical rotation and retention time (chiral GC) were identical to those obtained using the *Pseudomonas cepacia* lipase resolution method and, therefore, we were satisfied that the absolute stereochemistry of the optically pure compound is as shown; (-)-**53** was recrystallised from diethyl ether and the X-ray crystal structure of this more active enantiomer can be seen below, Figure 2.13.2.



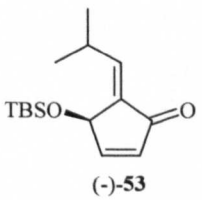


Figure 2.13.2 X-ray crystal structure of (-)-**53**

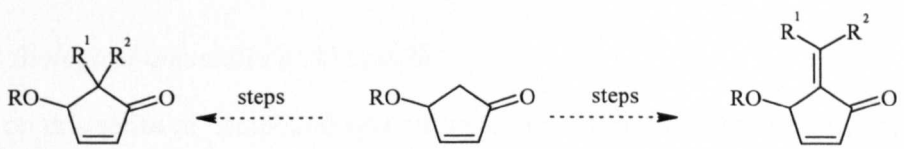
Biological data for the chiral compounds (+)-**53** and (-)-**53** compared with the racemic material can be seen in Table 2.13.2. The (+)-enantiomer appears to be an order of magnitude less active than the racemic material (entry 2, Table 2.13.2), but whilst the (-)-enantiomer is more active than the racemate it is slightly more toxic (entry 3). Despite the toxicity exhibited by these compounds *in vitro*, interestingly, it is not as evident in our *in vivo* assays and thus (-)-**53** was developed as one of the lead compounds.

Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	0.4	50	(±)-**53**
2	4	50	(+)-**53**
3	0.3	10	(-)-**53**

Table 2.13.2 Biological evaluation of the enantiomers of **53** against the Sendai virus

2.14 Synthesis and biological activity of the gem-dimethyl series

As mentioned at the beginning of this chapter the options for diversification away from **31** became immediately apparent based on my predecessors' work.[55] As well as the work discussed above, the compounds exemplified by **33**, were also considered.

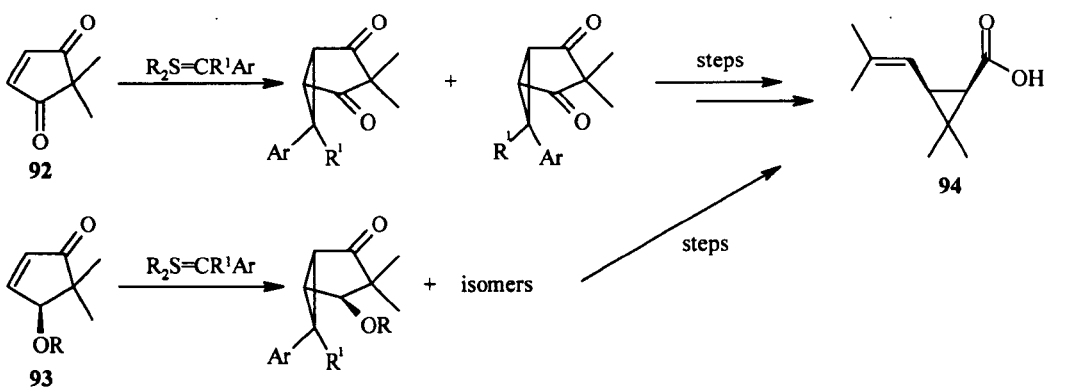


33 **31**, R=TBS **32**

As well as in the preparation of the madindolines (Section 2.4.1), 5,5-dialkyl-cyclopentenone analogues have also been used as versatile chiral building blocks for the synthesis of agriculturally useful products.[89, 90]

2.14.1 Krief's synthesis of (1R)-cis-chrysanthemic acid

In their work Krief *et al.* have elegantly shown this by revealing that enedione **92** and the chiral protected alcohol **93** can undergo stereoselective cyclopropanation of the enone to reveal the geminally disubstituted cyclopropane derivatives and their isomers. These bicyclic compounds were successfully utilised to develop an enantioselective synthesis of (1*R*)-*cis*-chrysanthemic acid **94**, Scheme 2.14.1.[89,90]

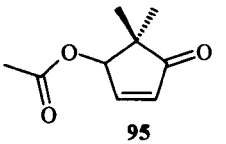


Scheme 2.14.1

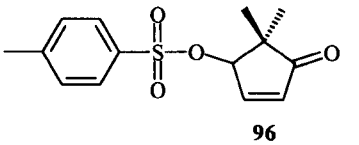
Based on the work of Krief, and the interesting properties and biological potency of these alkyl cyclopentenones, we were confident of a successful preparation of them and subsequent biological evaluation.

2.14.2 Biological anomalies of 95 and 96

Work on this series of compound was prompted by a very interesting biological result discovered by my predecessors in that acetate **95** and tosylate **96** seemed to show complete selectivity for only one biological response.



95

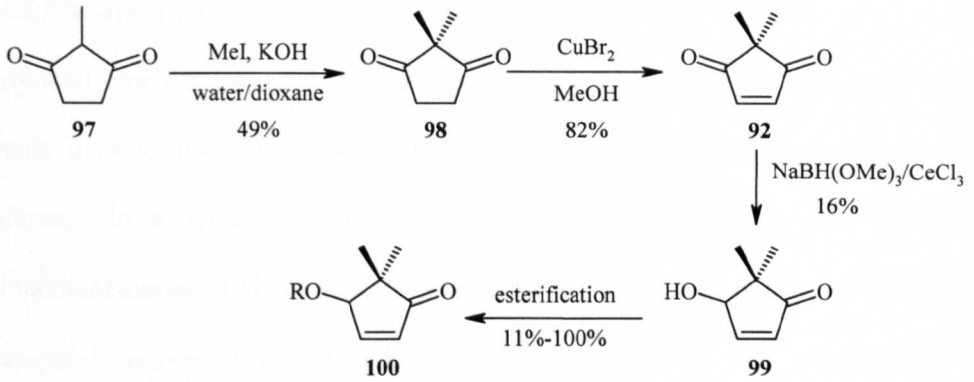


96

The acetate **95** originally showed complete selectivity for HSF activation whilst the tosylate **96** showed complete selectivity for NF-κB inhibition in our primary screen. Thus, based on these results, which seem to stem only from the protecting group used, we decided to make a small library of analogues varying the C-4 hydroxyl group. In doing so we hoped to repeat, and thus confirm these two results, and also see if we could improve upon them.

2.14.3 Synthesis of a 12-membered library of gem-dimethyl analogues

The synthesis of the parent alcohol **99**, *i.e.* the common intermediate of the analogue compounds, follows the work of Krief.[89, 90] The synthesis begins with α-methylation of 2-methyl-cyclopentane-1,3-dione **97** using methyl iodide and potassium hydroxide in a water/1,4-dioxane mixture (49%). Oxidation to the enedione system of **92** was achieved very successfully (82%) using copper(II) bromide in refluxing methanol. A careful (-78 °C) mono-reduction was undertaken to provide the familiar 4-hydroxy enone system **99** which was now ready to be esterified at the C-4 oxygen to generate analogues exemplified by **100**, Scheme 2.14.3.



Scheme 2.14.3

Unfortunately, over-reduction and thus diol formation often hampered the yield of the reduction step, **92** to **99**, despite the use of sodium trimethoxyborohydride, which is only capable of a single reduction per mole of reducing agent. Nevertheless, enough of the desired mono-reduced product **99** was available to continue with the synthesis of a small library, *via* parallel synthesis.

The final step of the sequence, derivatisation of alcohol **99**, utilised standard procedures (esterifying agent, triethylamine, 4-dimethylaminopyridine and dichloromethane)[69, 70] to provide the compounds shown in Table 2.14.3.2, which we used to assess the influence of the alcohol group on the biology of this system.

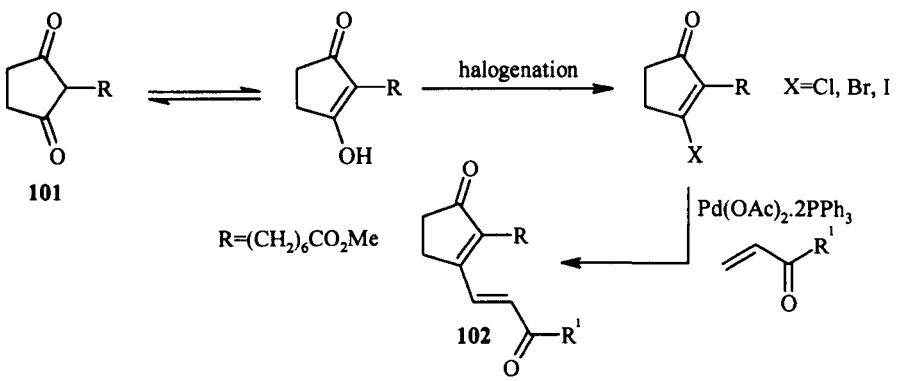
Notably, the parent alcohol itself **99**, nor the intermediate enedione **92**, showed any significant biological activity, Table 2.14.3.

Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	10	500	**99**
2	30	500	**92**

Table 2.14.3 Biological evaluation of **92** and **99** against the Sendai virus

2.14.3.1 Naora's synthesis of prostaglandin B_1

Compounds such as the starting material 2-methyl-1,3-cyclopentanediones **97** used in Scheme 2.14.3, have also been used as intermediates in the synthesis of natural products. In a review by Schick and Eichhorn it is shown that 2-alkyl-1,3-cyclopentanediones **101** can be halogenated and reacted further with an *α,β*-unsaturated ketone under palladium catalysis to afford the prostaglandin B_1 intermediate **102**, Scheme 2.14.3.1.[91] Thus, these compounds were proving to be extremely useful in our approach towards the synthesis of cyclopentenone prostaglandin analogues.

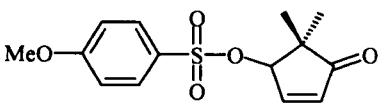


Scheme 2.14.3.1

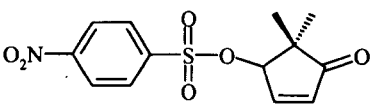
2.14.3.2 Synthesis of sulfonate esters

Returning to the synthesis and biological activity of our dimethyl analogues, the biology of the sulfonate derivatives were compared directly to the tosyl analogue **96**. Despite the fact that the selectivity for NF-*κ*B inhibition of the tosylate could not be repeated, we still desired to investigate the series to determine if its general activity could be improved upon.

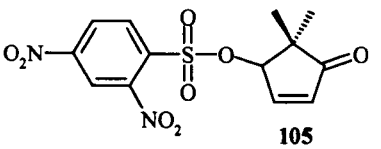
Various sulfonate esters were chosen which would vary either the electron demand or the steric demand of the system. Thus, increasing the electron-density of the benzene ring in the sulfonyl derivatives was achieved using *p*-methoxybenzenesulfonyl chloride but, unfortunately, the product **103** gave similar results (entry 2, Table 2.14.3.2), within the limits of the assay, as the less electron-rich tosylate system **96**.



103



104



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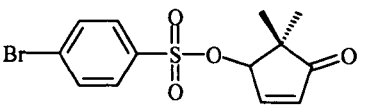
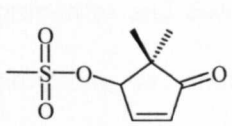
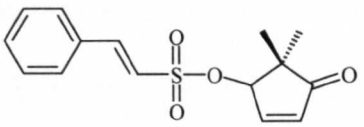


106

Conversely, however, it seems that removing electron density from the benzene ring with the nitro groups of **104** and **105** as well as the bromide analogue **106** (entries 3, 4 and 5, Table 2.14.3.2) had a negative effect on anti-viral activity. Such an effect was also mirrored by the decrease in toxicity of those compounds, suggesting an overall less active series of compounds. The mesyl, styryl and dansyl compounds **107**, **108** and **109** (entries 6, 7 and 8, Table 2.14.3.2), although differing in their electronic and steric properties, failed to provide us with a new lead compound. Nevertheless, it is interesting to note that the mesylate **107**, bearing an excellent leaving group, was approximately ten times less toxic than the tosylate. This suggests that the leaving group potential of the alcohol derivative and not the lipophilicity or sterics may play a part in the activity. Unfortunately, the corresponding triflate was too unstable to isolate.



107



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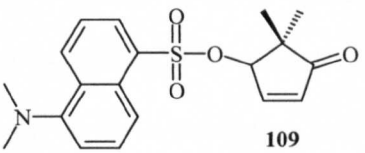


109

Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	1	50	**96**
2	2	100	**103**
3	10	100	**104**
4	30	500	**105**
5	5	100	**106**
6	5	500	**107**
7	5	100	**108**
8	2	500	**109**

Table 2.14.3.2 Biological evaluation of *gem*-dimethyl sulfonate ester analogues against the Sendai virus

2.14.3.3 In vivo biological activity of ***96***

Despite these results, other biological tests indicated that the overall biological profile of tosylate **96** showed it to be our best sulfonyl derivative, and thus we decided to take it on to further testing. Since **96** initially showed selectivity for NF-κB inhibition, in the anti-viral assay, we sent the compound for tests using an *in vivo* inflammation model. To this end, the racemate of tosylate **96** was tested in the murine carrageenan air pouch model and it revealed a bell shaped dose response to inflammation; it had a tendency to exacerbate inflammation at higher doses.[84] Like-wise naturally occurring prostaglandins, for example 15-deoxy-$\Delta^{12,14}$ PGJ_2, also exhibit a bell shaped dose response curve in the same model.[84]

Resolution of the enantiomers and subsequent biological evaluation has shown the (-)-enantiomer to be a potent anti-viral compound without exacerbation of inflammation, whereas the (+)-enantiomer appears to convey no anti-inflammatory

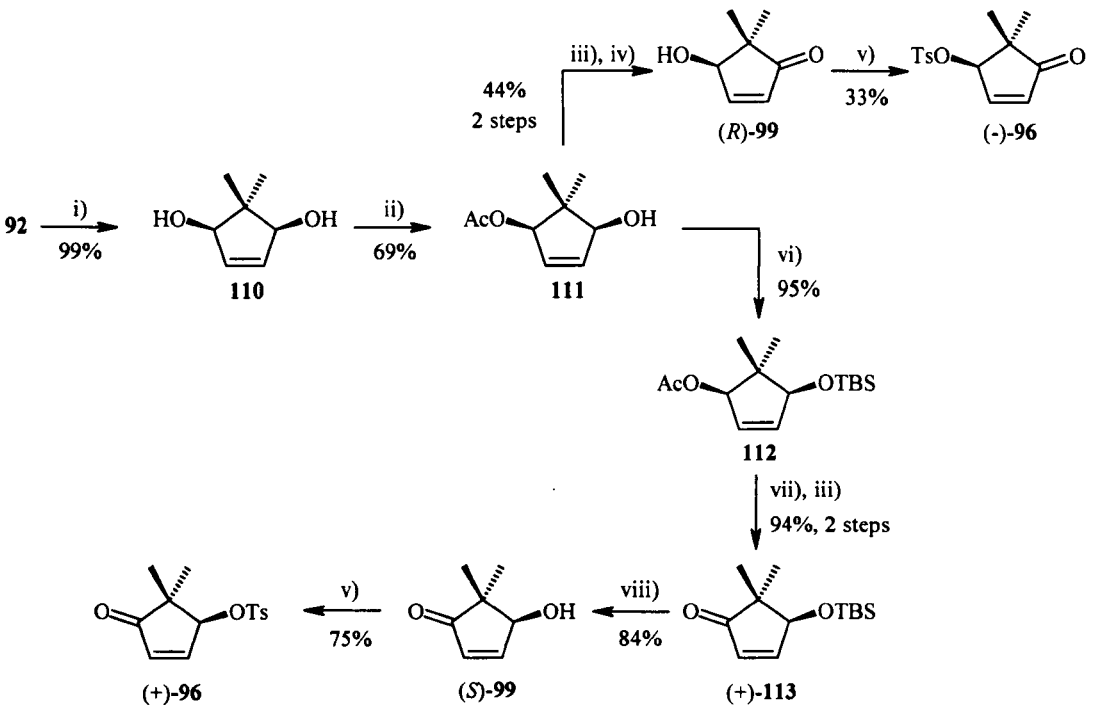
properties and does appear to exacerbate the inflammation reaction to some extent, providing yet another example of the different biological response generated by enantiomers. Thus, the (-)-enantiomer, at present, looks to be a promising anti-inflammatory candidate.

Another *in vivo* study carried out on this compound was the IL-1 driven monoarticular arthritis model in the rat and it showed completely to abolish paw swelling at 30 μg; unfortunately at this concentration, (-)-**96** also demonstrated adverse affects on the behaviour of the rat.[84]

2.14.3.4 Isolation of the enantiomers of ***96***

The asymmetric synthesis developed to prepare the enantiomers of tosylate **96** follows the work of Krief[90] and Yamada.[92]

The stereodivergent synthesis begins with the isolation of *syn*-meso-diol **110**, from the enedione in 99% yield. Enzymatic desymmetrisation was performed with lipase PS-C Amano II and vinyl acetate and provided the chiral acetate **111** in 69% yield, Scheme 2.14.3.4.



Scheme 2.14.3.4: *Asymmetric synthesis of* ***96*** *- Reagents*: i) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 °C, 99%, ii) lipase PS-C Amano II, vinyl acetate, toluene, 69%, iii) PDC, 4Å sieves, DCM, iv) LiOH, DME, 48%, v) *p*-toluenesulfonic anhydride, TEA, DMAP, DCM, vi) TBSCl, imidazole, DMF, 95%, vii) DIBAL, toluene, -78 °C, 100%, viii) 80% acetic acid, 84%.

Access to the (*R*)-series is carried out *via* an oxidation/deacetylation process to give alcohol (*R*)-**99** with an excellent enantiomeric excess of 97% (LIPODEX E-0.2 μm, 25 M × 0.25 mm, fused silica capillary column; retention time (t_r)=13.81 min.). The chiral tosylate (-)-**96** was prepared by tosylation with *p*-toluenesulfonic anhydride in dichloromethane in a modest yield of 33%.

Protection of the alcohol **111** with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide yielded silyl acetate **112** in 95% yield. Deacetylation using diisobutylaluminium hydride in toluene, followed by oxidation with pyridinium dichromate in dichloromethane yielded chiral silyl-ether **113** in 94% yield over two steps. Deprotection of the silicon protecting group using 80% acetic acid then yielded the chiral alcohol (*S*)-**99** with an enantiomeric excess of >99% (LIPODEX E-0.2 μm,

25 M × 0.25 mm, fused silica capillary column; retention time (t_r)=13.44 min.). Derivatisation of alcohol (*S*)-**99** with *p*-toluenesulfonic anhydride in dichloromethane gave rise to (+)-**96**, 75%.

The biological data for the enantiomers, compared with the racemate, can be seen below, Table 2.14.3.4.

Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	1	50	(±)-**96**
2	3	50	(+)-**96**
3	2.5	10	(-)-**96**

Table 2.14.3.4 Biological evaluation of the enantiomers of **96** against the Sendai virus

The enantiomers (entries 2 and 3, Table 2.14.3.4) display similar activity to each other, and possess the same order of magnitude an activity as the racemate, although (-)-**96** appears to be slightly more toxic. Despite this, the toxicity of (-)-**96** is not apparent *in vivo*, Section 2.14.3.3.

*2.14.3.5 Synthesis of ester derivatives of **100***

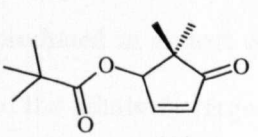
Unfortunately, despite these promising biological results both regarding anti-viral and anti-inflammatory responses *in vitro* and *in vivo* these compounds possessed certain properties that prevented them from progressing further. Since sulfonate esters are highly activated leaving groups, it was believed that they would be potent alkylating agents in the body. Despite the fact that the toxicity, associated with potent alkylating agents, was not seen in our *in vivo* studies, this series of compound was side-lined, believing that they would fail in preclinical trials.

Instead, various esters of the series were prepared to compare directly with acetate **95**. Unfortunately, as seen with the tosylate compound, re-testing of acetate **95** showed that it was not as selective as we first believed. However, a positive result came with the preparation of the pivaloyl derivative **114** (entry 2, Table 2.14.3.5). Increasing the lipophilicity and steric hindrance, by preparing the pivaloyl analogue, resulted in an increase in activity over that of the acetate **95**. Although we are unsure of the precise reasons why it is more active, the compound required more thorough testing, and was subsequently resolved into its enantiomers, following the chemistry highlighted in Scheme 2.14.3.4, by one of my colleagues. The benzoyl analogue **115** (entry 3), also more lipophilic and sterically demanding than the acetate, proved to be less active than the acetate and the pivaloylate.

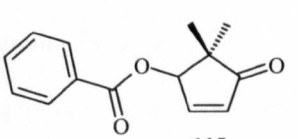
Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	4	100	**95**
2	1	50	**114**
3	10	100	**115**
4	2	100	**116**

Table 2.14.3.5 Biological evaluation of *gem*-dimethyl ester analogues against the Sendai virus

The dansyl derivative **109** and the isatoic derivative **116** were prepared not only for their potentially innate biological activity, but also as potential fluorescent probes in our high throughput screen being developed by the biologists at the time. Neither proved to be particularly interesting regarding their biological activity.



114



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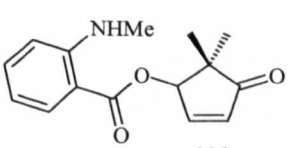


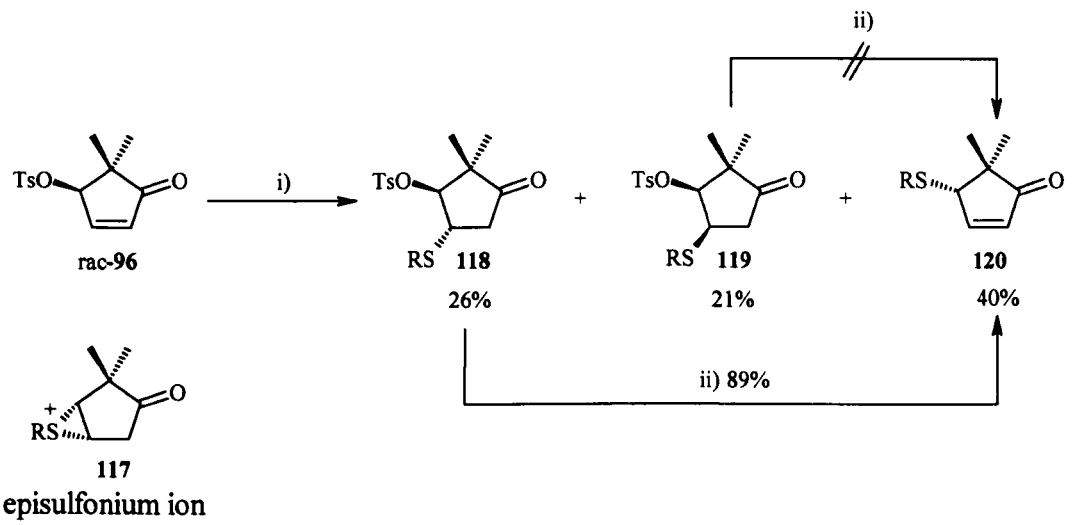
116

2.15 Development of 4-aza-analogues of 33

Work on a new series came about when we established that replacing oxygen for nitrogen, at the 4-position, in the cross-conjugated series of the type exemplified by **32**, was beneficial to activity.

2.15.1 Development of sulfur analogues

Previous work in the group had established that thio-nucleophiles could add into racemic tosylate **96** and rearrange *via* an episulfonium ion intermediate **117**, Scheme 2.15.1.[93]



Scheme 2.15.1: *Reagents*: i) *n*-$C_8H_{17}SH$, DBU, THF, rt, 10 min, ii) DCM, 40 °C, 1-6 h. R=*n*-octyl.

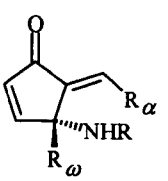
Addition is accompanied by concomitant elimination of *p*-toluenesulfonic acid to yield the desired sulfur analogue **120**, along with *anti*- and *syn*-diastereomeric adducts **118** and **119**. It is interesting to note that the *syn*- and *anti*-diastereomers are produced in almost equal amounts (21% and 26% respectively) despite the presence of the relatively large tosyl group at C-4 to direct the incoming nucleophile. This lack

of selectivity is thought to be due to the presence of the dimethyl groups at C-5 and is discussed later, see Section 2.16.

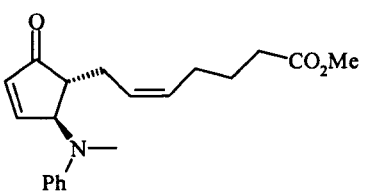
It was also discovered that the *anti*-diastereomer **118** could be converted cleanly into the desired thio-analogue **120**, presumably *via* episulfonium ion intermediate **117**, in an intramolecular S_N2 fashion by heating in dichloromethane. As expected, the *syn*-diastereomer **119** did not rearrange, due to the *syn*-orientation of the participating groups. Based on the isolation of **118** and **119**, and the fact that the ring system is a classical neopentyl system, incapable of undergoing standard S_N2 displacement,[94] we were confident that the mechanism is as shown *i.e. via* the episulfonium ion **117**.

2.15.2 Amino-prostaglandin analogues

We were further encouraged by the discovery that 12-amino alkylidenecyclopentenone prostaglandins **121**, developed by Florent *et al.*, exhibited highly potent biological activities.[95]



121



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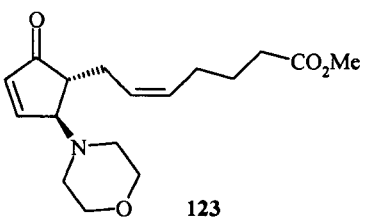


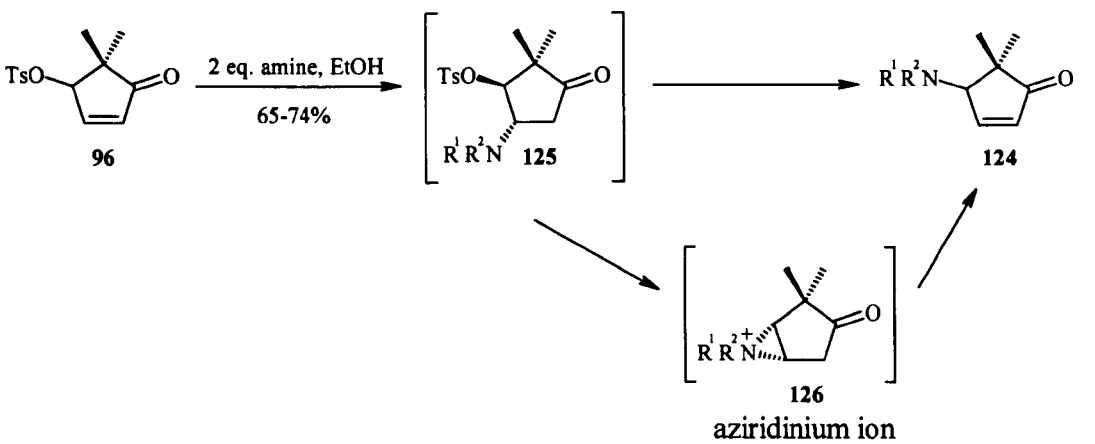
123

More importantly however, were the compounds of the Glaxo group, whereby 4-amino cyclopentenones possessing a prostaglandin side-chain at the 5-position were prepared as prostaglandin analogues, and subsequently patented **122** and **123**.[96] With

structures so similar to our dimethyl compounds we again felt confident of biological activity from this series.

2.15.3 Synthesis of 4-amino-5,5-dimethyl-cyclopentenones

Starting from racemic tosylate **96**, we set out to prepare three analogues to test the biological activity of this series. Initial experiments to prepare the amino analogues, following the methodology developed in the sulfur-series, whereby two equivalents of the amine and the tosylate **96** were heated under reflux in dichloromethane, failed to isolate the desired 4-amino compound **124**. However, changing to ethanol as solvent successfully afforded the rearranged product, *via* the aziridinium ion **126**, in good yields (65-74%), Scheme 2.15.3.

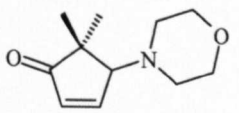


Scheme 2.15.3

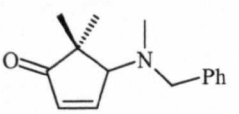
It is believed that the mechanism again follows an intramolecular S_N2 reaction pathway *via* the aziridinium ion **126**, since we were able to isolate the amino 1,4-conjugate adduct **125**; it is known that intermolecular nucleophilic addition is usually extremely difficult on such a neopentyl system.[94] The structure of the conjugate-adduct, **125**, was assigned due to the disappearance of the starting material alkene

signal at δ_H 6.27 ppm. (C(2)H) in the ^{1}H NMR (250 MHz) and the shifting of the *H*-C-4 signal to 4.94 ppm. and transforming to a doublet with a coupling constant reminiscent of an *anti*-relationship (*J* 8.2 Hz). We attempted to render the enone incapable of undergoing 1,4-conjugate additions to show that the intermolecular S_N2 pathway is not viable. However, protection of the carbonyl in **96** as its acetal, or reduction of it to the alcohol failed.

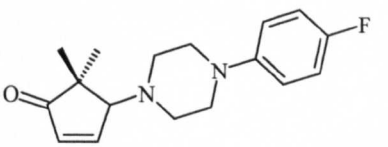
The three analogues prepared using the chemistry depicted in Scheme 2.15.3 are shown below.



127



128



129

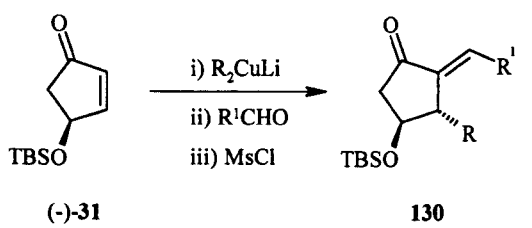
Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	1	50	**96**
2	25	>500	**127**
3	12	100	**128**
4	20	100	**129**

Table 2.15.3 Biological evaluation of 4-amino analogues of **96** against the Sendai virus

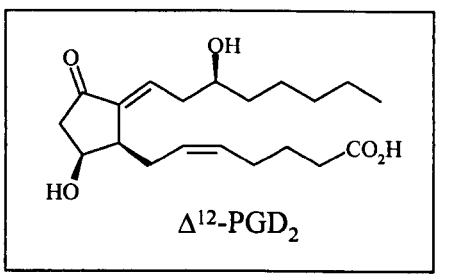
Unfortunately, when compared to the racemic tosylate **96** (entry 1, Table 2.15.3) the 4-amino analogues were significantly less active, but once again this is accompanied by a lack of toxicity. So it seems that, for this series of compounds, it really is the nucleofugacity of the group at the 4-position which conveys the activity.

2.16 Synthesis of dimethyl-PGD analogues

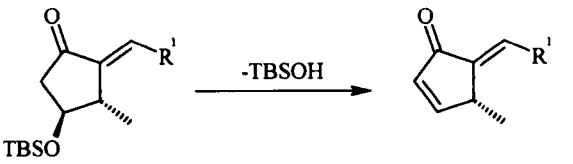
The next series of compounds developed intended to exploit the activity of the prostaglandins of the D-series. Work within the group had shown that following the 3-component coupling approach developed by Noyori (Section 1.3.2), Δ^{12}-PGD_2 analogues could be prepared from (-)-**31** that exhibited excellent anti-viral activity against the Sendai virus.



(-)-**31** **130**



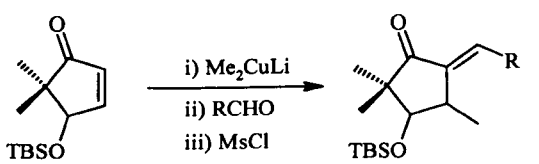
It was hoped that the *exo*-cyclic carbon-carbon double bond in **130** might provide the electrophilic enone necessary to accept the thiol nucleophile of our target IKK. We also believed, having gained significant experience of the chemistry of 4-silanyloxy cyclopentenones, that the 4-silanyloxy group may eliminate in the test conditions giving rise to PGJ-analogues. Thus, the activity may in fact be stemming from this elimination and the generation of the more active cross-conjugated cyclopentenone **131**, whilst the side-chains would convey the desired selectivity. Regardless of the mechanism involved, analogues of the type exemplified by **130** showed excellent activities in our assays.



130 R=Me **131**

As a result, we postulated that the activity would diminish if similar derivatives of **132** were prepared. Such derivatives, for example **133** and **134**, would be unable to eliminate the 3-silanyloxy group and perhaps the activity would not be as pronounced, and the compounds, therefore, be more selective.

In the event, utilising the chemistry developed within the group, two dimethyl analogues **133** and **134** were prepared to test this hypothesis. The silicon-protected starting material **132** was prepared using the chemistry developed for the dimethyl compounds and access into the dimethyl-PGD analogues was achieved *via* addition of a methyl cuprate (generated from the reaction of methyl lithium and copper(I) iodide in diethyl ether at 0 °C) into **132**. Isobutyraldehyde or benzaldehyde were added to the enolate, generated from the cuprate addition, following the addition of an ethereal solution of zinc chloride. Elimination of the crude alcohol was achieved using methanesulfonyl chloride to obtain the desired compounds **133** and **134** as a mixture of *syn*- and *anti*-diastereomers (26-34%).



132

133 R=*i*-Pr, 26%
134 R=Ph, 34%

Initially, it was uncertain if these two compounds were geometric isomers ((*E*) and (*Z*)) or diastereoisomers (*syn* and *anti*). Thus, in a test experiment, the reaction was split into two steps. It was found that after the addition of the cuprate, followed by aqueous work-up, a mixture of diastereomers (ca. 3.5:1, *anti*:*syn*) was obtained whereby the methyl group had added non-specifically into the enone system of **132**. Interestingly, only the *anti*-diastereomer is observed in the identical reaction with **31**. Therefore, upon observing this mixture in the dimethyl system, and further elaborating it to the final mixture of diastereomers (LDA, isobutyraldehyde, THF, -78 °C, with spontaneous dehydration upon warming to room temperature) we confirmed that products **133** and **134** were in fact mixtures of *syn*- and *anti*-diastereomers. The geometry of the double bond was assigned by comparison of the new compounds to analogous compounds using the chemical shift of the olefin proton as a guide.

It is believed that the presence of the two methyl groups in **132** causes perturbations in the cyclopentenone ring system. The incoming cuprate nucleophile is hindered by the silanyloxy group on one face and one of the methyl groups on the other thus giving rise to the mixture of diastereomers. The two products, **133** and **134**, were tested for activity as different diastereomeric ratios (ca. 4.5:1 for **133** and ca. 29:1 for **134**). The reason is that the compounds were purified by column chromatography to different extents; of course the *syn*/*anti* ratio is fixed by the addition of the methyl cuprate into **132** in the first step.

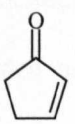
Entry	ID_{50} (μM)	TD_{100} (μM)	Compound
1	30	500	**133**
2	15	50	**134**

Table 2.16 Biological evaluation of PGD-analogues, **133** and **134**, against the Sendai virus

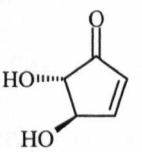
Interestingly, compounds **133** and **134** did not display the desired activity (Table 2.16), possibly because we prevented the ability for the 3-silanyloxy group to eliminate due to the inclusion of the methyl groups, suggesting that it is the eliminated, cross-conjugated system (type **131**) which conveys the activity.

2.17 Synthesis of a naturally occurring cyclopentenone NF-κB inhibitor

All lead compounds described to this point are very lipophilic, possessing high cLog P values; as a result they would be suitable only for topical applications. Thus, we desired to develop a series of compounds which would allow us to access more polar, hydrophilic molecules which may result in an increase in oral bioavailability.

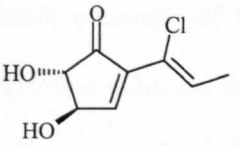


30

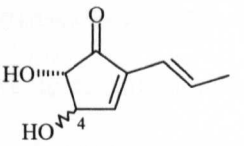


135

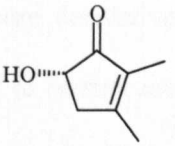
It has also been reported that cyclopentenone **30**[51] (*vide supra*) and the dihydroxy compound **135**[97-99] activate HSF and/or inhibit NF-κB with weak to modest potency, respectively. More recently, in their search for new inhibitors of the IL-6-mediated signal transduction in HepG2 cells, using secreted alkaline phosphatase (SEAP) as reporter gene, Erkel *et al.* isolated four novel compounds, **136** to **139**, from fermentations of the ascomycete strain A23-98.[100, 101]



136



137



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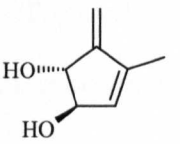


139

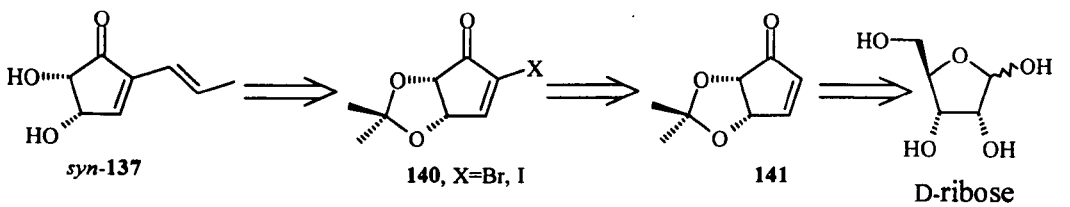
Amongst other things, cyclopentenones **136** and **137** were shown to inhibit NF-κB with IC_{50} values of 10-15 μM and 50-100 μM respectively. It was also suggested that these cyclopentenones inhibit the NF-κB pathway by preventing the phosphorylation and degradation of the IκBα protein, in the same manner as the cyclopentenone prostaglandins.[100]

Based on this evidence, we desired to synthesise **137**, to prove the structure and identify the absolute stereochemistry, and also to determine its activity in our assays. Compound **137** was isolated as a mixture of diastereomers, epimeric at C-4, and although the relative stereochemistry was determined by comparison with similar natural products,[102] the absolute stereochemistry was undetermined.

2.17.1 Retrosynthesis of the syn-diastereomers of 137

It was envisaged that the synthesis of these natural products could be achieved using palladium chemistry to incorporate the side-chain *via* the coupling of a suitably derived cyclopentenone and a geometrically pure derivative of the side-chain.

Thus, retrosynthetic cleavage of the sp^2-sp^2 carbon-carbon bond, Scheme 2.17.1, would result in **140** and indicates the need, therefore, to acquire a suitable preparation of stereochemically pure 4,5-dihydroxycyclopentenones, such as **141**, as well as a geometrically pure derivatives of the side-chain. The cyclopentenone ring system would also need to be successfully halogenated at the α-position (**140**, X=Br, I), ready for its palladium-catalysed coupling to the side-chain.



Scheme 2.17.1

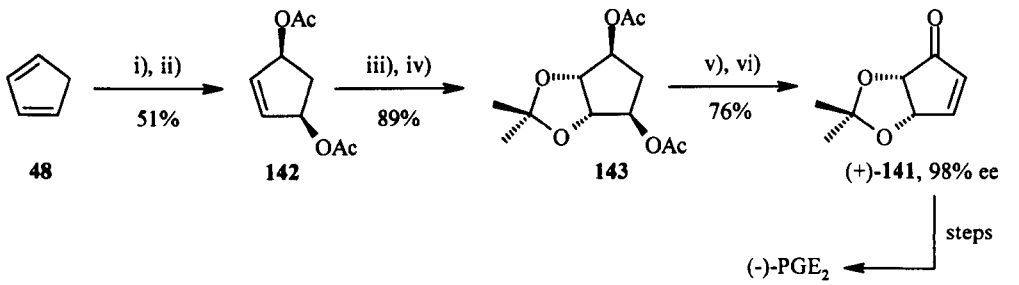
*2.17.2 Methods for the synthesis of the syn-diol cyclopentenone ring system of **141***

*2.17.2.1 Johnson's method for the synthesis of **141***

Various methods exist in the literature for the preparation of the protected *syn*-diol cyclopentenone moiety **141** in both enantiomeric forms.[103-110] For example, Johnson and co-workers developed a photochemical method for the synthesis of **141** during their synthesis of (-)-PGE_2.[103]

First, photochemical oxidation of cyclopentadiene **48** with singlet oxygen, followed by protection of the resulting *syn*-diol, with acetic anhydride and pyridine, generated the *bis*-acetoxy compound **142** (51%). Diastereoselective dihydroxylation of **142**, and orthogonal protection of the diol as its acetonide, generated **143**, in 89% yield for the two steps. Finally, the desired chiral cyclopentenone (+)-**141** was accessed *via* a two-step, enzyme catalysed desymmetrisation with electric eel acetylcholinesterase,

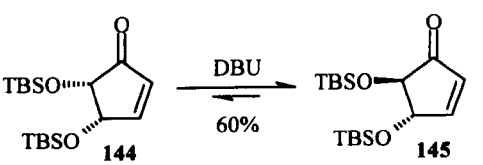
followed by oxidation using Jones reagent (CrO_3, H_2SO_4) with concomitant acetate elimination. Scheme 2.17.2.1.



Scheme 2.17.2.1: *Johnson's synthesis of (-)-PGE$_2$ - Reagents*: i) O_2, *hv*, rose bengal, thiourea, MeOH, ii) Ac_2O, pyridine, DMAP, DCM, iii) 1 mol % OsO_4, Me_3NO, THF, acetone, iv) acetone, catalytic TsOH, v) electric eel acetylcholinesterase, H_2O, vi) CrO_3, H_2SO_4, acetone.

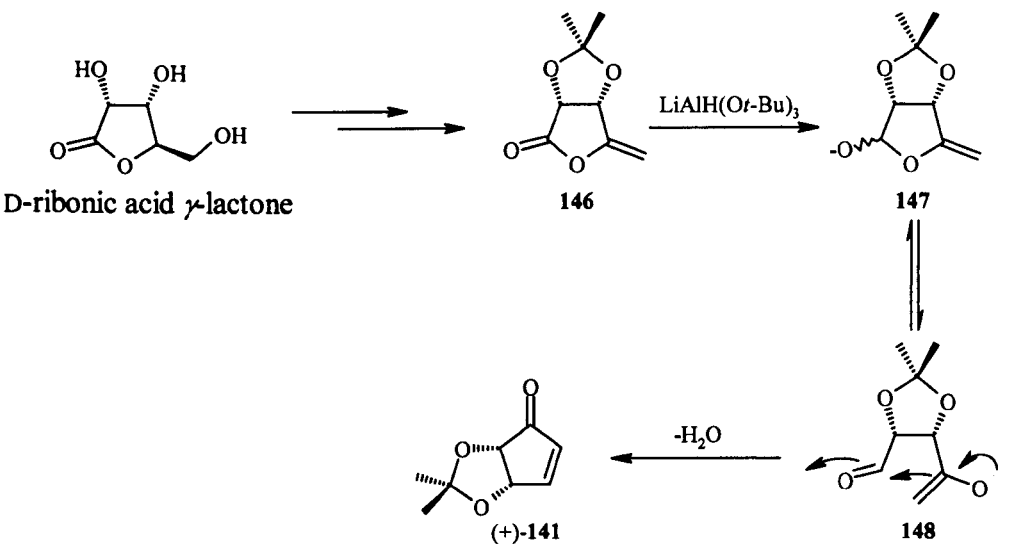
Johnson then successfully took (+)-**141** and elegantly transformed it into (-)-PGE_2 *via* a three-component coupling reaction, similar to Noyori's protocol, but cleverly lacking the problem of enolate equilibration mentioned in Section 1.3.2.

Johnson has modified his protocol to allow access into the 4,5-*anti*-diol system of **145**.[104] This modification takes the *bis*-protected *syn*-diol system of **144**, which upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane affords the α'-epimerised product. Such a reaction could serve to generate the *anti*-diastereomer, *anti*-**137**, of the natural product in our target synthesis.



*2.17.2.2 Prasit's method for the synthesis of **141***

A second approach, developed by Prasit, commences from D-ribonic acid γ-lactone and relies on its derivatisation to enol lactone **146**, and the subsequent rearrangement of **146** to cyclopentanone aldol products, Scheme 2.17.2.2.[105] Thus, reduction of enol lactone **146**, to the lactol **147**, allows ring-opening to occur, generating an electrophilic aldehyde and an enolate **148**. Intramolecular aldol condensation of this reactive species then gives rise to the desired product (+)-**141**.

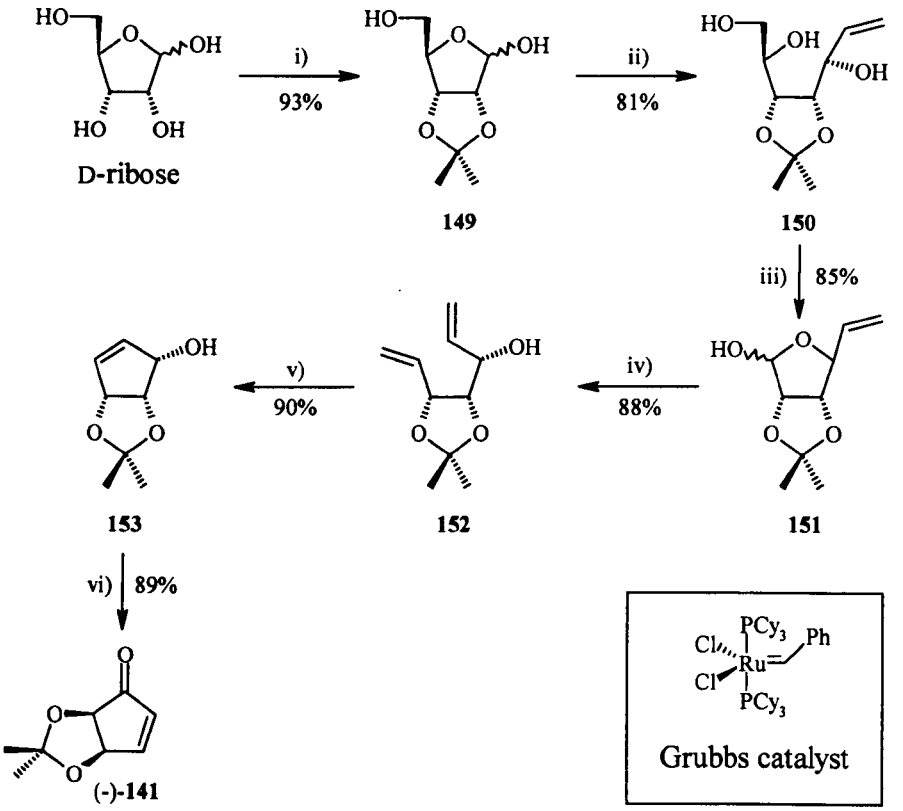


Scheme 2.17.2.2

*2.17.2.3 Jeong's method for the synthesis of **141***

Other carbohydrate-based syntheses of **141** utilise ring-closing metathesis as a key step to generate the cyclopentene ring.[106-108] Two such methods have been the focus of Jeong's research group, and in 2002 the group developed a new and improved synthesis of both enantiomers of **141** starting from a common starting material, namely D-ribose.[107, 108] The elegance of the stereodivergent synthesis developed by Jeong *et al.* was attractive to us since it would allow us to access both enantiomers of

our target **137** and their analogues, and hopefully help to confirm the absolute stereochemistry of the natural products.



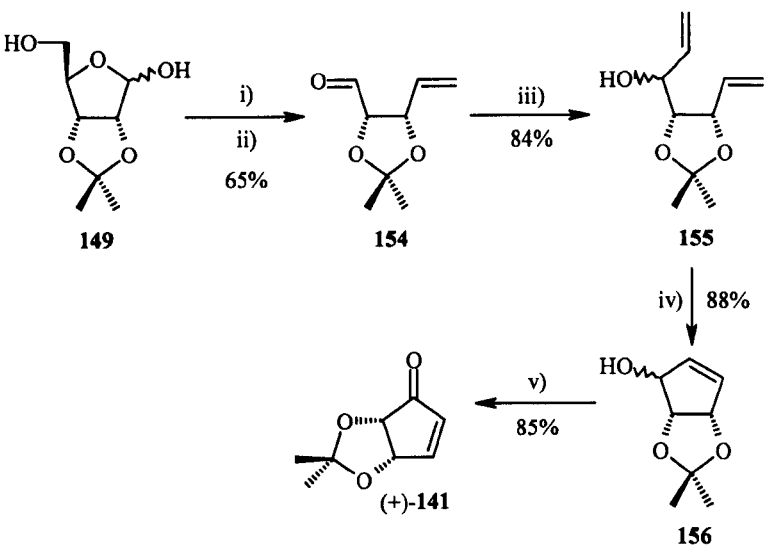
Scheme 2.17.2.3.1: *Reagents*: i) acetone, H_2SO_4, ii) vinylmagnesium bromide, THF, -78 °C, iii) $NaIO_4$, DCM, H_2O, iv) NaH, DMSO, CH_3PPh_3Br, THF, v) Grubbs' catalyst, $CHCl_3$, vi) MnO_2, DCM.

Jeong's approach begins with the protection of D-ribose to generate acetonide **149** in excellent yield (93%). Treatment of **149** with vinylmagnesium bromide, in tetrahydrofuran at -78 °C, gave triol **150** (81%), which was followed by oxidative cleavage of triol **150** with sodium periodate to give lactol **151** in 85% yield, Scheme 2.17.2.3.1.

Wittig reaction of **151** utilising the ylide generated from methyltriphenylphosphonium bromide and Corey's dimsyl anion (sodium hydride, dimethyl sulfoxide) produced

diene **152** in 88% yield. Ring-closing metathesis of diene **152** using Grubbs' first generation catalyst, gave allylic alcohol **153** (90%), which was converted into the cyclopentenone (-)-**141** in an overall yield of 45% from D-ribose.

Interestingly, reversing the order of addition of the Grignard and Wittig steps, allows access to the mirror image of (-)-**141**. Thus, commencing with a Wittig reaction on **149** (in this case using the ylide generated from methyltriphenylphosphonium bromide and potassium *t*-butoxide), followed by oxidative cleavage of the resulting diol with sodium periodate, afforded olefin **154** in 65% yield for the two steps.

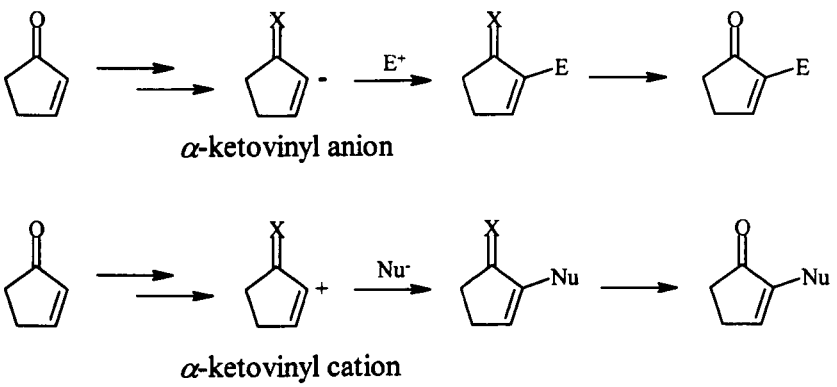


Scheme 2.17.2.3.2: *Reagents*: i) *t*-BuOK, CH_3PPh_3Br, THF, ii) $NaIO_4$, DCM, H_2O, iii) vinylmagnesium bromide, THF, -78 °C, iv) Grubbs' catalyst, $CHCl_3$, v) MnO_2, DCM.

Vinylmagnesium bromide in tetrahydrofuran at -78 °C converted aldehyde **154** into the diene **155** (84%), which was subjected to ring-closing metathesis, followed by oxidation to give cyclopentenone (+)-**141** in 38% yield from D-ribose (Scheme 2.17.2.3.2).

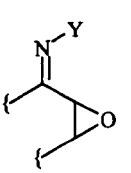
2.17.3 α-Substitution of cyclic α,β-unsaturated cyclopentenones

In a review by Amri, the synthetic methods utilised to obtain α-substituted cyclic enones is discussed.[111] Various methods are mentioned using the α-carbon of the cyclopentenone ring as latent anions or cations, along with named reactions, such as the Baylis-Hilman reaction, for the successful elaboration of the cyclic enones into α-substituted cyclic enones, Scheme 2.17.3.



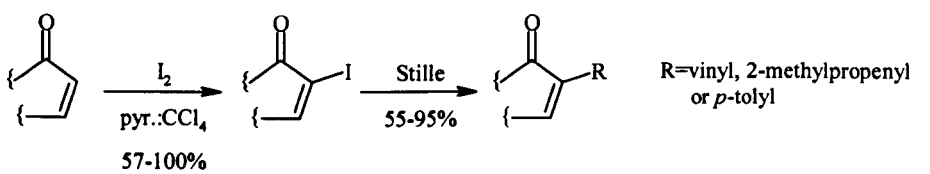
Scheme 2.17.3

However, such an approach is hampered by the fact that the intermediate α-keto ion equivalents are actually oximes **157**, tosylhydrazones **158** or *N,N*-dimethylhydrazones **159**, and thus in order to prepare the intermediate ionic equivalents above, prior derivatisation of the ring system is needed. Not only that, but such a strategy is only amenable for the preparation of analogues whose α-side-chain can be derived from an electrophilic or nucleophilic partner.



157 Y=OH
158 Y=NHTs
159 Y=NMe_2

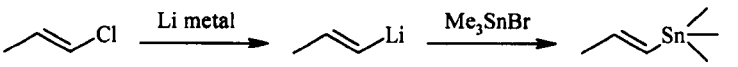
However, in our retrosynthetic analysis, Scheme 2.17.1, we postulated that α-substitution would occur, by way of α-halogenation, followed by palladium-catalysed coupling, in order to install the desired side-chains, both of the natural compounds and their analogues. Literature precedent pinpoints the poor reactivity of α-bromocyclopentenones in the palladium-catalysed Stille reaction.[112] Thus, as a result, Johnson has developed a method for the α-iodination of cyclic enones and their subsequent derivatisation in the Stille reaction in excellent yields.[113, 114]



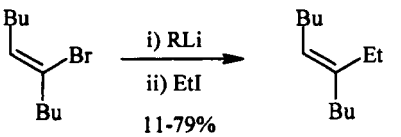
With the successful methodologies developed by Jeong and Johnson, for the preparation of cyclopentenone **141**, its iodination and subsequent derivatisation in the Stille reaction, we felt confident of developing an efficient synthesis to our chosen target **137**. All that remained was to synthesise, in a stereospecific manner, the alkenyl stannane that would become the target's side-chain.

2.17.4 Synthesis of geometrically pure alkenyl stannanes

The preparation of propenyl tin derivatives is described only sparsely in the chemical literature. However, Seyferth and Vaughan have reported on the successful isolation of both *cis*- and *trans*-propenyltrimethyl tin compounds, by the reaction of isomerically pure *cis*- and *trans*-propenyllithium reagents (obtained from the reaction of lithium with *cis*-1-bromopropene and *trans*-1-chloropropene respectively) with trimethyltin bromide.[115]



In a later report, Miller *et al.* investigated the effect of alkyllithium reagents on the alkylation of mono- and disubstituted vinyl bromides, for example, *cis*-5-bromo-5-decene, *via* halogen-metal exchange.[116]



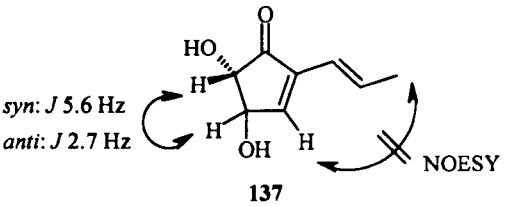
Thus, it was hoped that, following the work of Seyferth and Vaughan or by using *n*-tributyltin chloride, instead of ethyl iodide, as the alkylating agent in Miller's work, we could access the desired stannanes. Recently, the subject of sp^2 organometallic derivatives has been reviewed by Marek.[117]

2.18 Synthesis of a natural cyclopentenone isolated from ascomycete strain A23-98

2.18.1 Synthesis of the syn-diastereomers of 137

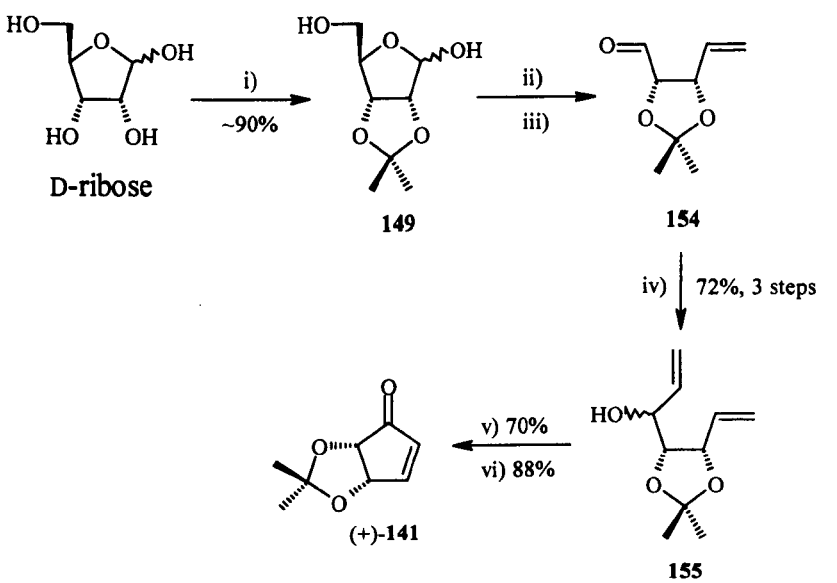
The structure of **137** has been proposed based only on NMR evidence.[101] The NMR evidence regarding the geometry of the *exo*-cyclic alkene unit in **137** was based on the *lack* of a NOESY correlation between the β-proton in the ring and the methyl group. The overlapping nature of the peaks in the ^1H NMR spectrum, corresponding to the protons in the side-chain, precluded the use of coupling constants to determine its geometry. Comparison of the coupling constant, $J_{4,5}$, for both *syn*- and *anti*-diastereomers, against structurally similar compounds, synthesised from the

chiral pool,[102] allowed the relative stereochemistry of the diol moiety to be determined, although the absolute stereochemistry was not determined.



137

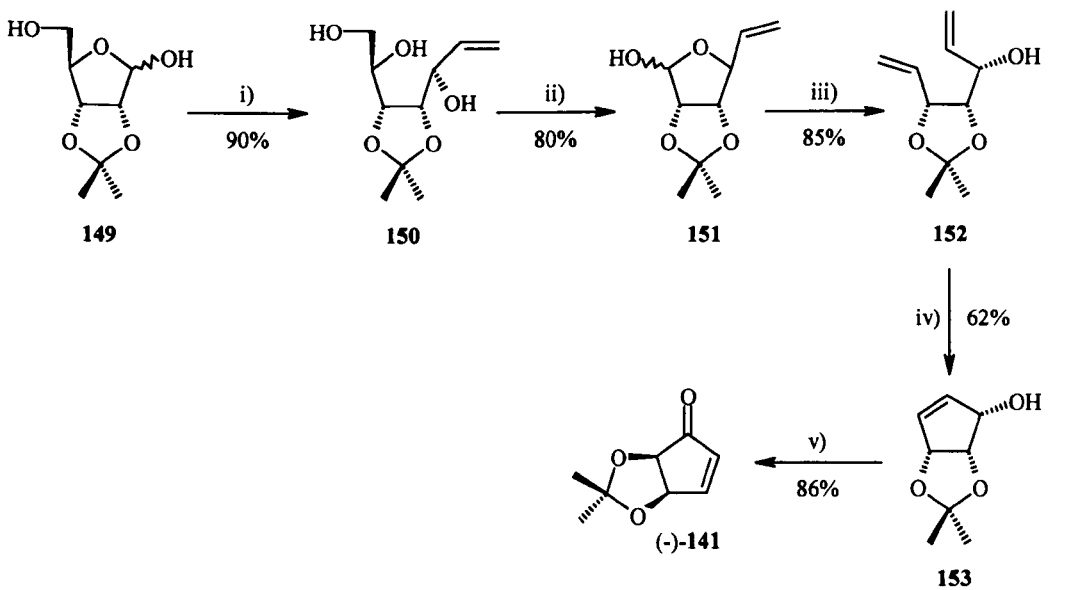
Our synthesis of *syn*-**137** began with the preparation of the chiral cyclopentenone nucleus (+)-**141**, based on the work of Jeong *et al.*,[107] in an overall yield of 40% from D-ribose. Thus, in the event, Scheme 2.18.1.1, a Wittig reaction is carried out on protected ribose **149** followed by sodium periodate cleavage of the resulting diol, to generate **154**.



Scheme 2.18.1.1: *Reagents*: i) acetone, H_2SO_4, ii) *t*-BuOK, CH_3PPh_3Br, THF, iii) $NaIO_4$, DCM, H_2O, iv) vinylmagnesium bromide, THF, -78 °C, v) Grubbs' catalyst, $CHCl_3$, vi) PDC, DCM.

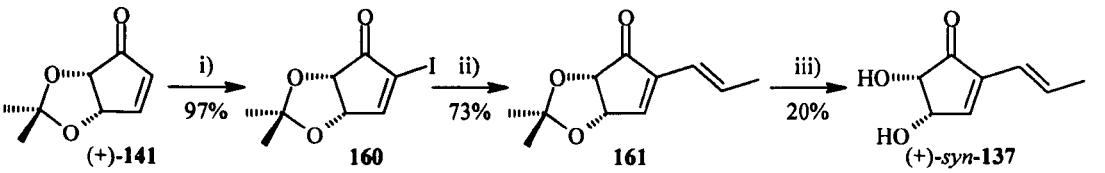
Grignard addition to the newly formed aldehyde **154**, using vinylmagnesium bromide, in tetrahydrofuran at -78 °C, then provided the *bis*-alkene **155** in 72% over the three steps. Subsequent ring closing metathesis of **155** and oxidation with pyridinium dichromate in dichloromethane, then gave a single enantiomer of cyclopentenone (+)-**141**.

Conversely, starting with the Grignard reaction (Scheme 2.18.1.2) gives rise to the other enantiomer, (-)-**141**, as shown, in an overall yield of 29% from D-ribose.



Scheme 2.18.1.2: *Reagents*: i) vinylmagnesium bromide, THF, -78 °C, ii) $NaIO_4$, DCM, H_2O, iii) NaH, DMSO, CH_3PPh_3Br, THF, iv) Grubbs' catalyst, $CHCl_3$, v) PDC, DCM.

Enone (+)-**141** underwent α-iodination to generate **160** in an excellent yield of 97%, following the work of Johnson.[113]



Scheme 2.18.1.3: *Reagents*: i) I_2, pyridine:CCl_4, ii) $(PhCN)_2PdCl_2$, CuI, $AsPh_3$, (*E*)-tributylpropenyl stannane, iii) PPTS, MeOH.

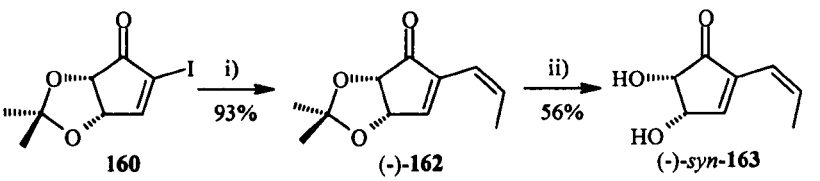
The preparation of *trans*-alkene **161**, *via* a palladium-catalysed Stille reaction[114] between vinyl iodide **160** and (*E*)-tributylpropenyl stannane (generated from the reaction between *trans*-1-bromopropene, *n*-tributyltin chloride and *t*-butyl lithium at -78 °C, in a manner similar to Miller)[116] resulted in a crude mixture of the protected, proposed natural product **161** (73%). It soon became evident however, that the NMR data of the acetonide protected product did not agree with those data reported for the natural compound.[101] The ^{1}H NMR spectrum of **161** showed two distinct signals for the *exo*-cyclic alkene protons in contrast to the literature data for the natural compound which stipulated these protons produced an AA' spin system centred at 6.05 ppm.[101]

Deprotection of the acetonide was, therefore, undertaken with pyridinium *p*-toluenesulfonate in methanol, albeit in a poor (20%) yield, and it was confirmed that the geometry of the double bond in the natural product was not *trans* as reported.[101] Therefore, in order to prove the structure of the natural product, and assess its biological activity, the *cis*-isomer was prepared by modifying the synthetic route already established.

2.18.2 Synthesis of the cis-isomer, (-)-syn-163

Stille coupling of **160** with (*Z*)-tributylpropenyl stannane (generated *via* hydrozirconation of *n*-tributyl(propynyl)stannane in tetrahydrofuran)[118] proceeded in

a gratifying ~75-93% yield, the yield depending on the purity of the stannane, Scheme 2.18.2.1. Deprotection with pyridinium *p*-toluenesulfonate in methanol gave the desired natural product *syn*-**163** in 50% overall yield from (+)-**141**; the ^{1}H NMR spectrum of (-)-*syn*-**163** was identical to that described for the natural compound. To illustrate the point, the distinctive alkene signals for (-)-*syn*-**163** and (+)-*syn*-**137** are shown in Figure 2.18.2.1. The structure of (-)-*syn*-**163** was confirmed by X-ray crystallography after its recrystallisation from methanol, Figure 2.18.2.2.



Scheme 2.18.2.1: *Reagents*: i) $(PhCN)_2PdCl_2$, CuI, $AsPh_3$, (*Z*)-tributylpropenyl stannane, ii) PPTS, MeOH.

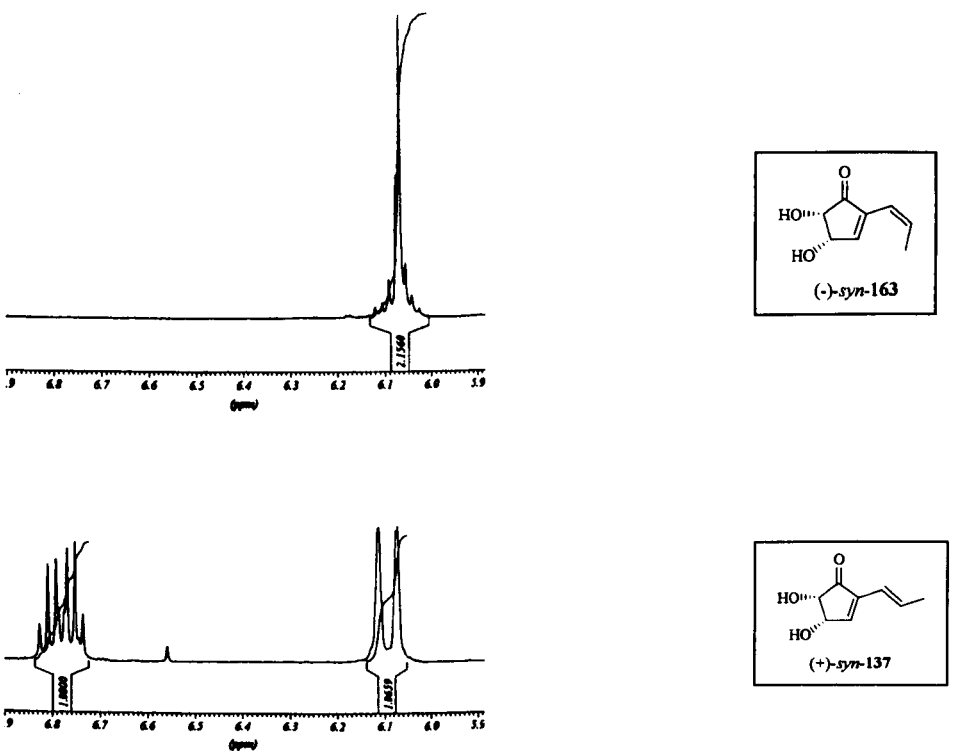
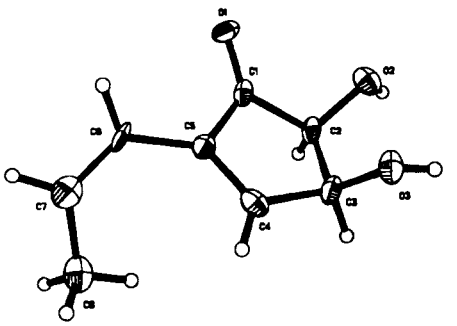
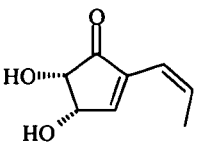


Figure 2.18.2.1: Comparison of the olefinic region of the ^{1}H NMR of *cis*- and *trans*-isomers *syn*-**163** and *syn*-**137**.



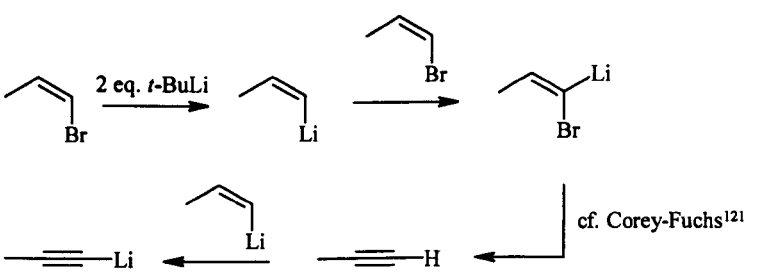


(-)-*syn*-**163**

Figure 2.18.2.2: X-ray crystal structure of (-)-*syn*-**163**

2.18.3 Stannane purity

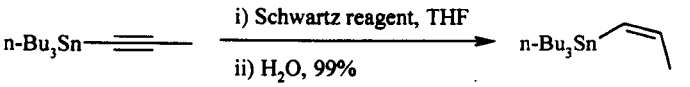
Using isomerically pure stannanes, almost quantitative yields can be obtained in this Stille reaction. However, when using *t*-butyl lithium/*n*-tributyltin chloride and *cis*-1-bromopropene to prepare the (*Z*)-stannane, following the procedure of Miller,[116] large amounts of *n*-tributyl(propynyl)stannane were formed (see proposed mechanism, Scheme 2.18.3).[119] The increased rate of transmetallation of alkynylstannanes over alkenylstannanes under the conditions of the Stille reaction, therefore, gives rise to lower yields of the desired product.[120]

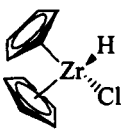


Scheme 2.18.3

Unfortunately, the similarity in boiling points and polarity makes the alkenyl and alkynyl stannanes inseparable by distillation or chromatography. If, however, Grignard methods are employed for the preparation of the stannane, the

propynylstannane is not formed, but isomeric mixtures are obtained, again leading to lower yields of the desired product in the subsequent Stille reaction.[117] Thus, to obtain isomerically pure (*Z*)-stannanes, and high yields for the Stille reaction, hydrozirconation of *n*-tributyl(propynyl)stannane, using Schwartz reagent must be employed.[118]



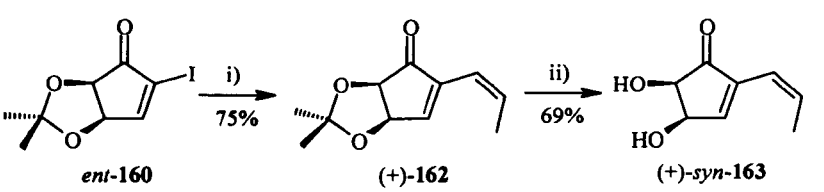


Schwartz reagent

It has been stipulated by Seebach that such a rearrangement can be prevented using two equivalents of *t*-butyl lithium at -120 °C in the Trapp-solvent mixture (THF:Et_2O:pentane, 4:1:1).[122] However, such a reaction did not provide the desired geometrically pure stannanes in our hands, the compound being contaminated with the rearranged product.

2.18.4 Synthesis of (+)-syn-163

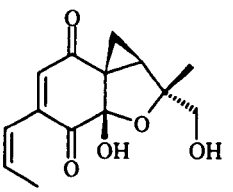
In the second phase of the work, we prepared (+)-cyclopentenone **163** from *ent*-**160**, using the same methodology, in an overall yield of 52%, Scheme 2.18.4.



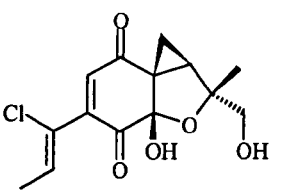
ent-**160** (+)-**162** (+)-*syn*-**163**

Scheme 2.18.4: *Reagents*: i) $(PhCN)_2PdCl_2$, CuI, $AsPh_3$, (*Z*)-tributylpropenyl stannane, ii) PPTS, MeOH.

Interestingly, by way of an analogy, Smith *et al.* have shown that the alkenyl side-chain of dechloromikrolin **164** possessed a (*Z*)-alkene unit and not an (*E*)-alkene side-chain as predicted by NMR studies and correlation with mikrolin **165**. This led to a revision of the proposed biosynthetic pathway, in particular the step at which chlorination took place.[123]



164



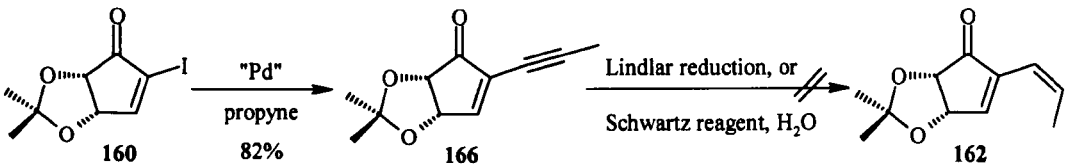
165

*2.18.5 Attempted reduction of alkyne **166***

Having now prepared the dechloro natural product and discovering that it possessed a *cis*-side-chain we realised that this structural feature may also be achieved *via* hydrogenation of a Sonogashira-coupled alkyne product such as **166**. Likewise, hydrozirconation of the alkyne **166** may also lend itself to a zirconated intermediate with which to install the chlorine atom of **136**, and thus develop a synthesis to both the chloro- and dechloro-natural products from a common, late-stage intermediate.

In the event, it was found that vinyl iodide **160** easily underwent a palladium catalysed Sonogashira coupling with propyne to afford the alkynyl product **166**, in excellent yield (82%).[124] Unfortunately, treatment of this product with Lindlar's catalyst (palladium, 5 wt. % on calcium carbonate, poisoned with lead)[125] failed to reduce the side-chain, resulting only in recovered starting material. Similarly, treatment of **166** with Schwartz reagent only succeeded in reducing the carbonyl

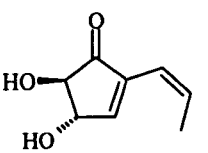
group of the enone.[118] However, alkyne **166** did provide us with a novel compound with which to probe structure activity relationships, Scheme 2.18.5.



Scheme 2.18.5

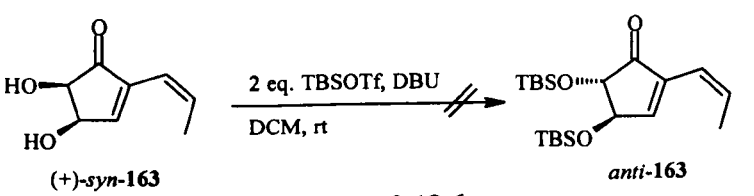
2.18.6 Synthesis of (+)-anti-163

In view of the revision of the structure of the natural product, we changed our second target structure to that of the *anti*-diol, *anti*-**163**, Scheme 2.18.6.4.



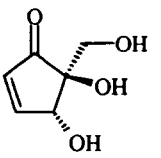
(+)-*anti*-**163**

Initial attempts at α'-epimerisation of the *cis*-isomer *syn*-**163**, *via bis*-silyl ether formation following the procedure of Johnson,[104] proved fruitless, Scheme 2.18.6.

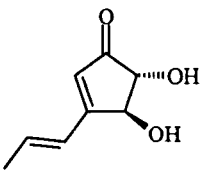


Scheme 2.18.6

The *anti*-diol moiety seen in **136** and *anti*-**137** is known in the chemical literature; most notably it is found in the *epi*-pentenomycin skeleton[126] and terrein.[127-129]



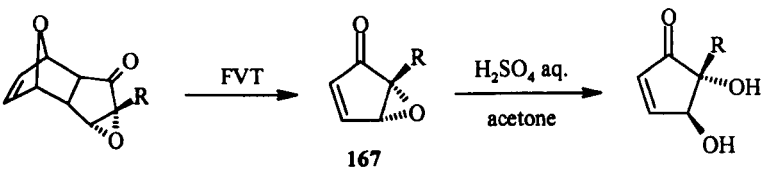
epi-pentenomycin I



terrein

2.18.6.1 Zwanenburg's synthesis of the anti-diol ring system

Along with these natural *anti*-diol compounds are the numerous approaches to this ring system as useful synthetic intermediates to a whole host of natural products. Zwanenburg has developed a method based on the transformations of cyclopentadienone epoxides **167**, and has shown their derivatisation to selected *anti*-diol intermediates, such as the *epi*-pentenomycins.[127]

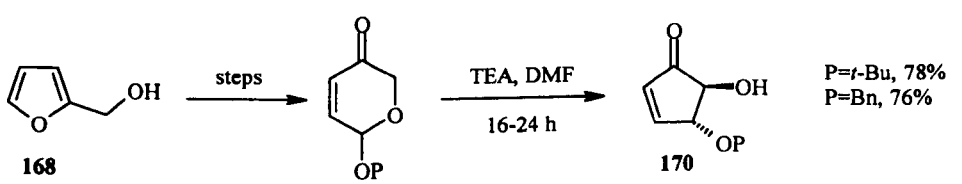


167

epi-pentenomycin
R=CH_2OH

2.18.6.2 Caddick's synthesis of the anti-diol ring system

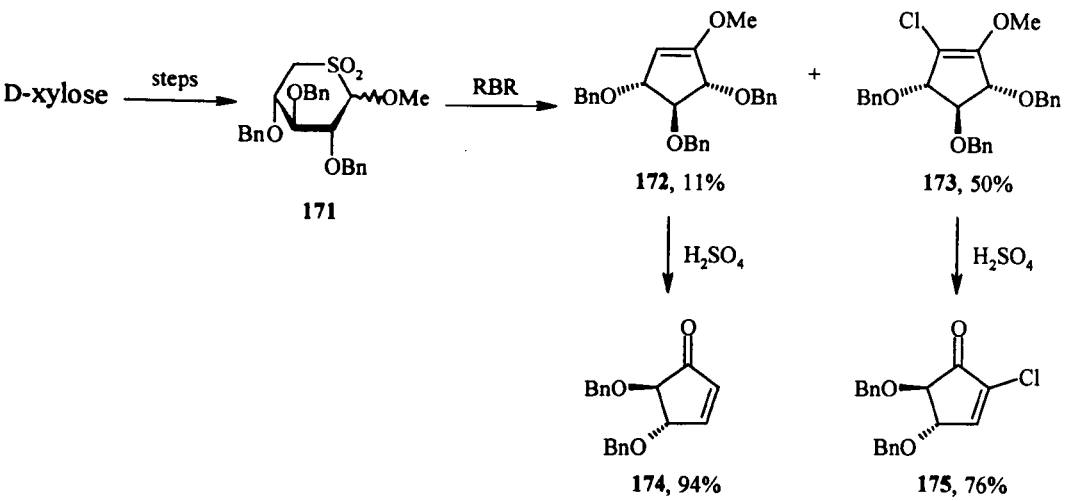
Yet another approach is that of Caddick *et al.* whereby pyranone **169**, generated from furfuryl alcohol **168**, is converted to the racemic *anti*-diol ring system of **170** under basic reaction conditions.[130-133]



168 **169** **170**

2.18.6.3 Taylor's synthesis of the anti-diol ring system

Finally, Taylor has shown that pentose and hexose sugars, for example D-xylose, can be converted into cyclopentenones **174** and α-chlorocyclopentenones **175** utilising the Ramberg-Bäcklund rearrangement of thiosugar-derived sulfones, **171**.[134]



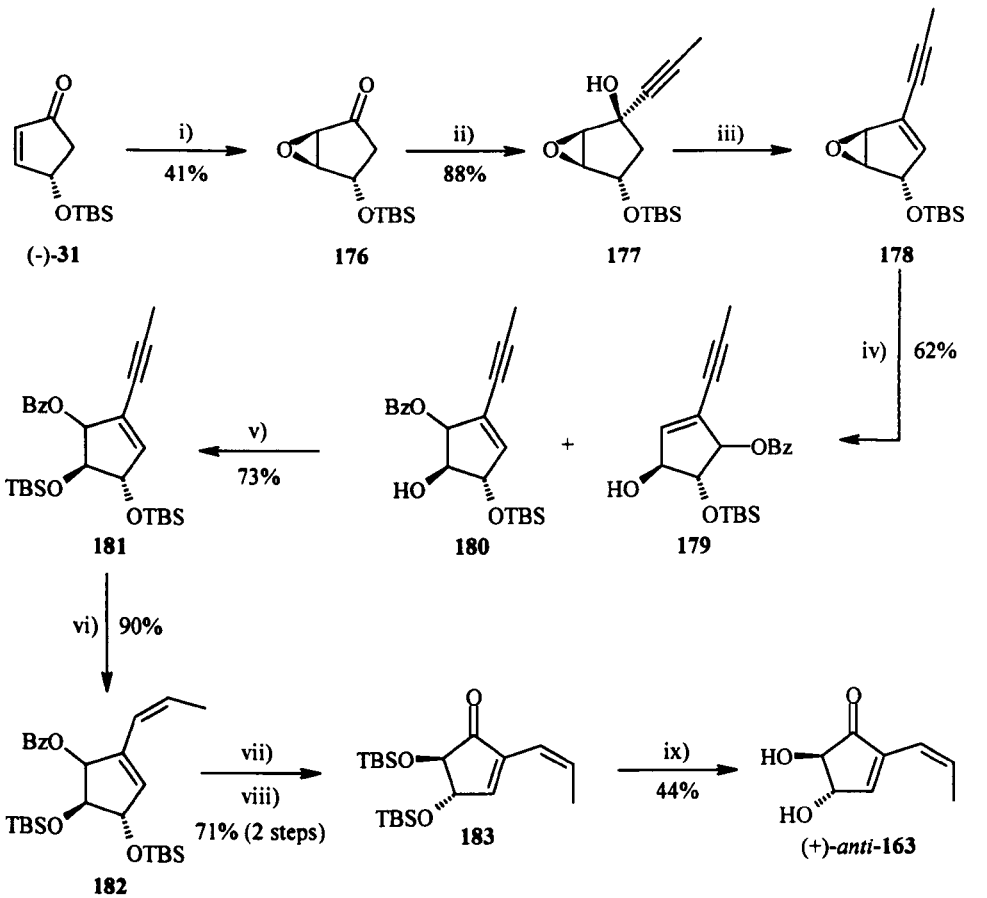
*2.18.6.4 Takahashi's approach towards the anti-diol ring system and the synthesis of anti-**163***

The method developed by Takahashi and co-workers for their new approach to nine-membered enediynes was ideally suited to apply to the synthesis of *anti*-**163**.[135-137]

Our synthesis, outlined in Scheme 2.18.6.4, commences with (*S*)-4-(*tert*-butyldimethylsilanyloxy)-cyclopent-2-enone (-)-**31**, and uses the work of Takahashi as a guide.

A modestly diastereoselective Weitz-Scheffer epoxidation (ca. 4.8:1, *anti*:*syn*), was performed in 41% yield to generate **176**. This was followed by Grignard addition of propynylmagnesium bromide, in tetrahydrofuran at -78 °C, in a gratifying 88% yield

to produce the tertiary alcohol **177**. Elimination of **177** utilising trifluoromethanesulfonic anhydride/2,6-lutidine at -78 °C yielded a mixture of products **178**, the desired eliminated compound, in admixture with the product tentatively assigned as the triflate derived alcohol of **177**.

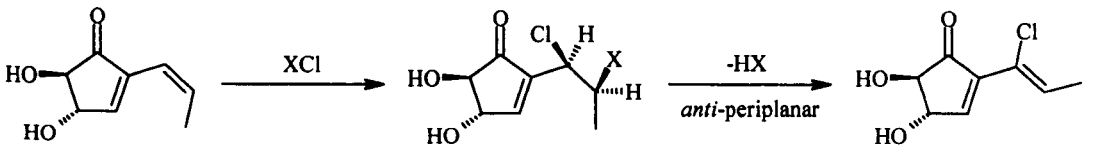


Scheme 2.18.6.4: *Reagents*: i) H_2O_2, NaOH, MeOH, ii) propynylmagnesium bromide, THF, -78 °C, iii) Tf_2O, 2,6-lutidine, 4Å molecular sieves, DCM, -78 °C, iv) $Pd(PPh_3)_4$, $PhCO_2H$, THF, 0 °C, v) TBSCl, imidazole, DMF, rt, vi) H_2, Lindlar's cat., quinoline, EtOAc, rt, vii) DIBAL, PhMe, -78 °C, viii) PDC, DCM, 4Å molecular sieves, rt, ix) AcOH:H_2O:THF, 3:1:1, 60 °C.

This mixture, when treated to a palladium-catalysed ring opening reaction, in the presence of benzoic acid, gave rise to two pairs of diastereomers **179** and **180** (62%). Protection of the alcohol as its silyl ether simplified the issue yielding one pair of diastereomers **181**, in a 73% yield. Reduction of the alkyne moiety proceeded exceedingly well on this occasion, affording diene **182** in 90% yield. Removal of the

benzoyl group using diisobutylaluminium hydride and oxidation employing pyridinium dichromate furnished compound **183**, whereupon acid-catalysed removal of the silyl protecting groups gave the diol (+)-*anti*-**163** (31% yield for the last three steps). The ^{1}H NMR spectrum of compound (+)-*anti*-**163** showed a coupling constant of 2.8 Hz between *H*-C-4 and *H*-C-5 (cf. 5.5 Hz for the *cis*-diol), and the *exo*-cyclic alkene protons gave the required AA' signal centred at 6.03 ppm, indicative of the (*Z*)-side-chain.

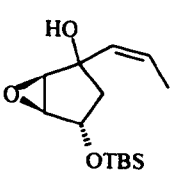
Having successfully developed a synthesis for both the *syn*- and *anti*-diastereomers of a natural product, isolated from ascomycete strain A23-98, it has subsequently been shown that the non-halogenated compounds are not *syn*- and *anti*-diols **137**. Instead, the reported physical data fit better to the data obtained for the *cis*-alkenes, *syn*- and *anti*-**163**. While the absolute configurations of the natural products were not ascertained and optical rotations were not reported, $[\alpha]_D$ values are now available for (+)-*syn*-**163**, (-)-*syn*-**163** and (+)-*anti*-**163**, should further information for the natural compounds become available. This may, therefore, have consequences regarding the proposed biosynthesis of these natural products *via* the pentaketide pathway,[138] in that chlorination may take place after the introduction of the *cis*-side-chain. Mechanistically, this appears sound, since the addition of XCl across the *cis*-side-chain of (+)-*anti*-**163**, followed by the elimination of HX *via* an *anti*-periplanar conformer, would present the enantiomer of the proposed, chlorinated natural product **136**.[123]



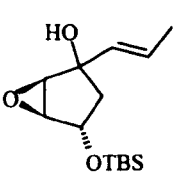
(+)-*anti*-**163** *ent*-**136**

2.18.7 Absolute stereochemistry of 177

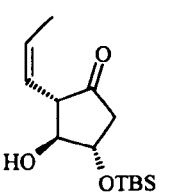
Interestingly, during the synthesis of *anti*-**163**, it was realised that at some stage during the synthesis, the alkyne, added into ketone **176** *via* propynylmagnesium bromide, would have to be reduced to the *cis*-alkene. Initially, reduction of **177** (using Lindlar's catalyst) was attempted but, unfortunately, resulted in the formation of two compounds, assigned by ^{1}H NMR as the *cis*- and *trans*-isomers **184** and **185** respectively. This result was unexpected since Lindlar's catalyst usually reduces alkynes stereospecifically to *cis*-alkenes, such as in the transformation **181** to **182** (Scheme 2.18.6.4); hence we eventually resorted to performing the reduction at a later stage. However, there does seem to be some precedent for the reduction of propargylic alcohols, using Lindlar's catalyst, resulting in mixtures of *cis*- and *trans*-alkenes.[139]



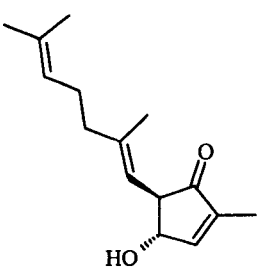
184



185



186



litseaverticillol A

Moreover, the expected reduction product **184** underwent a rearrangement whilst left in deuteriated chloroform, resulting in the pinacol-rearranged product **186**, a chemical

motif closely related to the natural product litseaverticillol A.[140] As a result, we are confident that the stereochemistry depicted in **177** is accurate, since the rearrangement of the reduced analogue **184** could only occur in such a stereochemical circumstance.

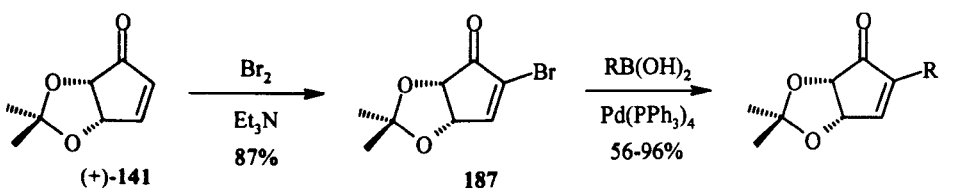
2.19 Preparation of structural analogues of 163

The synthesis of various analogues of the natural products was undertaken. This project was carried out in parallel to the synthesis of the natural compounds, attempting to concentrate on the steric and electronic properties of the side-chain. It was hoped that this might lead to improvements on the compounds ability to inhibit the formation of NF-κB, a known feature of the products isolated from ascomycete strain A23-98.[100, 101]

The synthesis of analogues began using commercially available boronic acids and α-halo cyclopentenone **140**, and thus, Suzuki reactions could take place directly once **140** had been prepared. At the time, synthesis of the geometrically pure stannanes, destined to become the natural products side-chain, were proving difficult to prepare due to the contamination of the desired stannanes with *n*-tributyl(propynyl)stannane, *vide supra*. Thus, we went ahead with the preparation of the analogues, initially using α-vinyl bromides **187** and the commercially available boronic acids, following the work of Chan and Mak.[141] It was later found that such α-bromocyclopentenones cannot undergo the desired Stille reaction with stannanes, and thus continuation of the project with the preparation of the natural products utilised α-iodocyclopentenones **160**.[112]

The preparation of the analogues began from (-)-**141** and (+)-**141** following α-bromination (using Br_2 and triethylamine in dichloromethane). This then gave rise to **187** and *ent*-**187** (ca. 85% yield), which is suitably functionalised to partake in Suzuki couplings to generate the aryl analogues **188, 189** and **190**, Scheme 2.19.[142-146]

As biological data for the parent cyclopentenones **141** and α-halo-cyclopentenones **140** began to accrue, it was clear that the more electron-deficient α-bromo compounds **187** and *ent*-**187** were more active than the parent cyclopentenones, (entries 10 and 11 cf. 2 and 3, Table 2.19). More importantly, the neutral α-phenyl compound **188** and the electron-rich *p*-methoxy phenyl compound **189** were not active within the limits of the test. Therefore, the preparation of both enantiomers of **190** was undertaken since the compound possessed electron-withdrawing properties similar to the α-bromo compound. NF-κB inhibitory activity for the synthesised compounds can be seen in Table 2.19.



(+)-**141** **187**

R= **188** Ph, **189** *p*-PhOMe, **190** *p*-PhCF$_3$

Scheme 2.19

Entry	NF-κB (μM)	Compound
1	50-100	**137**[a]
2	30	(+)-**141**
3	48	(-)-**141**
4	27	**160**
5	51	*ent*-**160**
6	79	(+)-**162**
7	80	(-)-**162**
8	>100	(-)-*syn*-**163**
9	13	**166**
10	12	**187**
11	24	*ent*-**187**
12	>100	**188**
13	>100	**189**
14	34	(+)-**190**
15	>100	(-)-**190**

Table 2.19 Biological evaluation against NF-κB inhibition of the natural product and analogues. [a] Reported in reference 100.

Along with the syntheses of the natural products isolated from ascomycete strain A23-98, we have shown how the biological activity can be affected by the synthesis of structural analogues.

Chapter 3:

Experimental

3 Experimental

3.1 General

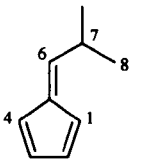
Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected; microanalyses were determined using a Carlo Elba elemental analyser. Nominal and accurate mass spectra were recorded on a VG7070E, CIPOS, Kratos Profile HV3 and TRIO1000. Specific optical rotations were measured at ambient temperature (20 ± 3 °C) using a 1 cm^3 cell with 0.1 dm path length, on an Optical Activity Ltd. AA-1000 polarimeter, operating at 589 nm corresponding to the sodium D line, and are recorded in units of 10^{-1} deg cm^2 g^{-1} (concentrations, c, are quoted in g/100 cm^3). Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FTIR spectrometer, over the range 4000-800 cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC200 (200 MHz), Bruker AC250 (250 MHz), Varian 300 Gemini 2000 (300 MHz) or a Bruker 400 Avance (400 MHz) instrument. ^{13}C NMR spectra were recorded on a Varian 300 Gemini 2000 (75.5 MHz) or a Bruker 400 Avance (100 MHz) instrument. All chemical shifts are quoted in ppm. relative to a calibration reference of tetramethylsilane (Me_4Si, 0 ppm.), residual $CHCl_3$, 7.26 ppm. or $CDCl_3$, 77.0 ppm. The following abbreviations were used to define the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad. The coupling constants (*J*) are measured in hertz (Hz). Chiral, capillary gas chromatography was performed on a Shimadzu GC-14A_H gas chromatograph with FI detection, using the following columns and conditions: Chrompack Chirasil-Dex CB, WCOT fused silica column, 25 M × 0.25 mm, 0.25 μm film thickness, programmed at 140 °C or a Lipodex E-0.2 μm, fused silica column, 25 M × 0.25 mm, programmed to rise from 100 °C to 180 °C over 2 °C/minute. Short path distillation was carried out using a

Kugelrohr apparatus and, where applicable, the boiling point quoted refers to the oven temperature.

Unless otherwise stated, all solvents were dried by the appropriate technique and all reactions were carried out under an atmosphere of nitrogen, in dried glassware, with the exclusion of water and oxygen.

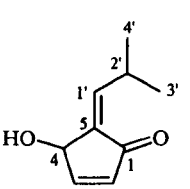
Reactions were monitored by thin layer chromatography (TLC), performed on aluminium backed silica gel, Merck 60 F_{254} plates, in a variety of solvents. The plates were visualised by UV light (254 nm), *p*-anisaldehyde or potassium permanganate. Column chromatography was conducted with ICN silica 32-6, 60Å mesh silica gel under bellows pressure.

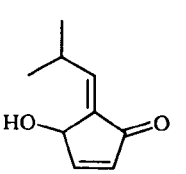
5-Isobutylidenecyclopenta-1,3-diene (49)



To a solution of freshly cracked cyclopentadiene (8.5 cm^3, 0.10 mol) and isobutyraldehyde (3.8 cm^3, 41.6 mmol) in methanol (42 cm^3) was added pyrrolidine (5.2 cm^3, 62.4 mmol). The reaction was stirred at room temperature for 2 minutes under an atmosphere of nitrogen, glacial acetic acid (3.8 cm^3) was added to the solution and the reaction mixture diluted with diethyl ether (180 cm^3) and water (180 cm^3). The aqueous layer was extracted with diethyl ether (2 × 100 cm^3) and the combined organic layers washed with water (20 cm^3), brine (20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title compound **49** (5.0 g, 100%) as a yellow oil; ν_{max}(film)/cm^{-1} 1340, 1466, 1650, 2961, 3047; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.13 (6H, d, *J* 6.9, C(8)H), 2.95-3.07 (1H, m, C(7)H), 6.22 (1H, d, *J* 10.2, C(6)H), 6.44-6.55 (4H, m, ring protons); δ_C (75 MHz; $CDCl_3$; Me_4Si) 23.1 (CH_3), 30.4, 119.3, 126.0, 130.8, 133.0 (CH), 143.7 (C), 149.8 (CH); *m/z* (CI) 121 ($[M+H]^+$, 100%); Found: $[M+H]^+$, 121.10158. C_9H_{13} requires $[M+H]^+$, 121.10172.

4-Hydroxy-5-[2'-methylprop-(*E*/*Z*)-ylidene]-cyclopent-2-enone (50) and (51)

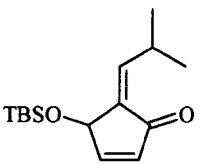


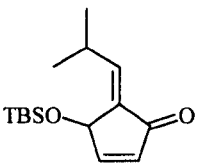


A solution of fulvene **49** (1.0 g, 8.3 mmol) and a catalytic amount of rose bengal in methanol (200 cm^3) was stirred at room temperature for 20 minutes with a steady flow of oxygen bubbling through it. After 20 minutes, the mixture was irradiated (500 W halogen lamp) with continuation of the flow of oxygen. After 13 hours, the irradiation and flow of oxygen were ceased and the methanol removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 2:3) to yield an inseparable mixture (ca. 1.2:1, *E*:*Z*) of the title compounds **50** and **51** (320 mg, 25%) as an orange oil; ν_{max}(film)/cm^{-1} 1657, 1701, 2870, 2963, 3399 br.; *m/z* (CI) 153 ($[M+H]^+$, 100%); Found: $[M+H]^+$, 153.09175. $C_9H_{13}O_2$ requires $[M+H]^+$, 153.09155; NMR data for the (*E*)-isomer: δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.10 (3H, d, *J* 6.7, CH_3), 1.12 (3H, d, *J* 6.7, CH_3), 2.92-3.01 (1H, m, C(2')H), 5.31 (1H, m, C(4)H), 6.40 (1H, d, *J* 6.0, C(2)H), 6.51 (1H, d, *J* 10.5, C(1')H), 7.46 (1H, dd, *J* 2.5 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.9, 22.2 (CH_3), 28.7, 70.4 (CH), 134.3 (C), 136.5, 149.7, 157.9 (CH), 195.2 (C).

NMR data for the (*Z*)-isomer: δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.03 (3H, d, *J* 6.7, CH_3), 1.06 (3H, d, *J* 6.7, CH_3), 3.81-3.87 (1H, m, C(2')H), 5.07 (1H, m, C(4)H), 6.17 (1H, d, *J* 10.0, C(1')H), 6.35 (1H, d, *J* 6.0, C(2)H), 7.38 (1H, dd, *J* 2.3 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 22.3, 22.4 (CH_3), 25.9, 72.3 (CH), 134.4 (C), 138.1, 145.7, 156.8 (CH), 195.3 (C).

4-(*tert*-Butyldimethylsilanyloxy)-5-[2'-methylprop-(*Z*)-ylidene]-cyclopent-2-enone (52) and 4-(*tert*-butyldimethylsilanyloxy)-5-[2'-methylprop-(*E*)-ylidene]-cyclopent-2-enone (53)



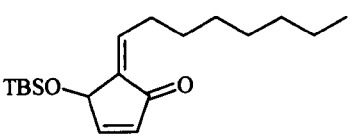


To a solution of *tert*-butyldimethylsilyl chloride (3.19 g, 21.2 mmol), triethylamine (8.0 cm^3, 57.0 mmol) and a catalytic amount of 4-dimethylaminopyridine (0.26 g, 2.1 mmol) in anhydrous dichloromethane (24 cm^3) was added a solution of alcohols **50** and **51** (2.48 g, 16.3 mmol) in anhydrous dichloromethane (24 cm^3) dropwise at 0 °C, under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature over 16 hours, then the reaction was quenched with water (60 cm^3) and the product was extracted with dichloromethane (3 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The products were purified by flash column chromatography (SiO_2; EtOAc:petroleum ether, 1:10) to yield the title compounds (*Z*)-**52** (392 mg, 9%) as a yellow oil and (*E*)-**53** (1.27 g, 30%) also as a yellow oil; (*Z*)-isomer: Found: C, 67.70; H, 9.93. $C_{15}H_{26}O_2Si$ requires C, 67.62; H, 9.84%; ν_{max}(film)/cm^{-1} 1659, 1704, 2859, 2958; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.14 (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.02 (3H, d, *J* 6.6, CH_3), 1.04 (3H, d, *J* 6.6, CH_3), 3.66-3.78 (1H, m, C(2')H), 5.13 (1H, m, C(4)H), 5.97 (1H, d, *J* 9.9, C(1')H), 6.32 (1H, d, *J* 5.5, C(2)H), 7.27 (1H, dd, *J* 2.5 and 5.5, C(3)H); δ_C (75 MHz; $CDCl_3$; Me_4Si) -4.2, -4.0 (CH_3), 18.1 (C), 22.3, 22.4,

25.7 (CH_3), 29.7, 72.7 (CH), 134.8 (C), 137.6, 148.6, 157.1 (CH), 195.3 (C); *m/z* (EI) 266 ($[M]^+$, 21%), 209 ($[M\text{-}C(CH_3)_3]^+$, 90).

(*E*)-isomer: Found: C, 67.68; H, 9.89. $C_{15}H_{26}O_2Si$ requires C, 67.62; H, 9.84%; ν_{max}(film)/cm^{-1} 1663, 1712, 2360, 2859, 2930, 2959; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.15 (3H, s, $SiCH_3$), 0.17 (3H, s, $SiCH_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.07 (3H, d, *J* 6.7, CH_3), 1.08 (3H, d, *J* 6.6, CH_3), 2.78-2.94 (1H, m, C(2')H), 5.36 (1H, m, C(4)H), 6.37 (1H, d, *J* 6.0, C(2)H), 6.45 (1H, d, *J* 10.4, C(1')H), 7.36 (1H, dd, *J* 2.3 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -4.0, -3.3 (CH_3), 18.3 (C), 22.3, 22.4, 26.1 (CH_3), 28.6, 71.1 (CH), 134.8 (C), 136.5, 144.9, 158.1 (CH), 195.4 (C); *m/z* (EI) 266 ($[M]^+$, 1%), 209 ($[M\text{-}C(CH_3)_3]^+$, 100); Found: $[M]^+$, 266.17006. $C_{15}H_{26}O_2Si$ requires $[M]^+$, 266.17020.

4-(*tert*-Butyldimethylsilanyloxy)-5-oct-(*Z*)-ylidenecyclopent-2-enone (54)



A solution of 5-octylidenecyclopenta-1,3-diene[147] (1.16 g, 6.6 mmol) and a catalytic amount of rose bengal in methanol (100 cm^3) was stirred at room temperature for 20 minutes with a steady flow of oxygen bubbling through it. After 20 minutes, the mixture was irradiated (500 W halogen lamp) with continuation of the flow of oxygen. After 13 hours, the irradiation and flow of oxygen were ceased, the reaction mixture was filtered and the methanol removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:petroleum ether, 3:7) to yield an inseparable mixture (ca. 2:1, *E*:*Z*) of the corresponding alcohols (0.36 g, 26%) as a

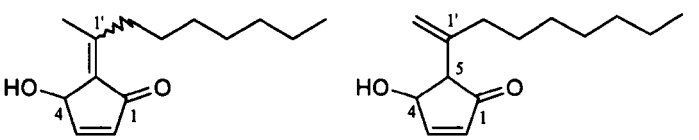
yellow oil; the cross-conjugated isomers were identified by the NMR signals at δ_H (400 MHz; $CDCl_3$; Me_4Si) (*E*)-isomer: 2.35-2.51 (2H, m, allylic CH_2), 5.28 (1H, br. s, C(4)H), 6.39 (1H, d, *J* 6.0, C(2)H), 6.70 (1H, t, *J* 7.7, C(1')H), 7.46 (1H, dd, *J* 2.4 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 70.4 (CH), 136.55 (C), 136.6, 139.8, 157.8 (CH), 194.5 (C).

(*Z*)-isomer: 2.73-2.83 (2H, m, allylic CH_2), 5.08 (1H, br. s, C(4)H), 6.35 (1H, d, *J* 6.4, C(2)H), 6.38 (1H, t, *J* 8.8, C(1')H), 7.37 (1H, dd, *J* 2.3 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 72.3 (CH), 136.8 (C), 138.2, 143.4, 156.5 (CH), 195.4 (C).

Mass spec. data; *m/z* (EI) 208 ($[M]^+$, 7%), 111 ($[M-C_7H_{15}+2H]^+$, 100), 110 ($[M-C_7H_{15}+H]^+$, 85), 109 ($[M-C_7H_{15}]^+$, 34); Found: $[M]^+$, 208.14626. $C_{13}H_{20}O_2$ requires $[M]^+$, 208.14633. To a solution of *tert*-butyldimethylsilyl chloride (0.18 g, 1.2 mmol), triethylamine (0.47 cm^3, 3.4 mmol) and a catalytic amount of 4-dimethylaminopyridine (15 mg, 0.12 mmol) in anhydrous dichloromethane (2 cm^3) was added a solution of the alcohols (200 mg, 0.96 mmol) in anhydrous dichloromethane (2 cm^3) dropwise at 0 °C, under a atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature over 94 hours. The reaction was quenched with water (4 cm^3) and the product extracted with dichloromethane (3 × 5 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:petroleum ether, 1:9) to yield the title compound **54** (8.6 mg, 3%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1667, 1715, 2857, 2928; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.14 (3H, s, $SiCH_3$), 0.17 (3H, s, $SiCH_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.26-1.30 (9H, m, alkyl chain), 1.47-1.56 (4H, m, alkyl chain), 2.32-2.40 (2H, m, allylic CH_2), 5.35 (1H, m, C(4)H), 6.38 (1H, d, *J* 6.1, C(2)H), 6.65 (1H, t, *J* 7.6, C(6)H), 7.36 (1H, dd, *J* 2.4 and 6.1, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -4.2, -

3.5, 14.0 (CH_3), 18.0 (C), 22.6 (CH_2), 25.8 (CH_3), 28.6, 29.1, 29.2, 29.3, 29.5 (CH_2), 70.9, 136.2 (CH), 136.8 (C), 138.8, 157.8 (CH), 194.6 (C); *m/z* (EI) 322 ($[M]^+$, 1%), 265 ($[M\text{-}C(CH_3)_3]^+$, 59); Found: $[M]^+$, 322.23281. $C_{19}H_{34}O_2Si$ requires $[M]^+$, 322.23282.

4-Hydroxy-5-[1'-methyloct-(*E*/*Z*)-ylidene]-cyclopent-2-enones (57 and 58) and 5-(1-heptylvinyl)-4-hydroxycyclopent-2-enone (59)

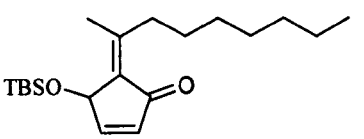


A solution of 5-[1'-methyloctylidene]-cyclopenta-1,3-diene[147] (2.5 g, 13.1 mmol) and a catalytic amount of rose bengal in methanol (250 cm^3) was stirred at room temperature for 15 minutes with a steady flow of oxygen bubbling through it. After 15 minutes, the mixture was irradiated (500 W halogen lamp) with continuation of the flow of oxygen. After 12.5 hours, the irradiation and flow of oxygen were ceased, the reaction mixture was filtered and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:petroleum ether, 3:7) to yield a mixture (ca. 1:1) of the title compounds **57**, **58** and **59** (1.06 g, 36%) as an orange oil; ν_{max}(film)/cm^{-1} 1635, 1698, 2856, 2926, 3410 br.; *m/z* (EI) 222 ($[M]^+$, 20%), 151 ($[M\text{-}C_5H_{11}]^+$, 45); Found: $[M]^+$, 222.16202. $C_{14}H_{22}O_2$ requires $[M]^+$, 222.16199; NMR data for the cross-conjugated isomer: δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (3H, t, *J* 6.6, CH_3), 1.28-1.30 (8H, m, alkyl chain), 1.42-1.51 (2H, m, alkyl chain), 2.08 (3H, s, allylic CH_3), 2.72-2.84 (2H, m, allylic CH_2), 4.97 (1H, m, C(4)H), 6.29 (1H, d, *J*

6.0, C(2)H), 7.31 (1H, dd, *J* 2.5 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.1, 21.6 (CH_3), 22.6, 28.4, 29.5, 31.7, 33.2, 37.3 (CH_2), 72.0 (CH), 131.2 (C), 137.9, 154.9 (CH), 156.5, 195.0 (C).

NMR data for the isomerised product: δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (3H, t, *J* 6.6, CH_3), 1.28-1.30 (8H, m, alkyl chain), 1.48-1.51 (2H, m, alkyl chain), 2.06-2.12 (2H, m, allylic CH_2), 3.30 (1H, d, *J* 6.5, C(5)H), 4.97 (1H, m, C(4)H), 4.73 (1H, s, -C=C*H*H), 5.18 (1H, s, -C=CH*H*), 6.33 (1H, d, *J* 5.8, C(2)H), 7.63 (1H, dd, *J* 2.3 and 5.8, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.1 (CH_3), 22.6, 27.2, 29.2, 29.3, 31.8, 37.8 (CH_2), 56.5, 71.3 (CH), 114.6 (CH_2), 135.6 (CH), 145.3 (C), 163.3 (CH), 206.8 (C).

4-(*tert*-Butyldimethylsilanyloxy)-5-[1'-methyloct-(*Z*)-ylidene]-cyclopent-2-enone (55)



To a solution of *tert*-butyldimethylsilyl chloride (0.30 g, 2.0 mmol), triethylamine (0.75 cm^3, 5.3 mmol) and 4-dimethylaminopyridine (20 mg, 0.20 mmol) in anhydrous dichloromethane (3 cm^3) was added a solution of alcohols **57**, **58** and **59** (338 mg, 1.52 mmol) in anhydrous dichloromethane (2 cm^3) dropwise at 0 °C, under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature over 94 hours then the reaction was quenched with water (5 cm^3) and the product extracted with dichloromethane (3 × 5 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by

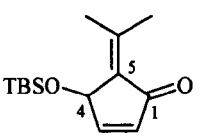
flash column chromatography (SiO_2; EtOAc:petroleum ether, 6:100) to yield the title compound **55** (38 mg, 7%) as a yellow oil; ν_{max}(film)/cm^{-1} 1643, 1698, 2857, 2929; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.06 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.24-1.48 (13H, m, aliphatic chain), 2.00 (3H, s, allylic CH_3), 2.75-2.80 (2H, m, allylic CH_2), 5.29 (1H, m, C(4)H), 6.26 (1H, d, *J* 6.0, C(2)H), 7.23 (1H, dd, *J* 2.5 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -3.4, -2.8, 14.4 (CH_3), 18.4 (C), 22.1 (CH_3), 23.0 (CH_2), 26.1 (CH_3), 28.6, 29.5, 30.1, 32.2, 33.6 (CH_2), 73.1 (CH), 131.9 (C), 137.9, 155.2, (CH), 155.5, 195.4 (C); *m/z* (EI) 336 ([M]$^+$, 29%), 279 ([M-$C(CH_3)_3$]$^+$, 87); Found: [M]$^+$, 336.24874. $C_{20}H_{36}O_2Si$ requires [M]$^+$, 336.24847.

General Procedure for cross-conjugated analogues

To a solution of freshly cracked cyclopentadiene and the appropriate aldehyde or ketone in reagent grade methanol was added pyrrolidine. The reaction was stirred at room temperature under an atmosphere of nitrogen, then glacial acetic acid was added to the solution and the reaction mixture diluted with diethyl ether and water. The aqueous layer was washed with diethyl ether and the combined organic layers washed with water, brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the fulvene product as a semi-pure yellow oil contaminated with diethyl ether. Due to their volatility the fulvenes were taken on to the next step without further purification. A solution of the fulvene and a catalytic amount of rose bengal in methanol was stirred at room temperature for 5 minutes with a steady flow of oxygen bubbling through it. After 5 minutes, the mixture was irradiated (500 W halogen lamp) with continuation of the flow of oxygen. Upon completion, the irradiation and flow of oxygen were ceased and the methanol removed *in vacuo*. The products were purified by flash column chromatography and the structures of the 4-hydroxy cross-conjugated

enones were identified by ^{1}H NMR; the isomers were taken on to next step without any further characterisation unless otherwise stated. To a solution of *tert*-butyldimethylsilyl chloride, triethylamine and a catalytic amount of 4-dimethylaminopyridine in anhydrous dichloromethane was added a solution of the alcohols in anhydrous dichloromethane, dropwise, at 0 °C, under an atmosphere of nitrogen; the reaction mixture was allowed to warm to room temperature. The reaction was quenched with water and the product extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*.

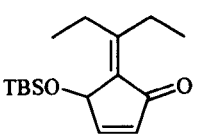
4-(*tert*-Butyldimethylsilanyloxy)-5-isopropylidenecyclopent-2-enone (62)



5-Isopropylidenecyclopenta-1,3-diene[147] (2.0 g, 18.9 mmol), catalytic rose bengal (19 mg, 0.02 mmol), methanol (400 cm^3). After 10 hours, the product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:1) to yield a mixture (ca. 1.3:1, out-of-conjugation isomer:cross-conjugated isomer) of the cross-conjugated enone as well as an isomer with an out-of-conjugation double bond (460 mg, 18%) as an orange oil. The 4-hydroxy cross-conjugated enone isomer was identified by the ^{1}H NMR (200 MHz) signals at 2.09 (3H, s, CH_3), 2.32 (3H, s, CH_3), 6.32 (1H, m, C(2)H), 7.33 (1H, dd, *J* 2.5 and 6.0, C(3)H); and the out-of-conjugation isomer identified by the ^{1}H NMR (200 MHz) signals at 1.80 (3H, m, CH_3), 3.30 (1H, d, *J* 6.6, C(5)H), 4.81 (1H, m, -C=C*H*H), 5.18 (1H, m, -C=CH*H*), 6.32 (1H, m, C(2)H), 7.64 (1H, dd, *J* 2.5 and 5.9, C(3)H). *tert*-Butyldimethylsilyl chloride (603 mg, 4.0 mmol),

triethylamine (0.6 cm^3, 4.3 mmol), 4-dimethylaminopyridine (53 mg, 0.43 mmol) in dichloromethane (18 cm^3), alcohols (460 mg, 3.3 mmol) in dichloromethane (15 cm^3). After 45 hours, the reaction was worked-up according to the general procedure and the product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:9) to yield the title compound **62** (0.29 g, 34%) as a pale yellow solid; m.p. 50-51 °C (from EtOAc:*n*-hexane); Found: C, 66.70; H, 9.87. $C_{14}H_{24}O_2Si$ requires C, 66.61; H, 9.58%; ν_{max}(film)/cm^{-1} 1649, 1699, 2857, 2930, 2954; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.08 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 2.01, (3H, s, CH_3), 2.30 (3H, s, CH_3), 5.31 (1H, m, C(4)H), 6.29 (1H, d, *J* 6.1, C(2)H), 7.24 (1H, dd, *J* 2.5 and 6.1, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -3.5, -3.0 (CH_3), 18.4 (C), 20.7, 24.4, 26.1 (CH_3), 72.9 (CH), 132.0 (C), 137.8 (CH), 150.8 (C), 155.4 (CH), 195.8 (C); *m/z* (EI) 252 ($[M]^+$, 4%), 195 ($[M\text{-}C(CH_3)_3]^+$, 95); Found: $[M]^+$, 252.15494. $C_{14}H_{24}O_2Si$ requires $[M]^+$, 252.15457.

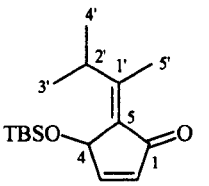
4-(*tert*-Butyldimethylsilanyloxy)-5-[1'-ethylpropylidene]-cyclopent-2-enone (63)



Cyclopentadiene (2.9 cm^3, 35.8 mmol), 3-pentanone (1.5 cm^3, 14.3 mmol), pyrrolidine (1.8 cm^3, 21.5 mmol), methanol (14 cm^3). After 1 hour, glacial acetic acid (1.8 cm^3) was added and the fulvene worked-up according to the general procedure. The fulvene, catalytic rose bengal in methanol (125 cm^3). After 10 hours, the reaction was worked-up according to the general procedure. The alcohol was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 2:3) to yield the desired alcohol (73

mg, 3%) as an orange oil; ν_{max}(film)/cm^{-1} 1633, 1682, 2360, 2971, 3388 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.08 (3H, t, *J* 7.6, CH_3), 1.15 (3H, t, *J* 7.6, CH_3), 2.37-2.52 (2H, m, CH_2), 2.70-2.88 (2H, m, CH_2), 5.22 (1H, m, C(4)H), 6.30 (1H, dd, *J* 1.0 and 6.0, C(2)H), 7.31 (1H, dd, *J* 2.5 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 12.7, 13.4 (CH_3), 23.8, 28.0 (CH_2), 72.1 (CH), 130.7 (C), 138.2, 155.3 (CH), 163.2, 195.7 (C); *m/z* (EI) 166 ([M]$^+$, 67%), 137 ([M-C_2H_5]$^+$, 97), 123 ([M-C_3H_7]$^+$, 95), 109 ([M-C_4H_{10}+H]$^+$, 100); Found: [M]$^+$, 166.09980. $C_{10}H_{14}O_2$ requires [M]$^+$, 166.09937. *tert*-Butyldimethylsilyl chloride (80 mg, 0.53 mmol), triethylamine (79 μl, 0.57 mmol), 4-dimethylaminopyridine (7 mg, 0.06 mmol) in dichloromethane (3.5 cm^3), alcohol (73 mg, 0.44 mmol) in dichloromethane (1 cm^3). After 65 hours, the reaction was worked-up according to the general procedure. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:9) to yield the title compound **63** (43 mg, 35%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1635, 1697, 2930, 2958; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.09 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.07 (3H, t, *J* 7.5, CH_3), 1.11 (3H, t, *J* 7.5, CH_3), 2.25-2.34 (1H, m, C*H*H), 2.42-2.51 (1H, m, CH*H*), 2.69-2.88 (2H, m, CH_2), 5.32 (1H, m, C(4)H), 6.27 (1H, d, *J* 6.1, C(2)H), 7.23 (1H, dd, *J* 2.5 and 6.1, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -3.5, -2.9, 12.6, 13.2 (CH_3), 18.4 (C), 23.7 (CH_2), 26.2 (CH_3), 27.6 (CH_2), 72.6 (CH), 130.8 (C), 137.9, 155.4 (CH), 161.8, 195.8 (C); *m/z* (EI) 280 ([M]$^+$, 36%), 223 ([M-$C(CH_3)_3$]$^+$, 64); Found: [M]$^+$, 280.18580. $C_{16}H_{28}O_2Si$ requires [M]$^+$, 280.18585.

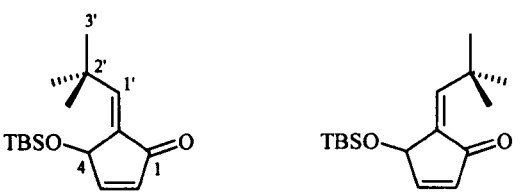
4-(*tert*-Butyldimethylsilanyloxy)-5-[1',2'-dimethylprop-(*E*)-ylidene]-cyclopent-2-enone (64)



Cyclopentadiene (3.0 cm^3, 36.3 mmol), 3-methyl-butan-2-one (1.6 cm^3, 14.5 mmol), pyrrolidine (1.8 cm^3, 21.5 mmol), methanol (36 cm^3). After 1 hour, glacial acetic acid (1.3 cm^3) was added and the reaction worked-up according to the general procedure. The fulvene, catalytic rose bengal in methanol (300 cm^3). After 35 hours, the product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:4) to yield a mixture (*E*/*Z*) of the 4-hydroxy cross-conjugated enone isomers as well as some of the isomer with an out-of-conjugation double bond (70 mg, 3%) as an orange oil. The 4-hydroxy cross-conjugated enone isomers were identified by the ^1H NMR (200 MHz) signals at 3.16 (1H, m, C(4)H), 4.40 (1H, m, C(4)H), 6.28-6.33 (2H, 2 × dd, 2 × C(2)H), 7.29-7.33 (2H, 2 × d, 2 × C(3)H); and the "out-of-conjugation" isomer identified by the ^1H NMR (200 MHz) signals at 3.35 (1H, d, *J* 6.5, C(5)H), 4.59 (1H, s, -C=C*H*H), 5.22 (1H, s, -C=CH*H*). *tert*-Butyldimethylsilyl chloride (95 mg, 0.63 mmol), triethylamine (0.18 cm^3, 1.26 mmol), 4-dimethylaminopyridine in dichloromethane (3 cm^3), alcohols (70 mg, 0.42 mmol) in dichloromethane (1 cm^3). After 72 hours, the reaction was worked-up according to the general procedure. The product was purified by preparative TLC (SiO_2; dichloromethane) to yield the cross-conjugated title compound **64** (12 mg, 10%) as a colourless oil; ν_{max}(film)/cm^{-1} 1638, 1697, 2856, 2929, 2958; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.12 (3H, s, $SiCH_3$), 0.14 (3H,

s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.05 (3H, d, *J* 6.9, CH_3), 1.08 (3H, d, *J* 6.6, CH_3), 2.19 (3H, s, C(5')H), 3.03-3.10 (1H, m, C(2')H), 5.32 (1H, m, C(4)H), 6.28 (1H, d, *J* 6.1, C(2)H), 7.21 (1H, dd, *J* 2.5 and 6.1, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -3.8, -3.1, 12.4 (CH_3), 18.3 (C), 20.4, 20.5, 26.1 (CH_3), 33.1, 72.2 (CH), 130.3 (C), 137.9, 155.2 (CH), 159.3, 196.7 (C); *m/z* (CI) 281 ($[M+H]^+$, 100%); Found: $[M+H]^+$, 281.19406. $C_{16}H_{29}O_2Si$ requires $[M+H]^+$, 281.19370.

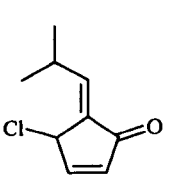
4-(*tert*-Butyldimethylsilanyloxy)-5-[2',2'-dimethylprop-(*E*)-ylidene]-cyclopent-2-enone (66) and 4-(*tert*-butyldimethylsilanyloxy)-5-[2',2'-dimethylprop-(*Z*)-ylidene]-cyclopent-2-enone (67)



Cyclopentadiene (4.8 cm^3, 58.0 mmol), pivalaldehyde (2.5 cm^3, 23.2 mmol), pyrrolidine (2.9 cm^3, 34.8 mmol), methanol (24 cm^3). After 2 hours, glacial acetic acid (2.2 cm^3) was added to the solution and the reaction worked-up according to the general procedure. The fulvene (2.6 g), catalytic rose bengal (0.13 g, 0.13 mmol), methanol (200 cm^3). After 15 hours, the product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 2:3) to yield an inseparable mixture (ca. 2:1, *E*:*Z*) of the 4-hydroxy cross-conjugated enone isomers (0.37 g, 10%) as an orange oil. The 4-hydroxy cross-conjugated enone isomers were identified by ^1H NMR (250 MHz) signals at; (*E*)-isomer: 5.42 (1H, m, C(4)H), 6.39 (1H, dd, *J* 1.1 and 6.0, C(2)H), 7.50 (1H, dd, *J* 1.7 and 6.0, C(3)H); (*Z*)-isomer: 5.03 (1H, m, C(4)H), 6.35

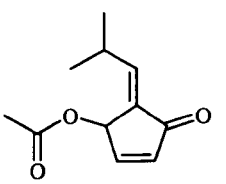
(1H, d, *J* 6.0, C(2)H), 7.38 (1H, dd, *J* 2.4 and 6.0, C(3)H). *tert*-Butyldimethylsilyl chloride (0.59 g, 3.9 mmol), triethylamine (1.1 cm^3, 7.7 mmol), 4-dimethylaminopyridine (41 mg, 0.13 mmol) in dichloromethane (15 cm^3), alcohols (0.43 g, 2.6 mmol) in dichloromethane (10 cm^3). After 5 days, the product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:10) to yield the title compounds (*E*)-**66** (72 mg, 10%) as a pale yellow oil and (*Z*)-**67** (95 mg, 13%) as a pale yellow oil; (*E*) isomer: ν_{max}(film)/cm^{-1} 1651, 1713, 2859, 2957; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.11 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.25 (9H, s, $-C(CH_3)_3$), 5.55-5.56 (1H, m, C(4)H), 6.37 (1H, d, *J* 6.0, C(2)H), 6.61 (1H, s, C(1')H), 7.46 (1H, dd, *J* 2.6 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -2.9, -2.3 (CH_3), 18.5 (C), 26.3, 29.7 (CH_3), 34.6 (C), 71.0 (CH), 133.2 (C), 135.6, 148.5, 158.5 (CH), 196.6 (C); *m/z* (CI) 281 ($[M+H]^+$, 100%); Found: $[M+H]^+$, 281.19406. $C_{16}H_{29}O_2Si$ requires $[M+H]^+$, 281.19370; (*Z*) isomer: ν_{max}(film)/cm^{-1} 1642, 1703, 2859, 2956; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.12 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.28 (9H, s, $-C(CH_3)_3$), 5.09-5.10 (1H, m, C(4)H), 6.21 (1H, s, C(1')H), 6.29 (1H, d, *J* 6.0, C(2)H), 7.27 (1H, m, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -3.7, -3.5 (CH_3), 18.5 (C), 26.1, 30.0 (CH_3), 33.7 (C), 74.2 (CH), 137.1 (C), 138.4, 152.7, 156.9 (CH), 193.8 (C); *m/z* (CI) 281 ($[M+H]^+$, 100%); Found: $[M+H]^+$, 281.19378. $C_{16}H_{29}O_2Si$ requires $[M+H]^+$, 281.19370.

4-Chloro-5-[2'-methylprop-(*E*)-ylidene]-cyclopent-2-enone (71)



To a solution of a mixture of alcohols **50** and **51** (50 mg, 0.33 mmol), triethylamine (46 μl, 0.33 mmol) and a catalytic amount of 4-dimethylaminopyridine in anhydrous dichloromethane (3 cm^3) was added *p*-toluenesulfonyl chloride (76 mg, 0.4 mmol). The reaction mixture was stirred at room temperature, under an atmosphere of nitrogen, for 42 hours. The reaction was quenched with water (3 cm^3) and the product extracted with dichloromethane (3 × 3 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:2) to yield the title compound **71** (11 mg, 10%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1712; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.10 (3H, d, *J* 6.6, CH_3), 1.15 (3H, d, *J* 6.5, CH_3), 2.86-2.98 (1H, m, C(2')H), 5.49 (1H, m, C(4)H), 6.45 (1H, d, *J* 5.9, C(2)H), 6.56 (1H, d, *J* 10.8, C(1')H), 7.43 (1H, dd, *J* 2.6 and 5.9, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.6, 22.1 (CH_3), 29.5, 54.3 (CH), 127.4 (C), 136.9, 147.2, 155.8 (CH), 193.6 (C); *m/z* (EI) 172 ($[M^{37}Cl]^+$, 11%), 170 ($[M^{35}Cl]^+$, 31), 135 ($[M-^{35}Cl]^+$, 51), 91 ($[M-^{35}Cl\text{-}H\text{-}C_3H_7]^+$, 100); Found: $[M^{35}Cl]^+$, 170.04990. $C_9H_{11}{}^{35}ClO$ requires $[M^{35}Cl]^+$, 170.04985.

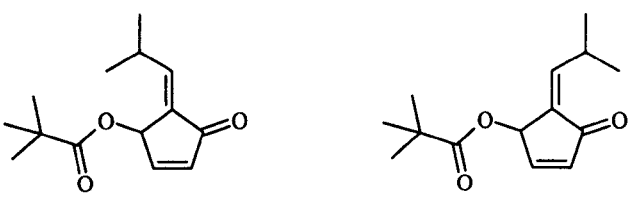
Acetic acid 5-[2'-methylprop-(*E*)-ylidene]-4-oxocyclopent-2-enyl ester (72)



To a solution of a mixture of alcohols **50** and **51** (50 mg, 0.33 mmol), triethylamine (46 μl, 0.33 mmol) and a catalytic amount of 4-dimethylaminopyridine in anhydrous dichloromethane (3 cm^3) was added acetic anhydride (38 μl, 0.4 mmol). The reaction

mixture was stirred at room temperature, under an atmosphere of nitrogen, for 42 hours. The reaction was quenched with water (3 cm^3) and the product extracted with dichloromethane (3 × 3 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:1) to yield the title compound **72** (7 mg, 11%) as a pale yellow oil; NMR (250 MHz) showed the product to be identical with the optically active material prepared *via* enzyme resolution.

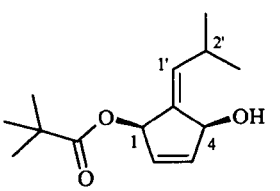
2,2-Dimethylpropionic acid 5-[2'-methylprop-(*E*)-ylidene]-4-oxocyclopent-2-enyl ester (73) and 2,2-dimethylpropionic acid 5-[2'-methylprop-(*Z*)-ylidene]-4-oxocyclopent-2-enyl ester (74)



To a solution of a mixture of alcohols **50** and **51** (75 mg, 0.49 mmol), triethylamine (0.2 cm^3, 1.5 mmol) and a catalytic amount of 4-dimethylaminopyridine in anhydrous dichloromethane (3 cm^3) was added pivaloyl chloride (0.12 cm^3, 0.98 mmol). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 16 hours. The reaction was quenched with water (5 cm^3) and the product extracted with dichloromethane (2 × 5 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:10) to yield the title compounds (*E*)-**73** (22 mg, 19%) as a pale yellow oil and (*Z*)-**74** (20 mg, 18%) as a pale yellow oil; (*E*)-

isomer: ν_{max}(film)/cm^{-1} 1668, 1732, 2872, 2966; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.07 (3H, d, *J* 6.6, CH_3), 1.09 (3H, d, *J* 6.6, CH_3), 1.22 (9H, s, -$C(CH_3)_3$), 2.51-2.61 (1H, m, C(2')H), 6.29-6.30 (1H, m, C(4)H), 6.50 (1H, dd, *J* 1.1 and 6.1, C(2)H), 6.55 (1H, d, *J* 11.0, C(1')H), 7.44 (1H, dd, *J* 2.5 and 6.1, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 22.2, 22.5, 27.4 (CH_3), 29.4 (CH), 39.2 (C), 71.3 (CH), 130.7 (C), 138.8, 146.2, 154.1 (CH), 178.6, 194.8 (C); *m/z* (CI) 237 ([M+H]$^+$, 100%); Found: [M+H]$^+$, 237.14886. $C_{14}H_{21}O_3$ requires [M+H]$^+$, 237.14906. (*Z*)-isomer: ν_{max}(film)/cm^{-1} 1656, 1713, 1732, 2871, 2967; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.00 (3H, d, *J* 6.6, CH_3), 1.04 (3H, d, *J* 6.6, CH_3), 1.22 (9H, s, -$C(CH_3)_3$), 3.81-3.92 (1H, m, C(2')H), 6.04 (1H, d, *J* 10.2, C(1')H), 6.17 (1H, m, C(4)H), 6.45 (1H, d, *J* 6.1, C(2)H), 7.32 (1H, dd, *J* 2.5 and 6.1, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 22.5, 22.6, 26.3 (CH_3), 27.4 (CH), 39.2 (C), 72.9 (CH), 131.0 (C), 140.3, 150.9, 153.1 (CH), 178.8, 195.1 (C); *m/z* (CI) 237 ([M+H]$^+$, 100%); Found: [M+H]$^+$, 237.14863. $C_{14}H_{21}O_3$ requires [M+H]$^+$, 237.14906.

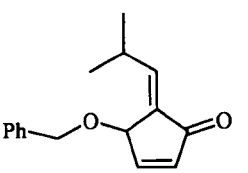
2,2-Dimethylpropionic acid 4-hydroxy-5-[2'-methylprop-(*E*)-ylidene]-cyclopent-2-enyl ester (77)



To a solution of diol **75** (1.3 g, 8.4 mmol),[76] pyridine (0.75 cm^3, 9.2 mmol) and a catalytic amount of 4-dimethylaminopyridine (0.13 g, 1.1 mmol) in anhydrous dichloromethane (85 cm^3) was added pivaloyl chloride (1.03 cm^3, 8.4 mmol) at 0 °C.

The reaction mixture was stirred at room temperature, under an atmosphere of nitrogen, for 16 hours. The reaction was quenched with water (50 cm^3) and the product extracted with dichloromethane (3 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:4) to yield the title compound **77** (414 mg, 21%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1152, 1722, 2959, 3390 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.01 (3H, d, *J* 6.6, CH_3), 1.02 (3H, d, *J* 6.6, CH_3), 1.18 (9H, s, $-C(CH_3)_3$), 2.84-2.97 (1H, m, C(2')H), 5.01 (1H, m, C(4)H), 5.67 (1H, d, *J* 10.8, C(1')H), 5.68 (1H, m, C(1)H), 5.98-6.00 (1H, m, C(3)H), 6.20-6.22 (1H, m, C(2)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 22.8, 23.4, 27.4 (CH_3), 29.0 (CH), 39.1 (C), 73.6, 77.9, 132.5 (CH), 138.2 (C), 139.1, 140.5 (CH), 178.9 (C); *m/z* (CI) 256 ($[M+NH_4]^+$, 7%), 238 ($[M]^+$, 1), 154 ($[M+H-COC(CH_3)_3]^+$, 100); Found: $[M+NH_4]^+$, 256.19077. $C_{14}H_{26}NO_3$ requires $[M+NH_4]^+$, 256.19125.

4-Benzyloxy-5-[2'-methylprop-(*E*)-ylidene]-cyclopent-2-enone (80)

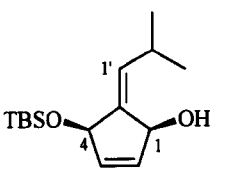


To a solution of alcohol **77** (50 mg, 0.21 mmol) in anhydrous tetrahydrofuran (2 cm^3) at 0 °C was added sodium hexamethyldisilazide (2 M solution in tetrahydrofuran, 0.21 cm^3, 0.42 mmol). After 30 minutes at 0 °C benzyl bromide (75 μl, 0.63 mmol) was added and the reaction mixture was allowed to warm to room temperature over 2 hours, under an atmosphere of nitrogen. The reaction was quenched with sat. aq.

ammonium chloride (5 cm^3) and the product extracted with diethyl ether (2 × 5 cm^3). The combined organic layers were washed with brine (5 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:12) to yield the benzyl pivaloylate (**78**, R=Piv, R^1=Bn) (40 mg, 58%) as a pale yellow oil. The product was tentatively assigned by ^1H NMR (250 MHz) and taken onto the next step without any further characterisation. To a solution of the benzyl pivaloylate (37 mg, 0.11 mmol) in anhydrous dichloromethane (1 cm^3) at 0 °C was added diisobutylaluminium hydride (1 M solution in dichloromethane, 0.25 cm^3, 0.25 mmol). The reaction mixture was stirred at room temperature, under an atmosphere of nitrogen, for 1.5 hours. The reaction was quenched with dichloromethane:methanol (1 cm^3, 1:1) followed by 2 M hydrochloric acid (1 cm^3). The layers were separated and the product was extracted with dichloromethane (2 × 2 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was dissolved in diethyl ether (3 cm^3), the undissolved solid filtered off and the solvent removed *in vacuo*. The crude product was dissolved in anhydrous dichloromethane (2 cm^3) and Dess-Martin periodinane (15% wt. solution in dichloromethane, 0.46 cm^3, 0.17 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour, then diluted with diethyl ether (2 cm^3) and a solution of sat. aq. sodium hydrogencarbonate and sat. aq. sodium thiosulfate (2 cm^3, 1:1); the mixture was allowed to stir for a further 15 minutes. The layers were separated and the product extracted with dichloromethane (2 × 2 cm^3). The combined organic layers were washed with brine (2 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 2:9) to yield the title compound **80** (10 mg, 36% over 2 steps) as a colourless oil; ν_{max}(film)/cm^{-1} 1661, 1709, 2869, 2926,

2960; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.07 (3H, d, *J* 6.6, CH_3), 1.09 (3H, d, *J* 6.4, CH_3), 2.84-2.95 (1H, m, C(2')H), 4.43 (1H, d, *J* 11.3, C*H*H), 4.50 (1H, d, *J* 11.3, CH*H*), 5.35 (1H, m, C(4)H), 6.49 (1H, d, *J* 6.1, C(2)H), 6.60 (1H, d, *J* 10.5, C(1')H), 7.28-7.38 (5H, m, Ph), 7.50 (1H, dd, *J* 2.3 and 6.1, C(3)H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 21.5 (2 × CH_3), 28.1 (CH), 68.1 (CH_2), 75.9, 127.6, 127.7, 128.3 (CH), 131.2 (C), 137.7 (CH), 137.7 (C), 145.8, 155.7 (CH), 194.6 (C); *m/z* (EI) 242 ($[M]^+$, 1%), 151 ($[M-CH_2Ph]^+$, 34), 91 ($[-CH_2Ph]^+$, 100); Found: $[M]^+$, 242.13069. $C_{16}H_{18}O_2$ requires $[M]^+$, 242.13068.

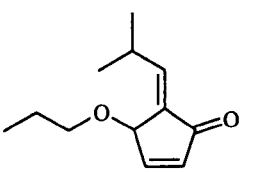
4-(*tert*-Butyldimethylsilanyloxy)-5-[2'-methylprop-(*E*)-ylidene]-cyclopent-2-enol (76)



To a solution of diol **75** (1.0 g, 6.5 mmol),[76] triethylamine (1.36 cm^3, 9.8 mmol) and a catalytic amount of 4-dimethylaminopyridine (0.1 g, 0.85 mmol) in anhydrous dichloromethane (65 cm^3) was added *tert*-butyldimethylsilyl chloride (1.1 g, 7.1 mmol) at 0 °C. The reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 4 days. The reaction was quenched with water (50 cm^3) and the product extracted with dichloromethane (2 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:9) to yield the title compound **76** (0.76 g, 44%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 2858, 2956,

3062, 3406 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.12 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.00 (3H, d, *J* 6.7, CH_3), 1.04 (3H, d, *J* 6.7, CH_3), 2.91-3.00 (1H, m, C(2')H), 4.86 (1H, s, C(1)H), 4.94 (1H, d, *J* 10.3, C(4)H), 5.56 (1H, d, *J* 10.0, C(1')H), 5.94-5.96 (1H, m, C(3)H), 6.02-6.04 (1H, m, C(2)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -3.83, -3.78, (CH_3), 18.6 (C), 23.5, 26.0, 26.3 (CH_3), 28.8, 73.6, 76.1, 136.3, 136.5, 138.8 (CH), 141.9 (C); *m/z* (CI) 286 ($[M+NH_4]^+$, 3%), 268 ($[M]^+$, 4), 251 ($[M+H-H_2O]^+$, 100); Found: $[M+NH_4]^+$, 286.21997. $C_{15}H_{32}NO_2Si$ requires $[M+NH_4]^+$, 286.22025.

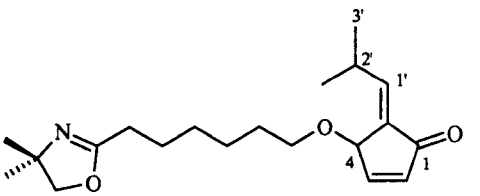
5-[2'-methylprop-(*E*)-ylidene]-4-propoxycyclopent-2-enone (81)



To a solution of alcohol **76** (150 mg, 0.56 mmol) in anhydrous tetrahydrofuran (5 cm^3) at 0 °C was added sodium hexamethyldisilazide (2 M solution in tetrahydrofuran, 0.56 cm^3, 1.12 mmol). After 30 minutes at 0 °C, *n*-propyl iodide (0.16 cm^3, 1.68 mmol) was added and the reaction mixture heated at 40 °C for 30 hours, under an atmosphere of nitrogen. The reaction was quenched with sat. aq. ammonium chloride (10 cm^3) and the product extracted with diethyl ether (2 × 5 cm^3). The combined organic layers were washed with brine (10 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:15) to yield propyl silyl ether (**78**, R=TBS, R^1=*n*-propyl) (100 mg, 57%) as a pale yellow oil. The structure of the

product was tentatively assigned by ^{1}H NMR (250 MHz) and taken onto the next step without any further characterisation. To a solution of the silyl ether (80 mg, 0.26 mmol) in anhydrous tetrahydrofuran (3 cm^3), at 0 °C, was added 4Å molecular sieves and tetra-*n*-butylammonium fluoride (1 M solution in tetrahydrofuran, 0.78 cm^3, 0.78 mmol). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 1 hour. The reaction was diluted with ethyl acetate (3 cm^3) followed by sat. aq. sodium hydrogencarbonate (3 cm^3). The layers were separated and the organic layer was washed with brine (3 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was dissolved in anhydrous dichloromethane (3 cm^3) and Dess-Martin periodinane (15% wt. solution in dichloromethane, 2.2 cm^3, 0.78 mmol) was added; the reaction mixture was stirred at room temperature for 2.5 hours. The reaction mixture was diluted with diethyl ether (3 cm^3) and a solution of sat. aq. sodium hydrogencarbonate and sat. aq. sodium thiosulfate (3 cm^3, 1:1) and the mixture allowed to stir for a further 15 minutes. The layers were separated and the product extracted with dichloromethane (2 × 3 cm^3). The combined organic layers were then dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:9) to yield the title compound **81** (10 mg, 20% over 2 steps) as a colourless oil; ν_{max}(film)/cm^{-1} 1663, 1710, 2872, 2962; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.93 (3H, t, *J* 7.4, CH_3), 1.09 (6H, app. t, *J* 6.7, 2 × CH_3), 1.55-1.66 (2H, m, CH_2), 2.83-2.92 (1H, m, C(2')H), 3.28-3.33 (1H, m, C*H*H), 3.40-3.46 (1H, m, CH*H*), 5.19 (1H, s, C(4)H), 6.47 (1H, d, *J* 6.1, C(2)H), 6.55 (1H, d, *J* 10.3, C(1')H), 7.53 (1H, d, *J* 6.1, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 10.6, 21.8, 21.9 (CH_3), 23.3 (CH_2), 28.5 (CH), 68.0 (CH_2), 76.4 (CH), 131.6 (C), 137.7, 145.7, 156.2 (CH), 194.9 (C); *m/z* (CI) 195 ([M+H]$^+$, 100%); Found: [M+H]$^+$, 195.13855. $C_{12}H_{19}O_2$ requires [M+H]$^+$, 195.13852.

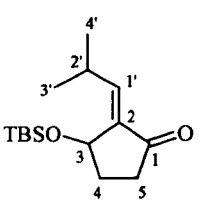
4-[6-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-hexyloxy]-5-[2'-methylprop-(*E*)-ylidene]-cyclopent-2-enone (82)



To a solution of alcohol **76** (100 mg, 0.37 mmol) in anhydrous tetrahydrofuran (4 cm^3) at 0 °C was added sodium hexamethyldisilazide (2 M solution in tetrahydrofuran, 0.28 cm^3, 0.56 mmol). After 30 minutes at 0 °C the iodo-alkyloxazoline (170 mg, 0.56 mmol) was added in anhydrous tetrahydrofuran (1 cm^3) and the reaction mixture was heated at 50 °C for 22 hours, under an atmosphere of nitrogen. The reaction was quenched with sat. aq. ammonium chloride (5 cm^3) and the product extracted with diethyl ether (2 × 5 cm^3). The combined organic layers were washed with brine (5 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:4) to yield the alkyl silyl ether (**78**, R=TBS, R^1=alkyl) (67 mg, 40%) as a colourless oil. The structure of the product was tentatively assigned by ^1H NMR (250 MHz) and taken onto the next step without any further characterisation. To a solution of the alkyl silyl ether (95 mg, 0.21 mmol) in anhydrous tetrahydrofuran (2 cm^3), at 0 °C, was added 4Å molecular sieves and tetra-*n*-butylammonium fluoride (1 M solution in tetrahydrofuran, 0.63 cm^3, 0.63 mmol). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 3 hours. The reaction was diluted with ethyl acetate (3 cm^3) followed by sat. aq. sodium hydrogencarbonate (3 cm^3). The layers were separated and the organic layer was washed with brine (3 cm^3), dried

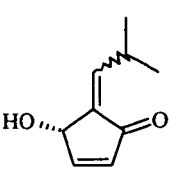
($MgSO_4$) and the solvent removed *in vacuo*. The crude product was dissolved in anhydrous dichloromethane (5 cm^3) and pyridinium dichromate (94 mg, 0.25 mmol) was added; the reaction mixture stirred at room temperature for 0.5 hour. The reaction mixture was filtered through a pad of silica gel and eluted with dichloromethane (3 × 5 cm^3) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:1) to yield the title compound **82** (14 mg, 20% over 2 steps) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1664, 1709, 2867, 2932, 2962; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.07 (3H, d, *J* 6.4, CH_3), 1.09 (3H, d, *J* 6.4, CH_3), 1.26 (6H, s, 2 × CH_3), 1.36 (2H, m, CH_2), 1.56-1.64 (6H, m, 3 × CH_2), 2.24 (2H, t, *J* 7.6, CH_2), 2.80-2.90 (1H, m, C(2')H), 3.30-3.36 (1H, m, C*H*H), 3.42-3.47 (1H, m, CH*H*), 3.90 (2H, s, CH_2), 5.18 (1H, s, C(4)H), 6.47 (1H, d, *J* 5.9, C(2)H), 6.54 (1H, d, *J* 10.5, C(1')H), 7.52 (1H, dd, *J* 1.9 and 5.9, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.8, 21.9 (CH_3), 25.8, 25.9, 28.0 (CH_2), 28.4 (CH_3), 28.5 (CH), 29.0, 29.9, 66.2 (CH_2), 66.8 (C), 76.4 (CH), 78.9 (CH_2), 131.6 (C), 137.7, 145.6, 156.2 (CH), 166.1, 194.9 (C); *m/z* (CI) 334 ($[M+H]^+$, 18%), 200 ($[C_{11}H_{20}NO+NH_4]$+, 96), 137 ($[M-C_{11}H_{20}NO-CH_3+H]^+$, 100); Found: $[M+H]^+$, 334.23887. $C_{20}H_{32}NO_3$ requires $[M+H]^+$, 334.23822.

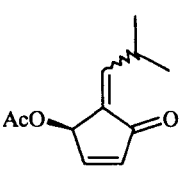
3-(*tert*-Butyldimethylsilanyloxy)-2-[2'-methylprop-(*E*)-ylidene]-cyclopentanone (84)



To a solution of a catalytic amount of $[(Ph_3P)CuH]_6$ (15 mg) in toluene (0.75 cm^3) was added phenyl silane (23 μl, 0.19 mmol) and enone **53** (42 mg, 0.16 mmol). After 5 hours, the reaction was diluted with diethyl ether (5 cm^3) and the organic layer washed with sat. aq. ammonium chloride (2 × 5 cm^3), sat. aq. sodium hydrogencarbonate (2 × 5 cm^3) and brine (2 × 5 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by preparative TLC (SiO_2; EtOAc:*n*-hexane, 1:4) to yield the title compound **84** (12 mg, 29%) as a colourless oil; ν_{max}(film)/cm^{-1} 1654, 1725, 2342, 2858, 2959; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.12 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.03 (3H, d, *J* 6.6, CH_3), 1.07 (3H, d, *J* 6.6, CH_3), 1.92-2.07 (2H, m, C(4)H), 2.16-2.58 (2H, m, C(5)H), 2.72-2.79 (1H, m, C(2')H), 4.98 (1H, m, C(3)H), 6.44 (1H, d, *J* 10.6, C(1')H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -4.8, -4.1 (CH_3), 17.9 (C), 22.1, 25.7, 28.3 (CH_3), 31.2, 35.7 (CH_2), 69.8, 77.2, 146.6 (CH), 149.5, 206.2 (C); *m/z* (CI) 286 ($[M+NH_4]^+$, 27%), 269 ($[M+H]^+$, 35), 154 ($[M+H\text{-}Si(CH_3)_2C(CH_3)_3]^+$, 62), 137 ($[M\text{-}OSi(CH_3)_2C(CH_3)_3]^+$, 100); Found: $[M+H]^+$, 269.19340. $C_{15}H_{29}O_2Si$ requires $[M+H]^+$, 269.19370.

(*S*)-4-Hydroxy-5-[2'-methylprop-(*E*/*Z*)-ylidene]-cyclopent-2-enones (50) and (51) and (*R*)-acetic acid 5-isobut-(*E*/*Z*)-ylidene-4-oxocyclopent-2-enyl ester





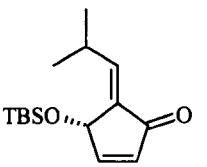
To a solution of a mixture of racemic alcohols **50** and **51** (1.15 g, 7.6 mmol) in toluene (350 cm^3) was added vinyl acetate (1.4 cm^3, 15.2 mmol) and *Pseudomonas*

cepacia lipase (5.0 g) and the reaction stirred at room temperature for 72 hours. The reaction mixture was filtered and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 3:7) to yield an inseparable mixture of the chiral alcohols **50** and **51** (620 mg, 42%) as a yellow oil, as well as both geometric isomers of the acetates (460 mg, 31%); ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) for the alcohols were identical to those of the racemic compounds, and were taken on to the next step as a mixture.

(*Z*)-acetate: ν_{max}(film)/cm^{-1} 1655, 1708, 1738, 2361, 2963; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.03 (3H, d, *J* 6.6, CH_3), 1.04 (3H, d, *J* 6.6, CH_3), 2.13 (3H, s, CH_3), 3.83-3.92 (1H, m, C(2')H), 6.13 (1H, d, *J* 10.1, C(1')H), 6.15-6.16 (1H, m, C(4)H), 6.44 (1H, d, *J* 6.1, C(2)H), 7.34 (1H, dd, *J* 2.5 and 6.1, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.5, 14.6, 22.6 (CH_3), 26.4, 73.4 (CH), 130.6 (C), 140.3, 151.4, 152.8 (CH), 171.5, 195.0 (C); *m/z* (CI) 195 ([M+H]$^+$, 100%); Found: [M+H]$^+$, 195.10201. $C_{11}H_{15}O_3$ requires [M+H]$^+$, 195.10211.

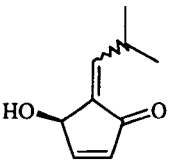
(*E*)-acetate: ν_{max}(film)/cm^{-1} 1666, 1715, 1738, 2872, 2964; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.08 (3H, d, *J* 6.6, CH_3), 1.09 (3H, d, *J* 6.6, CH_3), 2.13 (3H, s, CH_3), 2.53-2.57 (1H, m, C(2')H), 6.34-6.36 (1H, m, C(4)H), 6.51 (1H, d, *J* 6.0, C(2)H), 6.55 (1H, d, *J* 10.7, C(1')H), 7.45 (1H, dd, *J* 2.6 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.3, 22.17, 22.21 (CH_3), 29.5, 71.3 (CH), 130.8 (C), 138.8, 146.4, 153.7 (CH), 170.9, 194.5 (C); *m/z* (CI) 195 ([M+H]$^+$, 100%); Found: [M+H]$^+$, 195.10201. $C_{11}H_{15}O_3$ requires [M+H]$^+$, 195.10211.

(*S*)-4-(*tert*-Butyldimethylsilanyloxy)-5-[2'-methylprop-(*E*)-ylidene]-cyclopent-2-enone (53)



To a solution of *tert*-butyldimethylsilyl chloride (77 mg, 0.57 mmol), triethylamine (0.2 cm^3, 1.4 mmol) and a catalytic amount of 4-dimethylaminopyridine (6 mg, 0.05 mmol) in anhydrous dichloromethane (1 cm^3) was added a solution of optically active alcohols **50** and **51** (60 mg, 0.4 mmol) in anhydrous dichloromethane (3 cm^3) dropwise at 0 °C, under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature over 72 hours, then quenched with water (5 cm^3) and the product extracted with dichloromethane (3 × 5 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:10) to yield the title compound **53** (13 mg, 12%) as a yellow solid; $[\alpha]_D^{20}$ +212.5 (c1.3, $CHCl_3$); t_r 20.7 minutes, >99% ee (Chrompack Chirasil-Dex CB column); ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) analysis of the product were identical to the spectra of the racemic material.

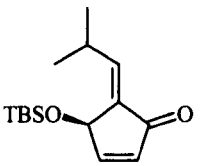
(*R*)-4-Hydroxy-5-[2'-methylprop-(*E*/*Z*)-ylidene]-cyclopent-2-enone (50) and (51)



To a mixture of the optically active acetates (460 mg, 2.37 mmol) in water (50 cm^3) was added *Pseudomonas cepacia* lipase (1.0 g) and the mixture was stirred overnight at room temperature. The product was extracted with diethyl ether (3 × 20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an inseparable mixture of the title compounds **50** and **51** (360 mg, 100%) as a pale yellow oil; $[\alpha]_D^{20}$ -154.5 (c0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 1660, 1699, 2871, 2962, 3397 br.; *m/z* (CI) 152 ($[M]^+$, 16%), 109 ($[M\text{-}CH(CH_3)_2]^+$, 96); Found: $[M]^+$, 152.08371. $C_9H_{12}O_2$ requires $[M]^+$, 152.08374; NMR data for the (*E*)-isomer: δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.10 (3H, d, *J* 6.7, CH_3), 1.12 (3H, d, *J* 6.7, CH_3), 2.92-3.01 (1H, m, C(2')H), 5.31 (1H, m, C(4)H), 6.40 (1H, d, *J* 6.0, C(2)H), 6.51 (1H, d, *J* 10.5, C(1')H), 7.46 (1H, dd, *J* 2.5 and 6.0, C(3)H).

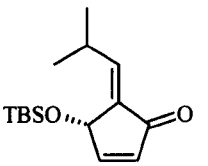
NMR data for the (*Z*)-isomer: δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.03 (3H, d, *J* 6.7, CH_3), 1.06 (3H, d, *J* 6.7, CH_3), 3.81-3.87 (1H, m, C(2')H), 5.07 (1H, m, C(4)H), 6.17 (1H, d, *J* 10.0, C(1')H), 6.35 (1H, d, *J* 6.0, C(2)H), 7.38 (1H, dd, *J* 2.3 and 6.0, C(3)H).

(*R*)-4-(*tert*-Butyldimethylsilanyloxy)-5-[2'-methylprop-(*E*)-ylidene]-cyclopent-2-enone (53)



To a solution of *tert*-butyldimethylsilyl chloride (0.46 g, 3.1 mmol), triethylamine (0.5 cm^3, 3.6 mmol) and a catalytic amount of 4-dimethylaminopyridine (38 mg, 0.31 mmol) in anhydrous dichloromethane (20 cm^3) was added a solution of alcohols **50** and **51** (360 mg, 2.4 mmol) in anhydrous dichloromethane (5 cm^3) dropwise at 0 °C, under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature over 72 hours, then quenched with water (20 cm^3) and the product extracted with dichloromethane (3 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:9) to yield the title compound **53** (160 mg, 38%) as a yellow solid; m.p. 41-42 °C (Et_2O); $[\alpha]_D^{20}$ -163.1 (c1.6, $CHCl_3$); t_r 20.2 minutes, >99% ee (Chrompack Chirasil-Dex CB column); ^1H NMR (250 MHz) analysis of the product was identical to the spectra of the racemic material.

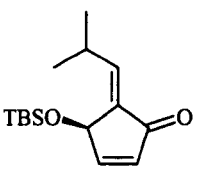
(*S*)-4-(*tert*-Butyldimethylsilanyloxy)-5-[2'-methylprop-(*E*)-ylidene]-cyclopent-2-enone (53)



To a solution of anhydrous diisopropylamine (0.33 cm^3, 2.4 mmol) in anhydrous tetrahydrofuran (2.4 cm^3) at -78 °C was added *n*-butyl lithium (2.5 M in hexanes, 0.94 cm^3, 2.4 mmol) dropwise under an atmosphere of nitrogen. The reaction mixture was allowed to warm to 0 °C for 15 minutes, then tetrahydrofuran (0.3 cm^3) was added and the reaction mixture cooled back down to -78 °C. (*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-2-enone **31** (0.5 g, 2.4 mmol)[88] in anhydrous tetrahydrofuran (0.6 cm^3) was added slowly and the reaction stirred at -78 °C for 25 minutes. Isobutyraldehyde (0.43 cm^3, 4.7 mmol) was added rapidly and the reaction stirred for 5 hours at -78 °C. The reaction was quenched with sat. aq. ammonium chloride (5 cm^3) and the product extracted with diethyl ether (3 × 5 cm^3). The combined organic layers were washed with 0.1 M hydrochloric acid (2 × 5 cm^3) and brine (2 × 5 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a crude yellow oil (0.67 g). This crude material was dissolved in pyridine (1.7 cm^3) and acetic anhydride (0.9 cm^3, 9.4 mmol) and 4-dimethylaminopyridine (42 mg, 0.34 mmol) were added. The reaction mixture was heated at 60 °C for 6 hours, then cooled to room temperature and water (8 cm^3) was added. The product was extracted with diethyl ether (3 × 10 cm^3) and the combined organic layers washed with 0.1 M hydrochloric acid (2 × 10 cm^3) and brine (2 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and the

solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:10) to yield the title compound **53** (34 mg, 5%) as a yellow solid; $[\alpha]_D^{20}$ +136.4 (c1.7, $CHCl_3$); t_r 20.7 minutes, >99% ee (Chrompack Chirasil-Dex CB column); ^1H NMR (200 MHz) analysis was identical to that of the compound made *via* enzyme resolution.

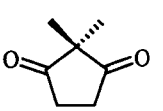
(*R*)-4-(*tert*-Butyldimethylsilanyloxy)-5-[2'-methylprop-(*E*)-ylidene]-cyclopent-2-enone (53)



To a solution of anhydrous diisopropylamine (0.33 cm^3, 2.4 mmol) in anhydrous tetrahydrofuran (2.4 cm^3) at -78 °C was added *n*-butyl lithium (2.5 M in hexanes, 0.94 cm^3, 2.4 mmol) dropwise under an atmosphere of nitrogen. The reaction mixture was allowed to warm to 0 °C for 15 minutes, then tetrahydrofuran (0.3 cm^3) was added and the reaction mixture cooled back down to -78 °C. (*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-2-enone **31** (0.5 g, 2.4 mmol)[88] in anhydrous tetrahydrofuran (0.6 cm^3) was added slowly and the reaction stirred at -78 °C for 30 minutes. Isobutyraldehyde (0.43 cm^3, 4.73 mmol) was added rapidly and the reaction stirred for 5 hours at -78 °C. The reaction was quenched with sat. aq. ammonium chloride (5 cm^3) and the product extracted with diethyl ether (3 × 5 cm^3). The combined organic layers were then washed with 0.1 M hydrochloric acid (2 × 5 cm^3) and brine (2 × 5 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a crude yellow oil

(1.3 g). This crude material was dissolved in pyridine (3.3 cm^3) and acetic anhydride (1.8 cm^3, 19.1 mmol) and 4-dimethylaminopyridine (80 mg, 0.65 mmol) added. The reaction mixture was then heated at 60 °C for 6 hours, then cooled to room temperature before water (16 cm^3) was added. The product was extracted with diethyl ether (3 × 10 cm^3) and the combined organic layers washed with 0.1 M hydrochloric acid (2 × 10 cm^3) and brine (2 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:10) to yield the title compound **53** (27 mg, 4%) as a yellow solid; $[\alpha]_D^{20}$ -133.0 (c1.2, $CHCl_3$); t_r 20.2 minutes, >99% ee (Chrompack Chirasil-Dex CB column); ^1H NMR (250 MHz) analysis was identical to that of the compound made *via* enzyme resolution.

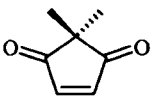
2,2-Dimethylcyclopentane-1,3-dione (98)



2-Methylcyclopentane-1,3-dione **97** (20.0 g, 0.18 mol) and potassium hydroxide (11.0 g, 0.20 mol) were suspended in 1,4-dioxane (125 cm^3) and water (42 cm^3). Methyl iodide (33.3 cm^3, 0.53 mol) was added in one portion and the reaction mixture heated under reflux for 20 hours. The reaction mixture was allowed to cool to room temperature and the product extracted with ethyl acetate (4 × 250 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 3:2) to yield the title compound **98** (11 g, 49%) as a pale yellow crystalline solid;

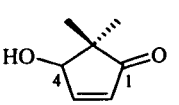
ν_{max}(film)/cm^{-1} 1732, 2356, 2871, 2931, 2975; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.15 (6H, s, 2 × CH_3), 2.80 (4H, s, 2 × CH_2); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.6 (2 × CH_3), 34.9 (2 × CH_2), 53.0 (C), 216.6 (2 × C); *m/z* (EI) 126 ([M]$^+$, 100%), 111 ([M-CH_3]$^+$, 85); Found: [M]$^+$, 126.06821. $C_7H_{10}O_2$ requires [M]$^+$, 126.06808.

2,2-Dimethylcyclopent-4-ene-1,3-dione (92)



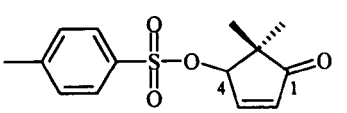
To a solution of saturated dione **98** (7.0 g, 56 mmol) in methanol (100 cm^3) was added copper(II) bromide (24.8 g, 0.11 mmol) and the reaction mixture heated under reflux for 4 hours. The reaction mixture was allowed to cool to room temperature, filtered through Celite, washed with dichloromethane (3 × 30 cm^3), and the solvent removed *in vacuo* to yield the title compound **92** (5.63 g, 82%) as a yellow oil; ν_{max}(film)/cm^{-1} 1704; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.17 (6H, s, 2 × CH_3), 7.20 (2H, s, 2 × CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.0 (CH_3), 46.8 (C), 147.4 (CH), 208.1 (C); *m/z* (EI) 124 ([M]$^+$, 100%); Found: [M]$^+$, 124.05212. $C_7H_8O_2$ requires [M]$^+$, 124.05243.

4-Hydroxy-5,5-dimethylcyclopent-2-enone (99)



To a solution of enedione **92** (300 mg, 2.4 mmol) and cerium(III) chloride heptahydrate (1.08 g, 2.9 mmol) in isopropanol (6 cm^3) at -78 °C was added sodium trimethoxy borohydride (371 mg, 2.9 mmol) portionwise over 5 minutes. After 30 minutes, the reaction was diluted with ethyl acetate (10 cm^3), followed by sat. aq. ammonium chloride (5 cm^3). The aqueous layer was extracted with ethyl acetate (3 × 10 cm^3) and the combined organic layers washed successively with water (2 × 10 cm^3) and brine (10 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 3:7) to yield the title compound **99** (50 mg, 16%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1704, 2973, 3418 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.08 (3H, s, CH_3), 1.16 (3H, s, CH_3), 4.59 (1H, m, C(4)H), 6.20 (1H, dd, *J* 1.4 and 5.8, C(2)H), 7.47 (1H, dd, *J* 2.2 and 5.8, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.1, 22.7 (CH_3), 48.2 (C), 79.7, 132.6, 160.9 (CH), 211.9 (C); *m/z* (EI) 126 ($[M]^+$, 31%), 111 ($[M-CH_3]^+$, 100); Found: $[M]^+$, 126.06797. $C_7H_{10}O_2$ requires $[M]^+$, 126.06808.

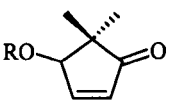
Toluene-4-sulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (96)



To a solution of alcohol **99** (18 mg, 0.14 mmol) and 4-dimethylaminopyridine (11 mg, 0.09 mmol) in anhydrous dichloromethane (0.5 cm^3) was added triethylamine (20 µl, 0.14 mmol) and *p*-toluenesulfonyl chloride (32 mg, 0.17 mmol). The reaction mixture was stirred at room temperature for 24 hours, diluted with water (1 cm^3) and the product extracted with dichloromethane (3 × 1 cm^3), dried ($MgSO_4$) and the solvent

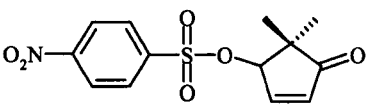
removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **96** (29 mg, 73%) as a pale yellow solid; Found: C, 59.98; H, 5.74. $C_{14}H_{16}O_4S$ requires C, 59.98; H, 5.75%; ν_{max}(film)/cm^{-1} 1598, 1727, 2976; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.03 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.48 (3H, s, $ArCH_3$), 5.19-5.20 (1H, m, C(4)H), 6.27 (1H, dd, *J* 1.4 and 6.0, C(2)H), 7.28 (1H, dd, *J* 2.3 and 6.0, C(3)H), 7.40 (2H, d, *J* 8.1, 2 × CH), 7.85 (2H, d, *J* 8.1, 2 × CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.7, 21.7, 22.3 (CH_3), 47.3 (C), 86.2, 127.9, 130.1 (CH), 133.3 (C), 134.9 (CH), 145.5 (C), 155.5 (CH), 208.5 (C); *m/z* (CI) 298 ($[M+NH_4]^+$, 43%); Found: $[M+NH_4]^+$, 298.11128. $C_{14}H_{20}NO_4S$ requires $[M+NH_4]^+$, 298.11130.

Preparation of analogues of 96 *via* parallel synthesis.



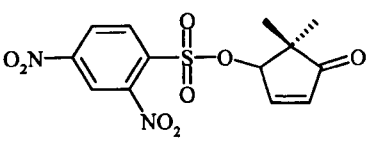
A stock solution of alcohol **99** (0.55 g, 4.4 mmol) in anhydrous dichloromethane (33 cm^3) was split between eleven reaction wells of a parallel synthesiser. To each well was added triethylamine (67 μl, 0.48 mmol) and a catalytic amount 4-dimethylaminopyridine followed by the appropriate alkylating agent (0.48 mmol). The reactions were stirred under an atmosphere of nitrogen for 45 hours. Water (3 cm^3) was added to each well and the mixtures passed through individual phase separators. The aqueous phase was then washed with dichloromethane (5 cm^3) and the organic solvent removed from each product *in vacuo*.

4-Nitrobenzenesulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (104)



The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **104** (88 mg, 71%) as an off-white solid; m.p. 117-118 °C (from dichloromethane); Found: C, 50.37; H, 4.18; N, 4.39. $C_{13}H_{13}NO_6S$ requires C, 50.15; H, 4.20; N, 4.47%; ν_{max}(film)/cm^{-1} 1189, 1352, 1538, 1725, 2978, 3109; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.08 (3H, s, CH_3), 1.13 (3H, s, CH_3), 5.37 (1H, m, C(4)H), 6.34 (1H, dd, *J* 1.3 and 5.8, C(2)H), 7.31 (1H, dd, *J* 2.3 and 5.8, C(3)H), 8.18 (2H, d, *J* 8.8, 2 × CH), 8.46 (2H, d, *J* 8.8, 2 × CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.7, 22.5 (CH_3), 47.3 (C), 87.4, 124.6, 129.2, 135.6 (CH), 142.0, 151.0 (C), 154.3 (CH), 207.7 (C); *m/z* (CI) 329 ($[M+NH_4]^+$, 16%), 109 ($[M\text{-}OSO_2\text{-}p\text{-}NO_2Ph]^+$, 100); Found: $[M+NH_4]^+$, 329.08023. $C_{13}H_{17}N_2O_6S$ requires ($[M+NH_4]^+$, 329.08075.

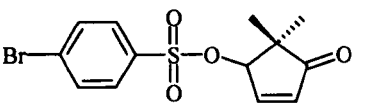
2,4-Dinitrobenzenesulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (105)



The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **105** (15 mg, 11%) as a yellow solid; m.p. 113 °C dec. (from dichloromethane); ν_{max}(film)/cm^{-1} 1190, 1351, 1539, 1557, 1724, 2359, 2918,

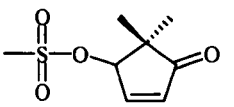
3107; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.16 (3H, s, CH_3), 1.25 (3H, s, CH_3), 5.64-5.65 (1H, m, C(4)H), 6.40 (1H, dd, *J* 1.1 and 6.0, C(2)H), 7.47 (1H, dd, *J* 2.3 and 6.0, C(3)H), 8.39-8.67 (3H, m, 3 × CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.8, 22.4 (CH_3), 47.6 (C), 89.7, 120.5, 126.9, 133.3 (CH), 135.1 (C), 136.1, 153.8 (CH), 183.8, 189.4, 207.4 (C); *m/z* (EI) 356 ($[M]^+$, 0.2%), 109 ($[M\text{-}OSO_2\text{-}2,4\text{-dinitro-Ph}]^+$, 100); Found: $[M]^+$, 356.03102. $C_{13}H_{12}N_2O_8S$ requires $[M]^+$, 356.03146.

4-Bromobenzenesulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (106)



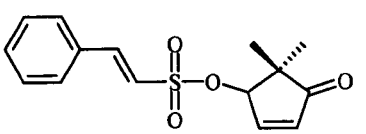
The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **106** (110 mg, 80%) as a white solid; m.p. 99-100 °C (from dichloromethane); Found: C, 45.45; H, 3.82. $C_{13}H_{13}{}^{79}BrO_4S$ requires C, 45.23; H, 3.79%; ν_{max}(film)/cm^{-1} 1189, 1372, 1723, 2975; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.06 (3H, s, CH_3), 1.08 (3H, s, CH_3), 5.25-5.26 (1H, m, C(4)H), 6.31 (1H, dd, *J* 1.4 and 5.9, C(2)H), 7.29 (1H, dd, *J* 2.3 and 5.9, C(3)H), 7.76 (2H, d, *J* 8.8, 2 × CH), 7.83 (2H, d, *J* 8.8, 2 × CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.1, 22.8 (CH_3), 47.7 (C), 87.0, 129.7 (CH), 130.0 (C), 133.3, 135.6 (CH), 135.7 (C), 155.4 (CH), 208.6 (C); *m/z* (EI) 346 ($[M^{81}Br]^+$, 3%), 344 ($[M^{79}Br]^+$, 3), 109 ($[M\text{-}OSO_2\text{-}p\text{-}^{79}BrPh]^+$, 100); Found: $[M]^+$, 343.97112. $C_{13}H_{13}BrO_4S$ requires $[M]^+$, 343.97180.

Methanesulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (107)



The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 3:2) to yield the title compound **107** (67 mg, 83%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1176, 1360, 1468, 1716, 2342, 2978; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.15 (3H, s, CH_3), 1.25 (3H, s, CH_3), 3.13 (3H, s, -SO_2CH_3), 5.43-5.44 (1H, m, C(4)H), 6.36 (1H, dd, *J* 1.3 and 5.9, C(2)H), 7.47 (1H, dd, *J* 2.4 and 5.9, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.0, 22.9, 38.8 (CH_3), 47.7 (C), 85.5, 135.6, 155.7 (CH), 208.9 (C); *m/z* (EI) 204 ([M]$^+$, 6%), 109 ([M-OSO_2CH_3]$^+$, 100); Found: [M]$^+$, 204.04592. $C_8H_{12}O_4S$ requires [M]$^+$, 204.04564.

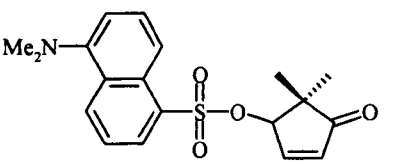
2-Phenylethenesulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (108)



The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **108** (57 mg, 20%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1168, 1361, 1716, 2360, 2977, 3063, 3426; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.16 (3H, s, CH_3), 1.21 (3H, s, CH_3), 5.31-5.32 (1H, m, C(4)H), 6.32 (1H, dd, *J* 1.4 and 5.9, C(2)H), 6.82 (1H, d, *J* 15.4, CH-alkene), 7.43-7.55 (6H, m, Ph and C(3)H), 7.68 (1H,

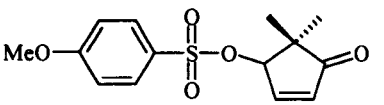
d, *J* 15.4, CH-alkene); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.8, 22.6 (CH_3), 47.4 (C), 86.2, 121.3, 128.6, 129.3, 131.7 (CH), 131.8 (C), 135.0, 145.4, 155.4 (CH), 208.4 (C); *m/z* (EI) 292 ($[M]^+$, 3%), 109 ($[M\text{-}OSO_2\text{-}CH{=}CH\text{-}Ph]^+$, 100); Found: $[M]^+$, 292.07700. $C_{15}H_{16}O_4S$ requires $[M]^+$, 292.07693.

5-Dimethylaminonaphthalene-1-sulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (109)



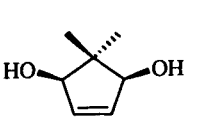
The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **109** (92 mg, 65%) as a bright yellow oil; ν_{max}(film)/cm^{-1} 1178, 1361, 1724, 2359, 2941; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.86 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.91 (6H, s, $-N(CH_3)_2$), 5.08-5.09 (1H, m, C(4)H), 6.20 (1H, dd, *J* 1.3 and 5.9, C(2)H), 7.19 (1H, dd, *J* 2.2 and 5.9, C(3)H), 7.24 (1H, d, *J* 8.1, CH), 7.57 (1H, app. t, *J* 7.9, CH), 7.62 (1H, app. t, *J* 8.1, CH), 8.28 (1H, d, *J* 8.1, CH), 8.32 (1H, d, *J* 7.9, CH), 8.65 (1H, d, *J* 7.9, CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.2, 22.3, 45.8 (CH_3), 47.9 (C), 87.2, 116.2, 119.8, 123.4, 129.3 (CH), 130.1, 130.2 (C), 131.0 (CH), 131.7 (C), 132.4, 135.1 (CH), 151.8 (C), 155.9 (CH), 208.7 (C); *m/z* (EI) 359 ($[M]^+$, 19%), 251 ($[H{+}OSO_2\text{-}5\text{-}NMe_2\text{-}Naphthyl]^+$, 100); Found: $[M]^+$, 359.11970. $C_{19}H_{21}NO_4S$ requires $[M]^+$, 359.11914.

4-Methoxybenzenesulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (103)



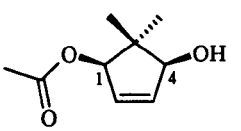
To a solution of alcohol **99** (40 mg, 0.32 mmol) and 4-dimethylaminopyridine (5 mg, 0.04 mmol) in anhydrous dichloromethane (3.5 cm^3) was added triethylamine (58 μl, 0.42 mmol) and *p*-methoxybenzenesulfonyl chloride (79 mg, 0.38 mmol). The reaction mixture was stirred at room temperature for 24 hours, diluted with water (3 cm^3) and the product extracted with dichloromethane (3 × 3 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **103** (54 mg, 58%) as a colourless oil; ν_{max}(film)/cm^{-1} 1579, 1595, 1717, 2359, 2974; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.05 (6H, s, 2 × CH_3), 3.91 (3H, s, -OCH_3), 5.19 (1H, m, C(4)H), 6.26 (1H, dd, *J* 1.4 and 5.9, C(2)H), 7.05 (2H, d, *J* 9.0, 2 × CH), 7.29 (1H, dd, *J* 2.3 and 5.9, C(3)H), 7.89 (2H, d, *J* 9.0, 2 × CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.1, 22.8 (CH_3), 47.7 (C), 56.1 (CH_3), 86.4, 115.0 (CH), 128.1 (C), 130.5, 135.2, 155.9 (CH), 164.5, 208.8 (C); *m/z* (EI) 296 ($[M]^+$, 11%), 171 ($[SO_2$-*p*-OMePh$]^+$, 100); Found: $[M]^+$, 296.07191. $C_{14}H_{16}O_5S$ requires $[M]^+$, 296.07184.

2,2-Dimethylcyclopent-4-ene-1,3-diol (110)



To a solution of enedione **92** (2.53 g, 20.4 mmol) and cerium(III) chloride heptahydrate (16.7 g, 44.9 mmol) in methanol (80 cm^3) at -78 °C was added sodium borohydride (1.7 g, 44.9 mmol) portionwise over 20 minutes. After 30 minutes, the reaction was allowed to warm to room temperature for 1 hour and the reaction quenched with sat. aq. ammonium chloride (80 cm^3). The aqueous layer was extracted with ethyl acetate (3 × 80 cm^3) and the combined organic layers dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title compound **110** (2.56 g, 99%) as a colourless crystalline solid. ν_{max}(film)/cm^{-1} 3258 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.04 (6H, s, 2 × CH_3), 1.62 (2H, br. s, 2 × -OH), 4.09 (2H, br. s, 2 × -C*H*OH), 6.02 (2H, s, -C*H*=C*H*-); δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.7 (CH_3), 46.6 (C), 83.2, 136.4 (CH); *m/z* (CI) 146 ($[M+NH_4]^+$, 86%), 128 ($[M]^+$, 63), 111 ($[M+H-H_2O]^+$, 100); Found: $[M+NH_4]^+$, 146.11792. $C_7H_{16}NO_2$ requires $[M+NH_4]^+$, 146.11809.

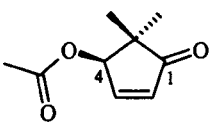
(1*R*,4*S*)-Acetic acid 4-hydroxy-5,5-dimethylcyclopent-2-enyl ester (111)



To a solution of diol **110** (4.0 g, 31.3 mmol) in toluene (40 cm^3) was added lipase PS-C Amano II (1.0 g) followed by vinyl acetate (14 cm^3, 156.5 mmol) and the reaction stirred at room temperature for 5 days. The enzyme was filtered off and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:1) to yield the title compound **111** (3.64 g, 69%) as a colourless oil; $[\alpha]_D$ -66.4 (c2.1, $CHCl_3$, lit.[92] -93.4 (c0.7, $CHCl_3$)); Found C, 63.24; H, 8.39. $C_9H_{14}O_3$ requires C, 63.51; H, 8.29%; ν_{max}(film)/cm^{-1} 1732, 3428 br.; δ_H (400

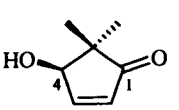
MHz; $CDCl_3$; Me_4Si) 0.99 (3H, s, CH_3), 1.11 (3H, s, CH_3), 2.07 (3H, s, CH_3), 4.09 (1H, br. s, C(4)H), 5.20 (1H, br. s, C(1)H), 5.92 (1H, dd, *J* 1.5 and 5.8, C(3)H), 6.11 (1H, dd, *J* 1.4 and 5.8, C(2)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 17.2, 21.4, 27.4 (CH_3), 45.7 (C), 83.3, 84.2, 132.7, 138.3 (CH), 171.0 (C); *m/z* (CI) 188 ($[M+NH_4]^+$, 49%), 153 ($[M+H-H_2O]^+$, 100), 111 ($[M-OCOCH_3]^+$, 55); Found: $[M+NH_4]^+$, 188.12809. $C_9H_{18}NO_3$ requires $[M+NH_4]^+$, 188.12866.

(*R*)-Acetic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (95)



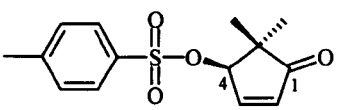
A solution of alcohol **111** (1.0 g, 5.9 mmol) and 4Å molecular sieves (2.6 g) in anhydrous dichloromethane (30 cm^3) was stirred at room temperature for 30 minutes under an atmosphere of nitrogen. Pyridinium dichromate (2.66 g, 7.1 mmol) was added and the reaction stirred at room temperature for 5 hours. The reaction mixture was filtered through a pad of silica and the solvent removed *in vacuo* to yield the title compound **95** (0.9 g, 91%) as a pale yellow oil; the ^1H NMR (250 MHz) spectrum was identical to that of the racemic compound and the compounds was taken onto the next step without further characterisation.

(*R*)-4-Hydroxy-5,5-dimethylcyclopent-2-enone (99)



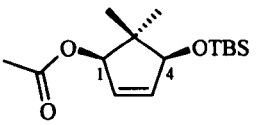
To a solution of acetate **95** (0.9 g, 5.4 mmol) in dimethoxyethane (270 cm^3) at 0 °C was added an aqueous solution of lithium hydroxide (1 M, 250 cm^3). After 5 minutes the reaction was diluted with ethyl acetate (250 cm^3) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 × 250 cm^3) and the combined organic layers washed with brine (250 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:2) to yield the title compound **99** (0.33 g, 48%) as a white solid; The ^1H NMR (200 MHz) spectrum was identical to that of the racemic compound; t_r 13.8 minutes, 97% ee (Lipodex E column).

(*R*)-Toluene-4-sulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (96)



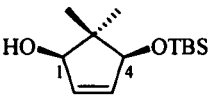
To a solution of alcohol **99** (300 mg, 2.4 mmol) and *p*-toluenesulfonic anhydride (1.17 g, 3.6 mmol) in anhydrous dichloromethane (25 cm^3) was added triethylamine (0.5 cm^3, 3.6 mmol) and a catalytic amount of 4-dimethylaminopyridine and the reaction stirred for 3 hours. The reaction was diluted with water (25 cm^3) and the layers separated. The aqueous layer was extracted with dichloromethane (2 × 25 cm^3) and the combined organic layers washed with brine (25 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **96** (222 mg, 33%) as a pale yellow solid; $[\alpha]_D^{20}$ -46.9 (c1.6, $CHCl_3$); The ^1H NMR (200 MHz) spectrum was identical to that of the racemic compound.

(1*R*,4*S*)-Acetic acid 4-(*tert*-butyldimethylsilanyloxy)-5,5-dimethylcyclopent-2-enyl ester (112)



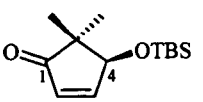
To a solution of alcohol **111** (1.5 g, 8.8 mmol) in anhydrous dimethylformamide (10 cm^3) was added imidazole (1.2 g, 17.6 mmol) and *tert*-butyldimethylsilyl chloride (1.6 g, 10.6 mmol) and the reaction stirred at room temperature for 16 hours. The reaction mixture was extracted with diethyl ether (3 × 10 cm^3) and the organic layers combined and washed with water (20 cm^3), brine (20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:10) to yield the title compound **112** (2.39 g, 95%) as a colourless oil; $[\alpha]_D^{20}$ +18.7 (c2.0, $CHCl_3$, lit.[92] +19.2 (c1.4, $CHCl_3$)); ν_{max}(film)/cm^{-1} 1742, 2957; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.08 (6H, s, $Si(CH_3)_2$), 0.87 (3H, s, CH_3), 0.91 (9H, s, $SiC(CH_3)_3$), 1.12 (3H, s, CH_3), 2.07 (3H, s, CH_3), 4.18 (1H, s, CH), 5.23 (1H, s, CH), 5.75-5.77 (1H, m, CH-alkene), 5.87-5.89 (1H, m, CH-alkene); δ_C (100 MHz; $CDCl_3$; Me_4Si) -4.4, -4.1, 17.6 (CH_3), 18.6 (C), 21.5, 26.2, 26.9 (CH_3), 47.7 (C), 83.1, 84.2, 130.6, 137.9 (CH), 171.4 (C); *m/z* (CI) 285 ($[M+H]^+$, 3%), 225 ($[M-OCOCH_3]^+$, 100); Found: $[M+H]^+$, 285.18807. $C_{15}H_{29}O_3Si$ requires $[M+H]^+$, 285.18860.

(1*R*,4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-5,5-dimethylcyclopent-2-enol



To a solution of acetate **112** (2.3 g, 8.1 mmol) in anhydrous toluene (80 cm^3) at -78 °C, under an atmosphere of nitrogen, was added diisobutylaluminium hydride (1 M solution in hexanes, 17.8 cm^3, 17.8 mmol) dropwise over 10 minutes and the reaction stirred at -78 °C for 0.5 hour. The reaction mixture was allowed to warm to room temperature then cooled back to -78 °C and quenched with methanol (0.6 cm^3). The product was extracted with diethyl ether (250 cm^3) and the organic layers combined and washed with brine (20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title compound (1.96 g, 100%) as a colourless crystalline solid; The ^1H NMR (200 MHz) spectrum was identical to that of the literature compound and taken on to the next step without further characterisation.[92]

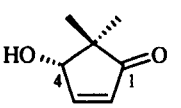
(*S*)-4-(*tert*-Butyldimethylsilanyloxy)-5,5-dimethylcyclopent-2-enone (113)



A solution of the chiral alcohol (1.96 g, 8.1 mmol) and 4Å molecular sieves (2.0 g) in anhydrous dichloromethane (50 cm^3) was stirred for 30 minutes under an atmosphere of nitrogen. Pyridinium dichromate (3.66 g, 9.7 mmol) was added and the reaction stirred at room temperature for 4.5 hours. The reaction mixture was filtered through a

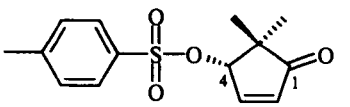
plug of silica and the solvent removed *in vacuo* to yield the title compound **113** (1.83 g, 94%) as a colourless oil; $[\alpha]_D^{20}$ +76.7 (c1.7, $CHCl_3$, lit.[92] +93.6 (c1.01, $CHCl_3$)); ν_{max}(film)/cm^{-1} 1720, 2957; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.13 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.01 (3H, s, CH_3), 1.12 (3H, s, CH_3), 4.51 (1H, m, C(4)H), 6.13 (1H, dd, *J* 1.3 and 5.9, C(2)H), 7.29 (1H, dd, *J* 2.1 and 5.9, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -4.4, -4.3 (CH_3), 18.5 (C), 21.3, 22.9, 26.1 (CH_3), 49.2 (C), 80.4, 132.1, 161.7 (CH), 212.1 (C); *m/z* (CI) 258 ($[M+NH_4]^+$, 27%), 241 ($[M+H]^+$, 56), 183 ($[M-C(CH_3)_3]^+$, 100); Found: $[M+NH_4]^+$, 258.18943. $C_{13}H_{28}NO_2Si$ requires $[M+NH_4]^+$, 258.18893.

(*S*)-4-Hydroxy-5,5-dimethylcyclopent-2-enone (99)



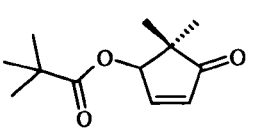
A solution of silyl ether **113** (1.5 g, 6.3 mmol) in 80% acetic acid (150 cm^3) was stirred at 40 °C for 22 hours. The solvent was removed *in vacuo* and the product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:1) to yield the title compound **99** (0.66 g, 84%) as a white solid; ^1H NMR (250 MHz) analysis was identical to that of the racemic compound; t_r 13.4 minutes, >99% ee (Lipodex E column).

(*S*)-Toluene-4-sulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (96)



To a solution of alcohol **99** (650 mg, 5.2 mmol) and *p*-toluenesulfonic anhydride (2.55 g, 7.8 mmol) in anhydrous dichloromethane (50 cm^3) was added triethylamine (1.1 cm^3, 7.8 mmol) and a catalytic amount of 4-dimethylaminopyridine; The reaction mixture was stirred for 16 hours, diluted with water (20 cm^3) and the layers separated. The aqueous layer was extracted with dichloromethane (2 × 20 cm^3) and the combined organic layers washed with brine (20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **96** (1.08 g, 75%) as a pale yellow solid; $[\alpha]_D^{20}$ +57.1 (c1.7, $CHCl_3$); The ^1H NMR (200 MHz) spectrum was identical to that of the racemic compound.

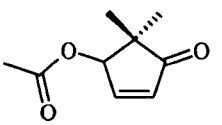
2,2-Dimethylpropionic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (114)



The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **114** (77 mg, 92%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1280, 1723, 2975; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.02 (3H, s, CH_3), 1.23 (3H, s, CH_3),

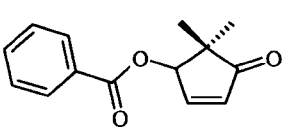
1.24 (9H, s, -C(CH_3)$_3$), 5.54-5.55 (1H, m, C(4)H), 6.30 (1H, dd, *J* 1.3 and 5.8, C(2)H), 7.41 (1H, dd, *J* 2.3 and 5.8, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.3, 23.8, 27.5 (CH_3), 39.4, 47.6 (C), 80.6, 134.6, 157.6 (CH), 178.4, 211.3 (C); *m/z* (EI) 210 ($[M]^+$, 0.5%), 57 ($[C(CH_3)_3]^+$, 100); Found: $[M]^+$, 210.12584. $C_{12}H_{18}O_3$ requires $[M]^+$, 210.12560.

Acetic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (95)



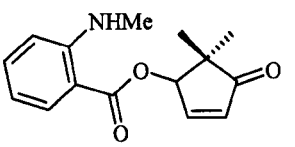
The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **95** (62 mg, 93%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1235, 1720, 1736, 2976; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.02 (3H, s, CH_3), 1.22 (3H, s, CH_3), 2.13 (3H, s, CH_3), 5.57-5.58 (1H, m, C(4)H), 6.28 (1H, dd, *J* 1.3 and 5.9, C(2)H), 7.40 (1H, dd, *J* 2.4 and 5.9, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 19.9, 20.7, 23.4 (CH_3), 47.1 (C), 80.5, 134.3, 156.9 (CH), 170.5, 210.5 (C); *m/z* (EI) 168 ($[M]^+$, 3%), 43 ($[CH_3CO]^+$, 100); Found: $[M]^+$, 168.07920. $C_9H_{12}O_3$ requires $[M]^+$, 168.07864.

Benzoic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (115)



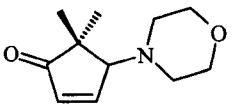
The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **115** (103 mg, 100%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1270, 1719, 2974; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.13 (3H, s, CH_3), 1.30 (3H, s, CH_3), 5.84 (1H, m, C(4)H), 6.35 (1H, dd, *J* 1.4 and 5.9, C(2)H), 7.45-7.48 (2H, m, 2 × CH), 7.54 (1H, dd, *J* 2.4 and 5.9, C(3)H), 7.57-7.62 (1H, m, CH), 8.04-8.07 (2H, m, 2 × CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.2, 23.4 (CH_3), 47.4 (C), 80.9, 128.6 (CH), 129.5 (C), 129.8, 133.5, 134.5, 156.9 (CH), 166.1, 210.5 (C); *m/z* (EI) 230 ([M]$^+$, 2%), 105 ([PhCO]$^+$, 100); Found: [M]$^+$, 230.09411. $C_{14}H_{14}O_3$ requires [M]$^+$, 230.09428.

2-Methylaminobenzoic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (116)



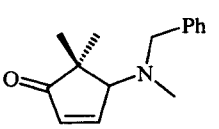
The product was purified by flash column chromatography (SiO_2; dichloromethane) to yield the title compound **116** (36 mg, 35%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1236, 1681, 1719, 3385; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.11 (3H, s, CH_3), 1.28 (3H, s, CH_3), 2.93 (3H, d, *J* 4.6, -NHC*H*$_3$), 5.76-5.77 (1H, m, C(4)H), 6.33 (1H, dd, *J* 1.5 and 5.8, C(2)H), 6.58 (1H, app. t, *J* 7.6, CH), 6.69 (1H, d, *J* 8.2, CH), 7.38-7.42 (1H, m, CH), 7.51 (1H, dd, *J* 2.3 and 5.8, C(3)H), 7.86 (1H, dd, *J* 1.8 and 8.2, CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.3, 23.3, 29.6 (CH_3), 47.5 (C), 80.2 (CH), 109.0 (C), 110.9, 114.5, 131.5, 134.3, 135.2 (CH), 152.4 (C), 157.4 (CH), 168.1, 210.7 (C); *m/z* (EI) 259 ([M]$^+$, 84%); Found: [M]$^+$, 259.12150. $C_{15}H_{17}NO_3$ requires [M]$^+$, 259.12085.

5,5-Dimethyl-4-morpholin-4-yl-cyclopent-2-enone (127)



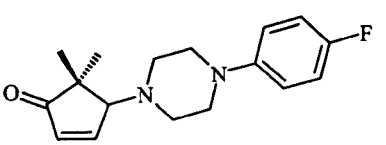
To a solution of tosylate **96** (50 mg, 0.18 mmol) in ethanol (18 cm^3) was added morpholine (35 μl, 0.40 mmol) and the reaction was heated under reflux for 48 hours. The reaction was allowed to cool and the solvent removed *in vacuo*. The crude product was dissolved in diethyl ether (5 cm^3) and sat. aq. sodium hydrogencarbonate (5 cm^3) added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 5 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:1) to yield the title compound **127** (23 mg, 66%) as a pale orange oil; ν_{max}(film)/cm^{-1} 1713; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.11 (3H, s, CH_3), 1.15 (3H, s, CH_3), 2.63 (4H, t, *J* 4.6, 2 × CH_2), 3.35 (1H, t, *J* 2.2, C(4)H), 3.65-3.75 (4H, m, 2 × CH_2), 6.24 (1H, dd, *J* 1.9 and 6.0, C(2)H), 7.65 (1H, dd, *J* 2.4 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.6, 26.6 (CH_3), 48.3 (C), 52.9, 67.6 (CH_2), 76.1, 133.3, 159.4 (CH), 213.0 (C); *m/z* (CI) 196 ($[M+H]^+$, 100%); Found: $[M+H]^+$, 196.13402. $C_{11}H_{18}NO_2$ requires $[M+H]^+$, 196.13374.

4-(Benzylmethylamino)-5,5-dimethylcyclopent-2-enone (128)



To a solution of tosylate **96** (33 mg, 0.12 mmol) in ethanol (12 cm^3) was added benzyl methylamine (34 μl, 0.26 mmol) and the reaction was heated under reflux for 48 hours. The reaction was allowed to cool and the solvent removed *in vacuo*. The crude product was dissolved in diethyl ether (10 cm^3) and sat. aq. sodium hydrogencarbonate (10 cm^3) added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 5 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:9) to yield the title compound **128** (20 mg, 74%) as a colourless oil; ν_{max}(film)/cm^{-1} 1712; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.08 (3H, s, CH_3), 1.19 (3H, s, CH_3), 2.30 (3H, s, -NCH_3), 3.62 (1H, t, *J* 2.2, C(4)H), 3.72 (2H, s, CH_2), 6.24 (1H, dd, *J* 1.9 and 6.0, C(2)H), 7.25-7.37 (5H, m, Ph), 7.66 (1H, dd, *J* 2.4 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.1, 26.4, 40.3 (CH_3), 48.2 (C), 60.2 (CH_2), 74.3, 127.1, 128.3, 128.4, 132.8 (CH), 139.4 (C), 160.6 (CH), 213.1 (C); *m/z* (CI) 230 ($[M+H]^+$, 100%); Found: $[M+H]^+$, 230.15525. $C_{15}H_{20}NO$ requires $[M+H]^+$, 230.15448.

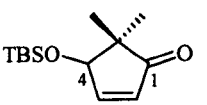
4-[4-(4-Fluorophenyl)-piperazin-1-yl]-5,5-dimethylcyclopent-2-enone (129)



To a solution of tosylate **96** (60 mg, 0.21 mmol) in ethanol (20 cm^3) was added 1-(4-fluoro-phenyl)-piperazine (83 mg, 0.46 mmol) and the reaction was heated under reflux for 19 hours. The reaction was allowed to cool and the solvent removed *in*

vacuo. The crude product was dissolved in diethyl ether (5 cm^3) and sat. aq. sodium hydrogencarbonate (5 cm^3) added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 5 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:3) to yield the title compound **129** (41 mg, 65%) as colourless oil; ν_{max}(film)/cm^{-1} 1236, 1510, 1712; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.13 (3H, s, CH_3), 1.17 (3H, s, CH_3), 2.74-2.83 (4H, m, 2 × CH_2), 3.06-3.15 (4H, m, 2 × CH_2), 3.44 (1H, t, *J* 2.2, C(4)H), 6.25 (1H, dd, *J* 1.8 and 6.0, C(2)H), 6.84-6.89 (2H, m, Ar), 6.93-6.99 (2H, m, Ar), 7.68 (1H, dd, *J* 2.5 and 6.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.5, 26.8 (CH_3), 48.3 (C), 51.0, 52.2 (CH_2), 75.7, 115.9, 118.3, 133.3 (CH), 148.3, 158.8 (C), 159.7 (CH), 213.2 (C); *m/z* (CI) 289 ($[M+H]^+$, 100%); Found: $[M+H]^+$, 289.17196. $C_{17}H_{22}FN_2O$ requires $[M+H]^+$, 289.17160.

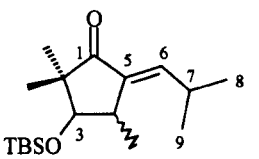
4-(*tert*-Butyldimethylsilanyloxy)-5,5-dimethylcyclopent-2-enone (132)



To a solution of alcohol **99** (260 mg, 2.1 mmol) in anhydrous dimethylformamide (20 cm^3) was added *tert*-butyldimethylsilyl chloride (0.37 g, 2.47 mmol) and the solution cooled to 0 °C. Imidazole (0.28 g, 4.1 mmol) was added over 30 minutes and the reaction allowed to warm to room temperature over 48 hours. The reaction was diluted with diethyl ether (20 cm^3) and the aqueous layer extracted with diethyl ether (3 × 20 cm^3). The combined organic layers were washed with water (20 cm^3) and

brine (20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:9) to yield the title compound **132** (235 mg, 47%) as a colourless oil. The ^1H NMR (200 MHz) spectrum was identical to the chiral compound and taken on to the next step without further characterisation.

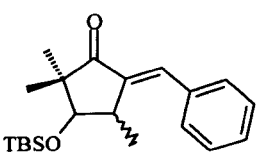
3-(*tert*-Butyldimethylsilanyloxy)-5-isobutylidene-2,2,4-trimethylcyclopentanone (133)



Methyl lithium (1.6 M in diethyl ether, 0.96 cm^3, 1.54 mmol) was added to a solution of copper(I) iodide (0.15 g, 0.79 mmol) in anhydrous diethyl ether (20 cm^3) at 0 °C and stirred for 15 minutes under an atmosphere of nitrogen. A solution of enone **132** (185 mg, 0.77 mmol) in anhydrous diethyl ether (1 cm^3) was added to the freshly prepared solution of Me_2CuLi, at 0 °C, and stirred for 30 minutes. A saturated ethereal solution of zinc chloride (0.69 M in diethyl ether, 2.2 cm^3, 1.54 mmol) was added to the reaction mixture followed by isobutyraldehyde (0.7 cm^3, 7.7 mmol) and the reaction stirred under an atmosphere of nitrogen for 15 minutes at 0 °C. The reaction was allowed to warm to room temperature, then cooled to 0 °C and quenched with 10% ammonium chloride solution (100 cm^3). The product was extracted with diethyl ether (2 × 20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 146 mg of a colourless oil. The crude product was taken up in anhydrous

dichloromethane (5 cm^3) and methanesulfonic acid (52 μl, 0.67 mmol), triethylamine (0.14 cm^3, 0.98 mmol) and a catalytic amount of 4-dimethylaminopyridine added and the reaction stirred at room temperature for 16 hours. Water (5 cm^3) was added and the product extracted with dichloromethane (2 × 5 cm^3), the combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:10) to yield a diastereomeric mixture (ca. 4.5:1, *anti*:*syn*) of the title compound **133** (81 mg, 34%) as a colourless oil; *anti*-isomer: ν_{max}(film)/cm^{-1} 1463, 1649, 1723, 2858, 2960; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.09 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.97 (3H, s, CH_3), 1.03 (3H, d, *J* 6.5, CH_3), 1.06 (3H, d, *J* 6.7, CH_3), 1.09 (3H, s, CH_3) 1.31 (3H, d, *J* 7.0, CH_3), 2.53-2.76 (2H, m, C(7)H and C(4)H), 3.52 (1H, d, *J* 5.9, C(3)H), 6.45 (1H, dd, *J* 2.8 and 10.6, C(6)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -4.3, -4.2 (CH_3), 18.2 (C), 18.5, 19.0, 22.1, 22.5, 22.8, 25.9 (CH_3), 28.0, 40.6 (CH), 49.7 (C), 84.3 (CH), 136.9 (C), 145.4 (CH), 209.6 (C); *m/z* (CI) 311 ($[M+H]^+$, 100%), 253 ($[M-C(CH_3)_3]^+$, 30); Found: $[M+H]^+$, 311.24077. $C_{18}H_{35}O_2Si$ requires $[M+H]^+$, 311.24063.

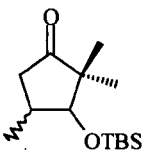
5-Benzylidene-3-(*tert*-butyldimethylsilanyloxy)-2,2,4-trimethylcyclopentanone (134)



Methyl lithium (1.6 M in diethyl ether, 1.58 cm^3, 2.52 mmol) was added to a solution of copper(I) iodide (0.24 g, 1.26 mmol) in anhydrous diethyl ether (20 cm^3) at 0 °C and stirred for 15 minutes under an atmosphere of nitrogen. A solution of enone **132** (150 mg, 0.63 mmol) in anhydrous diethyl ether (1 cm^3) was added to the freshly prepared solution of Me_2CuLi, at 0 °C, and stirred for 30 minutes. A saturated ethereal solution of zinc chloride (0.69 M in diethyl ether, 2.3 cm^3) was added to the reaction mixture followed by benzaldehyde (0.64 cm^3, 6.3 mmol) and the reaction stirred under an atmosphere of nitrogen for 30 minutes at 0 °C. The reaction was allowed to warm to room temperature, then cooled to 0 °C and quenched with 10% ammonium chloride solution (100 cm^3). The product was extracted with diethyl ether (2 × 20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 211 mg of a crude yellow oil. The crude product was taken up in dichloromethane (6 cm^3) and methanesulfonic acid (90 μl, 1.17 mmol), triethylamine (0.16 cm^3, 1.17 mmol) and a catalytic amount of 4-dimethylaminopyridine added and the reaction stirred at room temperature for 70 hours. Water (10 cm^3) was added and the product extracted with dichloromethane (2 × 5 cm^3), the combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; dichloromethane:*n*-hexane, 3:7) to yield a diastereomeric mixture (ca. 29:1, *anti*:*syn*) of the title compound **134** (56 mg, 26%) as pale yellow oil; *anti*-isomer; ν_{max}(film)/cm^{-1} 1463, 1626, 1716, 2857, 2929, 2958; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.11 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.06 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.21 (3H, d, *J* 7.0, CH_3), 3.11-3.18 (1H, m, C(4)H), 3.63 (1H, d, *J* 5.7, C(3)H), 7.31-7.50 (6H, m, Ph and C(6)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -3.9 (2 × CH_3), 16.9 (CH_3), 18.6 (C), 19.5, 23.1, 26.3 (CH_3), 41.8 (CH), 50.0 (C), 85.1, 128.8, 129.4, 130.6, 135.0 (CH), 135.3, 139.6, 210.1 (C); *m/z*

(CI) 345 ($[M+H]^+$, 100%); Found: $[M+^{23}Na]^+$, 367.2067. $C_{21}H_{32}{}^{23}NaO_2Si$ requires $[M+^{23}Na]^+$, 367.2069.

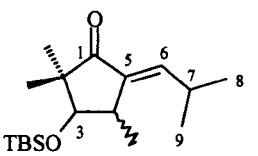
3-(*tert*-Butyldimethylsilanyloxy)-2,2,4-trimethylcyclopentanone



Methyl lithium (1.6 M in diethyl ether, 10.5 cm^3, 16.8 mmol) was added to a solution of copper(I) iodide (1.6 g, 8.4 mmol) in anhydrous diethyl ether (130 cm^3) at 0 °C and stirred for 15 minutes under an atmosphere of nitrogen. A solution of enone **132** (1.0 g, 4.2 mmol) in anhydrous diethyl ether (6 cm^3) was added to the freshly prepared solution of Me_2CuLi, at 0 °C, and stirred for 45 minutes. The reaction was allowed to warm to room temperature, then cooled to 0 °C and quenched with 10% ammonium chloride solution (100 cm^3). The product was extracted with diethyl ether (2 × 100 cm^3) and the combined organic layers washed with water (100 cm^3) and brine (100 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a diastereomeric mixture (ca. 3.5:1, *anti*:*syn*) of the title compound (0.98 g, 92%) as a pale yellow oil; *anti*-isomer; ν_{max}(film)/cm^{-1} 1745, 2858, 2930, 2958; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.09 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.92 (3H, s, CH_3), 0.93 (9H, s, $SiC(CH_3)_3$), 1.05 (3H, s, CH_3) 1.14 (3H, d, *J* 6.5, CH_3), 1.77 (1H, dd, *J* 11.8 and 18.9, C*H*H), 2.03-2.16 (1H, m, C(4)H), 2.56 (1H, dd, *J* 8.4 and 18.9, CH*H*), 3.47 (1H, d, *J* 9.0, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -3.8, -3.6, 18.3, 18.4 (CH_3), 18.6 (C), 22.7, 26.2 (CH_3), 35.7 (CH), 43.8 (CH_2), 51.0 (C), 85.6 (CH), 220.1 (C); *m/z* (CI) 257 ($[M+H]^+$, 29%),

274 ($[M+NH_4]^+$, 88), 199 ($[M-C(CH_3)_3]^+$, 100); Found: $[M+H]^+$, 257.19378. $C_{14}H_{29}O_2Si$ requires $[M+H]^+$, 257.19370.

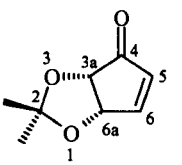
3-(*tert*-Butyldimethylsilanyloxy)-5-isobutylidene-2,2,4-trimethylcyclopentanone (133)



To a solution of anhydrous diisopropylamine (0.34 cm^3, 2.4 mmol) in anhydrous tetrahydrofuran (2.5 cm^3) at 0 °C was added *n*-butyl lithium (1.6 M in hexanes, 1.5 cm^3, 2.4 mmol) dropwise, under an atmosphere of nitrogen and the reaction stirred for 45 minutes. The reaction mixture was cooled to -78 °C and 3-(*tert*-butyldimethylsilanyloxy)-2,2,4-trimethylcyclopentanone (0.5 g, 2.0 mmol) in anhydrous tetrahydrofuran (0.5 cm^3) was added slowly and the reaction stirred at -78 °C for 1 hour. Isobutyraldehyde (0.36 cm^3, 4.0 mmol) was added dropwise and the reaction stirred for 4 hours, slowly warming to room temperature. The reaction was quenched with sat. aq. ammonium chloride (5 cm^3) and the product was extracted with diethyl ether (3 × 5 cm^3). The combined organic layers were washed with 0.1 M hydrochloric acid (2 × 5 cm^3), brine (2 × 5 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; dichloromethane:*n*-hexane, 1:1) to yield a diastereomeric mixture (ca. 4.5:1, *anti*:*syn*) of the title compound **133** (113 mg, 18%) as a colourless oil; The ^1H NMR (250

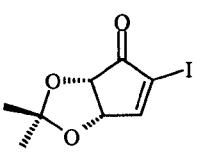
MHz) spectrum was identical to that of the compound made in the one-step procedure.

(3a*S*,6a*S*)-2,2-Dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (141)[107]



$[\alpha]_D^{20}$ +70.9 (c1.7, $CHCl_3$, lit.[107] +70.0 (c0.92, $CHCl_3$)); ν_{max}(film)/cm^{-1} 1584, 1717, 2933, 2999; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.42 (6H, s, 2 × CH_3), 4.47 (1H, d, *J* 5.5, C(3a)H), 5.26 (1H, dd, *J* 2.3 and 5.5, C(6a)H), 6.22 (1H, d, *J* 5.9, C(5)H), 7.61 (1H, dd, *J* 2.3 and 5.9, C(6)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.2, 27.4 (CH_3), 76.7, 78.6 (CH), 115.6 (C), 134.4, 159.6 (CH), 203.0 (C); *m/z* (CI) 172 ($[M+NH_4]^+$, 100%), 155 ($[M+H]^+$, 32); Found: $[M+H]^+$, 155.07055. $C_8H_{11}O_3$ requires $[M+H]^+$, 155.07082.

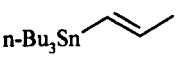
(3a*S*,6a*S*)-5-Iodo-2,2-dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (160)



To a solution of enone **141** (100 mg, 0.65 mmol) in carbon tetrachloride:pyridine (2.5 cm^3, 1:1) at 0 °C was added iodine (0.65 g, 2.6 mmol) in carbon tetrachloride:pyridine (2.5 cm^3, 1:1) dropwise, and the reaction mixture was stirred for 2.5 hours at room

temperature under an atmosphere of nitrogen. The reaction was diluted with diethyl ether (25 cm^3) and water (25 cm^3) and the layers separated. The aqueous layer was washed with diethyl ether (3 × 25 cm^3) and the combined organic layers washed with sat. aq. sodium thiosulfate (2 × 50 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:4) to yield the title compound **160** (116 mg, 64%) as a white solid; ν_{max}(film)/cm^{-1} 1380, 1568, 1732, 2356, 2939, 2997; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.39 (3H, s, CH_3), 1.42 (3H, s, CH_3), 4.53 (1H, d, *J* 5.6, C(3a)H), 5.22 (1H, dd, *J* 2.6 and 5.6, C(6a)H), 7.97 (1H, d, *J* 2.6, C(6)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.5, 27.4 (CH_3), 73.8, 79.7 (CH), 105.8, 115.9 (C), 164.8 (CH), 197.4 (C); *m/z* (CI) 298 ($[M+NH_4]^+$, 100%); Found: $[M+NH_4]^+$, 297.99380. $C_8H_{13}INO_3$ requires $[M+NH_4]^+$, 297.99405.

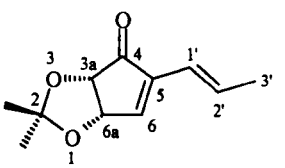
(*E*)-Tributylpropenylstannane



To a solution of *trans*-1-bromopropene (1.0 g, 8.3 mmol) in anhydrous diethyl ether (23 cm^3) at -78 °C was added *t*-butyl lithium (1.7 M in pentane, 10.8 cm^3, 18.3 mmol) slowly and the reaction mixture was stirred for 1 hour under an atmosphere of argon. Tributyltin chloride (2.25 cm^3, 8.3 mmol) was added and the reaction allowed to warm to room temperature over 16 hours. The reaction was quenched with methanol (1 cm^3) and water (50 cm^3) was added. The product was extracted with ethyl acetate (2 × 50 cm^3) and the combined organic layers dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by high vacuum distillation (125 °C, 0.1 mmHg)

to yield the title compound (2.69 g, 100%) as a colourless oil; ν_{max}(film)/cm^{-1} 874, 982, 1376, 1418, 1442, 1464, 1602, 2956; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (9H, t, *J* 7.2, 3 × CH_3), 1.26-1.57 (18H, m, 9 × CH_2), 1.84 (3H, d, *J* 5.4, CH_3), 5.87-6.03 (2H, m, 2 × CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 9.8 (CH_2), 14.0, 23.9 (CH_3), 27.6, 29.5 (CH_2), 129.3, 144.6 (CH).

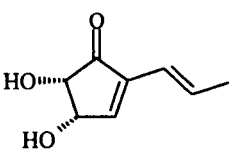
(3a*S*,6a*S*)-2,2-Dimethyl-5-prop-(*E*)-enyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (161)



To a solution of *α*-iodoenone **160** (150 mg, 0.54 mmol) in degassed 1-methyl-2-pyrrolidinone (4.0 cm^3) was added *bis*(benzonitrile)dichloropalladium(II) (11.5 mg, 0.03 mmol), copper(I) iodide (9.5 mg, 0.05 mmol) and triphenyl arsine (15.3 mg, 0.05 mmol). A solution of (*E*)-tributylpropenylstannane (0.20 g, 0.6 mmol) in 1-methyl-2-pyrrolidinone (1.0 cm^3) was added and the reaction stirred for 16 hours at room temperature under an atmosphere of nitrogen. The reaction was diluted with ethyl acetate (5 cm^3) and the product washed with aq. potassium fluoride (2 × 5 cm^3). The combined organic layers were washed with water (10 cm^3) and the combined aqueous layers back extracted with ethyl acetate (10 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:9) to yield the title compound **161** (76 mg, 73%) as a yellow solid; ν_{max}(film)/cm^{-1} 1345, 1374, 1456, 1653, 1717, 2936;

δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.38 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.84 (3H, dd, *J* 1.4 and 6.8, C(3')H) 4.50 (1H, d, *J* 5.6, C(3a)H), 5.19 (1H, dd, *J* 2.6 and 5.6, C(6a)H), 6.08 (1H, dd, *J* 1.4 and 15.7, C(1')H), 6.80 (1H, dq, *J* 6.8 and 15.7, C(2')H), 7.18 (1H, d, *J* 2.6, C(6)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 19.1, 26.3, 27.6 (CH_3), 76.6, 78.2 (CH), 115.1 (C), 120.5, 135.2 (CH), 141.2 (C), 150.0 (CH), 201.8 (C); *m/z* (CI) 212 ($[M+NH_4]^+$, 30%), 154 ($[M-C_3H_6O+NH_4]^+$, 40), 137 ($[M-C_3H_6O+H]^+$, 100); Found: $[M+NH_4]^+$, 212.12849. $C_{11}H_{18}NO_3$ requires $[M+NH_4]^+$, 212.12866.

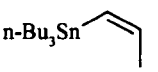
(3a*S*,6a*S*)-4,5-Dihydroxy-2-prop-(*E*)-enylcyclopent-2-enone (137)



To a solution of acetonide **161** (75 mg, 0.39 mmol) in methanol (3.5 cm^3) was added pyridinium *p*-toluenesulfonate (15 mg, 0.06 mmol) and the reaction heated under reflux for 6.5 hours. The solvent was removed *in vacuo* and the product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:1) to yield the title compound **137** (12 mg, 20%) as a pale yellow solid; m.p. 97-99 °C (MeOH); $[\alpha]_D^{20}$ +38.8 (c1.0, MeOH); ν_{max}(film)/cm^{-1} 983, 1158, 1652, 1708, 2956, 3250 br., 3452 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.85 (3H, dd, *J* 1.4 and 6.8, C(3')H) 2.71 (1H, br. s, -OH), 2.99 (1H, br. s, -OH), 4.17 (1H, d, *J* 5.6, C(5)H), 4.82-4.84 (1H, m, C(4)H), 6.10 (1H, d, *J* 16.0, C(1')H), 6.74-6.83 (1H, m, C(2')H), 7.24 (1H, d, *J* 3.2, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 19.2 (CH_3), 67.3, 72.6, 120.5, 135.3 (CH), 140.9 (C),

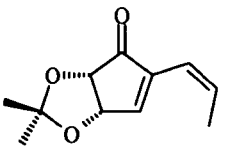
150.7 (CH), 205.2 (C); *m/z* (CI) 172 ($[M+NH_4]^+$, 100%), 154 ($[M]^+$, 23); Found: $[M+NH_4]^+$, 172.09704. $C_8H_{14}NO_3$ requires $[M+NH_4]^+$, 172.09737.

(*Z*)-Tributylpropenylstannane



To a solution of *n*-tributyl(propynyl)stannane (500 mg, 1.5 mmol) in anhydrous tetrahydrofuran (35 cm^3) was added *bis*(cyclopentadienyl)zirconium chloride hydride (0.77 g, 3 mmol). The reaction mixture was stirred for 30 minutes under an atmosphere of nitrogen, quenched with water (1 cm^3) and stirred for 30 minutes. Pentane (5 cm^3) was added and the mixture filtered through a plug of silica gel and the solvent removed *in vacuo*. The product was purified by high vacuum distillation (125 °C, 0.1 mmHg) to yield the title compound (0.5 g, 99%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 960, 1072, 1376, 1464, 1601, 2854, 2923, 2958; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.87-0.94 (9H, m, 3 × CH_3), 1.27-1.54 (18H, m, 9 × CH_2), 1.76 (3H, dd, *J* 1.3 and 6.4, CH_3), 5.80 (1H, dq, *J* 1.3 and 12.4, CH), 6.59 (1H, dq, *J* 6.4 and 12.4, CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 10.5 (CH_2), 14.0, 22.3 (CH_3), 27.7, 29.6 (CH_2), 129.5, 143.6 (CH).

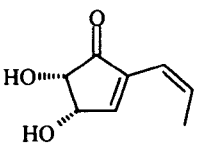
(3a*S*,6a*S*)-2,2-Dimethyl-5-prop-(*Z*)-enyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (162)



To a solution of *α*-iodoenone **160** (150 mg, 0.54 mmol) in degassed 1-methyl-2-pyrrolidinone (4.0 cm^3) was added *bis*(benzonitrile)dichloropalladium(II) (11.5 mg, 0.03 mmol), copper(I) iodide (9.5 mg, 0.05 mmol) and triphenyl arsine (15.3 mg, 0.05 mmol). A solution of (*Z*)-tributylpropenylstannane (0.27 g, 0.81 mmol) in 1-methyl-2-pyrrolidinone (1.0 cm^3) was added and the reaction stirred for 16 hours at room temperature under an atmosphere of nitrogen. The reaction was diluted with ethyl acetate (5 cm^3) and the product washed with aq. potassium fluoride (2 × 5 cm^3). The combined organic layers were washed with water (10 cm^3) and the combined aqueous layers back extracted with ethyl acetate (10 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:9) to yield the title compound **162** (97 mg, 93%) as a yellow solid; m.p. 32-34 °C (from EtOAc:*n*-hexane); $[\alpha]_D^{20}$ -73.7 (c1.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 1202, 1373, 1637, 1725, 2937, 2990; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.40 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.87 (3H, d, *J* 5.4, C(3')H) 4.50 (1H, d, *J* 5.6, C(3a)H), 5.28 (1H, dd, *J* 2.7 and 5.6, C(6a)H), 6.05-6.12, (2H, m, C(1')H and C(2')H), 7.38 (1H, d, *J* 2.7, C(6)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.1, 26.6, 28.0 (CH_3), 76.9, 77.6 (CH), 115.6 (C), 118.1, 134.8 (CH), 141.3 (C), 152.3 (CH), 202.5 (C); *m/z* (CI) 212 ($[M+NH_4]^+$, 51%), 154 ($[M-C_3H_6O+NH_4]^+$, 29), 137

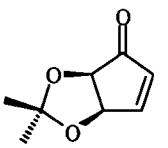
([M-C_3H_6O+H]$^+$, 100); Found: [M+NH_4]$^+$, 212.12812. $C_{11}H_{18}NO_3$ requires [M+NH_4]$^+$, 212.12866.

(3a*S*,6a*S*)-4,5-Dihydroxy-2-prop-(*Z*)-enylcyclopent-2-enone (163)



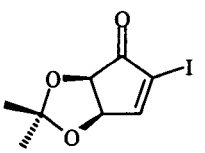
To a solution of acetonide **162** (60 mg, 0.31 mmol) in methanol (3.0 cm^3) was added pyridinium *p*-toluenesulfonate (12 mg, 0.05 mmol) and the reaction heated under reflux for 5.5 hours. The solvent was removed *in vacuo* and the product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 2:3) to yield the title compound **163** (27 mg, 56%) as a white solid; m.p. 108-109 °C (MeOH); $[\alpha]_D^{20}$ -17.6 (c1.0, MeOH); ν_{max}(film)/cm^{-1} 983, 1153, 1292, 1712, 2939, 3283 br., 3431 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.88 (3H, d, *J* 5.2, C(3')H), 2.90 (1H, br. s, -OH), 3.16 (1H, br. s, -OH), 4.18 (1H, d, *J* 5.5, C(5)H), 4.90 (1H, dd, *J* 3.2 and 5.5, C(4)H), 6.02-6.12 (2H, m, C(1')H and C(2')H), 7.45 (1H, d, *J* 3.2, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 15.8 (CH_3), 67.8, 71.2, 117.6, 134.6 (CH), 140.6 (C), 153.3 (CH), 205.7 (C); *m/z* (CI) 172 ([M+NH_4]$^+$, 100%), 155 ([M+H]$^+$, 23), 154 ([M]$^+$, 28), 137 ([M-OH]$^+$, 57); Found: [M+NH_4]$^+$, 172.09704. $C_8H_{14}NO_3$ requires [M+NH_4]$^+$, 172.09737.

(3a*R*,6a*R*)-2,2-Dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (141)[107]



$[\alpha]_D^{20}$ -70.5 (c1.7, $CHCl_3$, lit.[107] -70.8 (c0.92, $CHCl_3$)); ν_{max}(film)/cm^{-1} 1583, 1716, 2932, 2979; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.42 (6H, s, 2 × CH_3), 4.47 (1H, d, *J* 5.5, C(3a)H), 5.26 (1H, dd, *J* 2.3 and 5.5, C(6a)H), 6.22 (1H, d, *J* 5.9, C(5)H), 7.61 (1H, dd, *J* 2.3 and 5.9, C(6)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.2, 27.4 (CH_3), 76.7, 78.6 (CH), 115.6 (C), 134.4, 159.6 (CH), 203.0 (C); *m/z* (CI) 172 ($[M+NH_4]^+$, 100%), 155 ($[M+H]^+$, 28); Found: $[M+H]^+$, 155.07029. $C_8H_{11}O_3$ requires $[M+H]^+$, 155.07082.

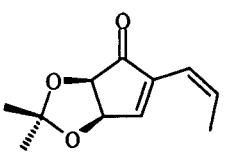
(3a*R*,6a*R*)-5-Iodo-2,2-dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (160)



To a solution of enone **141** (0.53, 3.4 mmol) in carbon tetrachloride:pyridine (12.5 cm^3, 1:1) at 0 °C was added iodine (3.45 g, 13.6 mmol) in carbon tetrachloride:pyridine (12.5 cm^3, 1:1) dropwise, and the reaction stirred for 1.5 hours at room temperature under an atmosphere of nitrogen. The reaction was diluted with diethyl ether (50 cm^3) and water (50 cm^3) and the layers separated. The aqueous layer was washed with diethyl ether (3 × 50 cm^3) and the combined organic layers washed with sat. aq. sodium thiosulfate (2 × 100 cm^3), dried ($MgSO_4$) and the solvent

removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:4) to yield the title compound **160** (0.69 g, 73%) as a white solid; Found: C, 34.45; H, 3.22. $C_8H_9IO_3$ requires C, 34.31; H, 3.24%; ν_{max}(film)/cm^{-1} 1380, 1569, 1733, 2939, 2996; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.39 (3H, s, CH_3), 1.42 (3H, s, CH_3), 4.53 (1H, d, *J* 5.6, C(3a)H), 5.22 (1H, dd, *J* 2.6 and 5.6, C(6a)H), 7.97 (1H, d, *J* 2.6, C(6)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.5, 27.4 (CH_3), 73.8, 79.7 (CH), 105.8, 115.9 (C), 164.8 (CH), 197.4 (C); *m/z* (CI) 298 ($[M+NH_4]^+$, 100%); Found: $[M+NH_4]^+$, 297.99408. $C_8H_{13}INO_3$ requires $[M+NH_4]^+$, 297.99405.

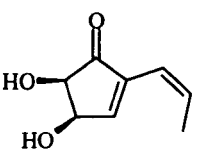
(3a*R*,6a*R*)-2,2-Dimethyl-5-prop-(*Z*)-enyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (162)



To a solution of α-iodoenone **160** (150 mg, 0.54 mmol) in degassed 1-methyl-2-pyrrolidinone (4.0 cm^3) was added *bis*(benzonitrile)dichloropalladium(II) (11.5 mg, 0.03 mmol), copper(I) iodide (9.5 mg, 0.05 mmol) and triphenyl arsine (15.3 mg, 0.05 mmol). A solution of (*Z*)-tributylpropenylstannane (0.27 g, 0.81 mmol) in 1-methyl-2-pyrrolidinone (1.0 cm^3) was added and the reaction stirred for 16 hours at room temperature under an atmosphere of nitrogen. The reaction was diluted with ethyl acetate (5 cm^3) and the product washed with aq. potassium fluoride (2 × 5 cm^3). The combined organic layers were washed with water (10 cm^3) and the combined aqueous layers back extracted with ethyl acetate (10 cm^3). The combined organic layers were

dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:9) to yield the title compound **162** (78 mg, 75%) as a yellow solid; m.p. 32-34 °C (from EtOAc:*n*-hexane); $[\alpha]_D^{20}$ +85.6 (c1.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 1203, 1373, 1636, 1732, 2937, 2990; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.40 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.87 (3H, d, *J* 5.4, C(3')H) 4.50 (1H, d, *J* 5.6, C(3a)H), 5.28 (1H, dd, *J* 2.7 and 5.6, C(6a)H), 6.05-6.12 (2H, m, C(1')H and C(2')H), 7.38 (1H, d, *J* 2.7, C(6)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.1, 26.6, 28.0 (CH_3), 76.9, 77.6 (CH), 115.6 (C), 118.1, 134.8 (CH), 141.3 (C), 152.3 (CH), 202.5 (C); *m/z* (CI) 212 ($[M+NH_4]^+$, 50%), 137 ($[M-C_3H_6O+H]^+$, 100); Found: $[M+NH_4]^+$, 212.12848. $C_{11}H_{18}NO_3$ requires $[M+NH_4]^+$, 212.12866.

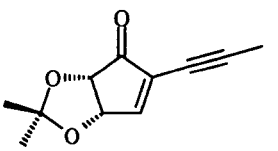
(3a*R*,6a*R*)-4,5-Dihydroxy-2-prop-(*Z*)-enylcyclopent-2-enone (163)



To a solution of acetonide **162** (65 mg, 0.34 mmol) in methanol (3.0 cm^3) was added pyridinium *p*-toluenesulfonate (13 mg, 0.05 mmol) and the reaction heated under reflux for 6.5 hours. The solvent was removed *in vacuo* and the product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 2:3) to yield the title compound **163** (36 mg, 69%) as a white solid; m.p. 106-108 °C (MeOH); $[\alpha]_D^{20}$ +25.0 (c1.0, MeOH); ν_{max}(film)/cm^{-1} 1152, 1292, 1712, 2940, 3285 br., 3430 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.88 (3H, d, *J* 5.2, C(3')H) 2.90 (1H, br. s, -OH), 3.16 (1H, br. s, -OH), 4.18 (1H, d, *J* 5.5, C(5)H), 4.90 (1H, dd, *J* 3.2 and 5.5, C(4)H), 6.02-6.12

(2H, m, C(1')H and C(2')H), 7.45 (1H, d, *J* 3.2, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 15.8 (CH_3), 67.8, 71.2, 117.6, 134.6 (CH), 140.6 (C), 153.3 (CH), 205.7 (C); *m/z* (CI) 172 ($[M+NH_4]^+$, 100%), 154 ($[M]^+$, 22), 137 ($[M-OH]^+$, 30); Found: $[M+NH_4]^+$, 172.09753. $C_8H_{14}NO_3$ requires $[M+NH_4]^+$, 172.09737.

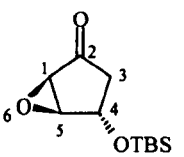
(3a*S*,6a*S*)-2,2-Dimethyl-5-prop-1-ynyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (166)



To a solution of *α*-iodoenone **160** (150 mg, 0.54 mmol) in degassed dimethylformamide (3.0 cm^3) was added tetrakis(triphenylphosphine)palladium (62 mg, 0.05 mmol), copper(I) iodide (21 mg, 0.1 mmol) and triethylamine (0.15 cm^3, 1.08 mmol). Propyne was bubbled through the solution for 10 minutes and the reaction stirred for 4 hours at room temperature under an atmosphere of propyne. The reaction was diluted with water (2 cm^3) and the product was extracted with diethyl ether (3 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:petroleum ether, 1:10) to yield the title compound **166** (60 mg, 58%) as a yellow solid; m.p. 74-76 °C (from EtOAc:petroleum ether); $[\alpha]_D^{20}$ +33.0 (c1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 1375, 1603, 1732, 2241, 2936, 2991; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.39 (3H, s, CH_3), 1.41 (3H, s, CH_3), 2.06 (3H, s, CH_3), 4.51 (1H, d, *J* 5.6, C(3a)H), 5.24 (1H, dd, *J* 2.2 and 5.6, C(6a)H), 7.48 (1H, d, *J* 2.2, C(6)H); δ_C (100

MHz; $CDCl_3$; Me_4Si) 5.0, 26.6, 27.9 (CH_3), 70.1 (C), 76.9, 77.2 (CH), 96.5, 115.8, 131.1 (C), 157.8 (CH), 199.9 (C); *m/z* (CI) 210 ($[M+NH_4]^+$, 100%), 152 ($[M-C_3H_6O+NH_4]^+$, 58), 135 ($[M-C_3H_6O+H]^+$, 71); Found: $[M+NH_4]^+$, 210.11328. $C_{11}H_{16}NO_3$ requires $[M+NH_4]^+$, 210.11301.

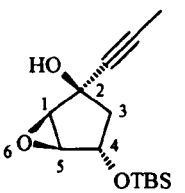
(1*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilanyloxy)-6-oxabicyclo[3.1.0]hexan-2-one (176)



To a solution of 4-(*tert*-butyldimethylsilanyloxy)-cyclopent-2-enone **31** (5.0 g, 23.6 mmol)[88] in methanol (100 cm^3) at 0 °C was added 30% aq. hydrogen peroxide (11.5 cm^3, 113 mmol). Sodium hydroxide (0.4 M, 61 cm^3, 24.4 mmol) was then added dropwise over 10 minutes, and the reaction stirred at 0 °C for 30 minutes. The reaction was quenched with sat. aq. sodium thiosulfate (100 cm^3) and diluted with diethyl ether (100 cm^3). The layers were separated and the aqueous layer extracted with diethyl ether (3 × 100 cm^3), the organic layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a diastereomeric mixture (ca. 4.8:1, *anti*:*syn*) of the title compound. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:6) to yield the title compound **176** (2.21 g, 41%) as a colourless oil; $[\alpha]_D^{20}$ +21.7 (c0.9, $CHCl_3$); Found: C, 58.12; H, 9.07. $C_{11}H_{20}O_3Si$ requires C, 57.85; H, 8.83%; ν_{max}(film)/cm^{-1} 1260, 1472, 1759, 2858, 2930, 2956; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.10 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.95 (1H, d, *J* 18.1, C*H*H), 2.59 (1H, dd, *J* 5.7 and

18.1, CH*H*), 3.39 (1H, d, *J* 2.2, C(5)H), 3.78 (1H, d, *J* 2.2, C(1)H), 4.59 (1H, d, *J* 5.7, C(4)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -4.8, -4.76 (CH_3), 18.0 (C), 25.7 (CH_3), 42.3 (CH_2), 54.2, 60.8, 67.7 (CH), 207.9 (C); *m/z* (CI) 246 ($[M+NH_4]^+$, 29%), 171 ($[M-C(CH_3)_3]^+$, 24), 143 ($[M-C(CH_3)_3-C_2H_6+2H]^+$, 100); Found: $[M+NH_4]^+$, 246.15305. $C_{11}H_{24}NO_3Si$ requires $[M+NH_4]^+$, 246.15254.

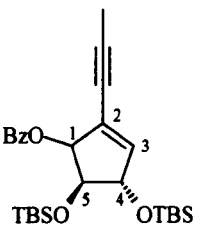
(1*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilanyloxy)-2-prop-1-ynyl-6-oxabicyclo[3.1.0] hexan-2-ol (177)



To a solution of ketone **176** (3.2 g, 14.0 mmol) in anhydrous tetrahydrofuran (140 cm^3) at -78 °C was added propynylmagnesium bromide (0.5 M in tetrahydrofuran, 42.1 cm^3, 21.0 mmol) slowly over 15 minutes and the reaction stirred at -78 °C for 20 hours. The reaction was quenched with sat. aq. ammonium chloride (100 cm^3) and the reaction mixture diluted with ethyl acetate (100 cm^3). The layers were separated and the aqueous layer extracted with ethyl acetate (3 × 100 cm^3), the organic layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 4:5) to yield the title compound **177** (3.31 g, 88%) as a colourless oil; ν_{max}(film)/cm^{-1} 1258, 1351, 1473, 2360, 2857, 2929, 2955, 3419 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.08 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.83 (1H, dd, *J* 5.3 and 13.7, C*H*H), 1.85 (3H, s, CH_3), 2.09 (1H, d, *J* 13.7, CH*H*), 3.41 (1H, d, *J* 2.5, C(5)H), 3.58

(1H, d, *J* 2.5, C(1)H), 4.38 (1H, d, *J* 5.3, C(4)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -4.5, -4.4, 4.0 (CH_3), 18.3 (C), 25.9 (CH_3), 46.6 (CH_2), 59.6, 62.1, 71.7 (CH), 73.4, 79.6, 83.3 (C); *m/z* (CI) 286 ($[M+NH_4]^+$, 49%), 269 ($[M+H]^+$, 28), 268 ($[M]^+$, 43), 251 ($[M-OH]^+$, 70); Found: $[M+NH_4]^+$, 286.18363. $C_{14}H_{28}NO_3Si$ requires $[M+NH_4]^+$, 286.18387.

(4*S*,5*S*)-Benzoic acid 4,5-bis-(*tert*-butyldimethylsilanyloxy)-2-prop-1-ynylcyclopent-2-enyl ester (181)

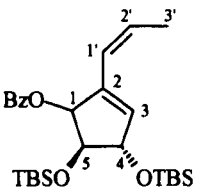


A solution of alcohol **177** (1.0 g, 3.73 mmol) and 4Å molecular sieves (1.0 g) in anhydrous dichloromethane (40 cm^3) at -78 °C was stirred for 1 hour under an atmosphere of nitrogen. 2,6-Lutidine (2.17 cm^3, 18.6 mmol) was added to the solution followed by trifluoromethanesulfonic anhydride (0.92 cm^3, 5.5 mmol) and the reaction stirred at -78 °C for 1 hour. The reaction was quenched with water (10 cm^3) and the reaction mixture filtered through Celite®. The product was extracted with dichloromethane (3 × 10 cm^3) and the organic layers combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:6) and tentatively assigned by ^1H NMR (200 MHz) as the eliminated alcohol **178** along with an inseparable, unidentified product (687 mg) as a pale yellow oil (ca. 3:1 in favour of the eliminated

alcohol). The mixture was taken onto the next step without further characterisation. A solution of this mixture (425 mg, 1.7 mmol) in anhydrous tetrahydrofuran (0.5 cm^3) was added to a stirred solution of tetrakis(triphenylphosphine)palladium (98 mg, 0.09 mmol) and benzoic acid (azeotropically dried with toluene, 0.23 g, 1.9 mmol), at 0 °C, under an atmosphere of nitrogen. The reaction was stirred at 0 °C for ten minutes followed by 1 hour at room temperature. The reaction mixture was passed through a plug of silica gel and eluted with diethyl ether and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:10) to yield two pairs of diastereoisomers **179** and **180** (392 mg, 62% over 2 steps) as a yellow oil. The mixture was taken onto the next step without further characterisation. To a solution of alcohols **179** and **180** (392 mg, 1.05 mmol) in anhydrous dimethylformamide (10 cm^3) was added imidazole (143 mg, 2.1 mmol) followed by *tert*-butyldimethylsilyl chloride (191 mg, 1.3 mmol) and the reaction stirred at room temperature for 18 hours. The reaction was quenched with water (20 cm^3) and the product extracted with diethyl ether (30 cm^3). The organic layer was washed with brine (20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:10) to yield one pair of diastereomers **181** (358 mg, 70%) as a colourless oil; ν_{max}(film)/cm^{-1} 1728, 2233, 2856, 2886, 2929, 2954; δ_H (400 MHz; $CDCl_3$; Me_4Si) -0.02 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.85 (9H, s, $SiC(CH_3)_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.81 (3H, s, CH_3), 4.29 (1H, t, *J* 5.0, C(5)H), 4.57 (1H, m, C(4)H), 5.82 (1H, d, *J* 5.0, C(1)H), 5.95 (1H, s, C(3)H), 7.45 (2H, dd, *J* 7.5, Ph), 7.57 (1H, tt, *J* 1.5 and 7.5, Ph), 8.10 (2H, d, *J* 7.5, Ph); δ_C (100 MHz; $CDCl_3$; Me_4Si) -4.2, -4.15 (× 2), -4.1, 4.7 (CH_3), 18.3, 18.4 (C), 26.1, 26.2 (CH_3), 73.8 (C), 80.3, 82.3, 86.7 (CH), 90.9, 125.3 (C), 128.7, 130.2 (CH), 130.6 (C),

133.3, 138.6 (CH), 166.1 (C); *m/z* (ES+) 509 ([M+^{23}Na]$^+$, 100%); Found: [M+^{23}Na]$^+$, 509.2514. $C_{27}H_{42}{}^{23}NaO_4Si_2$ requires [M+^{23}Na]$^+$, 509.2519.

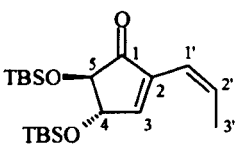
(4*S*,5*S*)-Benzoic acid 4,5-bis-(*tert*-butyldimethylsilanyloxy)-2-prop-(*Z*)-enylcyclopent-2-enyl ester (182)



To a solution of alkyne **181** (271 mg, 0.56 mmol) in ethyl acetate (11 cm^3) was added a solution of quinoline (0.1 M solution in ethyl acetate, 2.8 cm^3, 0.28 mmol) followed by Lindlar's catalyst (379 mg). The solution was evacuated and backfilled 4 times with hydrogen and the reaction stirred for 40 minutes under a balloon of hydrogen. The reaction mixture was filtered through a plug of silica gel and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:15) to yield the title compound **182** (245 mg, 90%) as a colourless oil; ν_{max}(film)/cm^{-1} 1724, 2343, 2360, 2857, 2894, 2929, 2955; δ_H (400 MHz; $CDCl_3$; Me_4Si) -0.01 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.94 (9H, s, $SiC(CH_3)_3$), 1.80 (3H, d, *J* 5.7, C(3')H), 4.33 (1H, t, *J* 4.8, C(5)H), 4.61 (1H, m, C(4)H), 5.68-5.78 (3H, m, C(3)H, C(1')H and C(2')H), 5.90 (1H, d, *J* 4.8, C(1)H), 7.44 (2H, dd, *J* 7.5, Ph), 7.56 (1H, tt, *J* 1.5 and 7.5, Ph), 8.07 (2H, dd, *J* 1.5 and 7.5, Ph); δ_C (100 MHz; $CDCl_3$; Me_4Si) -4.2, -4.15, -4.04, -4.01, 15.5 (CH_3), 18.3, 18.5 (C), 26.1, 26.3 (CH_3), 80.8, 83.4, 86.7, 122.4, 128.7, 130.1 (CH), 130.5 (C), 131.3, 132.6, 133.3 (CH), 138.2, 166.5 (C); *m/z* (ES+)

511 ([M+^{23}Na]$^+$, 100%); Found: [M+^{23}Na]$^+$, 511.2698. $C_{27}H_{44}{}^{23}NaO_4Si_2$ requires [M+^{23}Na]$^+$, 511.2676.

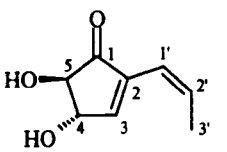
(4*S*,5*R*)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-2-prop-(*Z*)-enylcyclopent-2-enone (183)



To a solution of benzoate **182** (365 mg, 0.75 mmol) in anhydrous toluene (8 cm^3) at -78 °C, under an atmosphere of nitrogen, was added diisobutylaluminium hydride (1 M solution in hexanes, 1.65 cm^3, 1.65 mmol) slowly and the reaction stirred for 90 minutes. The reaction mixture was allowed to warm to room temperature, then cooled to -78 °C and quenched with methanol (1 cm^3) and water (5 cm^3). The product was extracted with diethyl ether (3 × 10 cm^3) and the combined organic layers dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 350 mg of a crude colourless oil. The crude alcohol (350 mg) was dissolved in dichloromethane (8 cm^3) and 4Å molecular sieves (350 mg) added. After 45 minutes at room temperature, pyridinium dichromate (0.71 g, 1.88 mmol) was added and the reaction stirred for 16 hours. The reaction was filtered through a plug of silica gel and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; diethyl ether:*n*-hexane, 1:15) to yield the title compound **183** (202 mg, 71% over two steps) as a colourless oil; $[\alpha]_D^{20}$ +86.2 (c1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1472, 1732, 2359, 2857, 2885, 2929, 2955; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.15 (3H, s, $SiCH_3$), 0.17 (3H, s,

$SiCH_3$), 0.18 (3H, s, $SiCH_3$), 0.20 (3H, s, $SiCH_3$), 0.94 (18H, s, 2 × $SiC(CH_3)_3$), 1.84 (3H, d, *J* 5.7, C(3')H), 4.18 (1H, d, *J* 2.7, C(5)H), 4.70 (1H, m, C(4)H), 5.94-6.03 (2H, m, C(1')H and C(2')H), 7.00 (1H, d, *J* 1.8, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) -4.6, -4.19, -4.18, -3.9, 16.0 (CH_3), 18.4, 18.7 (C), 26.15, 26.18 (CH_3), 77.4, 83.0, 118.3, 133.5 (CH), 139.3 (C), 152.7 (CH), 202.6 (C); *m/z* (CI) 383 ($[M+H]^+$, 100%), 325 ($[M-C(CH_3)_3]^+$, 49), 268 ($[M-2 \times (C(CH_3)_3)]^+$, 47); Found: $[M+H]^+$, 383.24393. $C_{20}H_{39}O_3Si_2$ requires $[M+H]^+$, 383.24377.

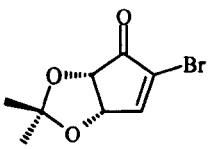
(4*S*,5*R*)-4,5-Dihydroxy-2-prop-(*Z*)-enylcyclopent-2-enone (163)



A solution of *bis*-silylether **183** (200 mg, 0.52 mmol) in acetic acid:water:tetrahydrfuran (2 cm^3, 3:1:1) was heated at 60 °C for 4 hours. Ethyl acetate (10 cm^3) was added to the cooled reaction mixture and the solution washed with sat. aq. sodium hydrogencarbonate (5 cm^3) and brine (5 cm^3). The aqueous layers were combined and washed with ethyl acetate (3 × 10 cm^3) and the organic layers combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 7:3) to yield the title compound **163** (36 mg, 44%) as a white solid; m.p. 52-56 °C (from EtOAc:*n*-hexane); $[\alpha]_D^{20}$ +22.6 (c0.9, MeOH); ν_{max}(film)/cm^{-1} 1050, 1132, 1292, 1417, 1715, 2361, 2921, 3372 br.; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.86 (3H, d, *J* 4.8, C(3')H), 4.28 (1H, d, *J* 2.8, C(5)H), 4.82 (1H, m, C(4)H), 5.98-6.08 (2H, m, C(1')H and C(2')H),

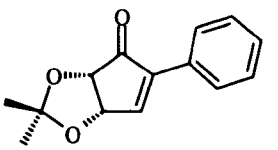
7.25 (1H, d, *J* 2.2, C(3)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 15.8 (CH_3), 75.6, 81.6, 117.3, 134.2 (CH), 139.2 (C), 153.2 (CH), 203.6 (C); *m/z* (CI) 172 ($[M+NH_4]^+$, 100%), 155 ($[M+H]^+$, 79), 154 ($[M]^+$, 20); Found: $[M+H]^+$, 155.07109. $C_8H_{11}O_3$ requires $[M+H]^+$, 155.07082.

(3a*S*,6a*S*)-5-Bromo-2,2-dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (187)



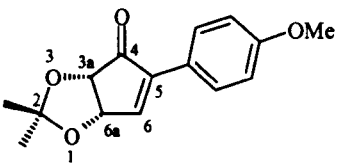
To a solution of enone **141** (200 mg, 1.3 mmol) in anhydrous dichloromethane (13 cm^3) at 0 °C was added bromine (72 µl, 1.4 mmol) dropwise and the reaction stirred for 30 minutes. Triethylamine (0.27 cm^3, 1.95 mmol) was added and the reaction stirred for 1 hour at 0 °C. The reaction was diluted with water (10 cm^3) and the layers separated. The aqueous layer was washed with dichloromethane (10 cm^3) and the combined organic layers washed with brine (10 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:10) to yield the title compound **187** (264 mg, 87%) as a white solid; ν_{max}(film)/cm^{-1} 1584, 1737, 2945, 2998; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.41 (3H, s, CH_3), 1.42 (3H, s, CH_3), 4.57 (1H, d, *J* 5.6, C(3a)H), 5.22 (1H, dd, *J* 2.5 and 5.6, C(6a)H), 7.71 (1H, d, *J* 2.5, C(6)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.7, 27.8 (CH_3), 75.7, 77.8 (CH), 116.2, 128.9 (C), 157.3 (CH), 195.6 (C); *m/z* (CI) 252 ($[M^{81}Br+NH_4]^+$, 95%), 250 ($[M^{79}Br+NH_4]^+$, 100); Found: $[M^{79}Br+NH_4]^+$, 250.00819. $C_8H_{13}{}^{79}BrNO_3$ requires $[M^{79}Br+NH_4]^+$, 250.00787.

(3a*S*,6a*S*)-2,2-Dimethyl-5-phenyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (188)



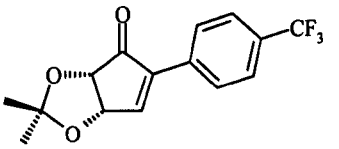
To a solution of α-bromoenone **187** (100 mg, 0.43 mmol) and phenylboronic acid (55 mg, 0.45 mmol) in degassed toluene (13 cm^3) was added tetrakis(triphenylphosphine)palladium (23 mg, 0.02 mmol) and potassium carbonate (89 mg, 0.65 mmol). The reaction was heated under reflux for 24 hours under an atmosphere of nitrogen. The reaction was allowed to cool and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:10) to yield the title compound **188** (61 mg, 62%) as a white solid; m.p. 99-100 °C (from EtOAc:*n*-hexane); $[\alpha]_D^{20}$ -36.2 (c0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 1716, 2341, 2359, 2992; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.42 (3H, s, CH_3), 1.45 (3H, s, CH_3), 4.65 (1H, d, *J* 5.6, C(3a)H), 5.31 (1H, dd, *J* 2.6 and 5.6, C(6a)H), 7.38-7.42 (3H, m, Ph), 7.67 (1H, d, *J* 2.6, C(6)H), 7.73-7.75 (2H, m, Ph); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.7, 28.0 (CH_3), 76.6, 78.6 (CH), 115.7 (C), 127.9, 129.0, 129.9 (CH), 130.6, 143.6 (C), 152.7 (CH), 201.4 (C); *m/z* (CI) 248 ($[M+NH_4]^+$, 23%), 173 ($[M+H-C_3H_6O]^+$, 100); Found: $[M+NH_4]^+$, 248.12860. $C_{14}H_{18}NO_3$ requires $[M+NH_4]^+$, 248.12866.

(3a*S*,6a*S*)-5-(4-Methoxyphenyl)-2,2-dimethyl-3a,6a-dihydrocyclopenta[1,3] dioxol-4-one (189)



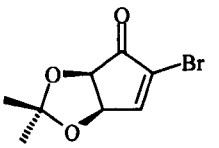
To a solution of *α*-bromoenone **187** (145 mg, 0.62 mmol) and *p*-methoxyphenylboronic acid (0.14 g, 0.93 mmol) in degassed toluene (19 cm^3) was added tetrakis(triphenylphosphine)palladium (72 mg, 0.06 mmol) and potassium carbonate (129 mg, 0.93 mmol). The reaction was heated under reflux for 23 hours under an atmosphere of nitrogen. The reaction was allowed to cool and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:10) to yield the title compound **189** (96 mg, 59%) as an off-white solid; m.p. 111-113 °C (from EtOAc:*n*-hexane); $[\alpha]_D^{20}$ -57.6 (c1.0, $CHCl_3$); Found: C, 69.15; H, 6.19. $C_{15}H_{16}O_4$ requires C, 69.22; H, 6.20%; ν_{max}(film)/cm^{-1} 1716, 2939, 2983; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.41 (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.83 (3H, s, -OCH_3), 4.62 (1H, d, *J* 5.6, C(3a)H), 5.28 (1H, dd, *J* 2.7 and 5.6, C(6a)H), 6.92 (2H, d, *J* 8.9, Ar), 7.58 (1H, d, *J* 2.7, C(6)H), 7.74 (2H, d, *J* 8.9, Ar); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.8, 28.0, 55.7 (CH_3), 76.6, 78.6, 114.4 (CH), 115.6, 123.1 (C), 129.3 (CH), 142.9 (C), 150.6 (CH), 161.1, 201.9 (C); *m/z* (CI) 278 ($[M+NH_4]^+$, 11%), 203 ($[M+H-C_3H_6O]^+$, 100); Found: $[M+NH_4]^+$, 278.13852. $C_{15}H_{20}NO_4$ requires $[M+NH_4]^+$, 278.13925.

(3a*S*,6a*S*)-2,2-Dimethyl-5-(4-trifluoromethylphenyl)-3a,6a-dihydrocyclopenta [1,3]dioxol-4-one (190)



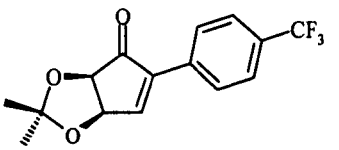
To a solution of α-bromoenone **187** (100 mg, 0.43 mmol) and *p*-trifluoromethylphenylboronic acid (104 mg, 0.55 mmol) in degassed toluene (13 cm^3) was added tetrakis(triphenylphosphine)palladium (46 mg, 0.04 mmol) and potassium carbonate (76 mg, 0.55 mmol). The reaction was heated under reflux for 41 hours under an atmosphere of nitrogen. The reaction was allowed to cool and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:4) to yield the title compound **190** (84 mg, 78%) as a pale yellow solid; m.p. 98-100 °C (from EtOAc:*n*-hexane); $[\alpha]_D^{20}$ -20.6 (c1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 1332, 1380, 1713; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.44 (3H, s, CH_3), 1.46 (3H, s, CH_3), 4.68 (1H, d, *J* 5.6, C(3a)H), 5.34 (1H, dd, *J* 2.6 and 5.6, C(6a)H), 7.67 (2H, d, *J* 8.2, Ar), 7.77 (1H, d, *J* 2.6, C(6)H), 7.86 (2H, d, *J* 8.2, Ar); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.2, 27.6 (CH_3), 76.1, 78.1 (CH), 115.6 (C), 125.6 (CF_3), 127.9 (2 × CH), 131.5, 133.6, 142.0 (C), 154.0 (CH), 200.5 (C); *m/z* (CI) 316 ($[M+NH_4]^+$, 61%), 299 ($[M+H]^+$, 3), 258 ($[M+NH_4-C_3H_6O]^+$, 100); Found: $[M+H]^+$, 299.08936. $C_{15}H_{14}F_3O_3$ requires $[M+H]^+$, 299.08951.

(3a*R*,6a*R*)-5-Bromo-2,2-dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (187)



To a solution of enone **141** (200 mg, 1.3 mmol) in anhydrous dichloromethane (13 cm^3) at 0 °C was added bromine (1M in dichloromethane, 1.4 cm^3, 1.4 mmol) dropwise and the reaction stirred for 30 minutes. Triethylamine (0.27 cm^3, 1.95 mmol) was added and the reaction stirred for 1.5 hours at 0 °C. The reaction was diluted with water (10 cm^3) and the layers separated. The aqueous layer was washed with dichloromethane (2 × 10 cm^3) and the combined organic layers washed with brine (10 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:10) to yield the title compound **187** (257 mg, 85%) as a white solid; ν_{max}(film)/cm^{-1} 1584, 1737, 1749, 2945, 2999; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.41 (3H, s, CH_3), 1.42 (3H, s, CH_3), 4.57 (1H, d, *J* 5.6, C(3a)H), 5.22 (1H, dd, *J* 2.5 and 5.6, C(6a)H), 7.71 (1H, d, *J* 2.5, C(6)H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.7, 27.8 (CH_3), 75.7, 77.8 (CH), 116.2, 128.9 (C), 157.3 (CH), 195.6 (C); *m/z* (CI) 252 ($[M^{81}Br+NH_4]^+$, 96%), 250 ($[M^{79}Br+NH_4]^+$, 100); Found: $[M^{79}Br+NH_4]^+$, 250.00770. $C_8H_{13}{}^{79}BrNO_3$ requires $[M^{79}Br+NH_4]^+$, 250.00787.

(3a*R*,6a*R*)-2,2-Dimethyl-5-(4-trifluoromethylphenyl)-3a,6a-dihydrocyclopenta [1,3]dioxol-4-one (190)



To a solution of α-bromoenone **187** (100 mg, 0.43 mmol) and *p*-trifluoromethylphenylboronic acid (123 mg, 0.65 mmol) in degassed toluene (13 cm^3) was added tetrakis(triphenylphosphine)palladium (46 mg, 0.04 mmol) and potassium carbonate (90 mg, 0.65 mmol). The reaction was heated under reflux for 65 hours under an atmosphere of nitrogen. The reaction was allowed to cool and the solvent removed *in vacuo*. The product was purified by flash column chromatography (SiO_2; EtOAc:*n*-hexane, 1:4) to yield the title compound **190** (123 mg, 96%) as a pale yellow solid; m.p. 101-102 °C (from EtOAc:*n*-hexane); $[\alpha]_D^{20}$ +17.0 (c1.5, $CHCl_3$); Found: C, 60.31; H, 4.36. $C_{15}H_{13}F_3O_3$ requires C, 60.41; H, 4.39%; ν_{max}(film)/cm^{-1} 1333, 1381, 1713; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.44 (3H, s, CH_3), 1.46 (3H, s, CH_3), 4.68 (1H, d, *J* 5.6, C(3a)H), 5.34 (1H, dd, *J* 2.6 and 5.6, C(6a)H), 7.67 (2H, d, *J* 8.2, Ar), 7.77 (1H, d, *J* 2.6, C(6)H), 7.86 (2H, d, *J* 8.2, Ar); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.2, 27.6 (CH_3), 76.1, 78.1 (CH), 115.6 (C), 125.6 (CF_3), 127.9 (2 × CH), 131.5, 133.6, 142.0 (C), 154.0 (CH), 200.5 (C); *m/z* (CI) 316 ($[M+NH_4]^+$, 100%), 258 ($[M-C_3H_6O+NH_4]^+$, 54), 240 ($[M-C_3H_6O]^+$, 53); Found: $[M+NH_4]^+$, 316.11669. $C_{15}H_{17}F_3NO_3$ requires $[M+NH_4]^+$, 316.11606.

Chapter 4:

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Chapter 5:

Appendix

Appendix I

Crystallographic data for (*R*)-4-(*tert*-butyldimethylsilanyloxy)-5-[2'-methylprop-(*E*)-ylidene]-cyclopent-2-enone, (-)-53

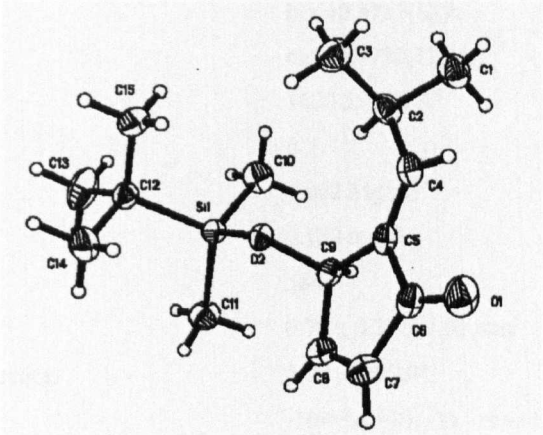

Table 1. Crystal data and structure refinement for tjs111m.

Identification code	tjs111m	
Empirical formula	C15 H26 O2 Si	
Formula weight	266.45	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.8583(5) Å	α= 90°.
	b = 10.5757(6) Å	β= 90°.
	c = 19.4971(12) Å	γ = 90°.
Volume	1620.35(17) $Å^3$	
Z	4	
Density (calculated)	1.092 Mg/m^3	
Absorption coefficient	0.139 mm^{-1}	
F(000)	584	
Crystal size	0.70 x 0.32 x 0.05 mm^3	
Theta range for data collection	2.09 to 28.29°.	
Index ranges	-10<=h<=10, -14<=k<=12, -21<=l<=25	
Reflections collected	10259	
Independent reflections	3780 [R(int) = 0.0398]	
Completeness to theta = 28.29°	96.0 %	
Absorption correction	None	
Max. and min. transmission	0.9931 and 0.9089	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3780 / 0 / 170	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0807	
R indices (all data)	R1 = 0.0385, wR2 = 0.0820	
Absolute structure parameter	0.06(10)	
Largest diff. peak and hole	0.300 and -0.168 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for tjs111m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5166(3)	6312(2)	3421(1)	43(1)
C(2)	5359(2)	5429(2)	2807(1)	30(1)
C(3)	3645(2)	4861(2)	2610(1)	43(1)
C(4)	6595(2)	4390(1)	2957(1)	27(1)
C(5)	7862(2)	3994(1)	2566(1)	25(1)
C(6)	8988(2)	2912(1)	2754(1)	29(1)
C(7)	10139(2)	2723(2)	2170(1)	36(1)
C(8)	9831(2)	3570(2)	1688(1)	33(1)
C(9)	8418(2)	4473(1)	1869(1)	24(1)
C(10)	6313(2)	7006(1)	1048(1)	36(1)
C(11)	8937(2)	5538(2)	247(1)	34(1)
C(12)	5170(2)	4714(1)	174(1)	26(1)
C(13)	4865(3)	5559(2)	-453(1)	51(1)
C(14)	5688(2)	3395(2)	-71(1)	39(1)
C(15)	3524(2)	4590(2)	586(1)	40(1)
O(1)	8952(2)	2305(1)	3284(1)	40(1)
O(2)	7084(1)	4413(1)	1374(1)	23(1)
Si(1)	6894(1)	5413(1)	722(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for tjs111m.

C(1)-C(2)	1.527(2)
C(2)-C(4)	1.495(2)
C(2)-C(3)	1.524(2)
C(4)-C(5)	1.322(2)
C(5)-C(6)	1.491(2)
C(5)-C(9)	1.5152(19)
C(6)-O(1)	1.2183(18)
C(6)-C(7)	1.467(2)
C(7)-C(8)	1.321(2)
C(8)-C(9)	1.507(2)
C(9)-O(2)	1.4257(15)
C(10)-Si(1)	1.8579(15)
C(11)-Si(1)	1.8578(16)
C(12)-C(15)	1.529(2)
C(12)-C(14)	1.530(2)
C(12)-C(13)	1.534(2)
C(12)-Si(1)	1.8770(15)
O(2)-Si(1)	1.6606(9)
C(4)-C(2)-C(3)	109.48(13)
C(4)-C(2)-C(1)	111.09(12)
C(3)-C(2)-C(1)	110.53(14)
C(5)-C(4)-C(2)	127.50(13)
C(4)-C(5)-C(6)	123.27(14)
C(4)-C(5)-C(9)	128.93(13)
C(6)-C(5)-C(9)	107.77(13)
O(1)-C(6)-C(7)	126.94(15)
O(1)-C(6)-C(5)	126.78(15)
C(7)-C(6)-C(5)	106.27(13)
C(8)-C(7)-C(6)	110.31(14)
C(7)-C(8)-C(9)	113.41(14)
O(2)-C(9)-C(8)	110.83(11)
O(2)-C(9)-C(5)	112.34(11)
C(8)-C(9)-C(5)	102.19(12)
C(15)-C(12)-C(14)	108.10(13)
C(15)-C(12)-C(13)	109.66(14)

C(14)-C(12)-C(13)	108.93(13)
C(15)-C(12)-Si(1)	110.24(10)
C(14)-C(12)-Si(1)	110.16(11)
C(13)-C(12)-Si(1)	109.72(11)
C(9)-O(2)-Si(1)	123.77(8)
O(2)-Si(1)-C(11)	110.43(6)
O(2)-Si(1)-C(10)	109.72(6)
C(11)-Si(1)-C(10)	108.58(8)
O(2)-Si(1)-C(12)	104.47(6)
C(11)-Si(1)-C(12)	111.61(7)
C(10)-Si(1)-C(12)	111.99(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for tjs111m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	54(1)	38(1)	37(1)	-7(1)	0(1)	11(1)
C(2)	38(1)	29(1)	23(1)	2(1)	2(1)	4(1)
C(3)	38(1)	45(1)	46(1)	-2(1)	-7(1)	9(1)
C(4)	35(1)	26(1)	20(1)	1(1)	-2(1)	-1(1)
C(5)	30(1)	23(1)	22(1)	-2(1)	-6(1)	-2(1)
C(6)	33(1)	25(1)	28(1)	-2(1)	-9(1)	-1(1)
C(7)	31(1)	38(1)	40(1)	0(1)	-4(1)	11(1)
C(8)	24(1)	45(1)	31(1)	-2(1)	0(1)	3(1)
C(9)	24(1)	23(1)	24(1)	0(1)	-3(1)	-2(1)
C(10)	46(1)	24(1)	38(1)	1(1)	0(1)	4(1)
C(11)	29(1)	40(1)	33(1)	6(1)	4(1)	-4(1)
C(12)	27(1)	30(1)	22(1)	2(1)	-2(1)	0(1)
C(13)	59(1)	55(1)	39(1)	16(1)	-22(1)	-7(1)
C(14)	42(1)	38(1)	37(1)	-10(1)	-1(1)	-3(1)
C(15)	25(1)	51(1)	45(1)	-9(1)	0(1)	-4(1)
O(1)	53(1)	35(1)	33(1)	7(1)	-8(1)	9(1)
O(2)	23(1)	25(1)	21(1)	2(1)	-3(1)	-2(1)
Si(1)	23(1)	22(1)	22(1)	2(1)	1(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for tjs111m.

	x	y	z	U(eq)
H(1A)	4401	7009	3301	64
H(1B)	6282	6652	3548	64
H(1C)	4691	5841	3809	64
H(2)	5797	5930	2409	36
H(3A)	3146	4439	3010	65
H(3B)	3806	4243	2241	65
H(3C)	2881	5534	2453	65
H(4)	6453	3966	3383	32
H(7)	10984	2083	2143	44
H(8)	10442	3606	1267	40
H(9)	8866	5355	1906	28
H(10A)	5246	6952	1307	54
H(10B)	6167	7587	661	54
H(10C)	7219	7320	1349	54
H(11A)	9799	5927	543	51
H(11B)	8775	6061	-162	51
H(11C)	9316	4692	110	51
H(13A)	5909	5608	-727	76
H(13B)	4543	6409	-301	76
H(13C)	3948	5201	-733	76
H(14A)	4780	3040	-356	58
H(14B)	5877	2846	327	58
H(14C)	6739	3453	-339	58
H(15A)	3188	5423	760	61
H(15B)	3705	4012	972	61
H(15C)	2622	4256	289	61

Table 6. Torsion angles [°] for tjs111m.

C(3)-C(2)-C(4)-C(5)	104.91(18)
C(1)-C(2)-C(4)-C(5)	-132.75(16)
C(2)-C(4)-C(5)-C(6)	-177.67(14)
C(2)-C(4)-C(5)-C(9)	0.3(2)
C(4)-C(5)-C(6)-O(1)	-3.5(2)
C(9)-C(5)-C(6)-O(1)	178.19(14)
C(4)-C(5)-C(6)-C(7)	176.22(14)
C(9)-C(5)-C(6)-C(7)	-2.13(16)
O(1)-C(6)-C(7)-C(8)	-179.00(15)
C(5)-C(6)-C(7)-C(8)	1.32(18)
C(6)-C(7)-C(8)-C(9)	0.1(2)
C(7)-C(8)-C(9)-O(2)	-121.24(15)
C(7)-C(8)-C(9)-C(5)	-1.36(17)
C(4)-C(5)-C(9)-O(2)	-57.33(19)
C(6)-C(5)-C(9)-O(2)	120.90(12)
C(4)-C(5)-C(9)-C(8)	-176.15(14)
C(6)-C(5)-C(9)-C(8)	2.07(14)
C(8)-C(9)-O(2)-Si(1)	-96.84(13)
C(5)-C(9)-O(2)-Si(1)	149.55(9)
C(9)-O(2)-Si(1)-C(11)	50.48(12)
C(9)-O(2)-Si(1)-C(10)	-69.17(12)
C(9)-O(2)-Si(1)-C(12)	170.61(10)
C(15)-C(12)-Si(1)-O(2)	59.05(12)
C(14)-C(12)-Si(1)-O(2)	-60.17(11)
C(13)-C(12)-Si(1)-O(2)	179.92(11)
C(15)-C(12)-Si(1)-C(11)	178.39(11)
C(14)-C(12)-Si(1)-C(11)	59.17(13)
C(13)-C(12)-Si(1)-C(11)	-60.74(14)
C(15)-C(12)-Si(1)-C(10)	-59.64(13)
C(14)-C(12)-Si(1)-C(10)	-178.85(10)
C(13)-C(12)-Si(1)-C(10)	61.24(14)

Symmetry transformations used to generate equivalent atoms:

Appendix II

Crystallographic data for (3a*S*,6a*S*)-4,5-dihydroxy-2-prop-(*Z*)-enyl-cyclopent-2-enone, (-)-*syn*-163

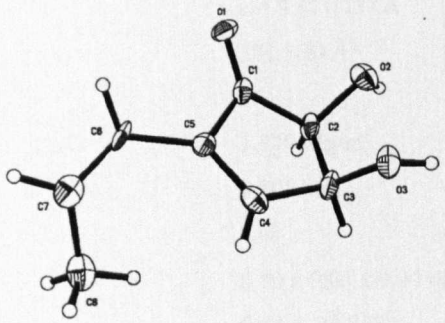

Table 1. Crystal data and structure refinement for tss319m.

Identification code	tss319m	
Empirical formula	C8 H10 O3	
Formula weight	154.16	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21**	
Unit cell dimensions	a = 7.940(10) Å	α= 90°.
	b = 5.159(6) Å	β= 105.635(18)°.
	c = 9.411(13) Å	γ = 90°.
Volume	371.3(8) $Å^3$	
Z	2	
Density (calculated)	1.379 Mg/m^3	
Absorption coefficient	0.105 mm^{-1}	
F(000)	164	
Crystal size	0.80 x 0.05 x 0.04 mm^3	
Theta range for data collection	2.25 to 28.26°.	
Index ranges	-10<=h<=7, -4<=k<=6, -12<=l<=9	
Reflections collected	1032	
Independent reflections	1016 [R(int) = 0.0327]	
Completeness to theta = 28.26°	79.2 %	
Max. and min. transmission	0.9958 and 0.9204	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1016 / 1 / 103	
Goodness-of-fit on F^2	0.696	
Final R indices [I>2sigma(I)]	R1 = 0.0460, wR2 = 0.0844	
R indices (all data)	R1 = 0.1234, wR2 = 0.0995	
Absolute structure parameter	4(4)**	
Largest diff. peak and hole	0.215 and -0.202 $e.Å^{-3}$	

**Note Absolute structure could not be determined

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for tss319m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8295(7)	7765(12)	5537(7)	19(2)
C(2)	7237(6)	10260(12)	5316(6)	20(1)
C(3)	7044(6)	10861(11)	6872(6)	22(2)
C(4)	8552(6)	9384(11)	7857(6)	20(2)
C(5)	9283(7)	7690(12)	7103(6)	19(2)
C(6)	10752(7)	5898(12)	7653(5)	22(2)
C(7)	12245(8)	6458(12)	8624(6)	28(2)
C(8)	12810(7)	8934(11)	9386(6)	30(2)
O(1)	8268(5)	6180(6)	4574(4)	23(1)
O(2)	5632(4)	10024(7)	4190(4)	26(1)
O(3)	5450(4)	9929(8)	7101(4)	26(1)

Table 3. Bond lengths [Å] and angles [°] for tss319m.

C(1)-O(1)	1.217(6)
C(1)-C(5)	1.472(8)
C(1)-C(2)	1.521(8)
C(2)-O(2)	1.426(6)
C(2)-C(3)	1.544(7)
C(3)-O(3)	1.424(6)
C(3)-C(4)	1.509(6)
C(4)-C(5)	1.351(7)
C(5)-C(6)	1.469(7)
C(6)-C(7)	1.320(7)
C(7)-C(8)	1.474(8)
O(1)-C(1)-C(5)	128.8(5)
O(1)-C(1)-C(2)	124.7(5)
C(5)-C(1)-C(2)	106.5(5)
O(2)-C(2)-C(1)	112.3(5)
O(2)-C(2)-C(3)	115.2(4)
C(1)-C(2)-C(3)	103.5(4)
O(3)-C(3)-C(4)	109.1(4)
O(3)-C(3)-C(2)	113.3(4)
C(4)-C(3)-C(2)	102.5(4)
C(5)-C(4)-C(3)	112.7(5)
C(4)-C(5)-C(6)	129.4(5)
C(4)-C(5)-C(1)	108.7(5)
C(6)-C(5)-C(1)	121.8(5)
C(7)-C(6)-C(5)	125.9(6)
C(6)-C(7)-C(8)	128.7(6)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for tss319m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	14(3)	10(4)	33(4)	6(3)	9(3)	1(3)
C(2)	16(3)	13(4)	30(3)	7(3)	7(3)	5(3)
C(3)	16(3)	16(4)	36(3)	0(3)	12(3)	3(3)
C(4)	17(3)	22(5)	21(3)	3(3)	4(3)	-8(3)
C(5)	15(3)	14(4)	28(4)	-2(3)	8(3)	-3(3)
C(6)	20(3)	15(4)	35(4)	1(3)	13(3)	11(3)
C(7)	28(4)	25(4)	35(4)	1(4)	14(3)	-1(4)
C(8)	25(4)	30(5)	37(4)	8(4)	10(3)	0(3)
O(1)	26(2)	15(3)	32(2)	-7(2)	13(2)	-3(2)
O(2)	24(2)	21(3)	30(2)	6(2)	4(2)	-6(2)
O(3)	19(2)	22(3)	38(3)	5(2)	9(2)	2(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for tss319m.

	x	y	z	U(eq)
H(2)	7949	11664	5030	23
H(3)	7176	12761	7080	26
H(4)	8945	9619	8895	24
H(6)	10613	4180	7276	27
H(7)	13068	5081	8864	34
H(8A)	11967	10294	8950	45
H(8B)	13966	9401	9278	45
H(8C)	12872	8752	10435	45
H(2O)	5478	11352	3654	39
H(3O)	4629	10932	6691	39

Table 6. Torsion angles [°] for tss319m.

O(1)-C(1)-C(2)-O(2)	29.9(8)
C(5)-C(1)-C(2)-O(2)	-149.3(4)
O(1)-C(1)-C(2)-C(3)	154.7(5)
C(5)-C(1)-C(2)-C(3)	-24.5(5)
O(2)-C(2)-C(3)-O(3)	27.6(7)
C(1)-C(2)-C(3)-O(3)	-95.3(5)
O(2)-C(2)-C(3)-C(4)	145.0(5)
C(1)-C(2)-C(3)-C(4)	22.1(5)
O(3)-C(3)-C(4)-C(5)	107.4(5)
C(2)-C(3)-C(4)-C(5)	-13.0(6)
C(3)-C(4)-C(5)-C(6)	-179.5(5)
C(3)-C(4)-C(5)-C(1)	-2.5(6)
O(1)-C(1)-C(5)-C(4)	-161.8(6)
C(2)-C(1)-C(5)-C(4)	17.4(6)
O(1)-C(1)-C(5)-C(6)	15.5(9)
C(2)-C(1)-C(5)-C(6)	-165.3(5)
C(4)-C(5)-C(6)-C(7)	-44.8(9)
C(1)-C(5)-C(6)-C(7)	138.5(6)
C(5)-C(6)-C(7)-C(8)	0.2(9)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for tss319m [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3O)...O(1)#1	0.84	2.29	3.018(6)	145.0
O(3)-H(3O)...O(2)#1	0.84	2.26	2.926(6)	136.7
O(2)-H(2O)...O(3)#1	0.84	2.04	2.838(6)	157.9

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y+1/2,-z+1

Appendix III

Biological Tests

The biological data for the compounds described in this thesis have all been compared using the same biological test to allow for direct comparisons to be made. The assay used was a viral screen to determine the activity of the test compounds as a function of concentration against the Sendai virus. Charterhouse Therapeutics has also developed specific screens to measure the effect of the test compounds on heat shock factor activation and NF-κB inhibition, along with a fast throughput screen based on *luciferase* production. Toxicity screens have also been set up, and the compounds in this thesis have been compared using the toxicity results from the Sendai virus screen. However, during the course of this Ph.D., the tests have evolved to allow for more accurate results to be obtained.

1. Viral tests

The viral tests comprises of specific cells being infected with the Sendai virus for one hour at 37 °C, then the viral inoculum is removed and the cells are treated with different concentrations of the test compound. Virus titers are determined by haemagglutinin titration because the haemagglutinin can aggregate with the virus only when it reaches a known concentration. Twenty-four hours after the injection, each cellular extract is tested at different concentrations. In each experiment, one knows the concentration of the virus as a function of the quantity of inhibitor introduced just by watching the aggregation. Thus, with this direct titration one can draw a graph of

the concentration of the virus as a function of the quantity of inhibitor injected.

2. Initial heat shock factor tests

This test was based on heat shock protein 70 (HSP70) production. Sendai virus infected or uninfected cells are treated with different concentrations of cyclopentenones. After a one hour absorption period, [^{35}S] labelled methionine is added to the culture for a further 24 hours. After this time, the amount of radioactivity incorporated into proteins is quantified and analysed by gel electrophoresis. The molecular weights are calculated by using Bio-RadM_T markers. The gel is dried and autoradiographed with an intensifying screen, then the intensity of the different spots for HSP70 is measured and a graph can be drawn correlating the intensities with the concentration of cyclopentenone introduced.

3. NF-κB

In this test, labelled DNA (DNA*) is used, and the activity of NF-κB is measured by studying how many DNA*- NF-κB complexes are formed. If the cyclopentenones are active, they inhibit the release of NF-κB and thus prevent its translocation into the nucleus and its binding to DNA.

The double stranded oligonucleotides which contain the NF-κB recognition sequence are end-labelled with [γ-^{32}P] ATP. The cells are then treated with the Sendai virus, along with different concentrations of the cyclopentenone test compound, and the cells are then stimulated with a known NF-κB promoter, for example, PMMA, TNF-α, virus infection etc., and are centrifuged to give a solution of nuclear proteins. A large excess of labelled-DNA is added to this solution, containing the nuclear

proteins, and the released NF-κB binds with labelled DNA to give the NF-κB-DNA* complex. This mixture is then resolved by electrophoresis, as in the HSP70 screen, and the intensity of the spots, corresponding to the labelled NF-κB-DNA* complex, is related to the NF-κB-inhibition potential of the compound being tested.