UNIVERSITY OF SOUTHAMPTON

Towards the total synthesis of desogestrel

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Doctor of Philosophy

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ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHS

DEPARTMENT OF CHEMISTRY

Doctor of Philosophy

TOWARDS THE TOTAL SYNTHESIS OF DESOGESTREL

by Robert Aldous Clarkson

Proposed is a total synthesis of the steroid desogestrel, utilizing a 1,4-addition/alkylation reaction to install the correct stereochemistry at C_8, C_{13} and C_{14} in a single-pot operation as well as a domino reaction to construct the B and C-steroid rings in a single operation. Detailed is the synthesis of a number of 1,4-addition precursors including the optimization of an achiral *Z*-allylic phosphonate and the subsequent 1,4-addition reactions of these compounds. It was discovered that, whilst a *Z*-allylic phosphonate took part in the 1,4-addition/alkylation as expected, the reaction with the *E*-double bond isomer afforded a 2 : 1 mixture of the 1, 4-addition/alkylation product : an intramolecular-cyclization bicyclic heptanone product. This intramolecular-cyclization reaction had plagued the 1,4-addition/alkylation reactions with phenyl allyl sulfoxide, and this discovery enabled the reaction to be conducted successfully within the allylic sulfoxide series by employing a *Z*-allylic sulfoxide. Also detailed are the subsequent reactions to convert the 1,4-addition/alkylation products into the domino cyclization precursors and the attempted domino reactions of these compounds. Whilst the domino reaction could not be realized, the C-ring cyclization was found to be extremely successful in the phosphonate series and subsequent optimization enabled yields of up to 92% to be obtained.

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Preface

The research described in this thesis was carried out under the supervision of Dr Bruno Linclau at the University of Southampton between October 2000 and July 2004. No part of this thesis has been previously submitted at this or any other university.

Acknowledgements

I thank first and foremost Dr Bruno Linclau for his continued help throughout this research project. I also thank Prof. Jeremy Kilburn for providing feedback from my quarterly reports, Mrs Joan Street and Dr Neil Wells for their assistance with the NMR facilities and Dr John Langley and Miss Julie Herniman for their assistance with the MS facilities. I also thank Dr Marinus Groen and Dr Jaap van der Louw from Organon N. V. (Oss) and the University of Southampton for funding. My thanks also extend to Miss Elena Boland for her continued help and support and also to the members of the Linclau group with whom I worked.

Abbreviations

The following abbreviations have been used throughout this thesis:

BEMP	–	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
br	–	broad
CAN	–	Cerium ammonium nitrate
CIMS	–	Chemical ionisation mass spectrometry
CSA	–	DL-camphor-10-sulfonic acid
d	–	doublet
DCC	–	Dicyclohexylcarbodiimide
de	–	diastereomeric excess
DEAD	–	Diethyl azodicarboxylate
DHA	–	Dehydroepiandrosterone acetate
DIBAL	–	Diisobutylaluminium hydride
DIPEA	–	Diisopropylethylamine
DMAP	–	Dimethylaminopyridine
DME	–	Dimethoxyethane
DMF	–	Dimethylformamide
DMSO	–	Dimethylsulfoxide
EDCI	–	1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
ee	–	enantiomeric excess
EIMS	–	Electron ionisation mass spectrometry
Ether	–	Diethyl ether
2-Ethylcyclopenteneone	–	2-Ethylcyclopent-2-ene-1-one
FSH	–	Follicle stimulating hormone
h	–	hour
HCA	–	Hexachloroacetone
HMPA	–	Hexamethylphosphoramide
HMPT	–	Hexamethyl phosphorus triamide
HPLC	–	High performance liquid chromatography

HRMS	–	High resolution mass spectrometry
IMHW	–	Intramolecular Horner-Wittig
L	–	litre
LAH	–	Lithium aluminium hydride
LDA	–	Lithium diisopropylamide
LH	–	Luteinizing hormone
LHMDS	–	Lithium hexamethyldisilazide (lithium bis(trimethylsilyl)amide)
m-CPBA	–	*meta*-Chloroperbenzioc acid (3-chloroperoxybenzoic acid)
2-Methylcyclopenteneone	–	2-Methylcyclopent-2-ene-1-one
min	–	minute
NMR	–	Nuclear magnetic resonance
o/n	–	overnight
OTf	–	Triflate/trifluoromethanesulfonate
ox	–	oxidation
PG	–	Protecting group
PMB	–	Pyridinium hydrobromide perbromide
PPTS	–	Pyridinium *p*-toluenesulfonate
*p*TSA	–	*para*-Toluenesulfonic acid
py	–	Pyridine
Q	–	Quaternary
q	–	quartet
rt	–	room temperature
s	–	singlet
t	–	triplet
TBAI	–	Tetrabutylammonium iodide
TBS/TBDMS	–	*tert*-Butyldimethylsilyl
TFA	–	Trifluoroacetic acid
THF	–	Tetrahydrofuran
TIPS	–	Triisopropylsilyl
TLC	–	Thin layer chromatography
TMEDA	–	Tetramethylethylenediamine
TMS	–	Trimethylsilyl

Chapter 1, Introduction

1.1 Steroids

1.1.1 Introduction to steroids

Steroids are a class of compounds whose structure is based on the tetracyclic ring system as illustrated in Figure 1. By convention, it is agreed that the rings are labelled with a letter and that this begins with the lower left hand ring, working towards the upper right hand ring. It is also convention to begin the carbon numbering in the A-ring, also illustrated in Figure 1.

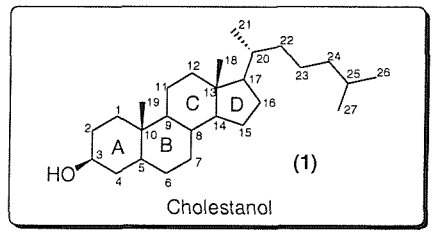


Figure 1

From the labelling convention, the upper and lower faces of the steroid can be clearly defined. For naming purposes, the upper face is defined as the β–face and the lower face is defined as the α–face (Figure 2).

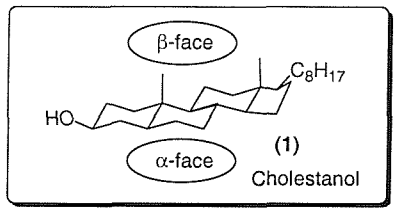


Figure 2

Additionally, the nor–prefix is used within steroid nomenclature to indicate the lack of a particular group, e.g. 19-nor is used to denote a missing methyl group at C_{10} (the C_{19} methyl group). This is illustrated in Figure 3 with the examples of testosterone (**2**) and 19-nortestosterone (nandrolone) (**3**). Other naming prefixes are used within steroid chemistry[1] but these have not been used within this thesis.

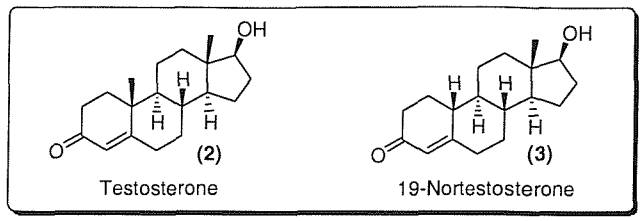
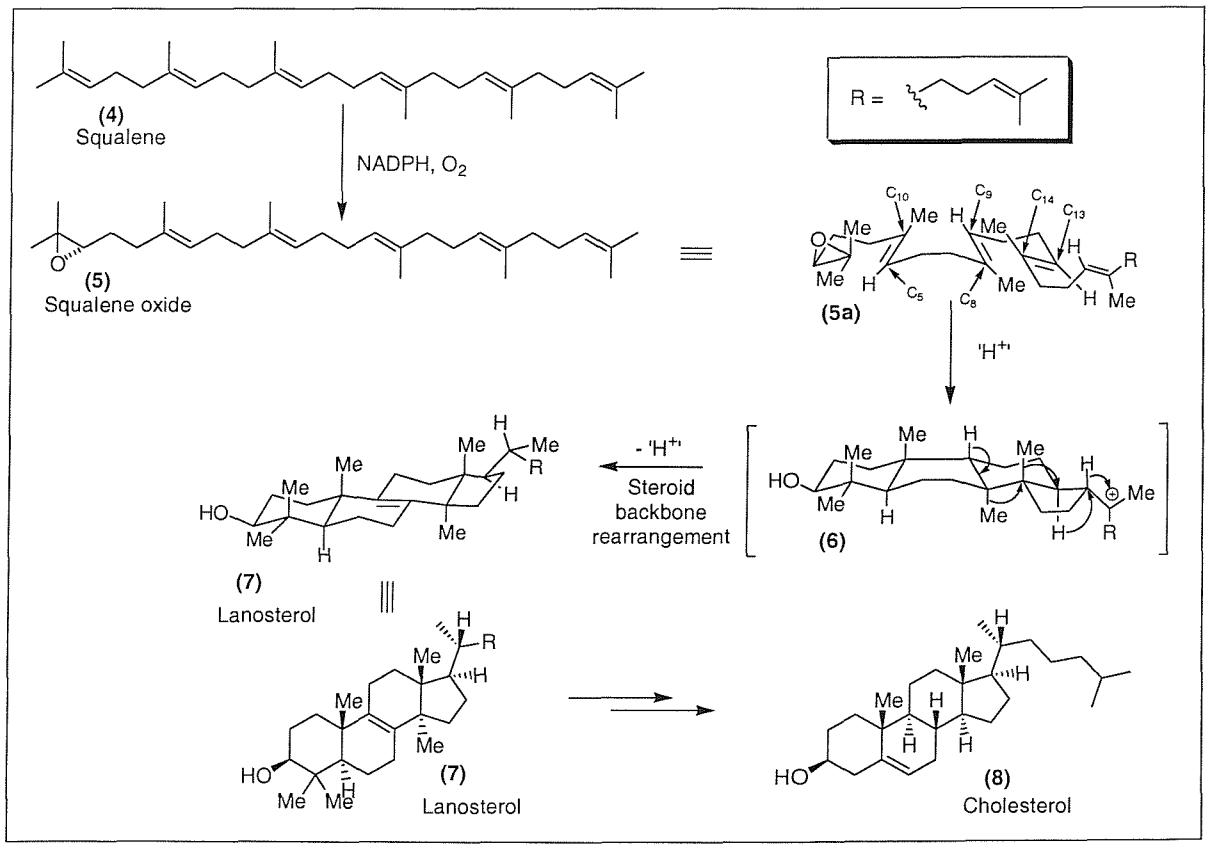


Figure 3

Steroids play an essential role in a great many physiological functions in both humans and animals and, as such, their importance cannot be understated.[1-8] Particular note should be made of the key functions steroids play within the reproduction process and also for the regulation of growth.

1.1.2 Steroid biosynthesis

The biosynthesis of steroids is shown in Scheme 1. The starting material is squalene oxide (**5**), and in nature this is made from two farnesyl pyrophosphate molecules. Syntheses based on the methodology used within nature are called biomimetric syntheses and these have been developed for steroid synthesis as well as other natural molecules.



Scheme 1

The first step in the biosynthesis forms squalene oxide as a single enantiomer via an enzymatic epoxidation of squalene **(4)**. This product can be drawn three dimensionally as the chair-boat-chair structure **(5a),** which undergoes a cationic polycyclization, leading to the tetracyclic cation intermediate **(6)**. The cation in **(6)** is not hydrated or reduced but undergoes a series of 1,2-shifts followed by an elimination to form lanosterol **(7)**. This step is called the steroid backbone rearrangement and is one of the most remarkable reactions in biological chemistry. The final steps to form cholesterol from lanosterol involve the elimination of the methyl groups at positions C_4 and C_{14} (lost as CO_2), the reduction of the double bond in the side chain and a transposition of the C_{8-9} double bond to C_{5-6}.[9]

Because Nature relies on squalene oxide as its steroid precursor, no group other than methyl can end up in the C_{13} position. Therefore, steroids with groups other than methyl in the C_{13} position are synthetic steroids.

1.1.3 Steroid hormones

Within the human body there are five classes of steroid hormones: androgens, oestrogens, progestogens, glucocorticoids and mineralocorticoids. Androgens are associated with the development and maintenance of male characteristics, fertility, muscle growth and mood effects. Oestrogens are associated with the development and maintenance of female characteristics, fertility, bone growth and mood effects. Progestogens are associated with the maintenance of pregnancy, regulation of the menstrual cycle and inhibition of ovulation. Glucocorticoids promote the formation of glycogen and enhance the degradation of fat and protein. They also enable animals to respond to stress. Mineralocorticoids maintain the balance of sodium and potassium ions in the body and as a consequence are associated with blood volume and pressure.[10]

Within each of these classes there are many examples of individual steroids, both natural and synthetic. Figure 4 shows one example each of a natural and synthetic steroid for each of the five classes of steroid hormone.

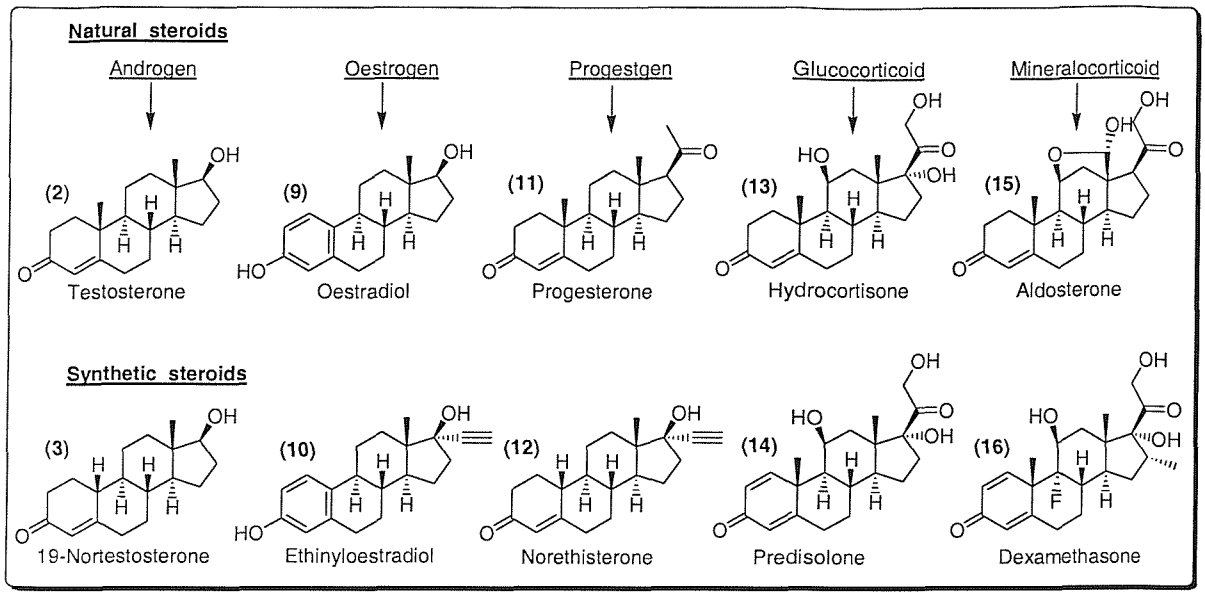


Figure 4

It is desirable to be able to synthesise natural steroids so that an adequate supply is available in order to fully investigate their physiological properties. Often the isolation of a steroid from natural sources can be an extremely inefficient process. Equally, access to totally synthetic steroids is also desirable as these compounds may exhibit increased potency compared with natural steroids, or have new and beneficial physiological effects.

1.1.4 Natural steroid sources for hemi-synthesis

Since steroids are such an important class of compound, it is hardly surprising to discover that work concerning the synthesis of these compounds has been underway for many years. As mentioned above, steroids have been constructed via totally synthetic methods but, all too often, these syntheses lead to isomeric mixtures of products. The steroid backbone itself often contains six asymmetric carbon centres, which means that up to 2^6 (64) stereoisomers are synthetically possible.[4] A frequently used approach to avoid this problem is to devise a hemi-synthesis from an abundant natural steroid. This does of course require a cheap and readily available natural steroid starting material; Figure 5 shows a number of these.

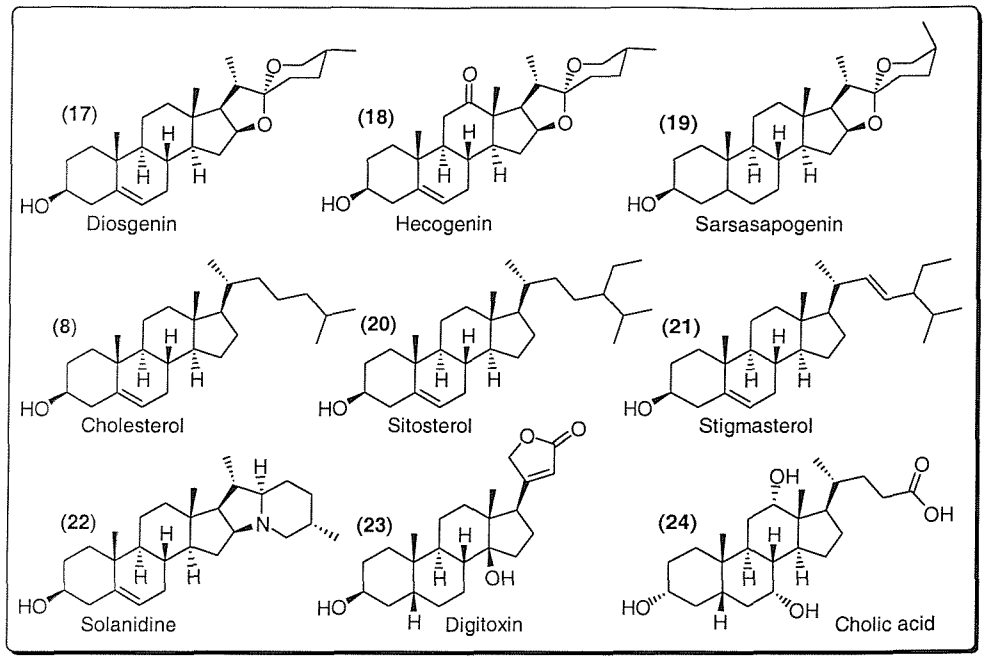


Figure 5

For example, the commercial synthesis of desogestrel is a hemi-synthesis starting from diosgenin (17). The full industrial desogestrel synthesis will be described below in section 1.4.5, page 28.

1.2 The role of steroid hormones during menstruation and pregnancy[11,12]

1.2.1 The menstrual cycle

The menstrual cycle involves a synchronized recurring sequence of changes to the lining of the uterus, key to which is the production and release of an egg from the ovary. The release of an egg is called ovulation and this occurs every 28–35 days in non-pregnant women. The function of the menstrual cycle is to provide a favourable environment for the implantation and development of a foetus. Implantation takes place very rarely however and the expanded endometrium (uterus) is broken down and excreted: this is known as menstruation. Day one is taken to be the first day of menstrual flow and this lasts around five days. After this time the endometrium begins to thicken and becomes permeated with blood vessels and glands in preparation for implantation. Up to day 14 the egg is developing in a protective sheath in the ovary known as a Graafian follicle and, upon release of the egg (about day 14), this follicle undergoes changes that turn it into a solid *corpus*

luteum ('yellow body'). If fertilization does not take place, the *corpus luteum* remains in the ovary for a further 14 days or so before it degenerates. This occurs at the same time that the endometrium breaks down and is excreted, thus completing the cycle.

All aspects of the menstrual cycle are controlled and synchronized by five hormones: gonadotrophin releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), oestrogen and progesterone as discussed below. GnRH is secreted by the hypothalamus. LH and FSH are both gonadotrophins (hormones that stimulate the gonads) and are secreted by the anterior pituitary gland, which is in the brain. Oestrogen and progesterone are both steroid hormones and are secreted by the ovary.

Figure 6 shows how the blood levels of each hormone change during the menstrual cycle. It is the relative concentrations of these hormones that are important, and as such no units are displayed on the Y-axis.

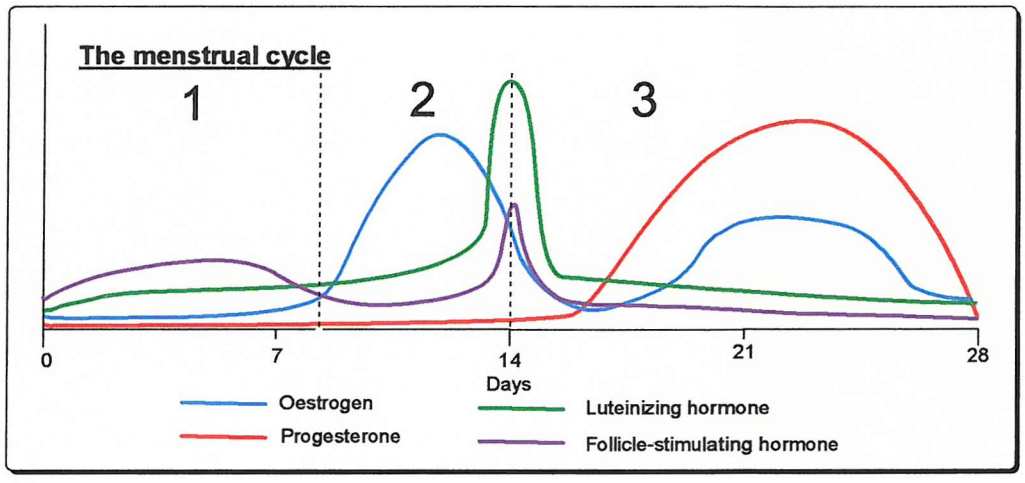


Figure 6

From day one, the hypothalamus releases GnRH (not shown on graph), which leads to the secretion of relatively low levels of LH and FSH (see section 1 of Figure 6). At this time there are many immature follicles in the ovary (one of which will become a Graafian follicle) and the FSH secretion stimulates the growth of these follicles. The cells of these growing follicles release oestrogen, which partly stimulates the rebuilding of the endometrium. As the oestrogen levels become higher, the oestrogen stimulates the hypothalamus to increase the output of GnRH. The increase in GnRH results in increased gonadotrophin (LH and FSH) release, and this in turn leads to a further increase in oestrogen production. The overall effect of this is to cause a surge in oestrogen and

gonadotrophin production, which in turn stimulates the release of an egg, and ovulation occurs (see section 2 of Figure 6).

Following the release of an egg from the follicle, the LH causes the formation of the *corpus luteum* from the follicle. The *corpus luteum* develops over the next few days and then begins production of yet more oestrogen and also of progesterone. The progesterone works in conjunction with the oestrogen to stop the secretion of LH and FSH so no other follicle can develop during the cycle. However, the *corpus luteum* still requires LH to function, without which it begins to degenerate and consequently the levels of progesterone and oestrogen also drop. The drop in these ovarian hormones causes spasms in the arteries of the uterine lining and this deprives the endometrium of blood. This results in menstruation and the beginning of a new cycle (see section 3 of Figure 6).

1.2.2 Pregnancy

In the event of fertilization, the *corpus luteum* does not degenerate but persists. This is due to the secretion of another hormone: chorionic gonadotrophin by the placenta. The *corpus luteum* is now able to continue secreting progesterone and low levels of oestrogen that maintain the development of the uterus and also prevent menstruation. The oestrogen and progesterone maintain the prevention of the production of FSH so no further follicles can develop during pregnancy.

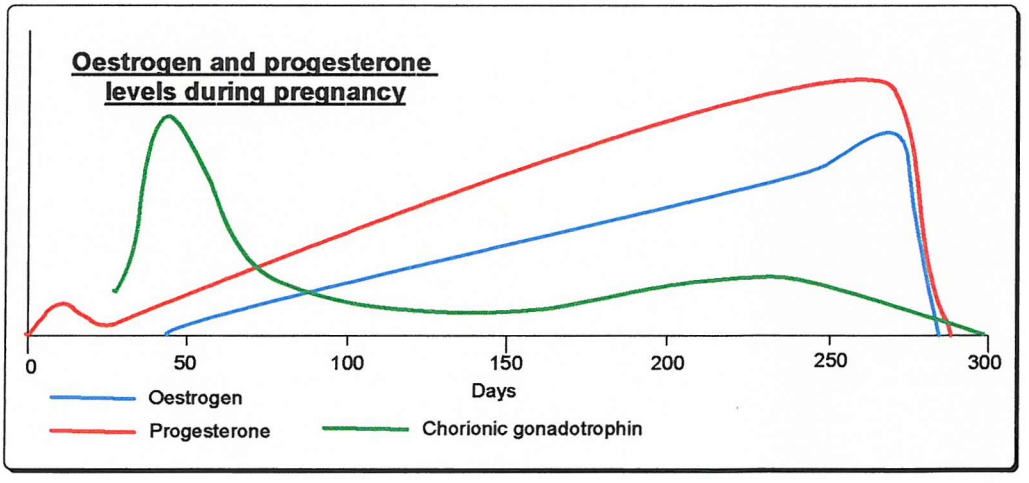


Figure 7

The requirement for progesterone continues throughout pregnancy and as a consequence, progesterone levels in the maternal blood supply rise continuously throughout pregnancy.

Abortion would result if either the ovary or pituitary were to be removed during pregnancy. Although not fully understood, it is expected that progesterone is used by the foetus to ensure an adequate supply of oxygen, salts and organic precursors to meet its needs.

Oestrogen levels also rise throughout the pregnancy term but they do not rise as high as the progesterone levels. The oestrogen is required by the mother to prepare for birth: for instance, to allow changes to the uterine musculature and also for the development and maintenance of the mammary glands for lactation. Figure 7 shows the variation in hormone levels during pregnancy.

1.3 The contraceptive pill

1.3.1 Contraception introduction

Contraceptives or other forms of fertility control have been practised for many thousands of years and the methods used have evolved alongside society.[13] The role of contraception is to reduce fertility but without permanent effects, i.e., it should be easily reversible. There are many forms of contraception, some more effective and reliable than others. A few examples are diaphragms, caps, spermicidal sponges, the rhythm method, withdrawal (*coitus interruptus*), intrauterine contraceptive devices (IUCDs) and steroidal contraceptives.

1.3.2 Background of steroidal contraceptives

Steroidal oral contraceptives are one of the most innovative pharmacological products of the 20th century and no other pharmacological agent has been more widely studied.[14] They were introduced in the 1950s but it was not until the 1960s that they became reliable and acceptably effective. The dose of steroid used is kept to an effective minimum to minimize any side effects and also to enable a rapid return to reproductive capacity. The mechanism by which all steroidal contraceptives function is via a progesterone-induced cessation of ovulation. This is discussed in greater detail in the next section.

There are two types of oral contraceptive: progestogen only preparations and combined oral contraceptives. Both types contain a progestogen but the combined oral contraceptive also

contains an oestrogen. The roles of these hormones in relation to contraception are fully explained in the next section. Steroidal contraceptives can also be administered as an injection or as sub-dermal implants. The advantage of non-oral steroidal contraceptives is that a greater variety of functional groups can be tolerated because the compounds pass straight into the blood supply and avoid being metabolised in the liver at the first pass. Non-oral steroidal contraceptives are still undergoing toxicology studies.[15]

1.3.3 Mode of action of oral contraceptives

During the female cycle, progesterone is produced after ovulation for the purpose of preventing additional eggs from developing by inhibiting the production of the gonadotrophins LH and FSH. The same is true during pregnancy; the persistent production of progesterone prevents further follicles from developing. The idea behind oral contraceptives was to supply a continuous source of a progestogen so that the body would inhibit the production of LH and FSH. Without these, ovulation could not occur and therefore there could be no pregnancy. The contraceptive pill does exactly this; it serves as an artificial source of a progestogen. Progestogen only contraceptives also cause additional antifertility effects such as decreased sperm transport and suppression of endometrial receptivity. The biggest weakness with this type of contraceptive is that the effects only last for 22–26 hours and hence must be taken daily. However, because this is such a tight window, if the woman is delayed in taking the pill, fertility can return and this is thought to be responsible for the increased failure rate of this type of oral contraceptive. Non-oral progestogen only contraceptives do not have this problem as the injection is effective for eight weeks and the implants are effective for up to five years.

In the combined oral contraceptives, the oestrogen is present in very small amounts and assists the progesterone to prevent the secretion of LH and FSH. The oestrogen is thought to promote the development of progesterone receptors, thus making the progestogens in the tablet more effective.

In wild animals and until fairly recently in humans, the female of the species would be pregnant or nursing for many of their fertile years. The overall effect of this was that women would be repeatedly exposed to higher levels of oestrogen and progesterone. In this

sense, the taking of oral contraceptives mimics the continuous exposure to steroids experienced during pregnancy.

1.3.4 Multiphasic oral contraceptives

The pill is taken for 21 days (or a multiple of this) and originally each combined oral contraceptive pill had the same composition (monophasic). Newer formulations were developed to reduce the steroidal intake but maintain contraceptive efficiency. They are called biphasic or triphasic oral contraceptives, and they work by altering the ratio of oestrogen to progestogen in each tablet. For instance, a biphasic preparation supplies equal progestogen and oestrogen for the first half of the cycle, after which the progestogen dose is stepped up. A triphasic oral contraceptive works in a similar way but has two changes and consequently three phases for each cycle. Overall, the oestrogen levels are lower and a more normal 'cycle' is achieved.[12]

1.3.5 Side effects of the contraceptive pill

Oral contraceptives have a variety of associated side effects. The first reported side effects were extremely serious in nature and affected the cardiovascular system: e.g., venous thromboembolism (blood clotting in the veins), heart attack and stroke.[16,17] The high doses of oestrogen were later found to be the problem and by reducing the formulation from 150 to 30 μg a day, the incidences of morbidity and mortality from thromboembolic effects among oral contraceptive users were significantly reduced.[18] The development of later generation steroids (see below) coupled with the introduction of multiphasic dosing routines have significantly reduced the risks, but there are still groups of women at increased risk; namely obese women or smokers. Although there is little evidence that steroidal contraceptives cause life-threatening conditions, it is more likely that they promote the effects of other unrelated conditions. It is for this reason that steroidal contraception is ill advised for women who are obese or smoke, or who have a history of cardiovascular disease.[19] Despite the above concerns, the risk of death from taking oral contraceptives is far lower than the same risk associated with driving. The risk is also lower than that from pregnancy, childbirth and abortion.

Other side effects of taking the oral contraceptive pill include weight gain, headaches, libido change, acne etc. These vary for each user, as well as with the type of contraceptive formulation used. Although these effects are not life-threatening, they are extremely important because they can affect user compliance thereby nullifying any contraceptive potential.

Not all of the side effects of taking oral contraceptives are negative however. Indeed oral contraceptive users have a reduced risk of developing ovarian and endometrial cancers compared with non-users, and these effects can persist for up to ten years after discontinuation of oral contraceptive use.[14] Oral contraceptives can also help women with menstrual disorders and can decrease the incidence of dysmenorrhoea and pre-menstrual syndrome. They work by improving the regularity of the menstrual cycle and can reduce the amount and duration of menstrual flow; this can in turn decrease iron deficiency anaemia. Certain oral contraceptives have been found to reduce the incidences of acne amongst users.

1.3.6 The evolution of oral contraceptives

The first steroid to be used as an oral contraceptive was norethisterone **(12)**, synthesised in 1951 (Figure 8). Norethisterone and all of the synthetic progestogens are derived from 19-nortestosterone **(3)**. Norethisterone is extremely similar in structure to 19-nortestosterone; the only difference is that norethisterone has an additional 17α-ethinyl group. It is this combination of the 17α-ethinyl and the 17β-hydroxyl groups that appear to mimic the 17β-acetyl group found in progesterone **(11)**.[20]

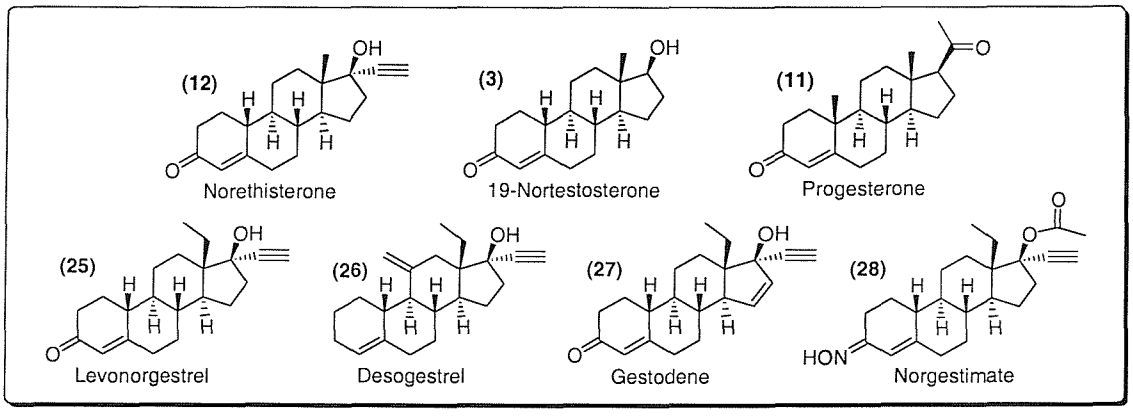


Figure 8

As mentioned above, the first generation of oral contraceptives had a number of serious side effects associated with them. In order to eliminate these problems, a few structural changes were made, from which the second generation of oral contraceptives were born (levonorgestrel, norgestrel[▪]). These new steroids had different selectivity profiles, which meant that they remained active progestogens but no longer caused the side effects previously observed. The second-generation steroids were also found to be more potent than the first generation compounds, which meant that smaller doses could be used to maintain contraceptive efficiency. The key structural difference between the first and second generation compounds was that the later compounds had an additional methyl group on C_{18} (a C_{13}-ethyl group) (see Figure 8, levonorgestrel **(25)** versus norethisterone **(12)**). It was this group that was believed responsible for the increased potency of the second generation compounds.[21] The different selectivity profile was not all for the better, however, as the second generation oral contraceptives were found to cause androgenic effects (e.g. facial hair) which were clearly not desirable in a pill for women. A solution was found to this problem by altering the dose of progestogen. This approach gave rise to what are now known as the bi- or triphasic oral contraceptives (details in section 1.3.4). Meanwhile, further research was underway into the development of new progestogens. These became the third generation of oral contraceptives, of which desogestrel **(26)** was the first on the market – introduced into Europe in 1981. Several years later two more third generation oral contraceptives were introduced: gestodene **(27)** and norgestimate **(28)** (Figure 8). Compared with norethisterone and levonorgestrel, the third generation oral contraceptives again had a higher binding affinity to progesterone receptors (*in vitro* studies) and fewer androgenic effects in the *in vivo* studies.[22] In terms of structure, gestodene is very similar to levonorgestrel, the only difference is an additional double bond between C_{15} and C_{16} in gestodene. Norgestimate and desogestrel both have two structural changes from levonorgestrel; norgestimate has both the C_{17}-β acetate and the C_3 oxime groups whereas desogestrel has no oxygenated C_3 functional group, but it does have an exocyclic methylene group at C_{11}. The C_{11} methylene group is responsible for the increased progestogenic but reduced androgenic activity of desogestrel.[22] The pharmacologically active form of desogestrel is its metabolite, 3-keto-desogestrel[18] **(29)** (Figure 9). 3-Keto-desogestrel can be injected, implanted, or it can be formed in the liver from orally administered desogestrel.

[▪] Levonorgestrel is the L-isomer of D,L-norgestrel.

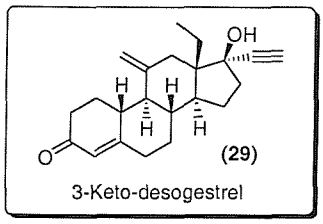


Figure 9

1.3.7 Antiprogestogens

The role abortion plays in birth control varies with a number of factors. In countries where contraception is not readily available or is not allowed on religious grounds, abortion is often used as a principal method of birth control. In the West however, abortion is typically used where contraception has failed. A number of different mechanical means can be used to induce abortion (depending upon the age of the embryo), but drugs can be used as an alternative method. These drugs are usually steroids and are called antiprogestogens. Antiprogestogens are compounds that exhibit high binding affinity to progesterone receptors (in progesterone target cells), and prevent endogenous progesterone from binding. Antiprogestogens however have no progestogenic activity and consequently the pregnancy cannot be maintained. Such antiprogestogen compounds have been proposed as potential once-a-month contraceptive pills.[12] The inclusion of a C_{11}-β-aryl group is thought to cause the antiprogestational activity associated with steroidal antiprogestogens such as mifepristone (RU486) **(30)** (Figure 10) and similar analogues.[20,23,24] The C_{17}-α-substituents are thought to increase the binding affinity to the progesterone receptor.

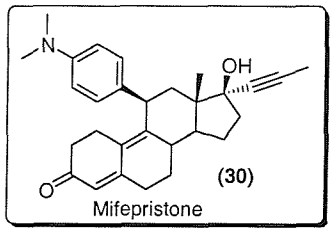


Figure 10

1.4 Previous syntheses of desogestrel

1.4.1 Synthetic challenges of desogestrel

The synthesis of desogestrel **(26)** (Figure 11) is faced with three main challenges:

The introduction of the C_{13}-ethyl group

The introduction of the C_{11}-methylene group

The construction of the A-ring with the C_{4-5} double bond (Δ^{4-5}) and with a C_{10}-H (i.e. no C_{19}).

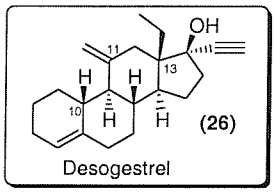


Figure 11

A general discussion of each of these challenges is given below, followed by a discussion of the existing desogestrel syntheses.

1.4.2 Introduction of the C_{13}-ethyl group

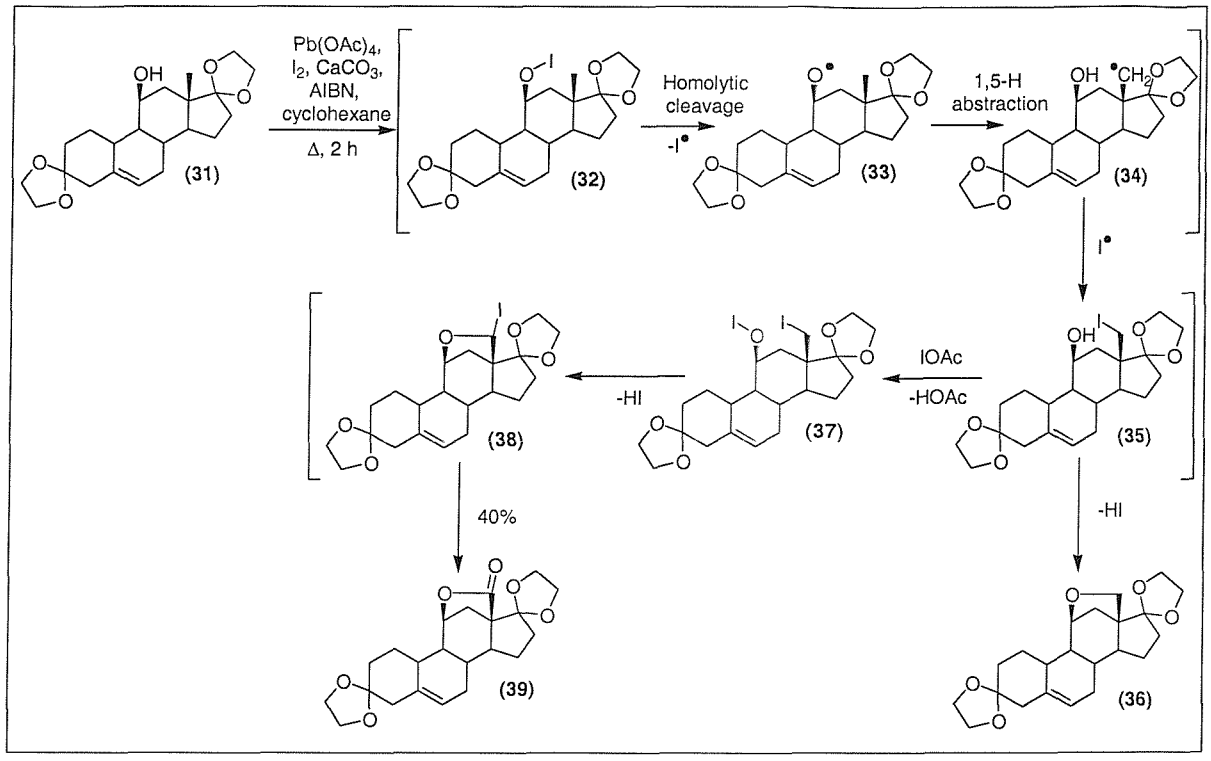
1.4.2.1 Hemi synthesis approaches

There are no naturally occurring steroids that have a C_{13}-ethyl group, and it was long thought that such steroids could not be made by hemi-synthesis from the 'steroidal pool'. However, this axiom changed when the intramolecular hypoiodite oxidation was discovered.[25] In this transformation, acetyl hypoiodite is generated by $Pb(OAc)_4$ mediated oxidation of I_2:

$$Pb(OAc)_4 + I_2 \rightarrow 2.IOAc + Pb(OAc)_2$$

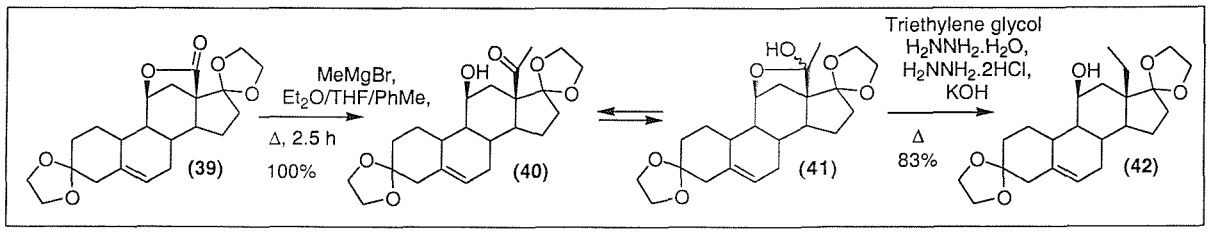
The acetyl hypoiodite was found to react with a C_{11}-β-hydroxyl group to form the C_{11}-β-OI species **(32)**, Scheme 2. Homolytic cleavage of the oxygen-iodine bond led to the formation of a C_{11}-β oxygen radical **(33)**, which abstracted a hydrogen from the C_{18}-methyl group. The primary C_{18} radical **(34)** then combined with an iodine radical to form the C_{13}-iodomethyl group **(35)**. This iodohydrin could eliminate hydrogen iodide to form the ether

(36), but this was quite slow in non-polar solvents. A second activation of the C_{11}-β-hydroxyl group with acetyl hypoiodite competed with this elimination to form the iodo hypoiodite (37). This compound then eliminated hydrogen iodide to form the iodo-ether (38). Subsequent *in situ* lead tetraacetate oxidation afforded the lactone (39).



Scheme 2

In the above example (Scheme 2, Zeelen and co-workers),[26] the lactone (39) was obtained in 40% yield from the C_{11}-β-hydroxy steroid (31). Further manipulation of the lactone afforded the C_{13} ethyl steroid (42) in 83% yield via a methyl Grignard addition to the lactone (39) followed by a Wolff-Kishner reduction of the C_{13}-acetyl group (in equilibrium with the hemiacetal (41)) (Scheme 3).



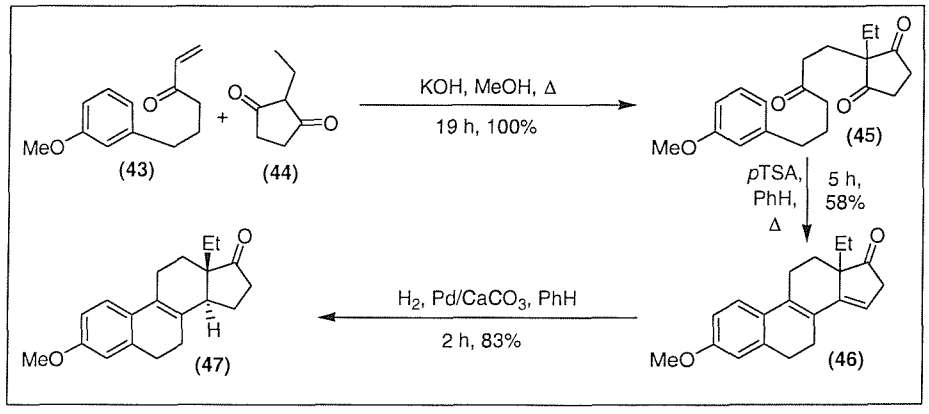
Scheme 3

Several C_{11}-C_{18} bridged steroids have been prepared via an elaboration of this hypoiodite reaction.[27,28]

1.4.2.2 Total synthesis approaches

A common method for the introduction of the C_{13}-ethyl group in total syntheses has been to use 2-ethyl-1,3-cyclopentanedione **(44)** as the D-ring precursor. Although different synthetic procedures have been employed in each case, the groups of Smith,[29] Saucy[30-32] and Corey[33] have all used this idea.

The synthesis devised by Smith and co-workers[29] utilised a Michael addition of the enolate of **(44)** onto the enone **(43)** to form the the triketone **(45)** (Scheme 4). Acid catalysed dehydration of **(45)** installed the four steroid rings and subsequent regio- and stereoselective hydrogenation introduced the C_{13}-C_{14} *trans*-hydrindane stereochemistry.

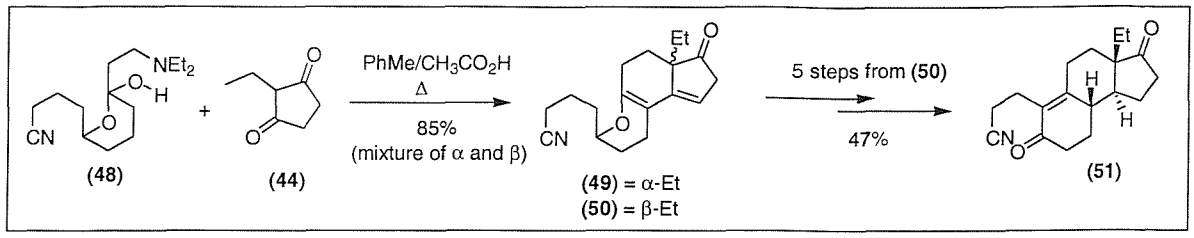


Scheme 4

This methodology afforded racemic products, but these could be resolved. Due to the apparent ease of the synthesis of the steroid **(47)**, this has been a frequently used starting material for C_{13}-ethyl steroids.[34-36]

The synthesis devised by Saucy and co-workers[30-32] used 2-ethyl-1,3-cyclopentanedione **(44)** in a condensation reaction with the amine **(48)** (available from γ-butyrolactone in 5 steps, 34%)[30] (Scheme 5). This reaction formed both the C_{13}-α and -β isomers **(49)** and **(50)**, but the β-isomer (major) could be separated by crystallization. A series of oxidation

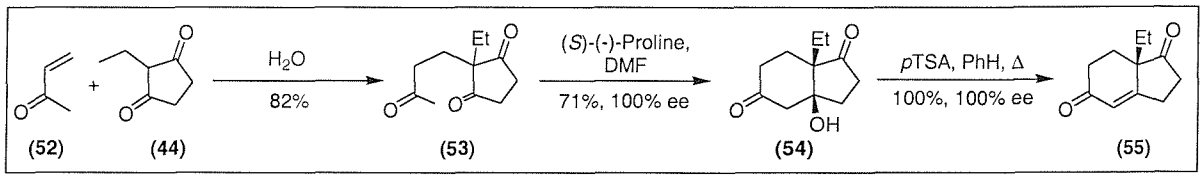
and reduction reactions formed the racemic diketone **(51)** in 47% yield.



Scheme 5

This sequence could also be used to synthesise optically pure steroids by changing the diethylamine group in **(48)** to an optically pure amine.[30]

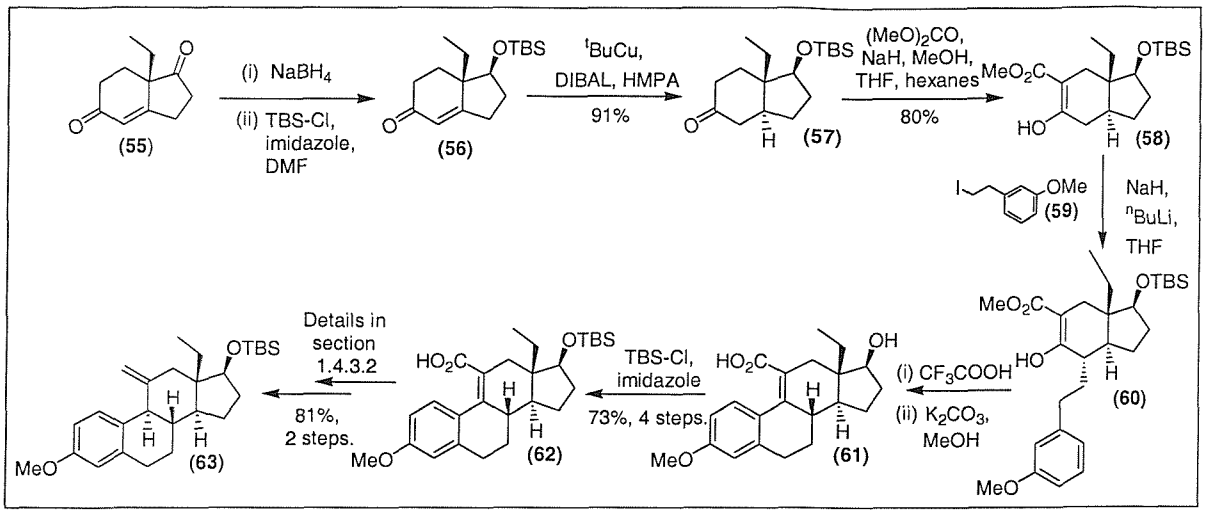
The Parrish-Hajos ketone **(55)**[37,38] has also been a frequently used precursor of C_{13}-ethyl steroids[39-43] and this is synthesised from 2-ethyl-1,3-cyclopentanedione **(44)** as shown in Scheme 6.



Scheme 6

From 2-ethyl-1,3-cyclopentanedione **(44)** and methyl vinyl ketone **(52)**, the triketone **(53)** was synthesised in 82% yield via a Michael addition conducted in aqueous media. A catalytic amount of (*S*)-(−)-proline was used in the asymmetric aldol reaction, leading to the optically pure *cis*-hydrindane **(54)** in 71% yield after crystallization. Subsequent acid catalysed dehydration afforded the optically pure Parrish-Hajos ketone **(55)** in 100% yield. Upon scale-up, this methodology was used to prepare the optically pure ketone **(55)** in 59% overall yield, starting from 42 g (0.33 mol) of 2-ethyl-1,3-cyclopentanedione.[39]

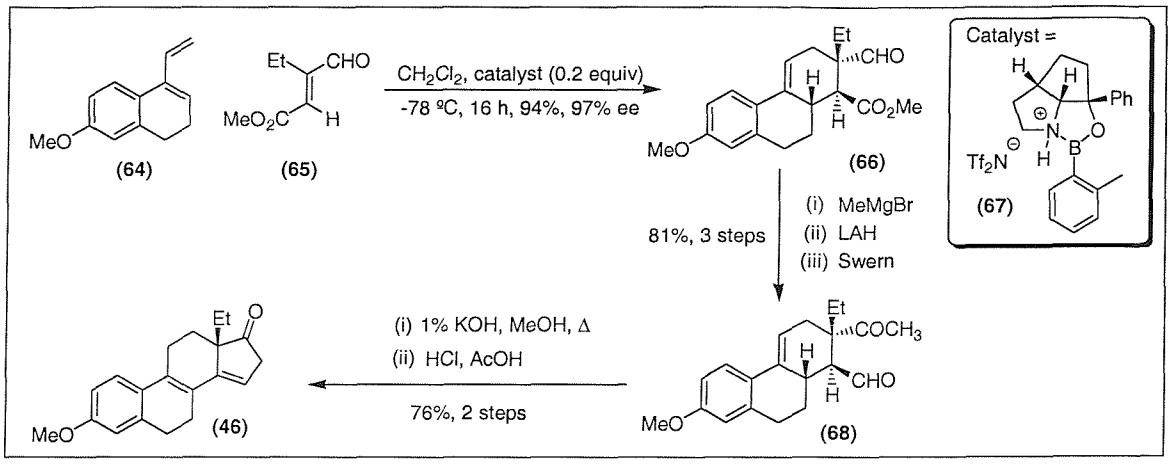
An example of steroid synthesis utilizing the Parrish-Hajos ketone **(55)** is shown below in Scheme 7. This illustrates the first part of Corey and Huangs' synthesis of desogestrel,[33] up to the A-ring precursor. The introduction of the C_{11}-methylene group is detailed in section 1.4.3.2 (page 25) and this information has not been duplicated here for clarity.



Scheme 7

From the Parrish-Hajos ketone (**55**), the ketone was selectively reduced in the presence of the enone using sodium borohydride and the product alcohol was protected as the ^{t}butyl dimethyl silyl ether (**56**). The stereoselective reduction of the α,β-double bond in (**56**) was achieved using a catalytic amount (0.3 equiv.) of ^{t}BuCu with a 2 equiv. excess of a DIBAL-HMPA complex. The *trans*-hydrindane (**57**) was formed in 91% yield but two other products were also formed in 2.8% and 0.9% yield. α-Methoxycarbonylation of (**57**) was achieved using dimethyl carbonate, sodium methoxide and sodium hydride in a 1 : 1 mixture of THF/hexane. Regioselectivity was clearly a problem here as the optimized conditions still led to a 6.3 : 1 mixture of regioisomers. Regio- and stereoselective alkylation of (**58**) was achieved by sequential double deprotonation with NaH followed by ^{n}BuLi and then treatment with the iodide (**59**). The tricyclic β-keto ester (**60**) was reacted crude with 10% TFA in CH_2Cl_2 to form the tetracyclic steroid skeleton, which had the correct steroid geometry at carbons 8, 13 and 14. This cationic cyclization is the same as that used in the Smith synthesis of steroids.[44] The TFA required for the cyclization also deprotected the C_{17}-silyl ether, forming the C_{17}-trifluoroacetate. The TBS group was re-introduced by cleavage of the trifluoroacetate with methanolic base (as well as C_{11}-ester hydrolysis), followed by reprotection of the C_{17}-hydroxyl group with TBS-Cl. Overall, the yield over four steps was 73%. The details of the functional group conversion to yield the C_{11}-methylene group are discussed below (section 1.4.3.2) and the later steps from (**63**) to desogestrel are discussed in section 1.4.4.2, page 27.

In a recent publication, Corey and co-workers[45] demonstrated that the C_{13}-ethyl group in desogestrel need not come from 2-ethyl-1,3-cyclopentanedione. As shown in Scheme 8 below, a Diels-Alder reaction between the diene **(64)** and the dienophile **(65)** yielded the ABC steroid precursor **(66)** in 94% and in 97% ee. A single recrystallization improved the ee to 100%. The success of this Diels-Alder reaction can be attributed to the newly developed catalyst **(67)**.[46]



Scheme 8

From **(66)**, addition of methyl magnesium bromide to the aldehyde followed by LAH reduction of the ester and a Swern oxidation of the two resultant alcohol groups afforded **(68)** in 81% yield. The D-ring was constructed using an aldol reaction followed by acid mediated dehydration. This afforded **(46)** in 76% yield, from which point literature methods were used to synthesise desogestrel.[33,47]

1.4.3 Introduction of the C_{11}-methylene group

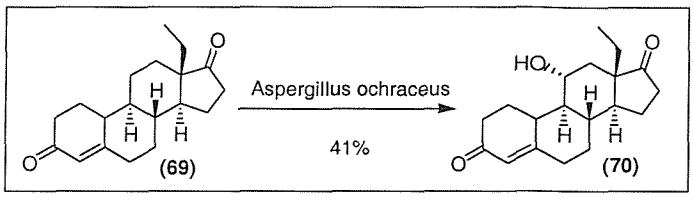
1.4.3.1 Via the C_{11}-ketone

In the previous syntheses of desogestrel, the most frequently used method for the introduction of the C_{11}-methylene group has been from a C_{11}-hydroxyl group, via the ketone. A number of methods are known for the insertion of a C_{11}-hydroxyl group,[48] and these shall be discussed in the following sections.

1.4.3.1.A Introduction of the C_{11}-hydroxyl group

1.4.3.1.A.i Microbial oxidation

Microbial oxidation[49] is used in the industrial synthesis of desogestrel to insert a C_{11}-α-hydroxyl group from the corresponding C_{11}-hydrocarbon. Gao and co-workers have also employed this procedure (Scheme 9).[50,51]

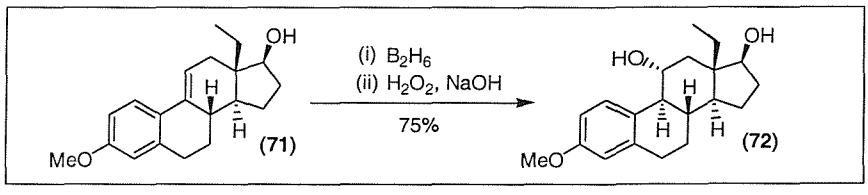


Scheme 9

The strain of mould used is extremely important for the selectivity as different strains can be used to oxidise other parts of the steroid.[49,52] Nevertheless, the biggest disadvantage with these oxidations is that by-products are often observed due to over-oxidation or non-selective oxidation. As a consequence, the yields are rarely excellent. The main advantage with this method is that it is a direct insertion of the hydroxyl group and therefore does not rely on any functional group interconversion, which can add several steps onto a synthesis.

1.4.3.1.A.ii Hydroboration/alkaline hydrogen peroxide

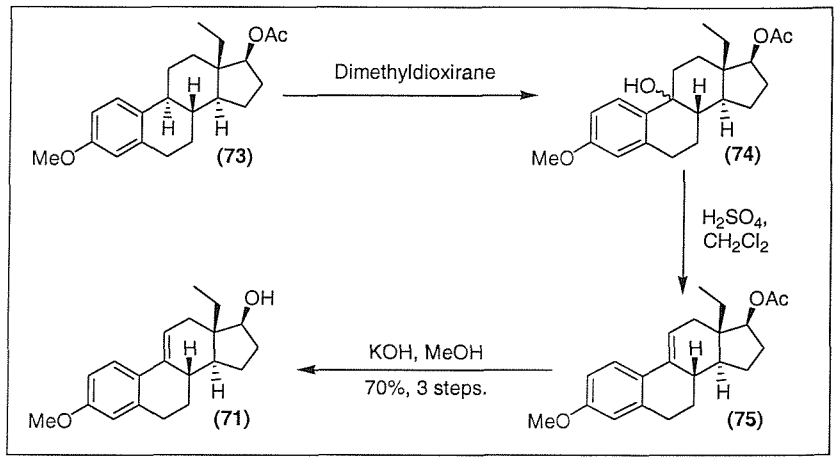
Another frequently employed method for the introduction of a C_{11}-α-hydroxyl group has been the hydroboration of a C_{9-11} double bond (Δ^{9-11}) followed by treatment with alkaline hydrogen peroxide to insert the hydroxyl group. This method has been used by the groups of Schwarz (Scheme 10),[47] Gao,[34] Stéphan[53] and Corey.[45]



Scheme 10

This hydroboration/alkaline hydrogen peroxide procedure is fairly efficient (75% yield), but there are several limitations. The first of which is that a C_{9-11} double bond is required and this could take several steps to install if it is not already present. Scheme 11 below shows

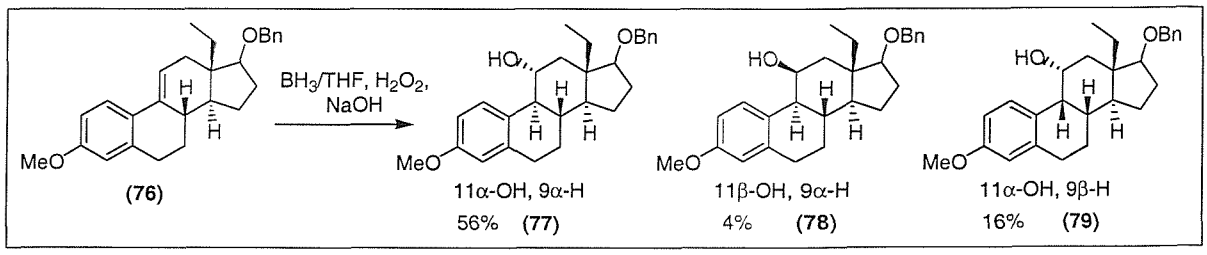
how Schwarz and co-workers installed this functional group from the corresponding C_{11}-hydrocarbon. The second limitation is that there can be no other double bonds susceptible to hydroboration in the starting material.



Scheme 11

The hydroboration precursor **(71)** was synthesised in three steps and 70% overall yield from the C_{13}-ethyl steroid **(73)** by treatment with dimethyldioxirane (generated *in situ* from acetone and potassium monopersulfate) followed by dehydration with sulfuric acid and finally deprotection of the acetate.

Another disadvantage with this method is that it is not reliable; Gao reported a yield of 56% (c.f. 75% in Scheme 10) as well as the formation of two by-products that were hard to separate (11β-OH, 9α-H and 11α-OH, 9β-H).[34] Details of these by-products are clearly shown in Scheme 12 below.

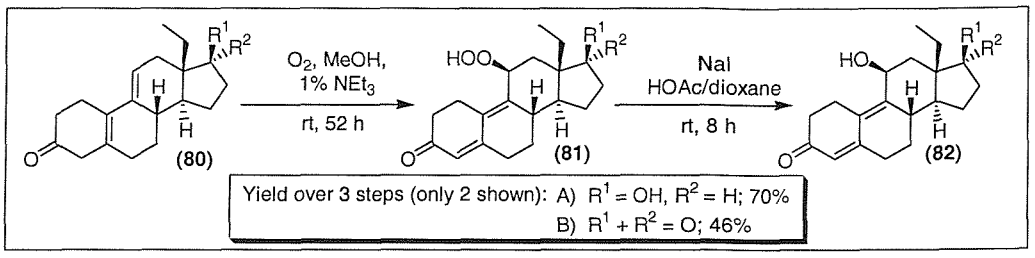


Scheme 12

1.4.3.1.A.iii Oxygen-peroxidation

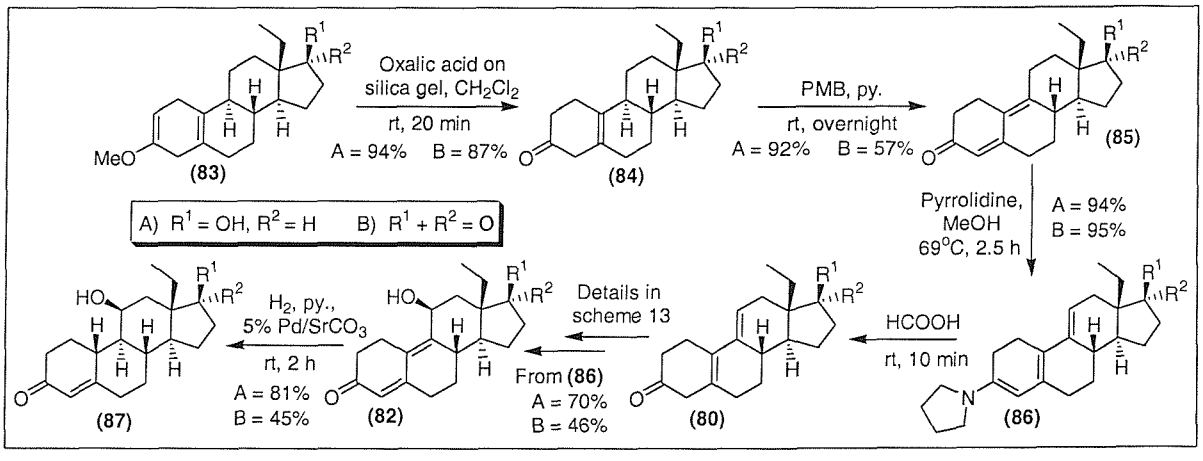
Oxygen-peroxidation is the only method that inserts the C_{11}-hydroxyl group in the β position. Joly and co-workers[48] developed the method in 1964, but Liu and co-workers[54,55]

are the only group to have employed this method towards the synthesis of desogestrel. Scheme 13 illustrates their procedure.



Scheme 13

The $C_{5\text{-}10}$, $C_{9\text{-}11}$ diene **(80)**, was unstable and was found to peroxidize upon exposure to oxygen. The resulting C_{11}-β-hydroperoxide **(81)** could be reduced with sodium iodide to give the C_{11}-β-alcohol **(82)** in at least 70% yield. As with the hydroboration procedure, a limitation of this method is the functional group requirements for C_{11}-oxo precursor. Scheme 14 shows how the $C_{5\text{-}10}$, $C_{9\text{-}11}$ diene functionality was introduced by Liu and co-workers.[54]



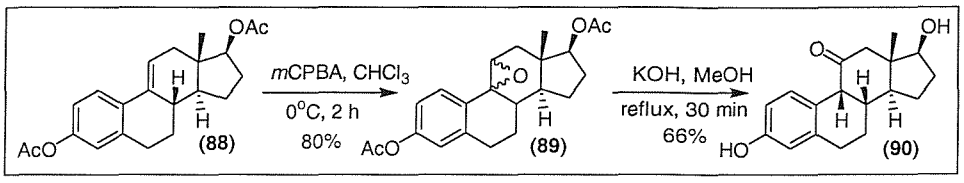
Scheme 14

From **(83)**, oxalic acid on silica gel was found to selectively hydrolyse the enol ether with no formation of any of the conjugated 4-ene-3-one product.

Dibromination/dehydrobromination of **(84)** with pyridinium hydrobromide perbromide (PMB) followed by pyrrolidine enamination and subsequent selective hydrolysis of the enamine with formic acid introduced the $C_{5\text{-}10}$, $C_{9\text{-}11}$ diene **(80)**. As detailed in Scheme 13 above, the oxygen-peroxidation step works quite efficiently but the subsequent hydrogenation of the $C_{9\text{-}10}$ double bond in **(82)** suffers from incomplete selectivity, thus placing another limitation upon this methodology.

1.4.3.1.A.iiii Epoxidation

There is another procedure to introduce a C_{11}-hydroxyl group but this has not yet successfully been used towards the synthesis of desogestrel. The method uses an epoxidation of a $C_{9\text{-}11}$ double bond followed by treatment with acid or base to insert the hydroxyl group. Liang and co-workers have conducted work in this area (Scheme 15).[56]



Scheme 15

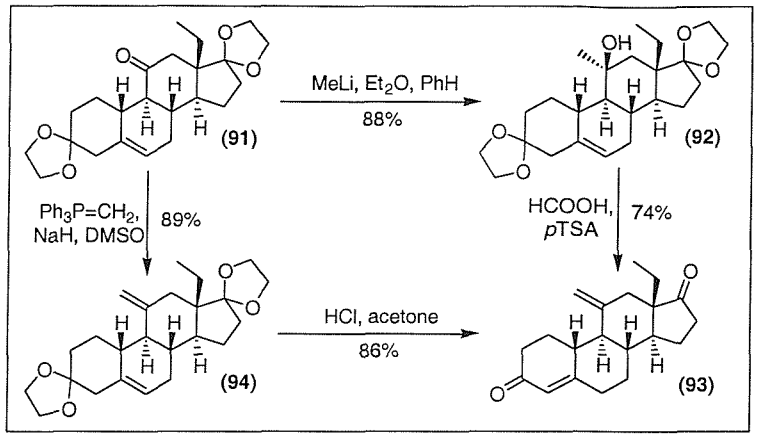
As with the hydroboration method, the use of *m*-CPBA means that the starting material can contain no other double bonds susceptible to epoxidation. The real downfall for this methodology however, is that the products do not contain the correct steroid geometry – C_9 always has the β configuration, even if the epoxide is synthesised stereoselectively.

1.4.3.1.B Oxidation to the ketone

From the C_{11}-hydroxyl group, several reagents have been used successfully in the oxidation to the ketone. Jones' reagent[50,54,55,57] has been the most commonly employed reagent because it can effectively oxidize both the α and β C_{11}-hydroxyl groups but activated DMSO methods[47,58] and PCC[34,51,53] oxidations have also been used effectively.

1.4.3.1.C Conversion to the methylene

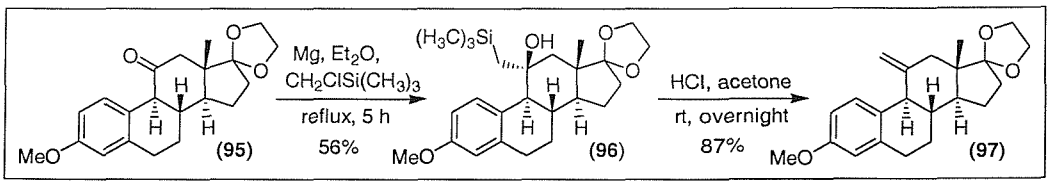
The C_{11}-methylene group can be formed from the C_{11}-ketone by one of three methods: addition of methyl magnesium iodide or methyllithium followed by dehydration in formic acid, Wittig reaction or Peterson olefination. Recently, Gao and co-workers compared the first two of these methods as shown in Scheme 16.[51]



Scheme 16

Treatment of the C_{11}-ketone **(91)** with methyllithium in ether and benzene proceeded in good yield. The stereochemical assignment of the C_{11}-methyl group in **(92)** was made by ^{1}H NMR analysis. The conditions required for dehydration of the newly formed hydroxyl group also removed the two acetal groups, leading to **(93)** in 65% yield over both steps. Alternatively, the Wittig reaction on **(91)** followed by acetal removal afforded **(93)** in 76% yield over both steps. No mention was made by Gao as to which is the favoured procedure, presumably the Wittig/deprotection route because of the higher yield.

The Peterson olefination has also been used to form the exocyclic methylene group as detailed in Scheme 17. This procedure uses a Grignard addition to form the β-hydroxy TMS group in **(96)**, which is eliminated upon treatment with acid.

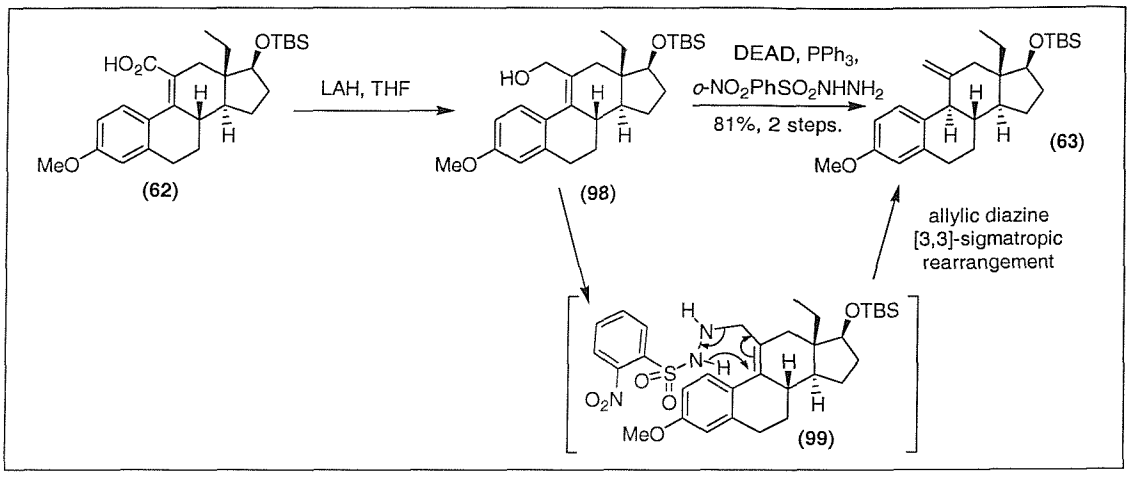


Scheme 17

This procedure was used in the original synthesis of desogestrel,[57] but has not been used much since due to the improved methods illustrated in Scheme 16.

1.4.3.2 Other methods

The only synthesis of desogestrel that does not insert the C_{11}-methylene group via the C_{11}-ketone is the synthesis devised by Corey and Huang.[33] Scheme 18 shows how the C_{11}-methylene group was obtained.



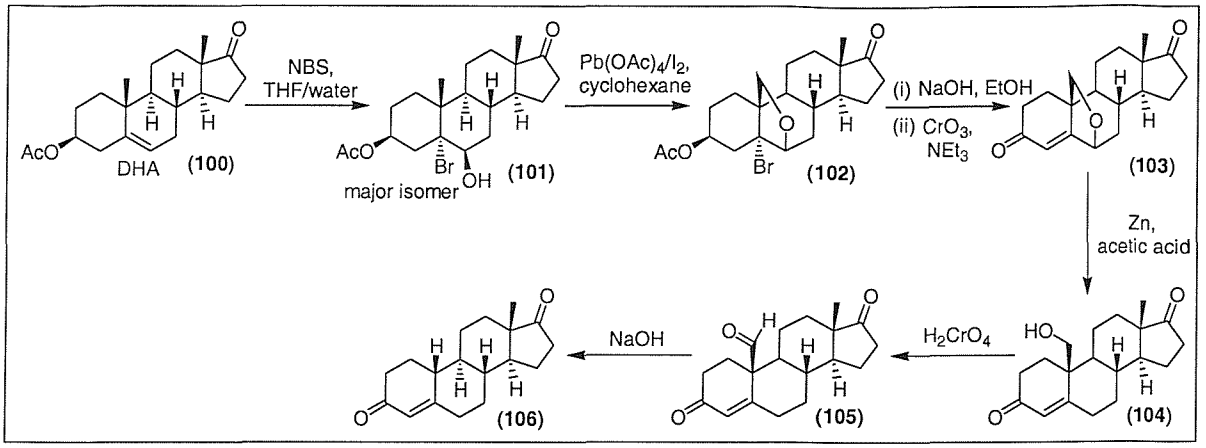
Scheme 18

From the C_{11}-acid **(62)**, LAH in THF was used in the reduction to the primary alcohol **(98)**. A Mitsunobu reaction was performed on the alcohol **(98)** to form the intermediate sulfonamide **(99)**, which underwent an allylic diazine-sigmatropic rearrangement[47] to form the exocyclic methylene group stereoselectively and in good yield (81%).

1.4.4 Modification/construction of the A-ring

1.4.4.1 Hemi synthesis approaches: removal of the C_{10}-methyl group

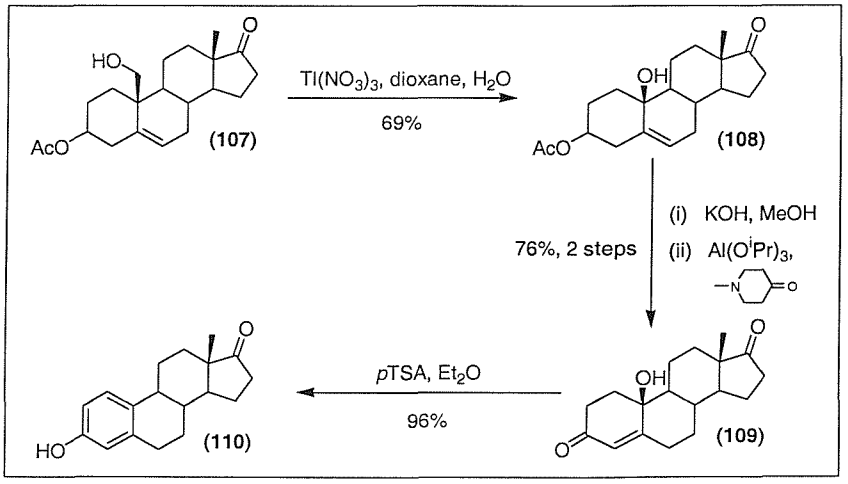
The synthesis of the desogestrel A-ring is fairly trivial when total synthesis approaches are used as detailed in the next section. In contrast, when hemi-synthetic approaches are used, the formation of C_{19}-norsteroids can be quite involving. Scheme 19 below details the seven-step method used in the industrial synthesis of desogestrel to remove the C_{10}-methyl group and Scheme 20 details a four-step thallium(III) mediated degradation of C_{19}-hydroxy steroids devised by Kočovsky and Baines.[59]



Scheme 19

From DHA **(100)** (see section 1.4.5, page 28, for the synthesis up to this point), the bromohydrin **(101)** is formed by reaction with NBS. Lead tetraacetate oxidation of this bromohydrin introduces the C_{6-19}-β ether functionality in **(102)** via another hypoiodite reaction. Acetate hydrolysis and dehydrohalogenation followed by acid mediated oxidation leads to the enone **(103)**. Zinc reduction of the ether group followed by chromic acid oxidation leads to the C_{10}-aldehyde **(105)** and this group is lost as formic acid following treatment with base.

The following synthesis devised by Kočovsky and Baines[59] is notably shorter than the route above, but this synthesis does start from a C_{19}-hydroxy steroid (c.f. **(104)** above), albeit a readily available precursor.

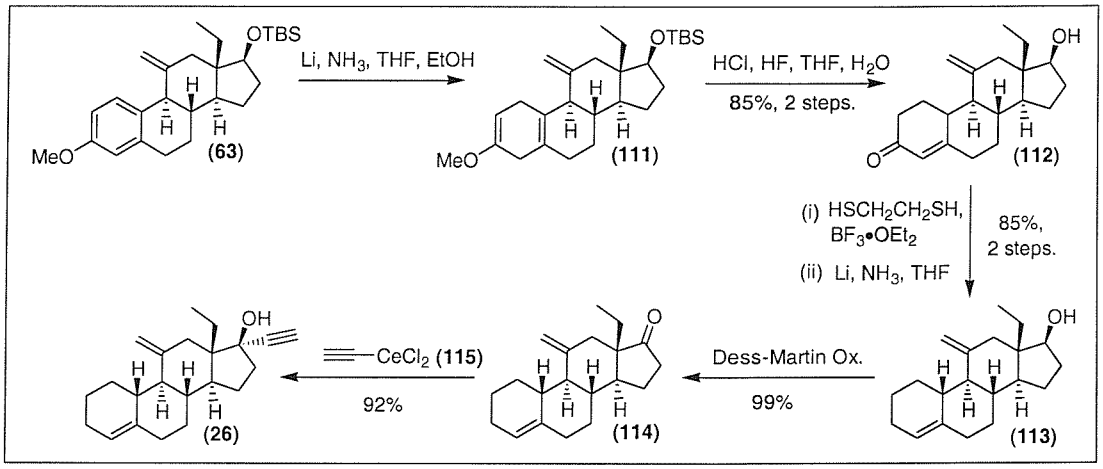


Scheme 20

From the C_{19}-hydroxy steroid **(107)**, the thallium compound causes a stereoelectronically controlled fragmentation of the C_{10}-group, leaving an allylic cation, which is quenched by water, affording the C_{10}-hydroxy steroid **(108)** in 69% yield. Saponification of the acetate in **(108)** followed by Oppenauer oxidation yielded **(109)** in 76% over both steps. Aromatization of the A-ring with *p*TSA in ether afforded estrone **(110)** in 96% yield. Kočovsky and Baines have demonstrated that this methodology is successful for a number of C_{19}-hydroxy steroids.

1.4.4.2 Total synthesis approaches

In the total syntheses of C_{19}-norsteroids, there are two commonly used procedures to install the A-ring: Modification of an aromatic A-ring, or the construction of the A-ring via a Robinson annulation. Towards the total synthesis of desogestrel, only the former method has been used. Scheme 21 demonstrates this methodology, illustrating the final steps to desogestrel in the Corey and Huang synthesis.[33]

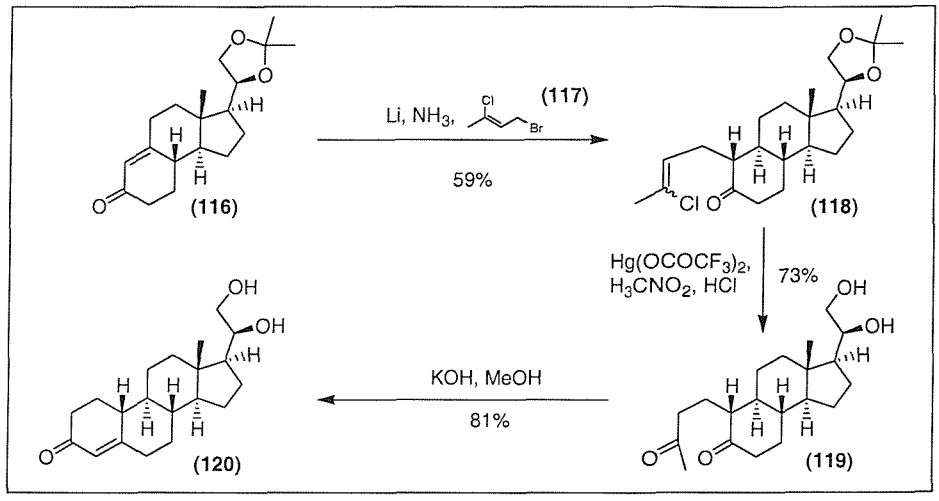


Scheme 21

De-aromatization of the A-ring in **(63)** was achieved using lithium in ammonia in the Birch reduction and the subsequent treatment with acid converted the 1-methoxy-1,4-hexanedione group in **(111)** to the α,β-enone in **(112)** as well as removing the silyl protecting group. At this point, Corey and Huang chose to use similar chemistry as used in the industrial synthesis of desogestrel (section 1.4.5), but in a different order. From **(112)**, the C_3-ketone was converted to the thioacetal, which was reduced using lithium in ammonia. The C_{17}-hydroxyl group in **(113)** was oxidized to the ketone using Dess-Martin periodinane and the

functionalization of the ketone (**114**) was effected using the *in situ* generated alkyno-lanthanide reagent (**115**).

The Robinson annulation is a common reaction in steroidal total syntheses and it has been used on separate occasions for the construction of the A, B and D rings.[7,60] The Robinson annulation or Robinson type chemistry has been used effectively for the construction of the A-ring in both C_{19}-norsteroids and regular steroids. Scheme 22 shows how Nemoto and co-workers[61-63] have used this reaction to construct the A-ring in a C_{19}-norsteroid synthesis.

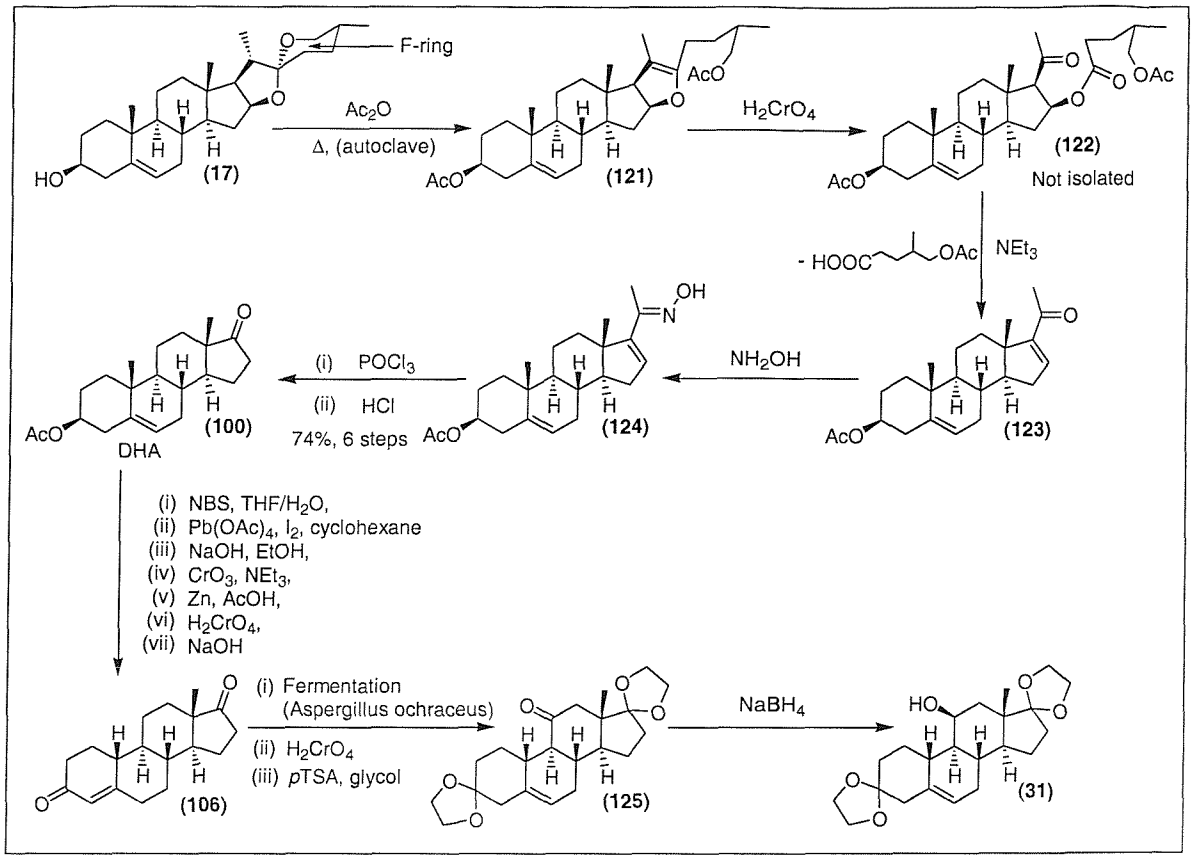


Scheme 22

Reductive alkylation of the enone (**116**) with 1-bromo-3-chlorobut-2-ene (**117**) was used to install the carbon framework for the A-ring, and hydrolysis of the vinyl chloride (**118**) afforded the diketone (**119**). The intramolecular aldol reaction completed the A-ring synthesis in 35% yield over all three steps.

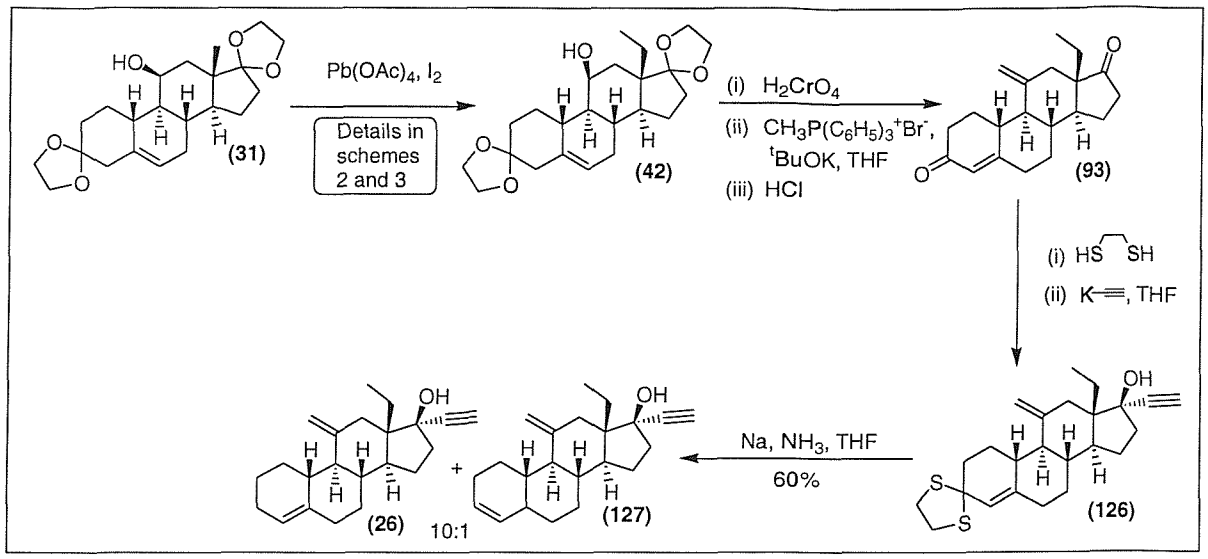
1.4.5 The complete industrial synthesis of desogestrel

The entire commercial synthesis of desogestrel has not been published by Organon, and as such, the overall yield cannot be calculated here. However, with the exception of the hypoiodite reactions, it is known that the yields of each individual step are excellent.[64] The synthesis is split into two schemes, where Scheme 23 shows the synthesis from the natural steroid Diosgenin (**17**) to the C_{13}-ethyl precursor (**31**) and Scheme 24 details the final steps to desogestrel, many of which have been touched upon already.



Scheme 23

From diosgenin **(17)**, dehydroepiandrosterone acetate (DHA) **(100)** is synthesised in six steps via the Marker process. The first step of the Marker process is to cleave the F-ring in diosgenin by heating the compound at 200 °C with acetic anhydride. Chromic acid oxidation of the C_{20-22} double bond in **(121)** converts this compound into the keto ester diacetate **(122)** and immediate treatment of the keto ester diacetate with base eliminates the C_{16} side chain, forming the enone **(123)**. Treatment of **(123)** with hydroxylamine forms the C_{17}-acetate-oxime **(124)**. $POCl_3$ is used to drive the Beckmann rearrangement of **(124)**, and DHA **(100)** is formed after acid hydrolysis. Overall, DHA can be prepared from diosgenin in 74% yield on an industrial scale.[1] The seven steps used to remove the C_{10}-methyl group have been detailed in Scheme 19. From the C_{19}-norsteroid **(106)**, the C_{11}-α-hydroxyl group is introduced by fermentation with the mould aspergillus ochraceus as discussed above (Scheme 9). Treatment with chromic acid oxidizes the hydroxyl to the ketone and selective acetalization of both the C_3 and C_{17} keto groups affords the C_{11}-oxo steroid **(125)**. The reduction of this remaining keto group with sodium borohydride is the most efficient way of achieving the C_{11}-β-hydroxyl in **(31)**, ready for the intramolecular hypoiodite reaction.

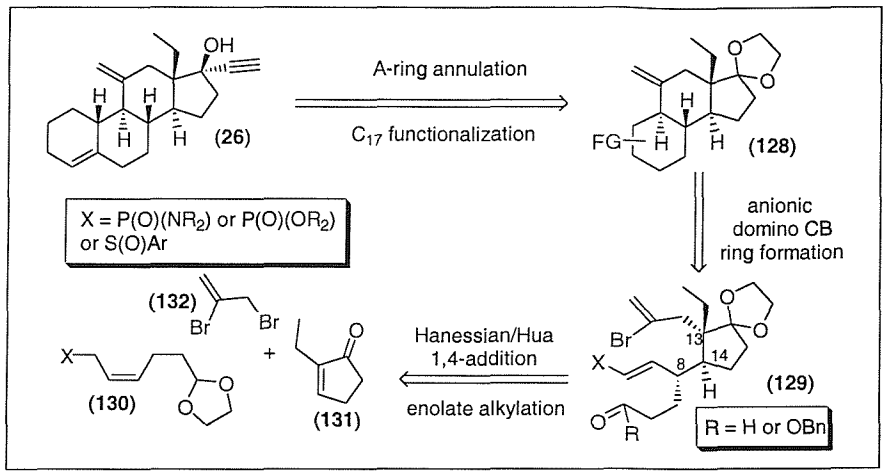


Scheme 24

Following the intramolecular hypoiodite reaction (detailed above in section 1.4.2.1, page 14), chromic acid oxidation of the C_{11}-β-hydroxyl group in **(42)** followed by Wittig chemistry introduced the exocyclic C_{11}-methylene group (section 1.4.3.1.C, page 23), and treatment with aqueous acid removed both of the acetal groups affording the diketone **(93)**. Selective protection of the enone as the thioacetal allowed the functionalization of the C_{17}-ketone with potassium acetylide, and then cleavage of the thioacetal group using sodium in ammonia led to a 10 : 1 mixture of desogestrel **(26)** and its C_{3-4} double bond isomer **(127)** in 60% yield.

1.5 Aim of the project

The aim of this research is to develop a novel method for steroid synthesis based on a domino cyclization approach. Scheme 25 shows the proposed retrosynthetic analysis towards desogestrel utilizing this methodology.



Scheme 25

The final steps in the proposed synthesis would be to install the A-ring from a residual functional group on the B-ring, and to introduce the C_{17}-α-ethinyl group. The tetracyclic product **(128)** would be formed by a domino reaction starting from **(129)**, which would be formed from a 1,4-addition with the *Z*-allylic phosphonamide, phosphonate or sulfoxide **(130)** onto the ethyl enone **(131)** with subsequent alkylation of the intermediate enolate. The proposed procedure offers a number of key advantages over the current desogestrel syntheses:

- Both the C_{13}-ethyl and the C_{11}-methylene groups would be present at the very beginning of the synthesis, and as such, no late stage introduction would be required;
- The *trans*-hydrindane stereochemistry at the CD-ring junction would be controlled during the 1,4-addition reaction and is reported to offer complete stereocontrol;[65-72]
- A Robinson annulation would be employed in the construction of the A-ring to complete the synthesis in a minimum number of steps.

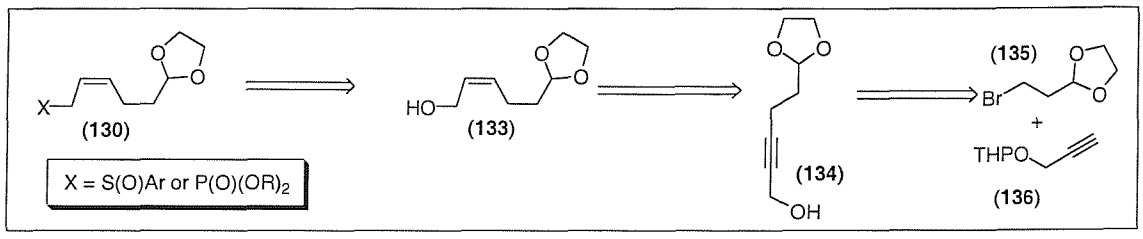
Each of the key steps are explained in more detail in the subsequent chapters: chapter 2 discusses the synthesis of the precursors for the 1,4-addition reaction, chapter 3 details the results of the Hanessian/Hua 1,4-addition reactions, conducted on a variety of 1,4-addition precursors. Chapter 4 discusses the results from the B and C-ring cyclizations and chapter 5 details future plans for the project. An overall summary is given in chapter 6, and the experimental details can be found in chapter 7.

Results and Discussion

Chapter 2, Synthesis of the allylic sulfoxide and phosphonate precursors for the conjugate addition reaction

2.1 Retrosynthetic analysis

The proposed retrosynthetic analysis for the sulfoxide and phosphonate conjugate addition precursors is shown in Scheme 26.



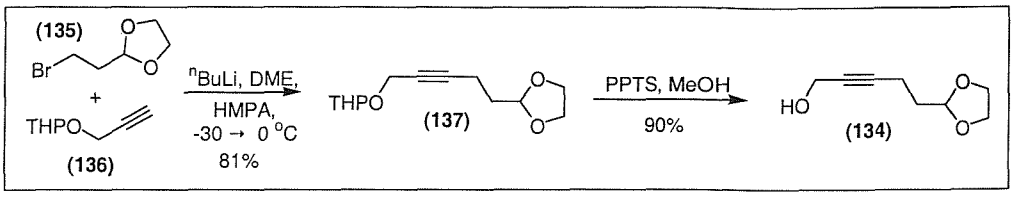
Scheme 26

This plan incorporated a degree of convergence, as the sulfoxide or phosphonate group in **(130)** would be introduced from the common precursor **(133)**. The *Z*-allylic alcohol **(133)** would be obtained via a stereoselective reduction of the propargylic alcohol **(134)**. The propargylic alcohol **(134)** is a known compound[73] and can be obtained from the bromide **(135)** and the THP protected propargylic alcohol **(136)**.

2.2 Synthesis of the common precursor (133)

2.2.1 Alkylation of propargyl alcohol

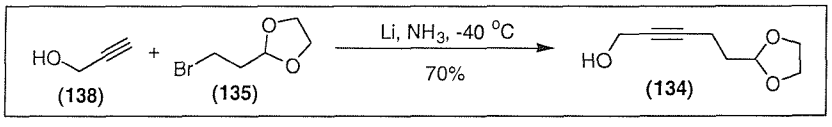
Deslongchamps and Roy[73] have previously synthesised the propargylic alcohol **(134)** in 73% yield via a two-step procedure (Scheme 27).



Scheme 27

The alkyne **(137)** was synthesised in 81% yield by deprotonation of the alkyne **(136)** with ^{n}BuLi at −30 °C followed by the addition of the commercially available bromide **(135)**. Deprotection of the alcohol in **(137)** with PPTS in methanol led to the propargylic alcohol **(134)** in 90% yield.

However, it was decided against using this route as it was reported only on a relatively small scale and used a significant amount of HMPA (3 equivalents). Instead, an alternative one-step synthesis of the propargylic alcohol **(134)** was investigated (Scheme 28).



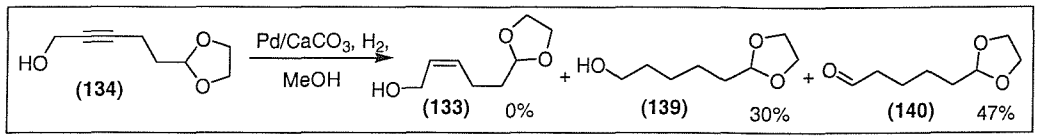
Scheme 28

By using lithium amide[74,75] to doubly deprotonate propargyl alcohol **(138)** and subsequent alkylation with the bromide **(135)**, the propargylic alcohol **(134)** could be reproducibly synthesised in 70% yield on a 25 g scale without the need for HMPA. This scale did require the use of 1.5 L of ammonia however. Increasing the concentration gave a thick mixture where mixing was inefficient, leading to poorer yields.

2.2.2 Selective reduction of the alkyne to *Z*-alkene

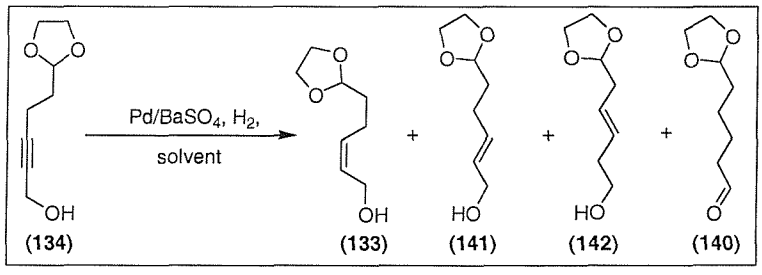
The *Z*-allylic alcohol **(133)** has been made previously[76] via a Lindlar reduction ($Pd/CaCO_3$) of the THP protected propargyl alcohol **(137)**. However, our synthesis as described in Scheme 28 required investigating the partial alkyne reduction using the propargylic alcohol **(134)**. Unfortunately, the partial reduction of the unprotected propargylic alcohol required major optimization efforts. Hydrogenation conditions were primarily investigated using both Lindlar catalyst and Rosenmund catalyst ($Pd/BaSO_4$). Using atmospheric H_2 pressure with the Lindlar conditions, the consumption of the starting material was complete within a

few hours, but the products contained no olefinic signals in the ^{1}H NMR. The two products isolated were identified as the fully reduced alcohol **(139)** (30%) and the aldehyde **(140)** (47%) (Scheme 29), which were both known compounds.[77]



Scheme 29

The use of different solvents in conjunction with the Lindlar catalyst changed the ratio of the products obtained but they did not afford any of the *Z*-alkene product **(133)**. The use of quinoline as a catalyst poison increased the amount of time for the staring material to be consumed but again, did not afford any *Z*-alkene product **(133)**. With Rosenmund catalyst, it was apparent that the reaction solvent had a dramatic influence on the reaction outcome (Scheme 30, Table 1).



Scheme 30

Entry	Solvent	Time (h)	Ratio of products **(133) : (141) : (142) : (140)**	Yield (%)
1	MeOH	18	-	Φ
2	EtOAc	4.5	9 : 44 : 16 : 31	89
3	Acetone	1.8	0 : 0 : 55 : 45	58
4	Et_2O	2	0 : 0 : 50 : 50	88
5	Hexane/EtOAc	3.5	0 : 0 : 83 : 17	95
6	Toluene	3	0 : 0 : 24 : 76	83
7	**DMSO**	**7**	**100 : 0 : 0 : 0**	**89**

Table 1

Φ = The starting alkyne was the only recognizable product obtained, recovered in 4% yield.

Although the reactions did not all take the same time, they were all stopped as soon as the alkyne (**134**) was no longer visible by TLC analysis.[■] Conducting the reaction in MeOH (entry 1) afforded no recognisable products other than the starting material. The use of EtOAc as the solvent, entry 2, led to the formation of four products; found to be the *Z*-allylic alcohol (**133**), the *E*-allylic alcohol (**141**), the homoallyl alcohol (**142**) and the aldehyde (**140**) in the ratio 9 : 44 : 16 : 31 respectively. The product ratios were obtained from the ^{1}H NMR analysis of the crude product. It was believed that the alkenes (**141**) and (**142**) both arose through a palladium catalysed isomerization of the *Z*-allylic alcohol (**133**).[78-81] Separation of the aldehyde from the alkene products was possible using column chromatography, and the homoallyl alcohol (**142**) was partially separable from the allylic alcohol products – an analytically pure sample was obtained using preparative HPLC. The *Z*- and *E*- allylic alcohols were not separable by either HPLC or silver nitrate chromatography.[82,83] The formation of the homoallylic alcohol (**142**) is remarkable and to our knowledge unprecedented in the literature.

Acetone (entry 3) was another extremely poor solvent for this partial hydrogenation as this yielded a 55 : 45 mixture of (**142**) and (**140**) in 58%. It is not clear why the use of this solvent returned such a poor yield of products. Using ether as the solvent (entry 4) led to almost the same ratio of products but in the better yield of 88%. Hexane alone was not polar enough to solubilize the propargyl alcohol (**134**) but a solution was formed following the addition of a minimal amount of EtOAc. This solvent mixture (entry 5) afforded an excellent yield of products but again, only the homoallyl alcohol (**142**) and the aldehyde (**140**) were isolated. In this instance the homoallyl alcohol (**142**) was found to be the major product (87 : 13, (**142**) : (**140**)). With toluene (entry 6), the same two products were isolated but the ratio of products was reversed (24 : 76, (**142**) : (**140**)). The best result came through the use of DMSO as the solvent. This reduction took the longest time, but it led exclusively to the *Z*-allylic alcohol (**133**) in very good yield (89%).

However, whilst up-scaling the DMSO-Pd/$BaSO_4$ mediated reduction (> 10 g scale), the reaction was not found to be reproducible. The reaction time varied from 4 to 11 hours and the yield varied from 55% to 76% but, crucially, the *Z* : *E* ratio of products obtained varied

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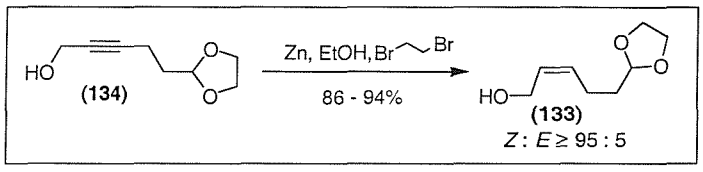
[■] A TLC eluent of 1 : 1 hexane/EtOAc afforded excellent separation of the starting alkyne from the products, providing a reliable method to follow the reaction progress.

from 97 : 3 down to 87 : 13. Presumably the heterogeneous conditions were responsible for the failure in the up-scaling of this reaction.

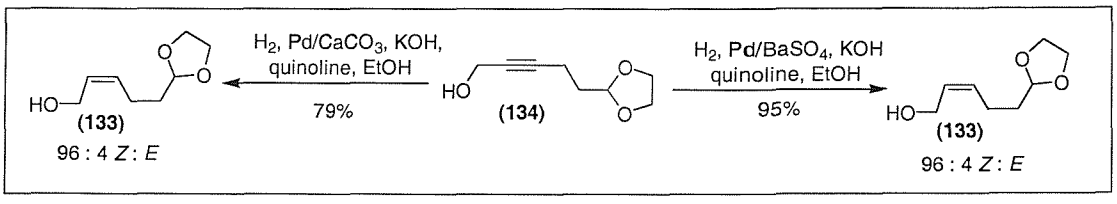
Alternative reduction conditions were found which involved the use of activated zinc instead of hydrogenation conditions.[84-90] Zinc-copper couple[84] was investigated initially but this only returned the starting material. Activation of zinc with 1,2-dibromoethane[85] selectively gave the *Z*-allylic alcohol in very good yield (86%) (Scheme 31). Further activation of the zinc using copper(I) bromide and lithium bromide[85,87] was investigated, but this led to the same product with no improvement in either yield or selectivity.



Scheme 31

Upon up-scaling this reaction, the *Z*-alkene product (**133**) was obtained in 86 to 94% yield, consistently with ≤ 5% of the *E*-double bond isomer. The success of this reduction is in part due to the presence of the propargyl alcohol moiety as this can co-ordinate to the metal, assisting the adsorption of the C≡C onto the metal surface.[85] The solvent is thought to be the hydrogen source for this reduction and it is believed to be introduced via an intramolecular proton transfer with an organometallic intermediate.[90]

After these investigations, a procedure was published in which KOH was used in conjunction with quinoline to poison the catalyst for the partial hydrogenation of an alkyne to give the *Z*-alkene.[91] This was subsequently investigated for the reduction of the alkyne (**134**) using both $Pd/CaCO_3$ and $Pd/BaSO_4$ with excellent results (Scheme 32).



Scheme 32

It was found that the reaction using the Lindlar catalyst took two days to go to completion but gave approximately 79% of (**133**) as a 96 : 4 mixture of *Z* : *E* isomers. The reaction

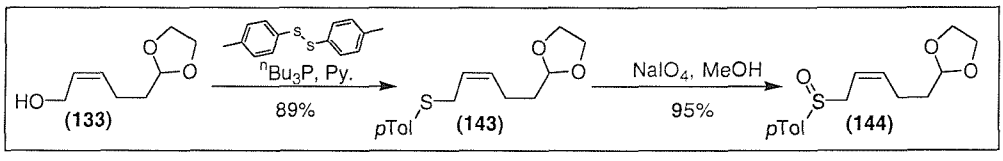
using the Rosenmund catalyst took overnight to go to completion but gave approximately 95% of **(133)**, also as a 96 : 4 mixture of *Z* : *E* isomers. Both of these yields are approximate because quinoline was present in the NMR spectra, even after chromatography. This reaction was not investigated for up-scaling as this route did not afford any major benefits over the optimised activated zinc method and because the quinoline proved to be difficult to remove entirely. The advantages this method would have over the activated zinc methodology are that the use of 1,2-dibromoethane (toxic) would be avoided and there would be no zinc to dispose of. Conversely there would be a need to recover or dispose of the palladium catalyst and also gaseous hydrogen is required.

2.2.3 Conclusion

A two-step synthesis was successfully developed for the common precursor **(133)**, which was amenable to scale-up.

2.3 Synthesis of the allylic sulfoxide (144)

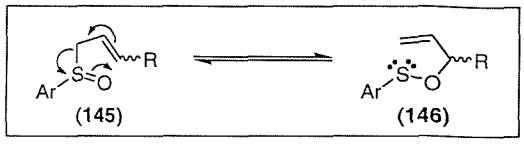
It was decided to synthesise a racemic sulfoxide for the initial investigations. The sulfoxide **(144)** was synthesised from the common precursor **(133)** via the sulfide **(143)** (Scheme 33).



Scheme 33

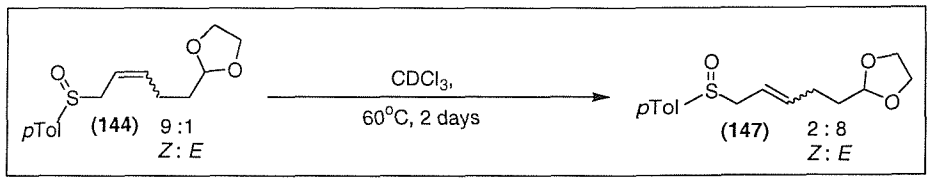
The sulfide **(143)** was synthesised in 89% yield by treatment of the allylic alcohol **(133)** with *p*-tolyl disulfide and tributylphosphine in pyridine. Diphenyl disulfide could be used in place of *p*-tolyl disulfide without any reduction in yield, but the *p*-tolyl group simplified the characterization. The oxidation to the racemic sulfoxide **(144)** was conducted using sodium metaperiodate in methanol.[92] This worked very well without overoxidation to the sulfone, affording the 1,4-addition precursor in 95% yield.

A drawback with allylic sulfoxides is their propensity to undergo a sulfoxide-sulfenate interconversion via a reversible [2,3]-sigmatropic rearrangement[93] (Scheme 34).



Scheme 34

This is an undesired process as *Z*-allylic sulfoxides get isomerized to the more stable *E*-double bond isomer. In addition, the sulfur atom in the sulfenate **(146)** is no longer a chiral centre; hence, a homochiral sulfoxide will racemize over time. Both consequences are obviously a concern regarding the case of chiral *Z*-allylic sulfoxides for the synthesis of desogestrel, as both the stereochemical integrity at C_8 and the enantioselectivity of the final product would be compromised. Furthermore, it was known that the sigmatropic rearrangement was much faster for unsubstituted allylsulfoxides compared with allylsulfoxides with further double bond substitution.[93] This was investigated with substrate **(144)** and it was found that the conversion of the *Z*-sulfoxide to the *E*-sulfoxide **(147)** was a relatively slow process (Scheme 35). A $CDCl_3$ solution sample of the sulfoxide **(144)** with 9 : 1, *Z* : *E* double bond geometry took 2 days at 60 °C to rearrange to 2 : 8, *Z* : *E*. These ratios can be calculated from the ^{1}H NMR of the mixture as both compounds exhibit clearly different signals for the S(O)C$\underline{H}_2$ environment. Heating the sample at 60°C for a longer time did not change the *Z* : *E* ratio but heating a toluene solution of **(144)** at 110 °C destroyed the compound. The compound could be stored in the freezer for several months without deteriorating.

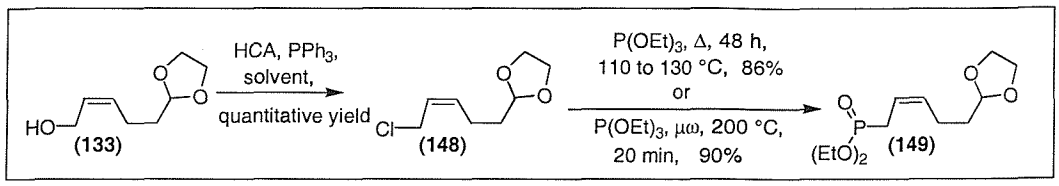


Scheme 35

These results prove that it should be possible to use enantiomerically pure *Z*-allylic sulfoxides for our purposes, provided that the temperature is kept below room temperature.

2.4 Synthesis of the phosphonate (149)

The phosphonate **(149)** was synthesised from the common precursor **(133)** via the allylic chloride **(148)** (Scheme 36).



Scheme 36

Several reagents were investigated for the conversion of the allylic alcohol **(133)** into the allylic chloride **(148)**. The use of triphosgene with pyridine[94] did not afford any recognizable products. Whilst PCl_3 in DMF[95] was effective in converting the alcohol into the chloride, the acidic conditions led to the partial deprotection of the aldehyde. The use of hexachloroacetone (HCA) with PPh_3[96-98] in the high boiling solvent sulfolane gave the best result, affording the allylic chloride **(148)** in quantitative yield. The procedure was later modified to use CH_2Cl_2 as the reaction solvent instead of sulfolane as this avoided a vacuum distillation step. Column chromatography was used to purify the product, but this was necessary even if the vacuum distillation step was included. On a larger scale, pre-adsorption of the crude reaction mixture onto silica assisted in the purification of the allylic chloride **(148)**.

Treatment of the *Z*-allylic chloride **(148)** with triethyl phosphite at 110 to 130 °C gave good yields of the *Z*-allylic phosphonate **(149)**, which was isolated by vacuum distillation. This reaction required longer reaction times than many literature examples, presumably because of the double bond geometry. The first step in the mechanism of the Michaelis-Arbuzov reaction is S_N2 displacement of the chloride by the nucleophilic phosphite.[99] It was thought that the *Z*-geometry of the double bond hindered the carbon of the CH_2Cl from S_N2 attack resulting, overall, in a longer reaction time.

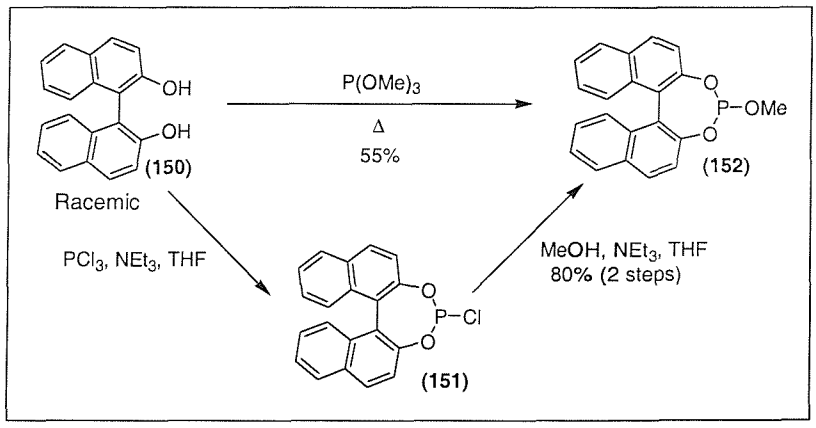
Microwave promoted Michaelis-Arbuzov reactions are known[100-102] and were also investigated. The optimum conditions were found to be 200 °C for 20 minutes using two equivalents of triethyl phosphite. This afforded the phosphonate **(149)** in 90% yield after chromatographic purification. These reactions were conducted in sealed tubes specific for

the microwave apparatus and, interestingly, despite the system being pressurised up to 18 bars, the ethyl chloride produced as a by-product did not interfere with the reaction. On a larger scale the microwave promoted reaction became less viable because the volume per tube had to be restricted to ~3 mL in order to keep the pressure within the operating limits. On a 10 g scale this equated to approximately 12 microwave vials, which was considerably more involving than the thermally promoted procedure for very little benefit.

Overall, from commercially available reagents, the phosphonate (**149**) could be synthesised on a 25 g scale in four steps and in 57% overall yield. This synthesis could be completed in five days, finishing with 22 g of the *Z*-allylic phosphonate.

2.5 Synthesis of the BINOL derived phosphonate (153)

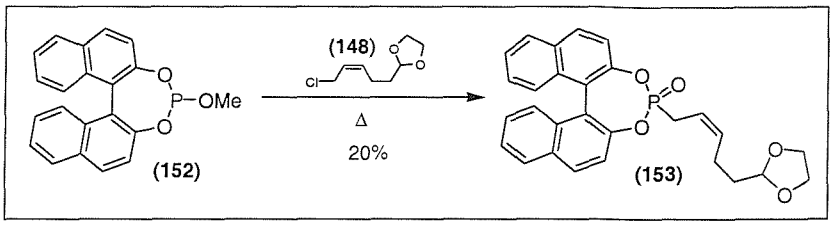
In order to achieve an enantioselective desogestrel synthesis, a chiral auxiliary ultimately needed to be used. As a model, racemic BINOL was employed initially. In order to synthesise the BINOL derived phosphonate (**153**), the phosphite (**152**) was required, for which two synthetic routes were attempted (Scheme 37).



Scheme 37

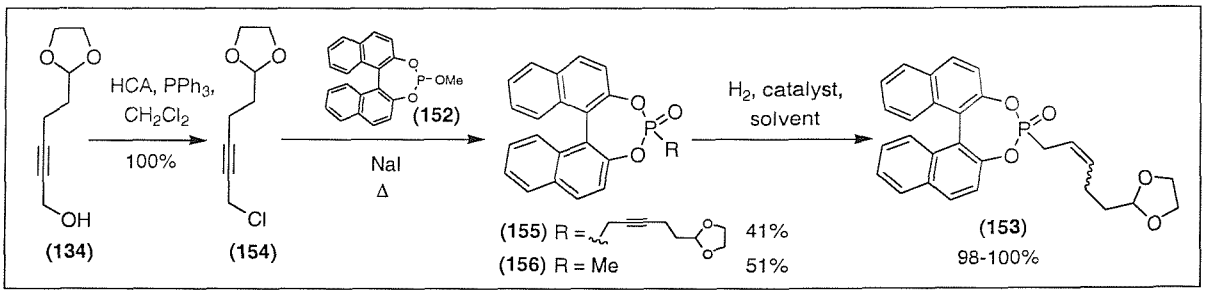
Although the phosphite (**152**) could be prepared in one step from BINOL by treatment with trimethyl phosphite, the reaction was low yielding (55%). It was found to be more efficient to adopt the two-step procedure via the chlorophosphite (**151**)[103-105] as this afforded the phosphite (**152**) in 80% yield from BINOL.

The phosphonate **(153)** was synthesised from the phosphite **(152)** as shown in Scheme 38. This reaction used the allylic chloride **(148)**, which had been synthesised from the common precursor **(133)** as described above.



Scheme 38

This reaction did not work very well however, as the phosphonate product **(153)** was only obtained in 20% yield and none of the allylic chloride was recovered. The addition of sodium iodide was investigated but this afforded no advantage. Microwave irradiation was not investigated on this substrate. It was thought that the poor result for the Michaelis-Arbuzov reaction might have been due to the large steric bulk of the BINOL group in conjunction with the *Z*-conformation of the double bond in the chloride. An alternative route was envisioned whereby the Michaelis-Arbuzov reaction would be conducted on the less sterically hindered propargylic chloride **(154)** and the partial reduction of the C≡C triple bond would be the final step (Scheme 39).



Scheme 39

The propargylic chloride **(154)**[73] was synthesised from the propargylic alcohol **(134)** in quantitative yield using the HCA/PPh_3/CH_2Cl_2 conditions described above. The yield for Michaelis-Arbuzov reaction did improve when the propargylic chloride **(154)** was used, but for the first time a side reaction was observed, which lead to the formation of the methyl phosphonate **(156)**. This product was formed by the reaction of chloromethane with the phosphite **(152)**. Chloromethane (boiling point = –24 °C) is synthesised during the reaction of the chloride **(154)** with the phosphite **(152)** but it is usually released from the reaction

mixture in its gaseous form. It was observed that this reaction mixture became extremely viscous as time increased and presumably this viscosity prevented the efficient release of chloromethane, despite its low boiling point. The use of a solvent would probably decrease the viscosity and may allow for more efficient removal of chloromethane. Microwave irradiation may also be beneficial in terms of elevated reaction temperatures and reduced reaction times but neither of these ideas were investigated.

The hydrogenation of the propargylic phosphonate **(155)** was investigated with a variety of catalysts and solvents. The results are summarised in Table 2.

Entry	Solvent	Catalyst[i]	Time (h)	Yield (%)[ii]	*Z* : *E* Ratio of **(153)**	Ratio of SM : P[iii]
1	EtOH	$Pd/BaSO_4$	1	-	None	§
2	EtOAc	$Pd/BaSO_4$	1	98	41 : 59	80 : 20
3	CH_2Cl_2	$Pd/BaSO_4$	1	99	52 : 48	0 : 100
4	CH_2Cl_2	$Pd/CaCO_3$	2	100	62 : 38	0 : 100
5	PhH	$Pd/CaCO_3$	1	100	72 : 28	0 : 100
6	DMSO	$Pd/CaCO_3$	2	100	84 : 16	0 : 100
7	DMSO	$Pd/BaSO_4$	1	100	>90 : 10	25 : 75
8	DMSO	$Pd/BaSO_4$	2	100	85 : 15	0 : 100
9	DMSO	$Pd/BaSO_4$	20	100	68 : 32	0 : 100

Table 2

[i] All catalysts were used in 5 mol%. § = 66% recovered starting material.
[ii] All yields are for isolated products but with no chromatographic purification except entry 1.
[iii] Alkyne starting material : alkene products.

With the exception of EtOH as solvent (entry 1), good recovery of products were observed in all cases. Of the remaining solvents investigated, PhH, CH_2Cl_2 and EtOAc all afforded poorer selectivity of the double bond in the alkene products than obtained with DMSO (entries 2 → 5). The use of Lindlar catalyst instead of Rosenmund catalyst improved the *Z* : *E* selectivity when CH_2Cl_2 was used as the solvent (entry 3 versus 4) but, in DMSO the results are nearly identical (entry 6 versus 8). The most important factor for this reduction in DMSO (and possibly other solvents) was that longer reaction times (entries 7 → 9) led to the synthesis of more of the undesired *E*-double bond isomer, presumably due to isomerization of the olefin in the presence of the palladium catalyst.[78-81] Overall, the double bond selectivity was not good enough to consider this hydrogenation route a viable option to the BINOL derived phosphonate **(153)**. Neither the activated zinc reduction nor the KOH/quinoline-poisoned palladium catalysed hydrogenation was investigated on this substrate.

2.6 Summary

An efficient procedure has been devised for the synthesis of two different 1,4-addition precursor compounds (a racemic sulfoxide and an achiral phosphonate), both from a common precursor. Optimization of the synthesis of the achiral phosphonate meant that the *Z*-allylic phosphonate **(149)** could be reliably synthesised in four steps and 57% overall yield from commercial reagents on a 25 g scale. This synthesis could be completed in five days, finishing with 22 g of the *Z*-allylic phosphonate. Similar chemistry was also applied to the synthesis of a BINOL derived phosphonate **(153)**, however, a satisfactory synthesis of diastereomerically pure *Z*-**(153)** has not been achieved.

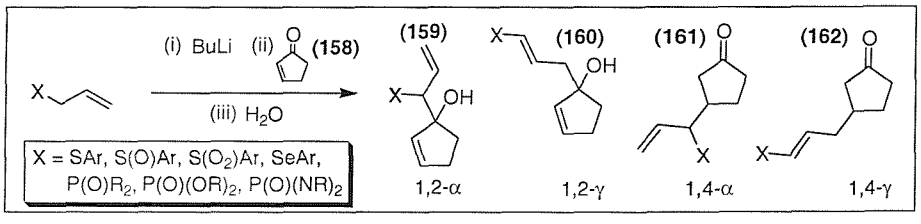
Chapter 3, The Hanessian/Hua 1,4-addition reaction

3.1 Introduction

The 1,4-addition reaction or Michael addition is an invaluable C-C bond forming reaction and is planned as the first key step in the proposed synthesis of desogestrel. The 1,4-addition utilizes a heteroatom stabilized allyl anion and quite different results can be obtained depending on the choice of this stabilizing group. In the following sections, the regioselectivity and stereoselectivity of the 1,4-addition reaction shall be discussed, followed by a number of examples of 1,4-addition reactions utilizing a chiral auxiliary.

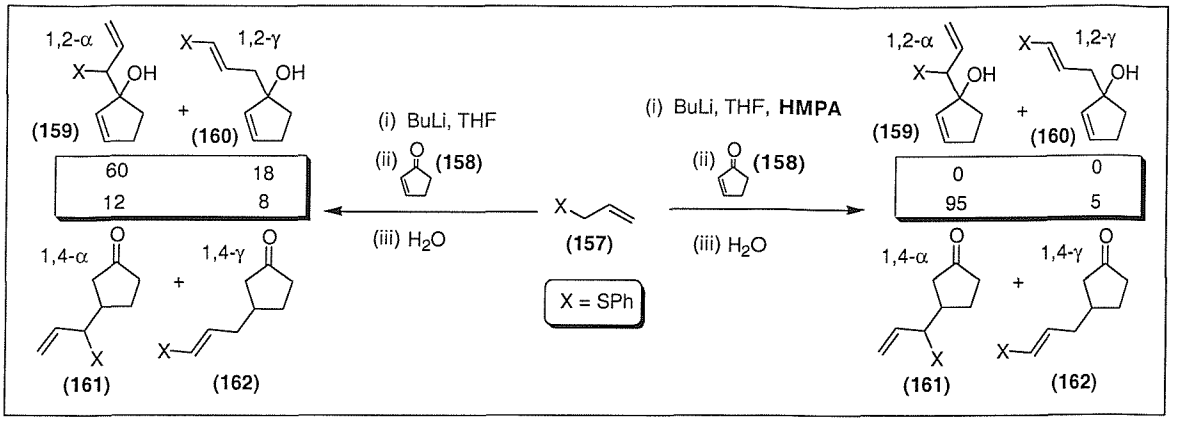
3.1.1 Regioselectivity during the 1,4-addition reaction

During the addition of heteroatom stabilized allyl anions to enones, regioselectivity can be a problem as four products are possible: 1,2-α-addition, 1,2-γ-addition, 1,4-α-addition and 1,4-γ-addition. These are summarised in Scheme 40.



Scheme 40

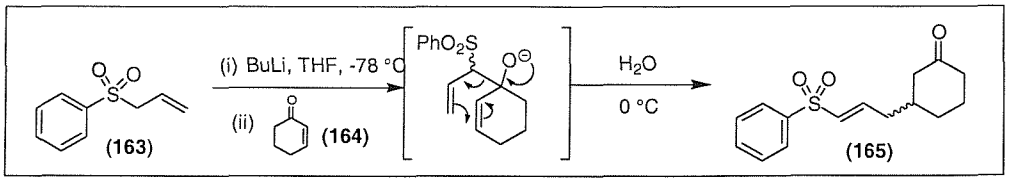
Haynes and others have shown that the heteroatom group directly affects the regioselectivity of the reaction. Sulfides and selenides are known to undergo 1,2-addition with a mixture of α and γ attack. If these additions are conducted in the presence of HMPA however, the 1,4-addition products are produced exclusively, with ~95 : 5, α : γ selectivity (Scheme 41).[106-109]



Scheme 41

Sulfoxides and phosphine oxides have been shown to undergo exclusive 1,4-γ-addition,[69,108,110] even at temperatures as low as −100 °C.[111] The addition of HMPA to these reactions did not affect the selectivity and it was even found to have a deleterious effect on the yields.[108,110] Additionally, conducting these reactions at temperatures as high as 0 °C had no detectable loss on diastereoselection.[108]

With sulfones,[111] carbonyl addition (1,2-α) takes place at low temperatures, but the product rearranges at 0 °C to give the 1,4-γ product (Scheme 42). Haynes and co-workers have demonstrated that more of the carbonyl adduct can be isolated if the temperature is kept below −70 °C.[111]

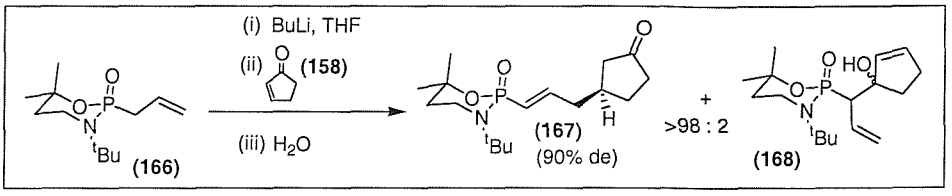


Scheme 42

HMPA has the same affect on sulfones as it has for sulfides and selenides i.e. HMPA stops the carbonyl addition and promotes conjugate addition.[111] In phosphonamide systems, Hanessian and co-workers have also found that the addition of HMPA improves the ratio of 1,4- to 1,2-addition.[65,67]

During the investigation of the conjugate addition of allyl-1,3,2-oxazaphosphorinane-2-oxides, Demark and co-workers[112] found that the 1,4-γ-addition product was produced with

a minor amount of the 1,2-α-addition product but neither of the 1,4-α- and 1,2-γ-addition products were detected (Scheme 43).

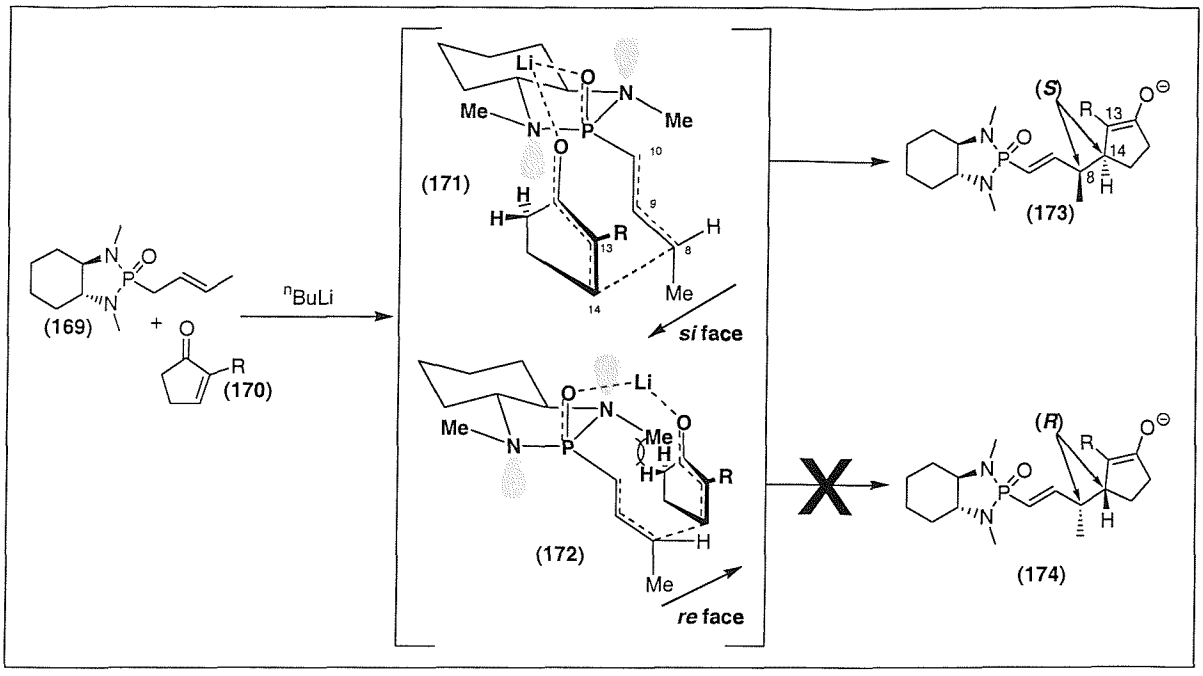


Scheme 43

Denmark's observations are consistent with the hard-soft, acid-base principle,[113] which states that hard nucleophiles would rather attack hard electrophiles and vice-versa. A hard nucleophile has no stabilizing effect (e.g. alkyl$^-$) and a soft nucleophile is stabilized (e.g. heteroatom-allyl group) the hard position of an enone is the carbonyl as no stabilization is offered whereas 1,4-addition forms the enolate, which is stabilized.

3.1.2 Stereoselectivity during the 1,4-addition reaction

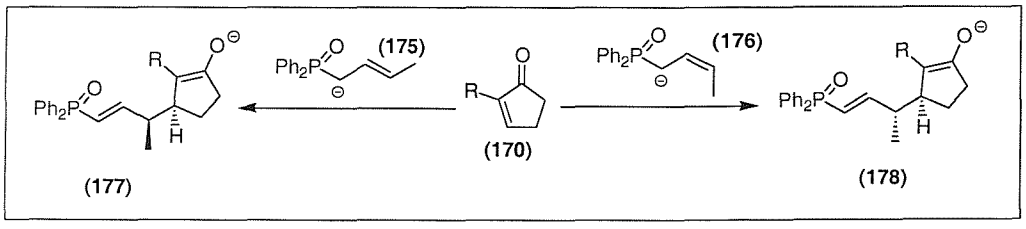
The 1,4-addition reaction using a *Z*-allylic phosphonate or sulfoxide is the first key step in the proposed synthesis of desogestrel, and this process would be used to introduce the stereochemistry at the carbons 8, 13 and 14 in a stereoselective manner. Hanessian and co-workers proposed that this 1,4-addition reaction proceeds via a *trans*-decalin transition state,[65-67] and that this accounts for the high levels of stereocontrol observed during the reaction. Scheme 44 shows an example of the 1,4-addition reaction from Hanessian's group and shows two transition states where the Michael nucleophile has approached the enone from either the *si* or *re* face. Hanessian and co-workers proposed that the *re*-transition state caused a steric clash between the α-CH_2 of the enone and the *N*-methyl group on the phosphonamide and that the reaction therefore proceeded via the *si*-transition state.



Scheme 44

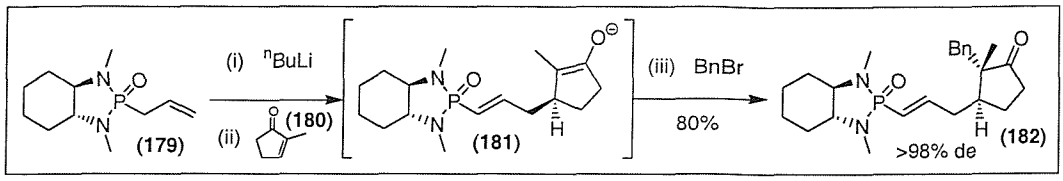
The *trans*-decalin transition state is directly responsible for the stereocontrolled introduction of the relative stereochemistry of C_8 and C_{14}, whilst the chiral auxiliary defines the absolute stereochemistry of these centres. Transition state **(171)** leads to the (*S*)-configuration at C_8 and C_{14}, whilst transition state **(172)** would lead to the (*R*)-configuration at C_8 and C_{14}. Both of these examples make use of a (*R*,*R*)-phosphonamide.

The particular C_8 configuration in **(173)** is a corollary of the geometry of the double bond in the 1,4-addition precursor. The closed *trans*-decalin transition state essentially translates the configuration of the double bond into the C_8 stereogenic centre. Haynes and co-workers[69,108,110,111,114] have conducted significant research in this area, demonstrating the different stereochemical outcomes for *E* or *Z* crotyl phosphine oxides (Scheme 45).



Scheme 45

The chirality at the position which becomes C_{13} in the steroid products is controlled during the 1,4-addition reaction via a diastereoselective alkylation of the intermediate enolate.[115] Scheme 46 shows an example from Hanessian's group.



Scheme 46

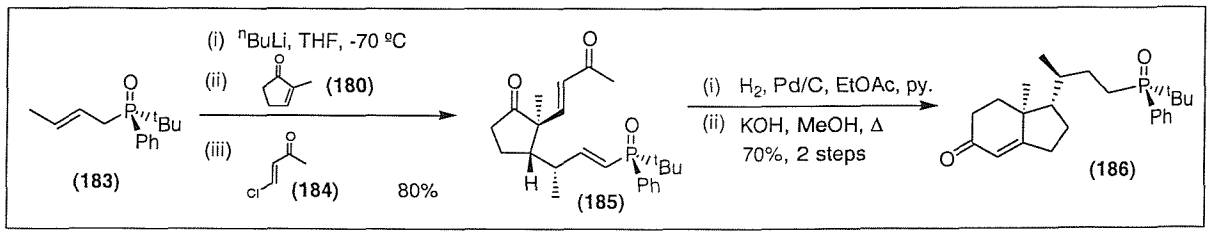
In the enolate **(181)**, the adjacent C_{14} moiety directs the attack of the electrophile to the least hindered back face. Many groups including Hanessian,[65,67,116] Haynes,[117-120] Jones[121,122] and Fuji[123] have employed this methodology in related 1,4-addition reactions.

3.1.3 Chiral auxiliaries

Chiral auxiliaries are used in 1,4-addition reactions to control the absolute stereochemistry of the products. There follows a number of examples of different chiral auxiliaries that have been employed in enantioselective 1,4-addition reactions. Included in this list is a homochiral sulfoxide. Although sulfoxides are not classed as auxiliaries, this example demonstrates the synthetic potential of this group.

As already illustrated in schemes 44 and 46 above, the phosphonamides used extensively in Hanessian's group lead to 1,4-addition products with excellent de's.

Haynes and co-workers[118] have utilized homochiral phosphine oxides to synthesise enantiopure hydrindenones suitable for conversion into vitamin D analogues (Scheme 47).

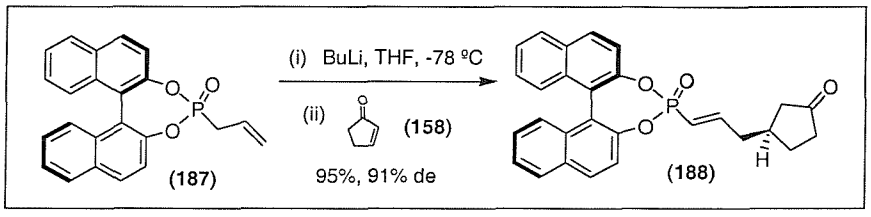


Scheme 47

From the optically active phosphine oxide **(183)**, the 1,4-addition onto 2-methylcyclopenteneone **(180)** and alkylation with the chloride **(184)** afforded the vinyl

phosphine oxide **(185)** in 80% yield. Subsequent hydrogenation of both C=C double bonds and an aldol ring formation formed the optically active hydrindenone **(186)** in 70% yield over both steps. This chemistry was successfully repeated using the opposite enantiomer of **(183)** to afford the opposite enantiomer of **(186)** in similar yield.

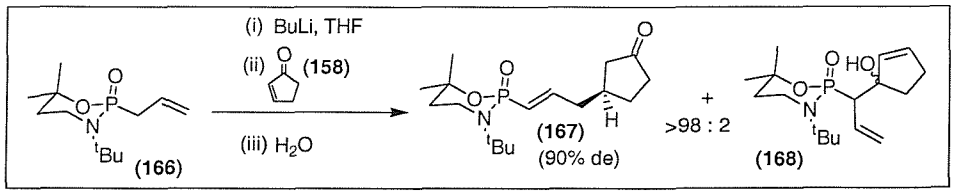
Fuji and co-workers have made use of a BINOL based auxiliary in their 1,4-addition reactions (Scheme 48).[123]



Scheme 48

The 1,4-addition reaction proceeded in excellent yield (95%) and with a very high degree of diastereoselectivity (91% de). Fuji and co-workers also investigated the effects of a number of different bases for the 1,4-addition reaction and found that lithium bases afforded better yields and greater diastereoselectivity.

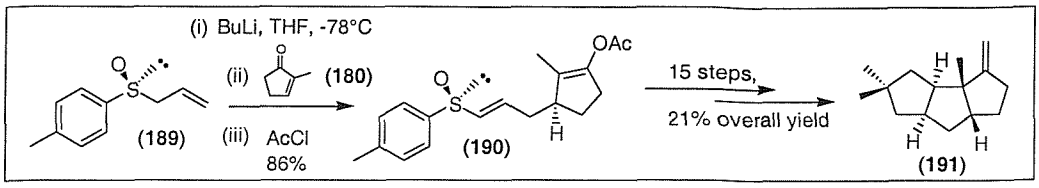
Denmark and co-workers have described high levels of stereocontrol in 1,4-addition reactions of anions derived from 2-allyl-1,3,2-oxazaphosphorinane-2-oxide **(166)** to simple cyclic enones (Scheme 49).[112]



Scheme 49

Denmark and co-workers found that the ^{t}butyl group afforded the best diastereoselectivity during the 1,4-addition step but other groups, both more and less sterically demanding, could also be tolerated, achieving de's of 88% (CEt_3) and 84% (^{i}Pr).

Hua has utilized a homochiral sulfoxide 1,4-addition approach on a number of occasions towards the synthesis of natural products[70,71,124] as shown in Scheme 50 (one example only).



Scheme 50

The 1,4-addition reaction was conducted on the enantiopure *p*-tolyl sulfoxide (**189**) and the intermediate enolate was trapped with acetyl chloride, leading to (**190**). From (**190**), (+)-hirsutene (**191**) was synthesised in 15 steps and in 21% yield.[70]

3.2 Synthesis of 2-ethylcyclopent-2-en-1-one (131)

For the desogestrel synthesis, the 2-ethylcyclopentenone (**131**) Michael acceptor was required and unlike 2-methylcyclopentenone (**180**), it was not commercially available, although several preparative procedures have been reported.[64,125,126] However, 2-methylcyclopentenone (**180**) was used as a model compound in the initial investigations. Eventually, (**131**) was synthesised using a variation of the Organon N. V. procedure[64] (Scheme 51).

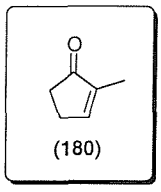
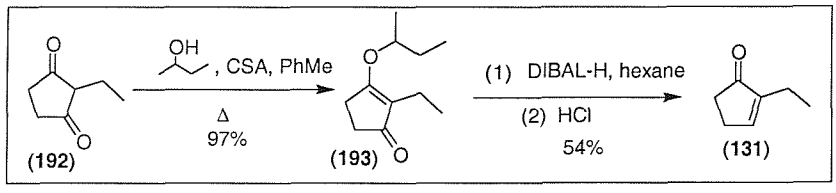


Figure 12



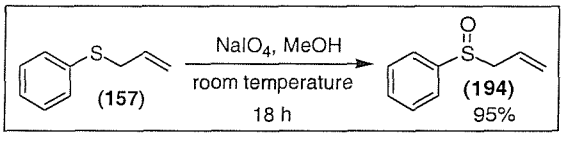
Scheme 51

Condensation of the diketone (**192**) with *sec*-butanol in refluxing toluene in the presence of an acid catalyst afforded the enol ether (**193**) in excellent yield after distillation. Reduction of the keto group followed by acid hydrolysis of the enol ether and subsequent elimination of the hydroxy group gave the enone (**131**) in 54% yield after purification. Although Organon N. V. conducted this procedure starting from 150 g of the diketone (**192**), it was successfully scaled down to work on both a 50 g and 25 g scale. Two changes were made during the scale down: 1) CSA was used as the acid catalyst in place of *p*TSA. This was easier to handle but did not change the course of the reaction. 2) The solvent for the reduction step was changed from toluene to hexane. This was because the enone product (**131**) was relatively volatile (boiling point = 47 – 49 °C/5 mmHg) and losses were being

suffered as this compound partially co-evaporated on the rotary evaporator. The change to hexane meant milder evaporation conditions could be used and consequently the yield for the enone improved (42% → 54%).

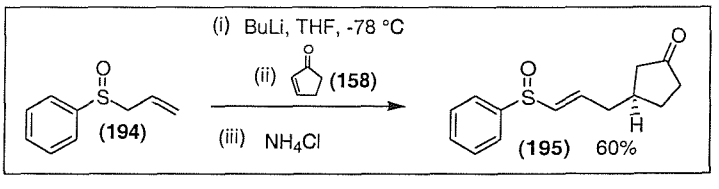
3.3 1,4-Addition reactions with phenyl allyl sulfoxide

Phenyl allyl sulfoxide (**194**) was chosen for model 1,4-addition reactions because it was cheap and quick to obtain and several reports exist with successful 1,4-addition reactions conducted with this compound[110,127] or the *p*-tolyl analogue.[70,122,124,128-131] Phenyl allyl sulfoxide was synthesised from the commercially available sulfide (**157**) using sodium metaperiodate in methanol as reported by Antonjuk and co-workers[92] (Scheme 52) and others.[132,133] These conditions worked excellently (95% yield) with no over-oxidation to the sulfone. Hydrogen peroxide could also be used as the oxidant when used in conjunction with hexafluoroisopropanol[134] (91% yield) but these conditions were less cost effective.



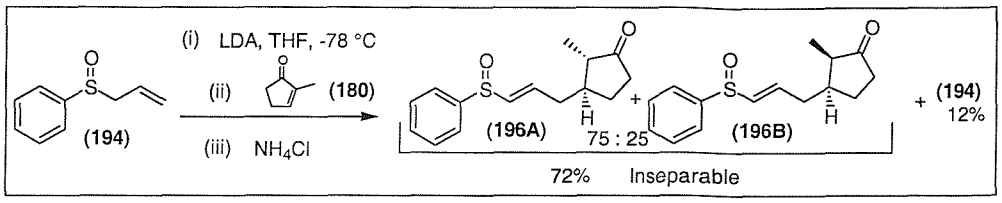
Scheme 52

Initially, a simple cyclic enone was used for the 1,4-addition reaction and the enolate formed during the reaction was quenched with a proton source instead of being alkylated with an electrophile (Scheme 53).



Scheme 53

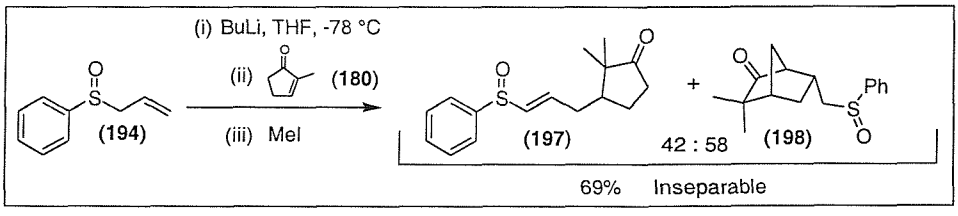
The 1,4-addition product (**195**) was produced as a single diastereoisomer in 60% yield, which was an encouraging result for our first reaction of this type. The same reaction was then attempted using (**180**) (Scheme 54).



Scheme 54

The reaction using the methyl enone **(180)** returned a small amount of the starting allylic sulfoxide (12%) as well as affording the 1,4-addition product **(196)** in 72% yield. This 1,4-addition product was obtained as an inseparable 75 : 25, **(196A)** : **(196B)** mixture of diastereoisomers. Hanessian and co-workers observed a similar mixture of diastereoisomers with their 1,4-addition reactions when they used the methyl enone **(180)** and quenched the enolate with ammonium chloride.[67] They reported a solution to this selectivity problem by simply quenching the enolate with methanol instead of ammonium chloride. This was tried for the reaction in Scheme 54 but the product was less pure than before. This was not considered problematic though, because in the synthesis towards desogestrel the enolate would need to be alkylated not quenched, and it was known from the literature that the stereoselectivity was much better for these reactions.[67,123]

Methyl iodide was chosen as the electrophile for a trial 1,4-addition reaction because of its high reactivity and because C_{13} in the 1,4-addition product would no longer be a chiral centre (Scheme 55). This was considered advantageous because it was expected to simplify the analysis of the products.



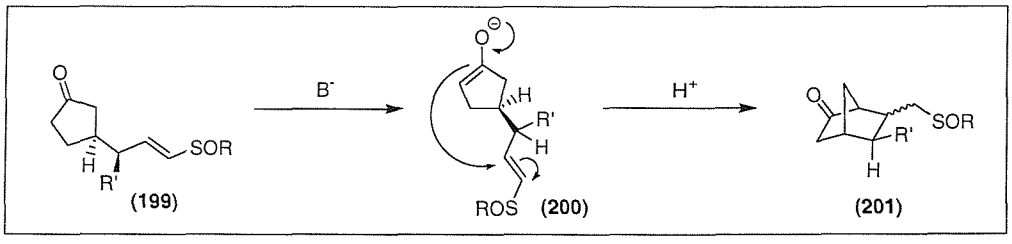
Scheme 55

This 1,4-addition reaction afforded two products; the 1,4,addition/alkylation product **(197)** and a byproduct, which was identified as the bicyclic heptanone product **(198)**. Only one diastereoisomer of **(198)** was isolated, but the stereochemistry is unknown. This 1,4-addition/alkylation reaction was attempted many times and combined yields were obtained in the range of 31% to 69%, where the ratio of **(197)** : **(198)** varied from 65 : 35 to 17 : 83.

Although these products could not be separated by chromatography, full NMR characterization was possible for each compound by comparison of the different mixtures.

The structure of **(198)** was established as the bicyclic heptanone product following the observations made previously by the groups of Haynes,[120] Pivnitski[127] and Jones.[135] Of these groups however, only Jones and co-workers[135] observed the formation of the bicyclic heptanone products during the 1,4-addition reaction itself. The other examples arose through separate and intentional reactions on the 1,4-addition product. Additionally, the intramolecular cyclizations observed by Jones's group only took place when the 1,4-addition reaction was being conducted on an allylic sulfone and it did not occur in the analogous sulfoxide reactions. It is still unclear why this intramolecular cyclization was observed for the reaction in Scheme 55.

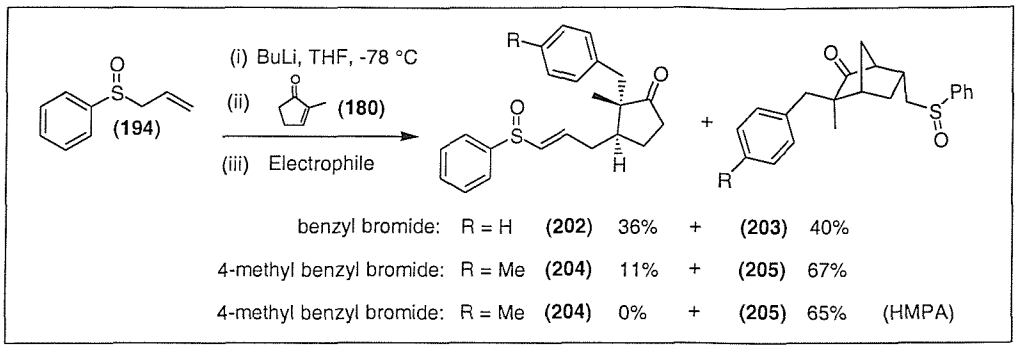
Haynes and co-workers[120] proposed a mechanism for the formation of bicyclic heptanone products (Scheme 56).



Scheme 56

Treatment of the 1,4-addition product **(199)** with base formed the enolate **(200)**, which attacked the α,β-unsaturated sulfoxide, leading to the bicyclic product **(201)** after work-up.

It was decided to investigate the 1,4-addition/alkylation reaction sequence with different electrophiles in the hope that these would lead exclusively to 1,4-addition products.

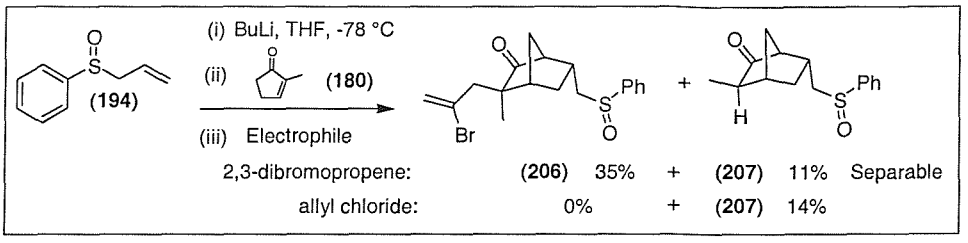


Scheme 57

Alkylating the intermediate enolate with benzyl bromide afforded a separable mixture of the 1,4-addition product **(202)** and the bicyclic heptanone product **(203)** in near equal amounts. The reaction with 4-methyl benzyl bromide also gave a separable mixture of similar products but the ratio was much more in favour of the bicyclic product. The 1,4-addition products **(202)** and **(204)** were isolated as single diastereoisomers with the C_{13}-benzyl group and the C_{14}-side chain positioned '*trans*' to each other. Although this was expected, it was a crucial finding because it meant that after cyclization of the C-ring, the CD-hydrindane system would be set up with the correct *trans*-stereochemistry required for the steroid skeleton. The bicyclic heptanone products **(203)** and **(205)** were isolated as single diastereoisomers but with unknown stereochemistry.

A variety of reaction temperatures and times were attempted in order to optimise the reaction with 4-methyl benzyl bromide but, despite these efforts, the best yield obtained for the 1,4-addition product was only 11%. In fact, the reaction could be considered quite reliable if the bicyclic heptanone product **(205)** was required, since significant temperature differences during the addition of reagents made little difference to the amounts of products produced. The only occasion when a significant difference in the types of product produced arose was when the electrophile was added as an HMPA solution instead of a THF solution. With the electrophile/HMPA solution, no 1,4-addition product was isolated at all. This could be because the HMPA might be stabilizing the lithium cation during the enolate formation (Scheme 56), and this is making the enolate more reactive towards the cyclization.

It seemed improbable at this stage that this reaction could be optimized for the 1,4-addition product but it was decided to investigate more electrophiles, especially 2,3-dibromopropene, as this was the electrophile required in the desogestrel synthesis (Scheme 58).



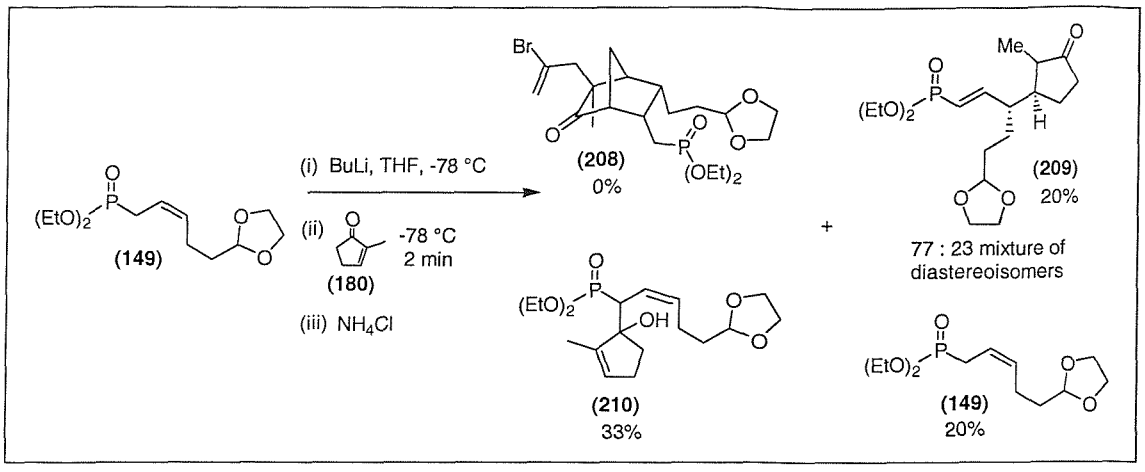
Scheme 58

When 2,3-dibromopropene was used as the electrophile, no 1,4-addition compound was produced. Instead, the bicyclic heptanone product **(206)** was synthesised in 35% yield along with the non-alkylated bicyclic heptanone product **(207)** in 11% yield. When allyl chloride was used as the electrophile, the only compound to be isolated was the non-alkylated bicyclic heptanone product **(207)**. The use of allyl iodide instead of allyl chloride did not change the course of reaction, as the non-alkylated product **(207)** was still the only compound to be isolated.

The 1,4-addition chemistry with phenyl allyl sulfoxide was not working as expected, contrary to the successful literature reports.[70,110,122,124,127-131] It was decided to switch the focus to work on the 1,4-addition reaction with a phosphonate. During this work, an explanation for the *in situ* cyclization was proposed (page 62). Based on those findings, the use of an allylic sulfoxide was reinvestigated and described in section 3.7, page 67.

3.4 1,4-Addition reactions with the phosphonate (149)

The conjugate addition of the *Z*-allylic phosphonate **(149)** was initially investigated again with quenching of the intermediate enolate (Scheme 59).



Scheme 59

This reaction led to a mixture of products, although the formation of the bicyclic heptanone product **(208)** was not observed. Of the addition products isolated, a 3 : 2 ratio of 1,2-α : 1,4-γ was observed **(210)** : **(209)**. These observations are consistent with Denmark's findings insofar as no 1,4-α- and 1,2-γ-addition products were detected.[112] The major product from the reaction was the carbonyl addition product **(210)** and it was thought that this might have been because the temperature was kept too low after the addition of the enone[111] or because not enough time elapsed between the addition of the enone and the quenching reagent. This reaction was the only instance where products with regiochemistry other than 1,4-γ-addition was observed, but for all of the subsequent reactions, the temperature was raised to 0 °C before the addition of the electrophile.

The 1,4-γ-addition product **(209)** was formed in a total of 20% and this was found to be approximately a 3 : 1 mixture of diastereoisomers, separable by preparative HPLC. The major diastereoisomer **(209A)** (Figure 13) had *trans*-geometry across the cyclopentane ring.

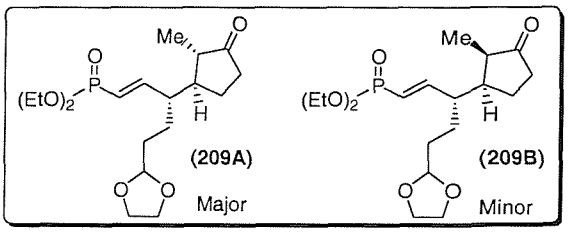
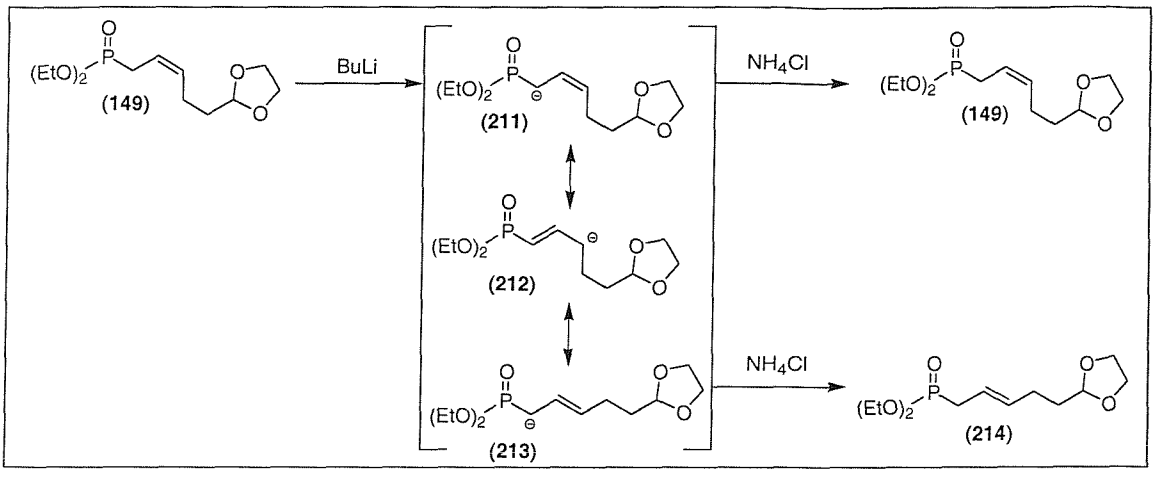


Figure 13

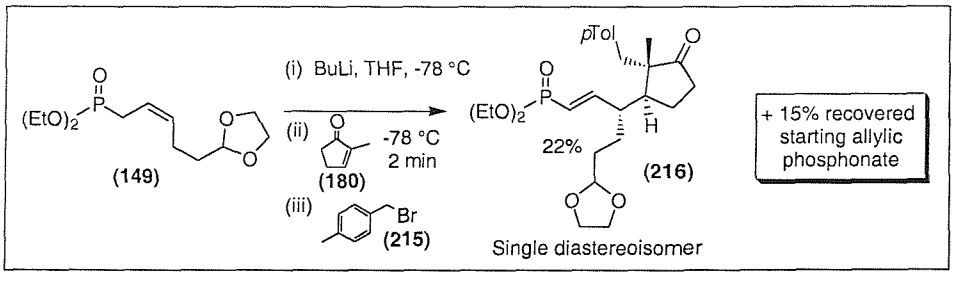
The third product that was obtained from this reaction was the allylic phosphonate starting material **(149)**. This was recovered in 20% yield and NMR analysis proved that the double

bond geometry was unchanged. It was expected that this material did not undergo deprotonation during the reaction because the potential for double bond isomerization (Scheme 60) would probably have afforded a mixture of the *Z* and *E* allylic phosphonates but a mixture was not observed.



Scheme 60

Following the partial success of the 1,4-addition/quench reaction, it was necessary to investigate how the system behaved with electrophiles in 1,4-addition/alkylation experiments. Again, model electrophiles were selected and 4-methyl benzyl bromide was chosen because this was a reactive electrophile with characteristic signals in the NMR (Scheme 61).

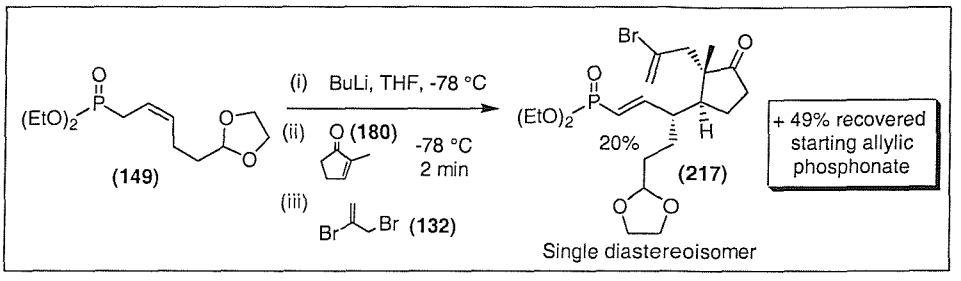


Scheme 61

Only one product was isolated from this reaction and this was found to be the vinyl phosphonate **(216)** obtained as a single diastereoisomer in 22% yield. The allylic phosphonate starting material **(149)** was also recovered in 15% yield. Apart from the low yield, the formation of **(216)** as a single diastereoisomer was an excellent result because it demonstrated that the 1,4-addition/alkylation sequence could be successfully conducted to

obtain single diastereoisomers without the occurrence of competing intramolecular cyclization reactions.

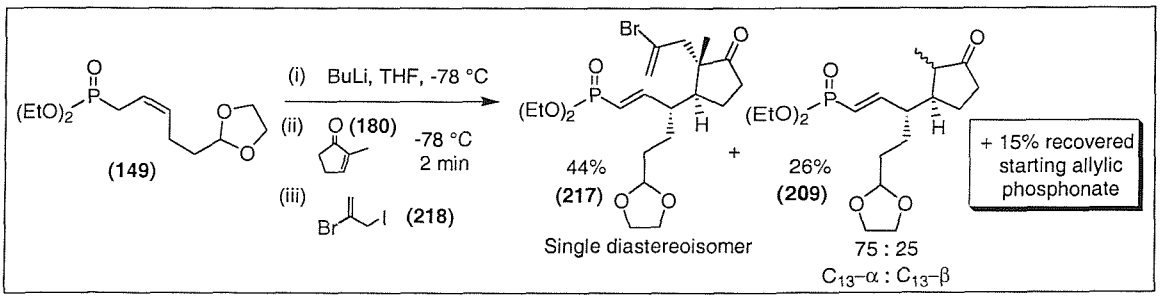
Following the success with the model electrophile, the reaction was repeated using 2,3-dibromopropene **(132)**; the electrophile required for the synthesis of desogestrel (Scheme 62).



Scheme 62

This reaction afforded the 1,4-addition product **(217)** as a single diastereoisomer in 20% yield along with the recovery of 49% of the starting material. Despite the reduced reactivity of this electrophile compared with 4-methyl benzyl bromide, a similar yield of the 1,4-addition product was achieved. This was another excellent result as the product **(217)** could be taken forward for the C-ring cyclization. The problems with this reaction included the poor yield of the 1,4-addition product and the high yield of recovered starting material.

In an attempt to improve the yield of the 1,4-addition product, the corresponding allylic iodide **(218)** was used as the electrophile and the temperature of the reaction was varied at different points (Scheme 63). The iodide **(218)** was synthesised from the bromide **(132)** via a Finkelstein reaction.[136]

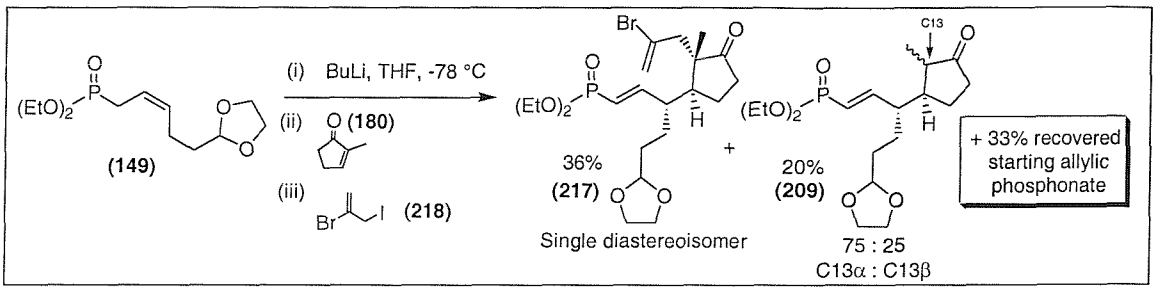


Scheme 63

It was found that this reaction afforded 44% of the 1,4-addition product **(217)** as well as 26% of the non-alkylated 1,4-addition product **(209)** in a 75 : 25 **(209A)** : **(209B)** ratio. 15% of the allylic phosphonate starting material **(149)** was also recovered.

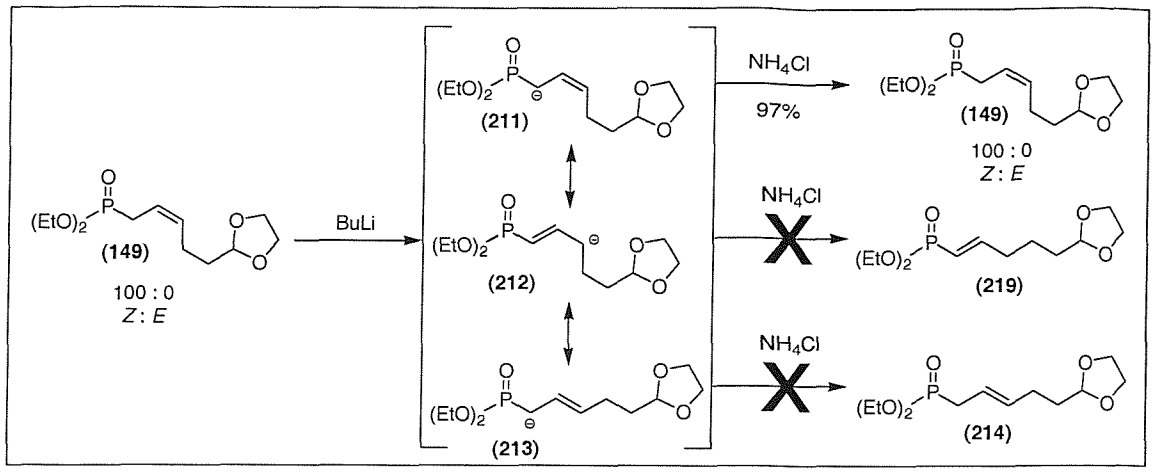
When this reaction was repeated, the point at which the reaction was warmed to 0 °C was changed from after the addition of the electrophile to after the addition of the ^{n}BuLi. This did not change the result however, as 44% of the 1,4-addition product was still obtained.

In order to consume more of the starting material and thus increase the yield of the 1,4-addition product, the reaction was repeated using an excess (1.3 equivalents) of ^{n}BuLi (Scheme 64).



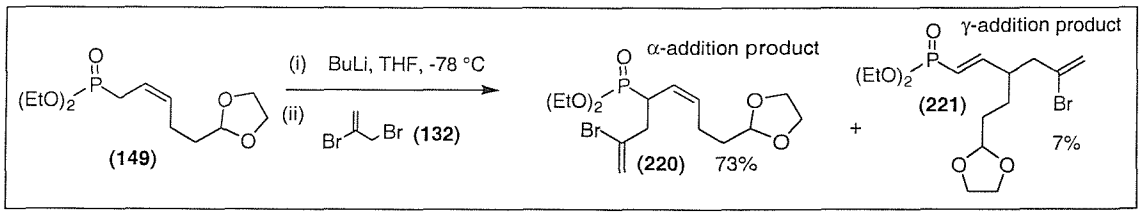
Scheme 64

This afforded 36% of the 1,4-addition product, which was similar to, but no better than, the previous results. A further 20% of the non-alkylated 1,4-addition material **(209)** was also isolated as a 75 : 25 mixture of **(209A)** : **(209B)**. Crucially, this reaction still afforded 33% of the starting allylic phosphonate to be recovered from the reaction with unchanged double bond geometry. This was surprising as it seemed unlikely that there would have been incomplete deprotonation of the allylic phosphonate starting material when 1.3 equivalents of BuLi had been used, and it was expected that subsequent protonation would at least partially give rise to the *E*-allylic phosphonate, and/or lead to the more stable α,β-unsaturated phosphonate **(219)** (Scheme 65).



Scheme 65

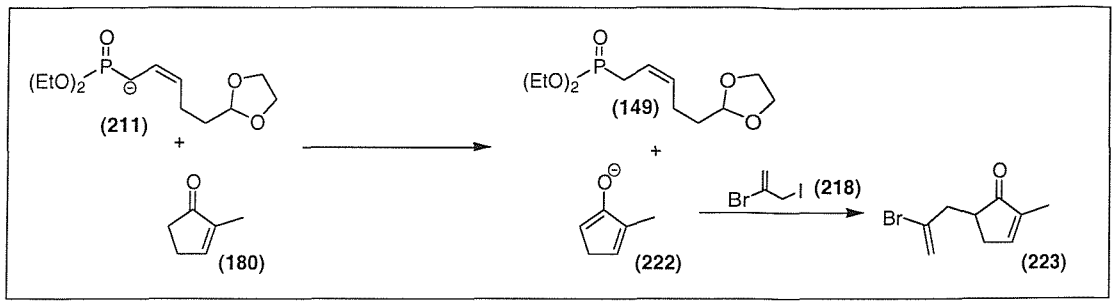
To test whether the deprotonation/protonation sequence would scramble the double bond geometry, the *Z*-allylic phosphonate **(149)** was deprotonated with ^{n}BuLi at –78 °C for 30 minutes and then protonated (Scheme 65). The *Z* : *E* ratio was unchanged which meant that the anion **(211)** must have been configurationally stable at this temperature. This indicated that the allylic phosphonate in all of the 1,4-addition reactions could have been fully deprotonated and that a different factor was responsible for the high return of the starting material. In a bid to identify this factor, the deprotonated phosphonate was alkylated with **(132)** directly (Scheme 66).



Scheme 66

This reaction afforded 73% of the α-addition product **(220)** and 7% of the γ-addition product **(221)**. None of the starting material **(149)** was recovered and no other products were detected other than base-line material. It became clear from the 80% conversion of starting material into products that one equivalent of base and of the electrophile was sufficient for this reaction. Also, since this was the first result where all of the starting allylic phosphonate had been consumed, it confirmed that the 1,4-addition process itself was responsible for the high recovery of the allylic phosphonate material during the 1,4-addition reaction.

In an effort to explain the high recovery of the starting allylic phosphonate material during the 1,4-addition reaction, Scheme 67 below shows an alternative reaction route with the potential to compete with the 1,4-addition.

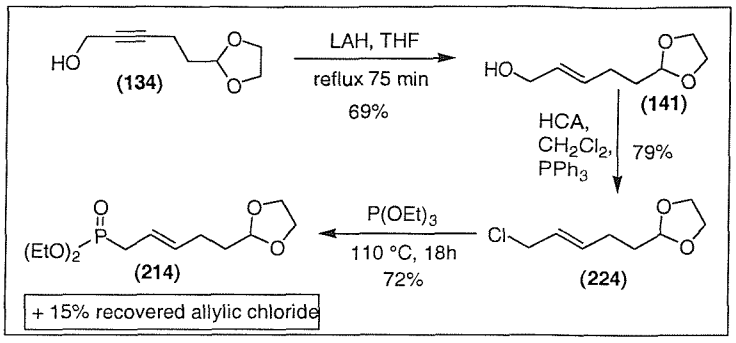


Scheme 67

Instead of undergoing a 1,4-addition, this route proposes that the enone **(180)** could be deprotonated by the phosphonate anion **(211)**. In this event, the allylic phosphonate **(149)** would be reformed and the enolate of the enone would be formed **(222)**. This enolate should be rather unreactive and would most likely be quenched, returning to the enone **(180)**, but the possibility of alkylation with **(218)** also exists, leading to the enone **(223)**. Despite the significant amounts of apolar products that were separated from the 1,4-addition product after each reaction, the enone **(223)** was never isolated and identified. Attempts were made to analyse the apolar material but the ^{1}H NMR and MS data were too complicated to interpret.

3.5 Synthesis of the phosphonate (214)

All of the phosphonate 1,4-addition/alkylation products isolated thus far had been obtained as single diastereoisomers, but they were also all oils. This meant that X-ray analysis had not and could not be used to ascertain the configuration of the C_8-stereocentre. Clearly, obtaining the natural steroid stereochemistry at this position was crucial for the project and it was reasoned that the best way to investigate the C_8-stereochemistry was to synthesise the C_8-epimeric compound. Since the C_8-stereocentre was controlled by the double-bond geometry in the allylic phosphonate starting material, the C_8-epimeric 1,4-addition/alkylation compound would be obtained from the *E*-allylic phosphonate **(214)**. The synthesis of this compound is shown in Scheme 68.

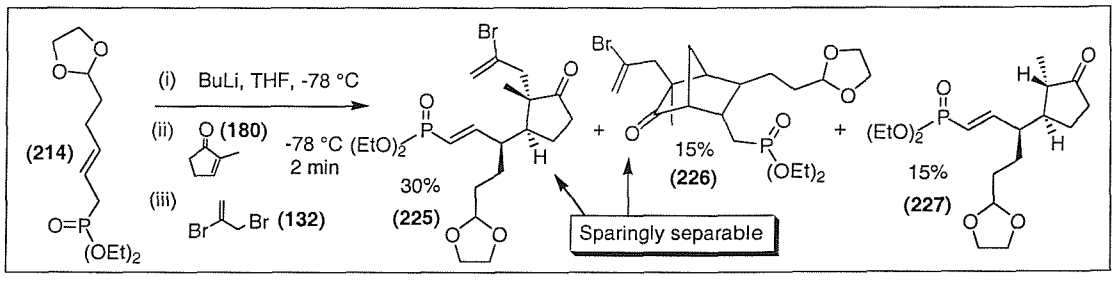


Scheme 68

The *E*-allylic alcohol **(141)** was synthesised from the propargylic alcohol **(134)** by reduction of the C≡C triple bond with LAH in THF. Wang and co-workers[137] have previously reported this compound, but no experimental conditions or analytical data were published. Formation of the allylic chloride **(224)** from the allylic alcohol **(141)** proceeded smoothly using HCA and PPh_3[96-98] in CH_2Cl_2 as described in section 2.4 (page 39). The Michaelis-Arbuzov reaction was not left until completion, but in 18 hours 72% of the phosphonate **(214)** was isolated along with 15% of the starting allylic chloride.

3.6 1,4-Addition reactions with the phosphonate (214)

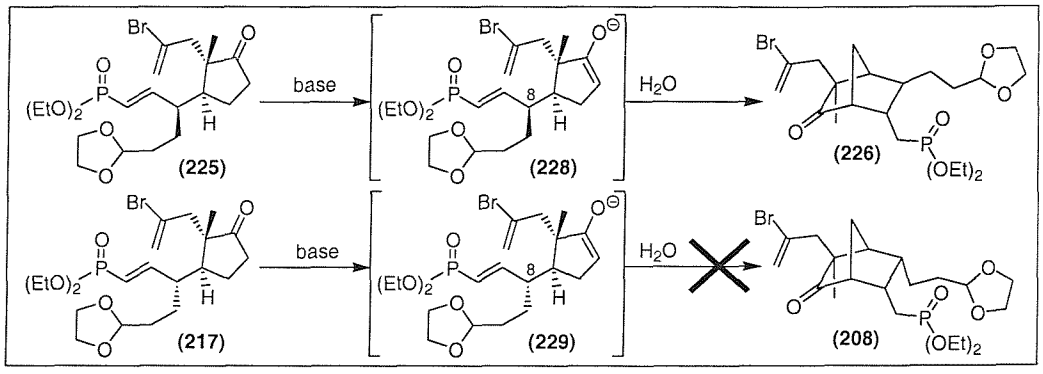
The 1,4-addition on the *E*-allylic phosphonate **(214)** was conducted under the same conditions as used above, using the electrophile **(132)** to alkylate the intermediate enolate (Scheme 69).



Scheme 69

Three products were isolated from the reaction mixture and no allylic phosphonate starting material **(214)** was recovered. The three products were identified as the 1,4-addition/alkylation product **(225)**, the non-alkylated 1,4-addition product **(227)** and, to our great surprise, the bicyclic heptanone product **(226)**. This was the only example in the

phosphonate series to undergo the same intramolecular cyclization commonly observed with the 1,4-addition reactions on phenyl allylic sulfoxide (**194**), and naturally we were curious as to why. The double bond geometry was the only difference between the allylic phosphonates (**149**) and (**214**), therefore it seemed logical that the difference in reactivity stemmed from this factor. It was supposed that, in both cases, the 1,4-addition went as expected, leading to (**225**) and (**217**) respectively (Scheme 70). According to Haynes' mechanism (Scheme 56), the enolates (**228**) and (**229**) would be formed (see below), which then could attack the α,β-unsaturated phosphonate to give the bicycloheptanone species. However, only (**226**) was observed, and not the formation of (**208**). This suggests that the C_8 configuration plays a key role in the cyclization process, presumably in relation to conformational aspects.



Scheme 70

Indeed, the explanation as to why the C_8 configuration was responsible for the intramolecular cyclization could be visualized in the energy minimized three-dimensional representations of the enolates (**228**) and (**229**) in Figure 14.[■]

[■] The program used to enegy minimize these structures was CS Chem3D Ultra V 6.0, CambridgeSoft.Com, www.camsoft.com

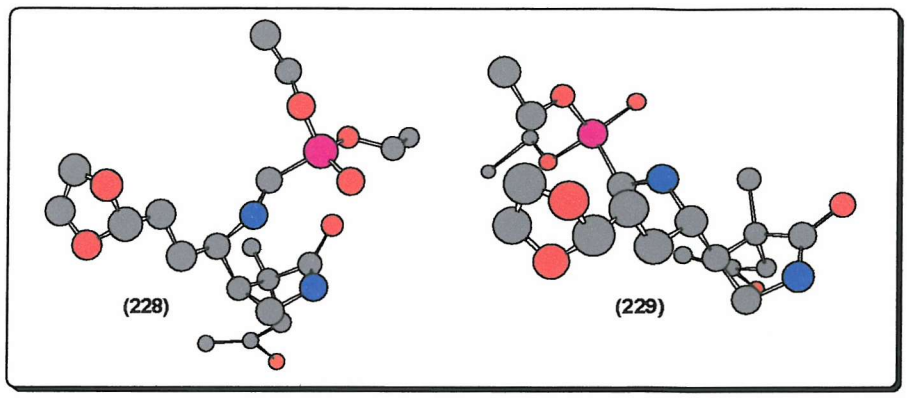
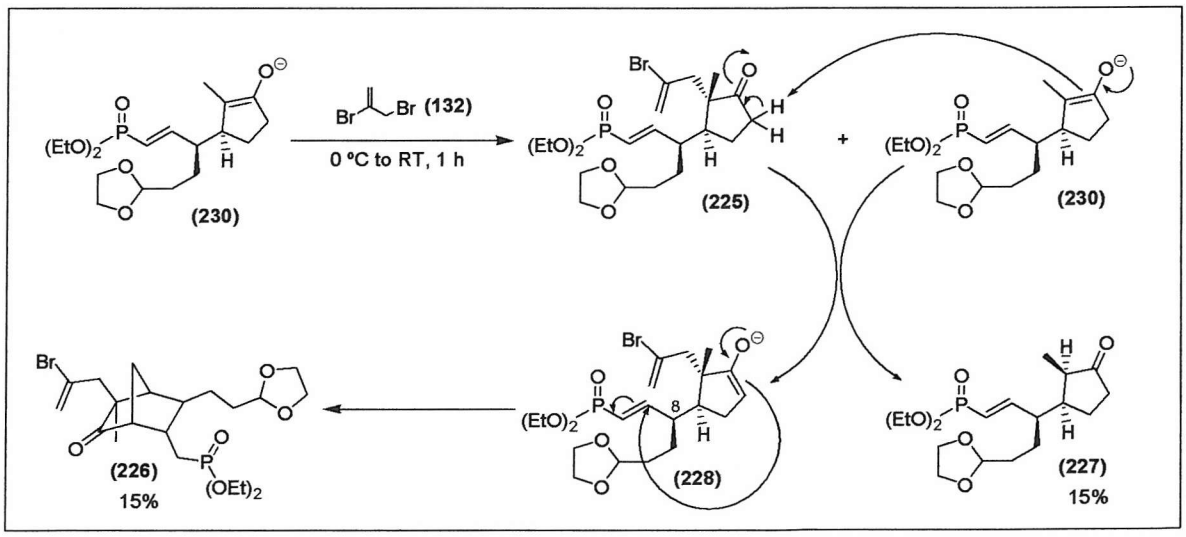


Figure 14

During the intramolecular cyclization, a new bond was formed from C_{16} to C_9. In Figure 14 these two carbon centres are coloured blue for clarity. The enolate **(228)** underwent the intramolecular cyclization leading to the bicyclic heptanone product **(226)** (Scheme 70). The three dimensional structure of **(228)** clearly shows that, as a consequence of the C_8-configuration, C_9 is placed very close to C_{16}, thus aiding the bond formation. Conversely, in the enolate **(229)**, the C_8-configuration affects the conformation in such a way that C_9 and C_{16} are too distant for intramolecular reaction to occur.

Although it is still unclear how the enolate **(228)** is formed, the following process is suggested (Scheme 71).



Scheme 71

The enolate **(230)** is the immediate result of the 1,4-addition process and, assuming the alkylation of this compound is a relatively slow process, **(230)** could exist at the same time

as the 1,4-addition/alkylation product **(225)**. In this event it would be possible for the enolate **(230)** to abstract a hydrogen from **(225)**, leading to both the enolate **(228)** and the protonated adduct **(227)**. If we make the assumption that the cyclization of **(228)** to **(226)** is a very fast process, it would explain why **(227)** and **(226)** were obtained in identical yields. However, in the corresponding process starting from the Z-allylic phosphonate **(149)**, we would expect a similar amount of protonated adduct, which is not observed. This may be due to a faster alkylation process, although this is still quite speculative.

From these observations, it became apparent that the formation of the bicyclic heptanone products in the sulfoxide series could probably be avoided by using an allylic sulfoxide with a *Z*-double bond. Indeed, this proved successful as detailed in the next section (3.7, page 67).

Returning to the 1,4-addition reaction conducted on the *E*-allylic phosphonate **(214)**, the 1,4-addition/alkylation product **(225)** and the bicyclic heptanone product **(226)** were found to be sparingly separable but analytically pure samples of each compound were obtained after repeated preparative HPLC. This enabled a direct comparison of the two C_8-epimeric 1,4-addition/alkylation compounds, which proved that the two compounds were different. The ^{1}H NMR for each of the 1,4-addition products obtained from the *Z*- and *E*-allylic phosphonates are displayed in Figure 15. The x-axis is identical in each spectra allowing for a direct comparison.

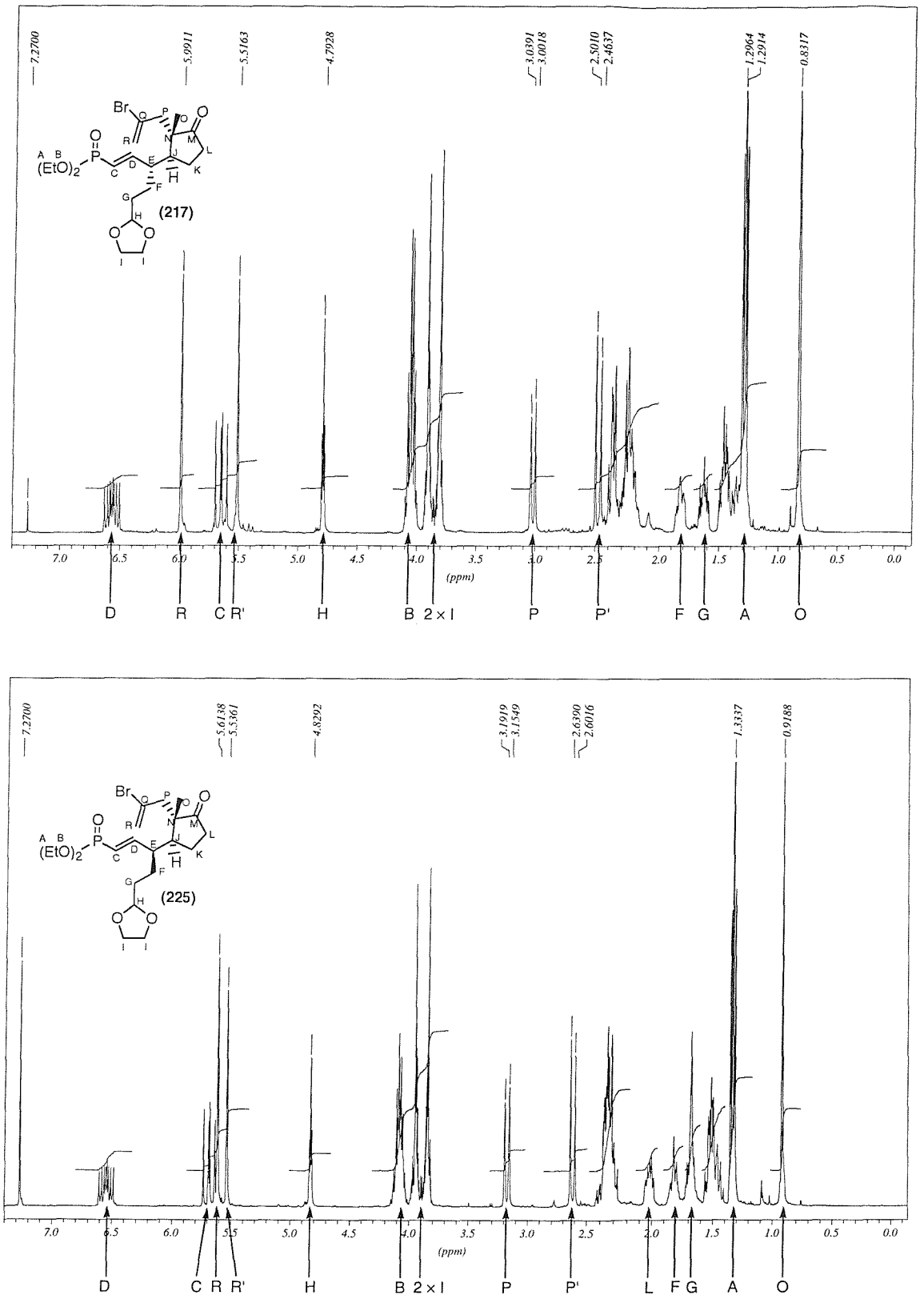

7.2700
5.9911
5.5163
4.7928
3.0391
3.0018
2.5010
2.4637
1.2964
1.2914
0.8317
(217)
(ppm)
D R C R' H B 2×I P P' F G A O
7.2700
5.6138
5.5361
4.8292
3.1919
3.1549
2.6390
2.6016
1.3337
0.9188
(225)
(ppm)
D C R R' H B 2×I P P' L F G A O

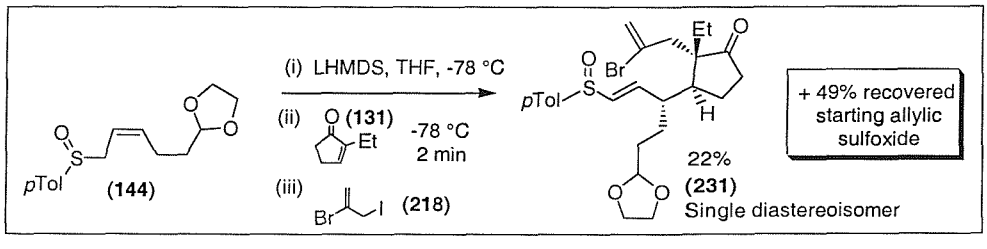
Figure 15

As would be expected, the spectra are similar but clearly different. Significant differences are displayed in the high-field region (δ = 1.4 to 2.5 ppm) and also for one of the CH_R signals at low-field. Although the only structural difference between the compounds is the configuration at C_8, this change affects the folding of the compounds and leads to the remarkable differences in the spectra. (For a visual example of how the C_8-configuration affects the overall conformation of the molecule, see the enolates in Figure 14 (page 64).)

Proving that the 1,4-addition/alkylation compounds derived from the *Z*- and *E*-phosphonates were different was a crucial result, as it proved that the C_8-stereochemistry could be reliably predicted. Clearly, if the two 1,4-addition/alkylation compounds had been identical, then the formation of the C_8-stereocentre was not controlled by the double bond geometry. These results are also believed to be the first examples that the 1,4-addition process is stereospecific on more complex allylic phosphonates than the crotyl examples used by Haynes and co-workers and Hanessian and co-workers.

3.7 1,4-Addition reactions with the sulfoxide (144)

The results with the *Z*- and *E*- allylic phosphonate 1,4-additions prompted us to re-investigate the sulfoxide-mediated approach. Hence the *Z*-allylic sulfoxide **(144)** was subjected to the 1,4-addition/alkylation reaction with 2-bromo-3-iodopropene as the electrophile. The ethyl enone **(131)** was also available at the time of this work and this was the only enone to be investigated (Scheme 72).



Scheme 72

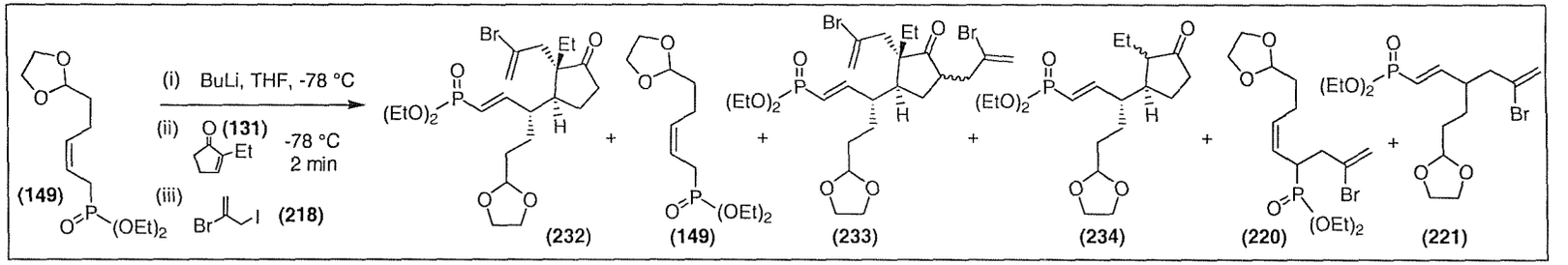
This reaction yielded the 1,4-addition compound **(231)** as a single diastereoisomer in 22% yield. The allylic sulfoxide starting material was also recovered in 49% yield but no other products were isolated. This result clearly showed that the presence of the *Z*-double bond did prevent the formation of bicyclic heptanone products. Although the allylic sulfoxide

starting material was recovered with unchanged double bond geometry, it was not possible to re-use this material without extensive chromatographic purification since the heating required for a distillation would have scrambled the double bond geometry.

The choice of base was important for this 1,4-addition reaction. Whereas ^{n}BuLi was the base of choice for the phosphonate 1,4-additions and either ^{n}BuLi or LDA could be used with equal results with phenyl allylic sulfoxide, when the sulfoxide **(144)** was treated with ^{n}BuLi, only a complex mixture of products was obtained. The problem was overcome by using either LDA or LHMDS – these bases gave almost identical results. Non-lithium bases were not investigated here as Fuji and co-workers[123] had previously shown that different countercations led to a decrease in both the yield and diastereoselectivity of the 1,4-addition reaction. This is thought to be because the lithium cation enables a tighter chelation of the transition state compared with the larger sodium or potassium cations. Unfortunately there was insufficient time to investigate/optimize the reaction in Scheme 72 further.

3.8 Phosphonate 1,4-addition reactions with the enone (131)

Given the successful trials with 2-methylcyclopenteneone **(180)**, the 1,4-addition/alkylation reaction was subsequently investigated using the 2-ethylcyclopenteneone substrate **(131)**. This reaction was conducted many times but the yield always remained between 14 and 31%. Table 3 shows these results and Scheme 73 shows the different products obtained.



Scheme 73

Entry	Scale (mmol)	T before enone addition (°C)	T after enone addition (°C)	Time before **(218)** addition (min)	Solvent$^{\Theta}$	Yields of products					
						(232)	**(149)**	**(233)**	**(234)**	**(220)**	**(221)**
1	7.13	–78	0	2	HMPA	14	51	1	0	0	0
2	30.68	–78	0	10	HMPA	14	60	1	0	0	0
3	2.08	–78	0	5	THF	14	53	*	0	0	0
4	0.82	–78	0	15	THF	14	43	5	9	0	0
5	1.85	0	0	60	THF	16	46	2	2	0	0
6	0.86	0	0	2	THF	16	37	4	0	0	0
7	7.45	–78	–78	2	HMPA	17	44	2	0	21	10
8	1.66	–78	0	15	THF	17	47	2	8	0	0
9¶	1.65	–78	0	15	THF	18	30	6	5	0	0
10	41.79	–78	0	10	HMPA	18	61	1	0	0	0
11	27.17	–100	–50	15	HMPA	20	40	2	0	12	11
12	1.83	–78	0	15	HMPA	25	35	2	6	0	0
13	22.20	–100	0	10	HMPA	28	58	*	0	0	0
14	1.86	–78	0	15	THF	28	35	*	0	0	0
15	13.85	–78	+18	45	THF	31	30	*	0	0	0

Table 3

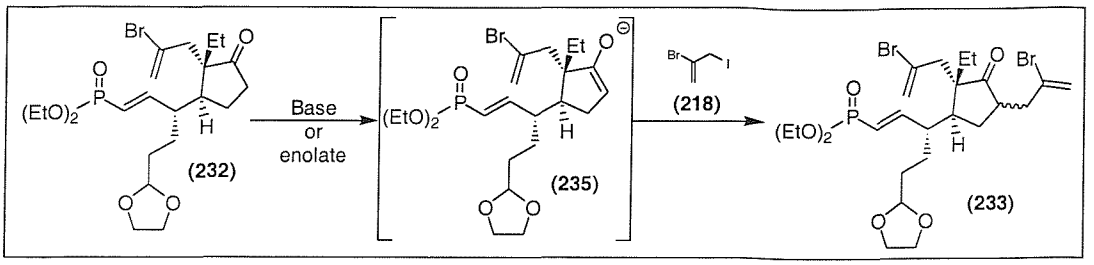
T = Temperature ¶ = 1.4 eq ^{n}BuLi * = Not isolated Θ = Solvent used during the electrophile addition

It was not possible to display 100% mass balance of the products because material was often destroyed by the harsh reaction conditions and lost as base-line material during chromatographic purification. Additionally, products were occasionally isolated by HPLC analysis that could not be assigned a structure. The NMR of these compounds was typically extremely messy – possibly the indication of a number of compounds despite eluting from the HPLC column as a single peak.

Entries 1 to 4 and 5 versus 6 show that the time allotted between the addition of the enone and the electrophile did not influence the yield of the 1,4-addition/alkylation product (**232**). Entries 1 to 4 also show that the yield of the 1,4-addition/alkylation product was not influenced by the solvent in which the electrophile was dissolved.

Varying the temperature of the reaction before the addition of the enone did not seem to influence the course of the reaction (entries 6 versus 1 and 13 versus 12 or 14). The temperature of the reaction after the enone addition was important however. Although the yield of the 1,4-addition/alkylation product was not significantly different, entries 7 and 11 showed that when the reaction was kept at –50 °C or lower after the addition of the enone, the side-products (**220**) and (**221**) were synthesised. These must have been synthesised through the direct reaction of the allylic phosphonate anion with the electrophile, i.e. complete addition of the allylic phosphonate anion to the enone was not occurring at low temperatures.

The use of an excess of BuLi (entry 9) did not change the amount of (**232**) obtained but it did afford a higher than normal recovery of the *bis*-alkylated 1,4-addition product (**233**). This *bis*-alkylated compound was not always isolated but it was almost always produced in 1 to 2% yield during the 1,4-addition reaction and it could be partially separated from the 1,4-addition/alkylation product (**232**) by preparative HPLC. This *bis*-alkylated compound must have been formed from the 1,4-addition/alkylation compound by the formation of the enolate followed by reaction with the electrophile (**218**) (Scheme 74). This process is similar to that proposed for the intramolecular cyclization leading to the bicyclic heptanone products as discussed in Scheme 71 above.



Scheme 74

The other compound often commonly observed during this 1,4-addition investigation was the non-alkylated 1,4-addition compound **(234)**. It is interesting to note that when this compound was not synthesised, the reactions were generally on a much larger scale than when the compound was synthesised. For the larger scale reactions, because the amount of reagents required for each reaction was so large, the reagents were commonly dried immediately prior to use. For the smaller scale reactions, it was common practice to use reagents that had been dried and then stored. This suggests that the non-alkylated 1,4-addition compound **(234)** was being produced because of moisture getting into reagents that had been dried and then stored.

Overall, the greatest yield obtained for the 1,4-addition compound **(232)** using the ethyl enone **(131)** was 31% compared with 44% achieved for the same 1,4-addition reaction using the methyl enone **(180)**. It was thought that the larger ethyl group caused an increased 1,3-diaxial interaction in the transition state and that this was responsible for the poorer yield (Figure 16).

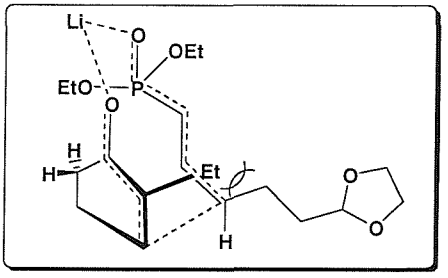
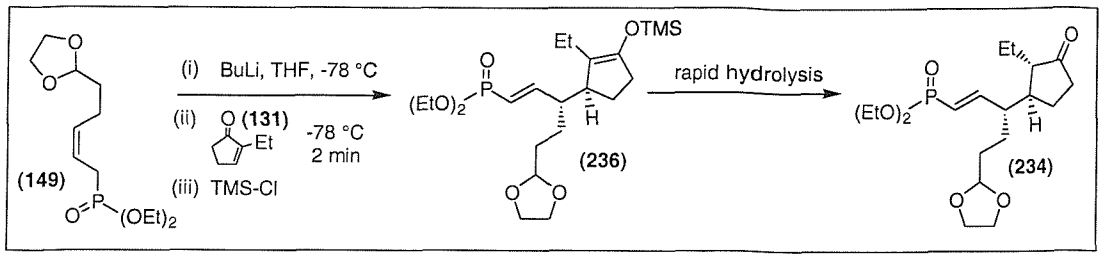


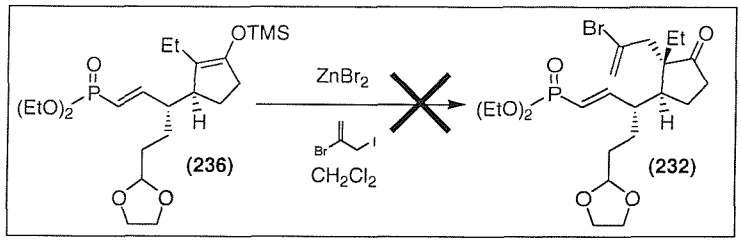
Figure 16

As an alternative to the alkylation of the enolate formed during the 1,4-addition reaction, attempts were made to trap the enolate as a silyl enol ether **(236)** (Scheme 75).



Scheme 75

TLC analysis suggested that the silyl enol ether **(236)** had been successfully synthesised but this compound was very labile, which meant that the isolation and characterization was not successful, even with carefully base-washed glassware. The compound isolated in these instances was the non-alkylated 1,4-addition product **(234)**. Despite the lability of this silyl enol ether, attempts were made to utilize this compound in order to obtain the alkylated 1,4-addition compound. These methods involved the use of zinc(II) bromide to form the metal enolate and then alkylation of this as shown in Scheme 76.

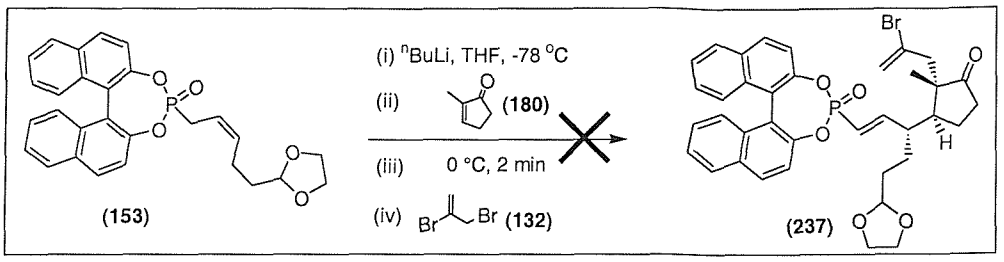


Scheme 76

The silyl enol ether used for these investigations was purified by basic column chromatography immediately prior to use or, in one instance, generated *in-situ*. These precautions did not appear to help however, as the only product to be isolated in all cases was the non-alkylated 1,4-addition product **(234)**.

3.9 1,4-Addition reactions with the BINOL derived phosphonate (153)

The 1,4-addition reaction with the BINOL phosphonate **(153)** (Scheme 77) was only investigated twice, but in both instances only base-line products were obtained. This was surprising because Fuji and co-workers[123] had reported a number of successful results using this type of compound, although their compounds were less complex.



Scheme 77

Work was not continued with the BINOL series of compounds because a lot of repetition of the 1,4-addition work was required at a time when it was more important to devote further studies towards the later steps in the synthesis towards desogestrel, even if it meant a racemic synthesis instead of an enantioselective synthesis would be the end result. If work were to return to this area then it would be worthwhile investigating the BINOL 1,4-addition with quenching of the enolate instead of alkylation. Although the reasons for this reaction failing are unclear, alkylation of the enolate complicates matters.

3.10 Summary

The 1,4-addition reaction has been investigated on a number of sulfoxide and phosphonate substrates. With a simple sulfoxide, the reaction was successful if the intermediate enolates were quenched with a proton source but it was found that if electrophiles were used, the 1,4-addition/alkylation products would be formed in conjunction with a bicyclic heptanone cyclization product. It was later observed that the intramolecular reaction leading to the bicyclic products could be avoided by using a 1,4-addition precursor with a *Z*-double bond. This was because the R-group on the double bond prevented the enolate from approaching the electrophilic site required for the intramolecular cyclization. Within the phosphonate series, the 1,4-addition/alkylation products from a *Z* and an *E*-allylic phosphonate were shown to have different stereochemistry and by comparison with the literature, this provided a strong indication that the proposed methodology would lead to steroid products with the desired stereochemistry. The ethyl enone **(131)** was also synthesised and used in 1,4-addition reactions. Although the yield was lower than with the analogous reactions using the methyl enone, up to 31% was possible which was acceptable considering the complexity of the product. Of all of the 1,4-addition/alkylation products synthesised, no diastereomeric mixtures were observed. This was an excellent finding because it meant that the

stereochemistry required for the steroid CD-*trans*-hydrindane system could be installed without the need for the separation of diastereoisomers.

Chapter 4, Steroid C and B-ring formation

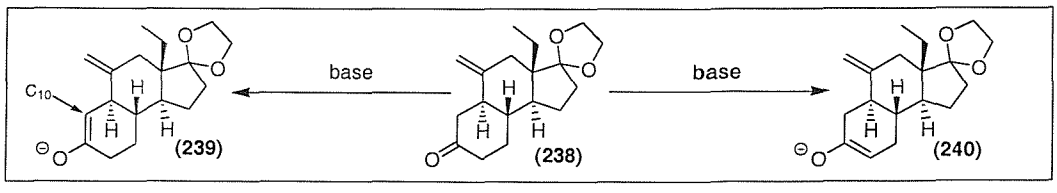
4.1 Introduction to the domino reaction

Domino reactions are defined by: "The process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step."[138] These type of reactions are not particularly rare, for instance, the biosynthesis of steroids from squalene oxide (section 1.1.2, page 2) is an example. The benefits of using domino reactions are both economic and ecological (reduced amounts of solvents, reagents, adsorbents and consequently waste).

Clearly, attempting to utilize a domino reaction in a total synthesis is only worthwhile if the reactions from the domino product to the target molecule do not involve an excessive number of steps that could be avoided if the domino reaction was not used. Towards the total synthesis of desogestrel this would not be the case, but clearly, the functional group requirements are different for both the phosphonate and sulfoxide series, therefore these are discussed below in different sections. In each case the domino reaction was expected to construct both the B and C-steroid rings in a single step operation.

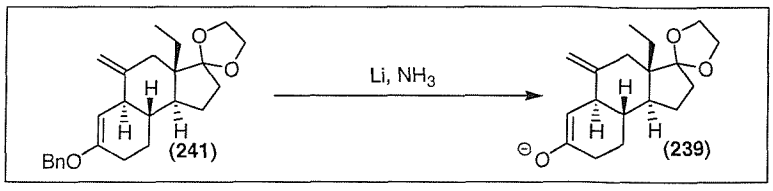
4.1.1 Phosphonate

From the phosphonate based domino product, the crucial reagent required for the construction of the A-ring was the enolate **(239)**, as this would lead exclusively to C_{10}-alkylated products. Clearly this enolate could not be synthesised cleanly from the ketone **(238)** since a mixture of the enolates **(239)** and **(240)** would be expected as shown in Scheme 78.



Scheme 78

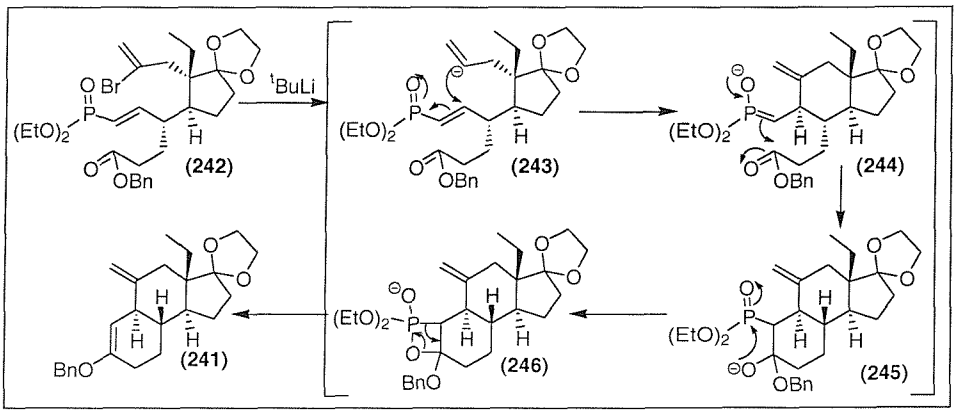
To circumvent this problem, a synthetic equivalent of the enolate **(239)** was required as the domino product, for which the benzyl enol ether **(241)** was considered (Scheme 79).



Scheme 79

A Birch type mechanism is employed in the deprotection of the benzyl ether and this leads exclusively to the enolate **(239)**.

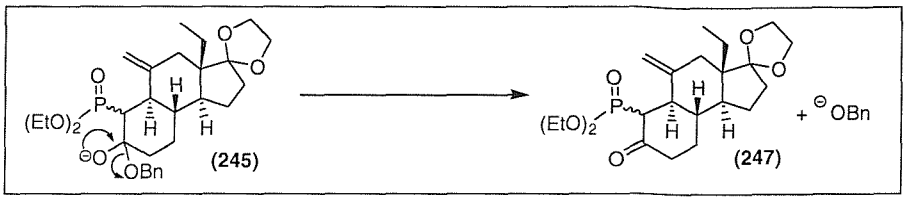
The domino route to the benzyl enol ether **(241)** comprising this benzyl group in the starting material is shown below in Scheme 80.



Scheme 80

Bromine-lithium exchange of the vinyl bromide **(242)** with ^{t}BuLi was expected to induce the intramolecular addition onto the α,β-unsaturated phosphonate, forming the C-ring. The anion **(244)** would then attack the carbonyl of the ester, forming the B-ring **(245)**. Intramolecular Horner-Wittig (IMHW) reactions on esters leading to enol ethers are precedented,[139-141] and it was expected that this would afford the tetracyclic product **(241)**.

An alternative reaction route from **(245)** could also be expected as shown in Scheme 81 below.

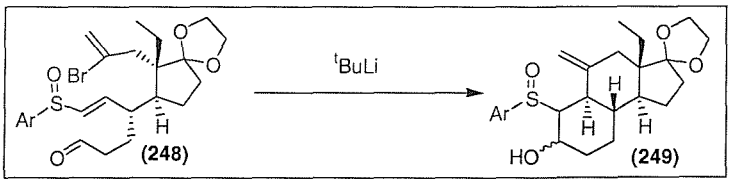


Scheme 81

Instead of undergoing the IMHW reaction, the oxyanion **(245)**, may simply reform the keto-group, eliminating benzoxide. This synthetic pathway is also precedented[142-145] and it was not clear which route the domino reaction would adopt. However, both the domino products **(241)** and **(247)** could lend themselves to the A-ring annulation with ease as discussed in chapter 5.1.2.1 (page 95), so this was not expected to impact upon the overall project.

4.1.2 Sulfoxide

The sulfoxide-based domino reaction was expected to be a simpler process than the phosphorus based analogue because with no HWE reaction possible, an extra functional group remains in the domino product. This can be seen in the proposed domino reaction in Scheme 82.



Scheme 82

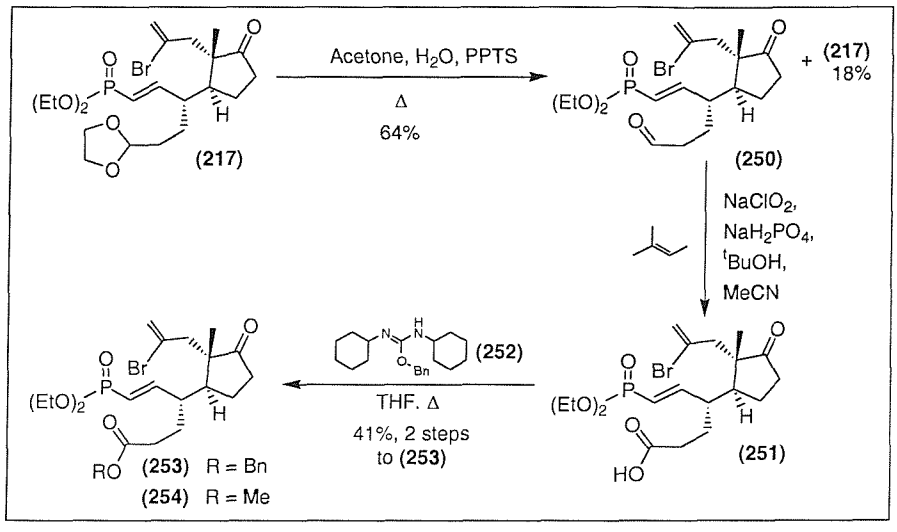
Following the domino reaction, the C_5-hydroxyl group in the domino product **(249)** was anticipated to be a useful handle on which to base the A-ring annulation reactions.

4.2 Synthesis of the phosphonate domino precursor

Initial experiments were executed using the 1,4-addition/alkylation adduct where 2-methylcyclopentenone was used as the enone.

4.2.1 Acetal to benzyl ester transformations

From the 1,4-addition product **(217)** (Scheme 83), a number of functional group transformations were required to form the domino precursor **(255)** (Scheme 84). As shown in Scheme 83, the acid **(251)** was formed by cleavage of the acetal **(217)** and subsequent oxidation of the resulting aldehyde **(250)**. The acid **(251)** was then benzylated to form the benzyl ester **(253)**.



Scheme 83

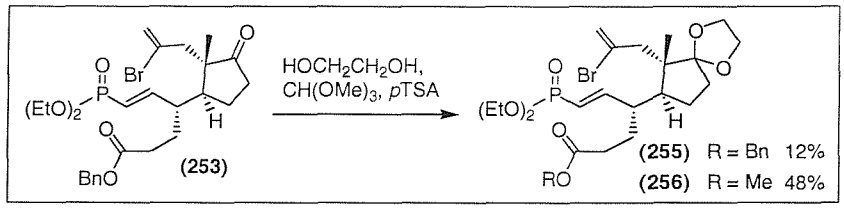
The best method found for the cleavage of the acetal in **(217)** was refluxing the compound with PPTS in wet acetone for 23 hours.[146] This afforded a 64% yield of the aldehyde **(250)** as well as 18% of the acetal starting material **(217)**. Unpredictably, extending the reaction time to 48 hours or reducing the reaction time to 2 hours resulted in a reduced amount of the aldehyde product (43% and 20% respectively). The remaining product in each case was the acetal starting material. Mixtures of the acetal **(217)** and the aldehyde **(250)** could be separated by preparative HPLC. Mineral acids were also investigated for this acetal cleavage but these reagents were found to be too harsh, as only complex mixtures of products were recovered. *p*TSA was investigated as a stronger acid catalyst alternative to PPTS, but after 5 days at reflux only 7% of the aldehyde was obtained with a 64% recovery of the acetal starting material. Patel and co-workers[147-149] have reported a one-pot procedure for the synthesis of esters from acetals using vanadium pentoxide with hydrogen peroxide in alcoholic media. This method was attempted twice in order to form both the benzyl ester

(**253**) and the methyl ester (**254**) but in both cases, the reaction failed and only the starting material was recovered.

After separation of the aldehyde (**250**) from the acetal (**217**), the aldehyde was smoothly oxidized to the acid (**251**) using sodium chlorite.[150,151] The benzylation was only investigated once for this compound and the benzyl-isourea (**252**) was used.[152-154] The yield over both steps was 41%. The poor yield was attributed to the poor quality of the isourea reagent that was used for the esterification.

4.2.2 C_{17}-ketone protection

The final step in the synthesis of the domino precursor required the protection of the C_{17}-ketone. Despite this being a common transformation, only one set of conditions returned acetal products. A multitude of acid catalysts[146,155-162] were investigated, using both Dean Stark apparatus or powdered activated molecular sieves to remove the water, all unsuccessfully. Equally unsuccessful were transacetalization conditions[163] and Noyori conditions.[164,165] The success came through the use of trimethylorthoformate[166] as an internal drying agent but these conditions also caused partial transesterification of the acetal products, affording both the benzyl ester product (**255**) and the methyl ester product (**256**) (Scheme 84).



Scheme 84

The major product isolated was the methyl ester (**256**) in 48% yield and the benzyl ester (**255**) was isolated in 12% yield. The transesterification reaction from (**255**) to (**256**) was possible because the methanol required to drive this reaction was produced as a by-product from trimethylorthoformate. It was thought that the benzyl ester (**255**) could be synthesised in better yield by substituting tribenzylorthoformate[167] for trimethylorthoformate, although this was not investigated for this substrate.

At the time of conducting this chemistry, the possibility of the domino reaction leading to the β-keto-phosphonate product ((**257**), Figure 17) had not been considered. For this reason, this reaction was considered a failure since it was believed that the benzyl ester was required for construction of the A-ring. Of course, if the β-keto-phosphonate product (**257**) were to be formed, it would not matter which ester was used.

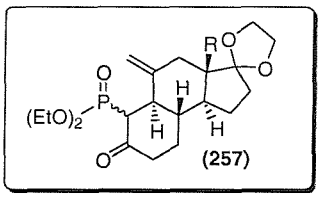


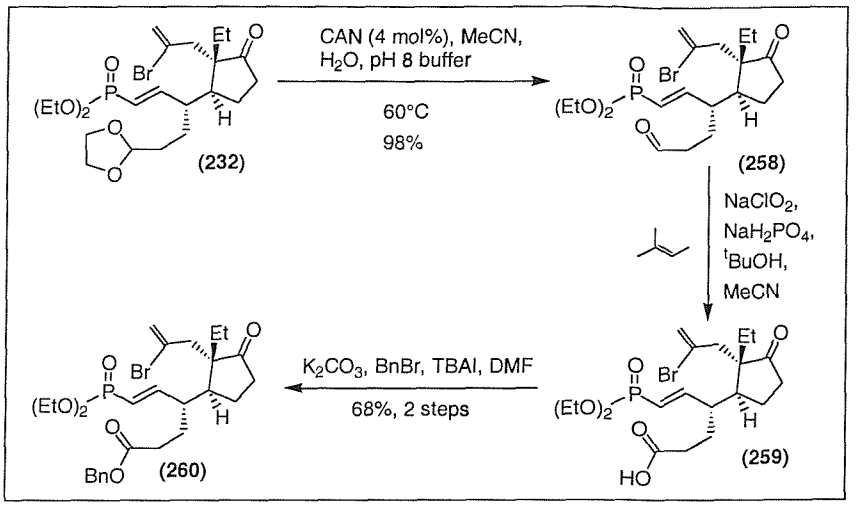
Figure 17

4.3 Synthesis of the phosphonate domino precursor

Further studies or optimization of results within the C_{13}-methyl series of compounds was discontinued because all of the material had been consumed. It was thought to be a better use of time to bring through more material with the C_{13}-ethyl group since this would allow progression towards desogestrel.

4.3.1 Acetal to benzyl ester transformations

The reagents and conditions used for the above acetal to ester conversion were employed for the acetal (**232**), but quite unsatisfactory results were obtained. Full optimization of this three step route afforded the benzyl ester product (**260**) in a considerably improved yield (Scheme 85).

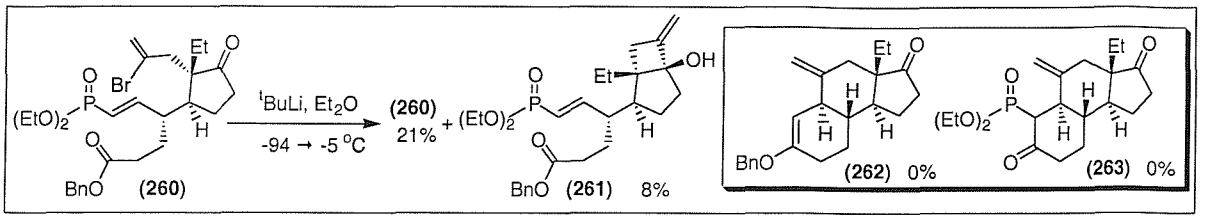


Scheme 85

The use of PPTS for the acetal cleavage as described above was investigated with **(232)** as the substrate, but this only afforded 41% of the aldehyde **(258)** and 36% of the recovered acetal starting material **(232)**. Wet butanone was investigated as an alternative solvent to acetone because this had a higher boiling point (80 °C) but this gave a near identical result (42%). A better result was achieved using iron(III) chloride hexahydrate in a refluxing CH_2Cl_2/acetone solvent system.[168] This method led to an improved yield of 51% but suffered from a long and involving work up due to the persistent iron salts. Finally, it was found that the best conditions for the acetal hydrolysis involved using cerium ammonium nitrate (CAN) as reported by Markó and co-workers.[169,170] The acetal was stirred in a buffered suspension (pH 8) of CAN in an acetonitrile/water solvent system at 60 °C until the reaction had gone to completion. The only drawback was that the reaction would often appear to have gone to completion as judged by TLC, but still have up to 10% of the acetal remaining. If this happened then the reaction could be repeated on the crude mixture without incurring any loss in the yield (up to 98% was possible). Sodium chlorite was employed for the oxidation of the aldehyde **(258)** to the acid **(259)** as described above. The benzyl isourea method was again employed for the benzylation reaction but this only afforded 49% of the benzyl ester **(260)**.[152-154] Other methods investigated included BnBr/NEt_3,[171] BnOH/DMAP with either DCC[172] or EDCI[173] and also BnBr/KF.$2H_2O$/tetrabutylammonium sulfate[174] but these all yielded the benzyl ester **(260)** in 50 to 58% yield. The best result of 68% was achieved using a DMF suspension of benzyl bromide, tetrabutylammonium iodide and potassium carbonate.[175] Hence, the overall yield for the three step sequence was improved from 26% (as obtained in section 4.2.1) to 67%.

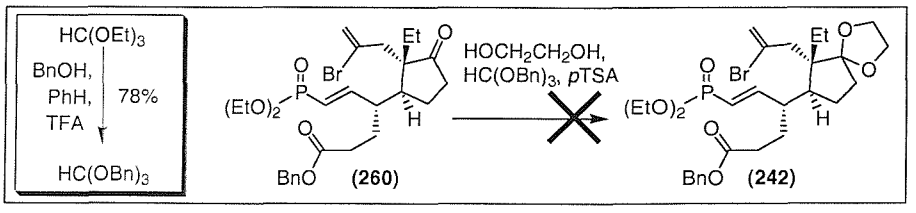
4.3.2 Attempted domino reaction

The domino reaction was initially attempted on the benzyl ester **(260)** (Scheme 86). This involved cooling an ether solution of the ester to ~−100 °C, treating this solution with 2.2 equivalents of ^{t}BuLi and finally allowing the reaction to warm slowly to ~0 °C.



Scheme 86

Six compounds were isolated form this reaction but unfortunately none of them were identified as the domino products **(262)** or **(263)**. Only two of the six products could be identified, the major one of which turned out to be the recovered benzyl ester starting material **(260)**, in 21% yield. The other compound identified was assigned the [3.2.0] bicyclic structure **(261)** based on NMR and MS data. This assignment was made following the identification of a similar compound in later studies. The formation of this compound is the result of bromine/lithium exchange with subsequent attack of the carbanion onto the ketone. The result appeared to indicate that the desired 6-exo C-ring cyclization was less favoured than the formation of the four-membered ring, hence C_{17}-ketone protection was necessary. The best method found earlier involved the use of an orthoformate drying agent. To avoid the earlier transesterification problems, tribenzylorthoformate was synthesised and used in place of trimethylorthoformate (Scheme 87).



Scheme 87

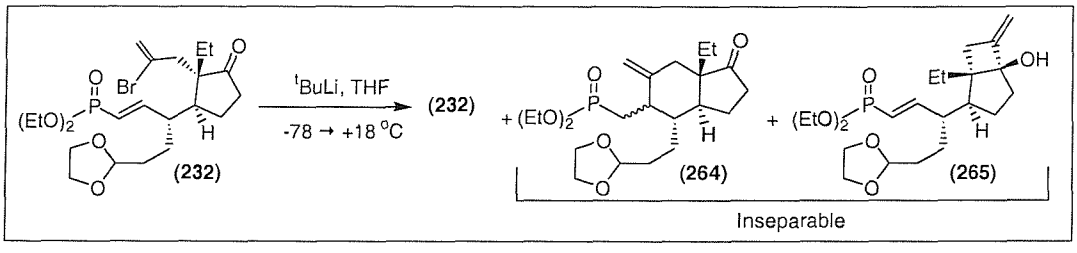
Tribenzylorthoformate was synthesised from triethylorthoformate in 78% yield.[167] The protection reaction did not work however. The only product to be recovered was the

starting material in 63%. Presumably the keto group was too sterically hindered for the reaction to take place.

4.4 C-ring formation

4.4.1 Initial cyclization reactions

As it was suspected that the C-ring cyclization would be a more difficult process than the B-ring formation, it was decided to concentrate on the first step of the domino cyclization. It was also decided to continue the investigation with the C_{17}-ketone unprotected. The 1,4-addition/alkylation product **(232)** was chosen as the starting material because it was appropriately functionalized and it was directly available. The initial investigation looked at the choice of base and the effect of a number of additives known to be salutary in halogen/metal exchange–intramolecular cyclizations.[176-184] The products are shown in Scheme 88 and the results are shown in Table 4.



Scheme 88

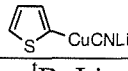
Entry	Base	Other reagent	Yield of recovered **(232)** (%)	Yield of **(264)** + **(265)** mixture (%)	Ratio of **(264)** : **(265)**
1	^{n}BuLi	–	95	–	–
2	^{n}BuLi§	–	93	–	–
3		–	96	–	–
4	^{t}BuLi	–	–	30	41 : 59
5	^{t}BuLi¶	–	–	35	40 : 60
6	^{t}BuLi	TMSCl	–	38	41 : 59
7	^{t}BuLi	CuI	–	30	24 : 76
8	^{t}BuLi	HMPA	19	48	24 : 76
9	^{t}BuLi	TMEDA	–	34	24 : 76

Table 4

§ = 2.2 equiv of ^{n}BuLi used. ¶ = −78 °C → +18 °C in one hour.

As shown above, the choice of the base was crucial for this reaction. If bromine/lithium exchange had occurred but no further reaction took place, then the product obtained after work up would be the allyl cyclopentanone (**266**) shown in Figure 18 below. This product was not isolated however, which means that both ^{n}BuLi and lithium 2-thienylcyanocuprate were not strong enough to initiate any reaction. The high yield of recovered starting material also suggested that no addition of ^{n}BuLi to the ketone or the unsaturated phosphonate took place.

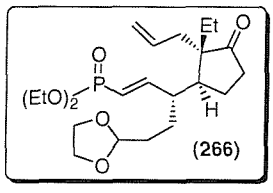
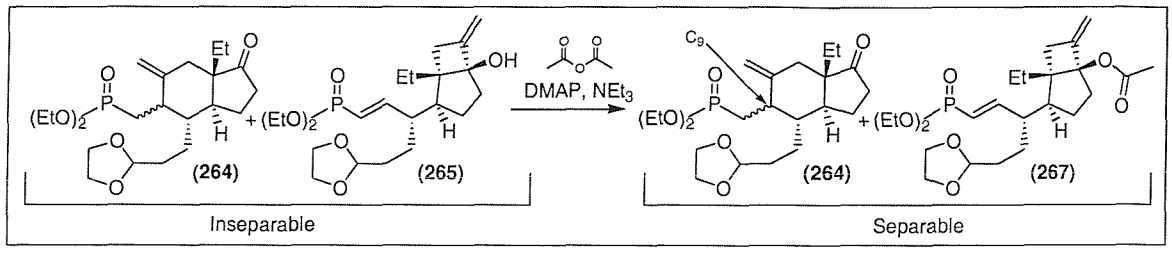


Figure 18

In contrast, ^{t}BuLi was able to promote this reaction as evidenced by the formation of both the desired *trans*-hydrindane compound (**264**) and the undesired bicyclo-[3.2.0]-heptane (**265**). Standard conditions for this reaction are represented by entry 4: ^{t}BuLi was added to a −78 °C THF solution of the phosphonate (**232**). After this addition the reaction was left in the cold bath to warm to room temperature slowly overnight. Conducting the reaction under these standard conditions afforded a 30% yield of a 41 : 59 inseparable mixture of (**264**) : (**265**). No other products were recovered, but a large amount of base-line material was removed during the chromatographic purification. Warming the reaction to room temperature over one hour improved the yield to 35% but did not influence the ratio of products obtained. Of the additives investigated, only TMSCl did not change the ratio of products obtained. Unfortunately all of the other additives gave even more of the undesired product (**265**). Of particular mention here is copper iodide. It was expected that the inclusion of this reagent would improve the soft addition onto the vinyl phosphonate (leading to (**264**)) but it appeared to have the opposite effect. Of the other additives tested, HMPA had the most impact, as this improved the yield from 30% to 48% and also afforded the recovery of 19% of the starting material. Interestingly, if the individual yields of products (**264**) and (**265**) are calculated based on the ratio of products obtained, entry 4 (control) afforded 12% of (**264**) and 18% of (**265**). If the same calculations are done for entry 8 (HMPA), (**264**) = 12% and (**265**) = 36%. Hence, 12% of the *trans*-hydrindane (**264**) was produced in both cases, indicating that HMPA had no influence during the formation of

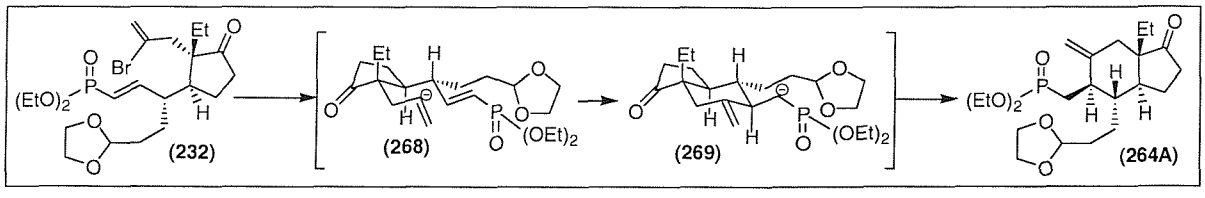
this reagent. The amount of the bicyclo-[3.2.0]-heptane **(265)** that was produced doubled when HMPA was used however.

The ratios of the *trans*-hydrindane compound **(264)** and the bicyclo-[3.2.0]-heptane **(265)** reported above were calculated from the ^{1}H and ^{31}P NMR spectra of mixtures of these compounds because they were inseparable by chromatography. Confirmation of the proposed structures was achieved by acylation of the mixture to afford the *trans*-hydrindane product **(264)** unchanged and the acetate **(267)**, which could then be separated by chromatography (Scheme 89).



Scheme 89

All of the above compounds were obtained as single diastereoisomers. Although the stereochemistry of **(264)** has not been proven, it is expected that the hydrogen atom on C_9 adopts the α-position, i.e. **(264A)** in Scheme 90. This configuration is expected because it would be obtained through the lowest energy transition state. Scheme 90 shows a three dimensional projection of this cyclisation including the expected transition state.



Scheme 90

Clearly, these results indicated that selective formation of the *trans*-hydrindane product was not a simple task. Therefore the key message from this investigation was that the C_{17}-ketone had to be protected for a successful cyclization reaction.

4.4.2 C_{17}-ketone protection

The first protecting group to be investigated for the C_{17}-ketone protection of **(232)** was the O,O-acetal. As mentioned in section 4.2.2, trimethylorthoformate/glycol/*p*TSA[166] had been used successfully to protect the C_{17}-ketone when the C_{13}-methyl was present, but these conditions did not work with the C_{13}-ethyl group. Conducting the same reaction in refluxing CH_2Cl_2 was also ineffective.[185] The more common conditions of using an acid catalyst in glycol with a Dean Stark separator[186] were also investigated on this substrate, but this only returned the starting material. Noyori conditions were also investigated using *in-situ* generated reagents[187] but this also returned only the starting material. It was extremely surprising to find that these reactions were all failing, especially because literature examples were being followed for compounds typical of the *trans*-hydrindane **(270)** in Figure 19, where the C_{13}-ethyl group was present.[30,47,50,51,58,185,188] It was suspected that the reduced rigidity of the 1,4-addition product **(232)** (Figure 20) compared with the *trans*-hydrindane system of **(270)** was responsible for the poor results.

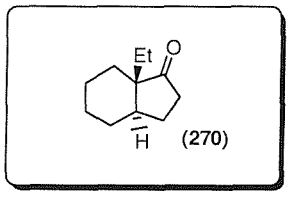


Figure 19

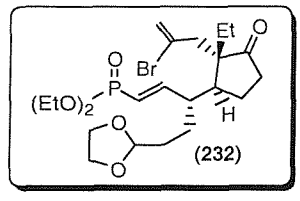
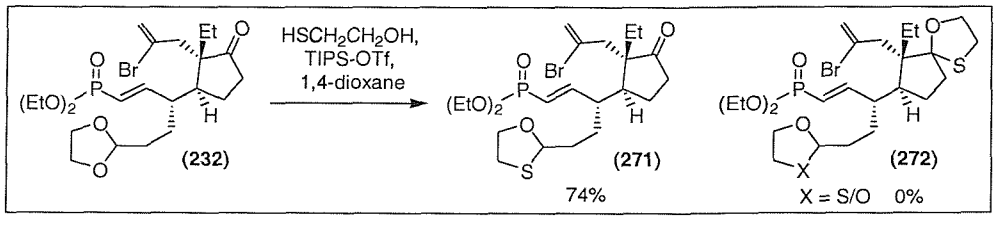


Figure 20

Protection of the ketone as an enamine was investigated but this was also unsuccessful, affording only the starting material.[189] A reaction did take place when 2-mercaptoethanol was used in an attempt to form the C_{17}-hemithioacetal,[190,191] but this was not a synthetically useful reaction; Instead of forming the C_{17}-hemithioacetal **(272)**, acetal exchange took place leading to the hemithioacetal product **(271)** in Scheme 91. **(271)** was obtained as a 1 : 1 mixture of diastereoisomers in 74% yield and no other products were produced.



Scheme 91

Different conditions for the S,O-mixed acetal formation did not influence the product obtained. Transacetalization conditions[192] with 2,2-dimethyl-1,3-oxathiolane[193] **(273)** (Figure 21) were investigated but this still gave 70% of the hemithioacetal **(271)** as well as 15% of the O,O-acetal starting material **(232)**.

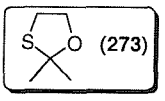
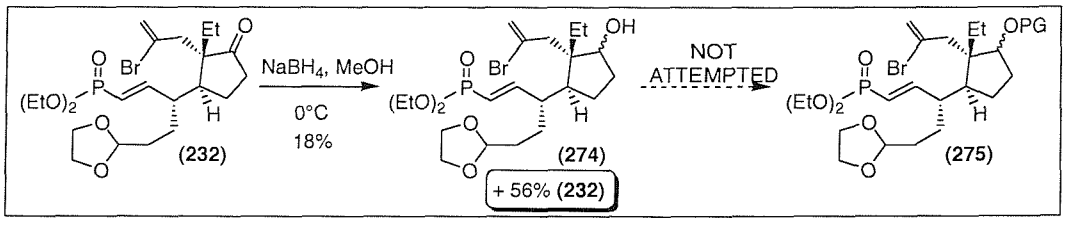


Figure 21

Protection of the ketone as either a hydrazone[194,195] or as a cyanohydrin[8,196] is well documented[197] but both of these functional groups would be suitable electrophiles for a cyclization to take place, and hence were not considered.

As an alternative to a direct protection, the reduction of the ketone to the alcohol was considered (Scheme 92). The alcohol could then be protected with a number of protecting groups.

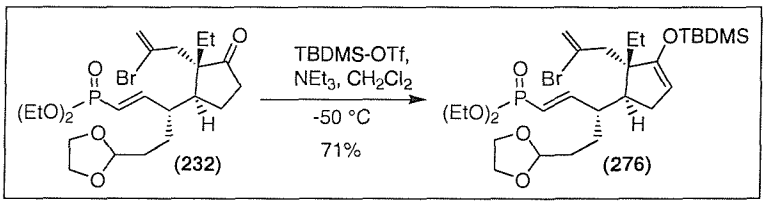


Scheme 92

Sodium borohydride was considered to be the reagent of choice for the reduction of steroidal C_{17}-ketones.[198-200] Whereas the reaction should have been complete within a few hours at 0 °C, TLC indicated that the reaction was incomplete. Extra time, heat and more sodium borohydride did not drive the reaction to completion. Once the reaction was worked up, it was found that 18% of the alcohol **(274)** had been synthesised and this existed as a mixture of diastereoisomers. 56% of the ketone starting material was also recovered. LAH was investigated as a stronger reducing agent[201,202] but this led to decomposition of the starting material.

4.4.3 Protection of the C_{17}-ketone as a silyl enol ether

Another method of ketone protection involved forming the silyl enol ether. Conducting the reaction under standard conditions for TMS enol ether formation (TMS-OTf/NEt_3/CH_2Cl_2, 0 °C)[189,203] only returned the starting ketone in 57% yield. Given the relatively high lability of TMS enol ethers, the protection of the C_{17}-ketone was attempted as a TBDMS enol ether using TBDMS-OTf.[204] However, no silyl enol ether product was obtained and an even worse yield of recovered starting material was obtained (31%). The poor yield of recovered starting material suggested that the reaction conditions were too harsh. To investigate this eventuality, the reaction was repeated at −50 °C. After 1 hour the reaction was worked up and purified by column chromatography using pre-neutralized silica gel. These conditions afforded the silyl enol ether product (**276**) in 62% yield. Increasing the concentration from 0.18 M to 0.28 M increased the yield to 71%.



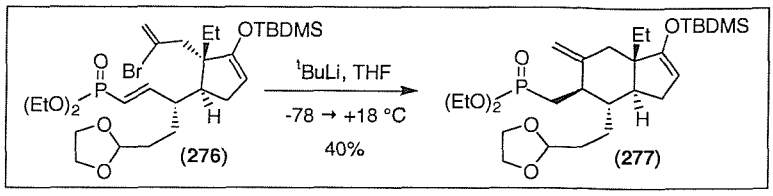
Scheme 93

Although yields of around 70% were obtained for most attempts of this reaction, extremely low yields (<10%) were obtained if the reaction was attempted on impure starting material. This was disappointing because, had it been successful, the lengthy and involving preparative HPLC purification of the 1,4-addition product would no longer have been required.

Having obtained the C_{17}-protected 1,4-addition compound, the C-ring cyclization was investigated once more.

4.4.4 C-ring formation

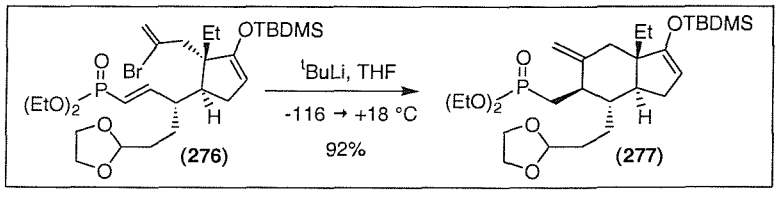
Immediately the results were encouraging. The very first attempt used the same control conditions as in section 4.4.1 (page 83) returned the desired cyclized product (**277**) as the only product and in 40% yield.



Scheme 94

The yield for this reaction was still fairly low. This was thought to have been because of the high reactivity of the ^{t}BuLi. To achieve more control over this reagent, the temperature of the phosphonate solution was lowered to −100 °C (MeOH/liquid N_2) and the reaction was repeated. Immediately the yield went up to 60%. Also investigated was the amount of time the reaction was given to warm from low temperature: The ^{t}BuLi addition was conducted at −100 °C, after which, the reaction was placed in a 0 °C cold bath for one hour. After purification, a total of 58% of *trans*-hydrindane products[▪] were obtained, almost identical to the previous experiment. Because the yields were virtually the same, it was concluded that the amount of time the reaction had to warm from low temperature was not an important factor.

Lowering the temperature of the reaction from −78 °C to −100 °C had led to a marked increase in the yield, it therefore seemed a logical to choice to try an even lower temperature. By forming an ethanol/liquid N_2 slurry, a temperature of −116 °C was achieved[205] and the reaction was repeated at this temperature. Occasionally the reaction mixture would become frozen at this temperature, in which case it had to be removed from the cold bath and stirred until homogeneous. The reaction could then be replaced into the cool bath and the ^{t}BuLi addition continued. This procedure could be used without incurring any problems or even a loss in the yield of products obtained.



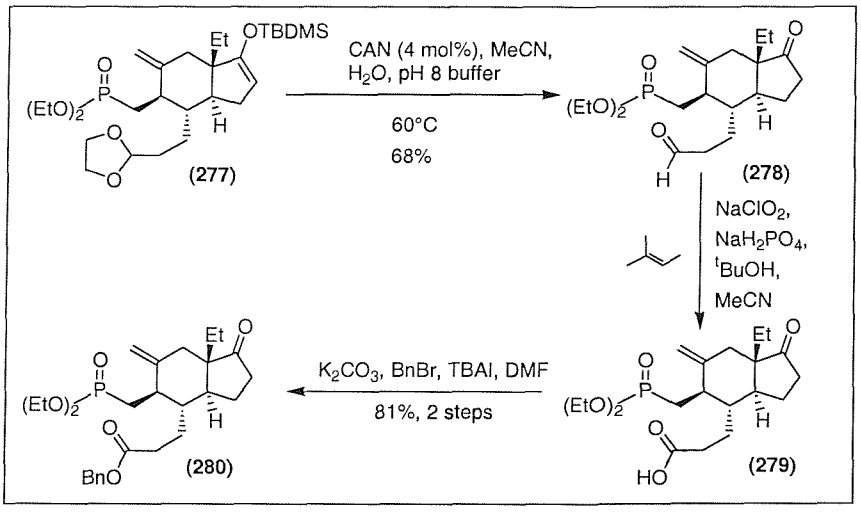
Scheme 95

▪ During this work up, the reaction mixture was treated with a quick acid wash. This caused some of the silyl enol ether to hydrolyse back to the ketone, but both products were isolated and the individual yields were combined.

On a small scale (0.34 mmol) a yield of 71% was obtained, but on a larger scale (2.00 mmol) both yields of 91 and 92% were obtained. In all three cases only one product was obtained and as a single diastereoisomer. This result was obviously of great importance, and was hoped would pave the way for a successful domino process.

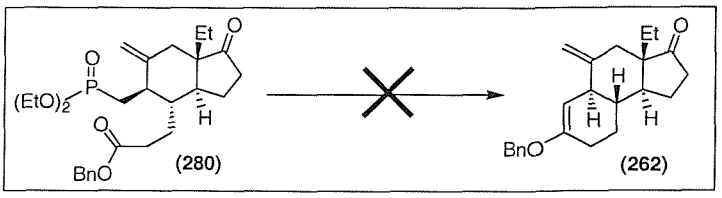
4.5 Attempted B-ring cyclizations starting from (277)

Although the domino process was the ideal goal, it seemed pertinent to attempt the B-ring cyclization as a separate operation from the C-ring cyclization. Hence, the acetal was hydrolysed under Marko's conditions[169,170] as discussed above. The silyl enol ether did not survive these conditions as expected, and the dicarbonyl compound **(278)** was obtained in 68% yield. The aldehyde **(278)** was oxidized to the acid **(279)** using the sodium chlorite conditions as discussed above.[150,151] The benzylation of the acid worked extremely well, affording the B-ring precursor **(280)** in 81% yield from the aldehyde **(278)**.



Scheme 96

The intramolecular Horner-Wittig (IMHW) reaction on **(280)** was attempted with a variety of bases and under a range of conditions but this cyclization could not be realized.



Scheme 97

DIPEA, sodium hydride (–40 °C) and the monomeric phosphazene base BEMP all returned the starting material in 75 to 99% yield. Sodium methoxide did not give the B-ring cyclized product nor return the starting material but caused transesterification, leading to the methyl ester (**281**) (Figure 22). The use of stronger bases such as LDA and ^{t}BuOK or using more forcing condition such as sodium hydride at room temperature all caused the destruction of the starting material and did not afford any recognizable products.

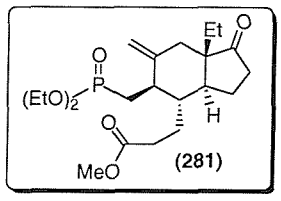
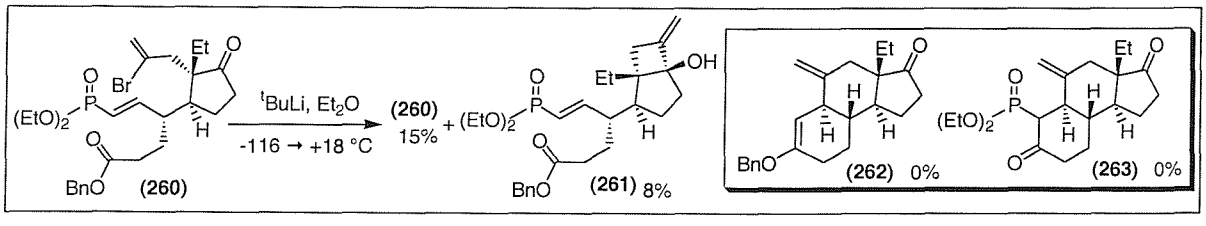


Figure 22

There are literature examples for similar IMHW reactions,[139-141,206] however all involved β-keto phosphonates. Despite the failure for the B-ring cyclization to take place starting from (**280**), it was anticipated that this transformation still could be successful as part of a domino process, as the C-ring cyclization gives rise to a deprotonated phosphonate, which would be able to react with the ester group.

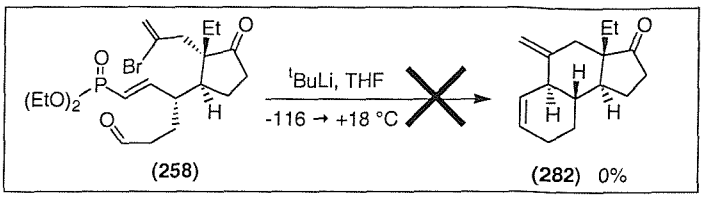
4.6 Attempted domino reactions

The domino cyclization was attempted again with (**260**) as the substrate, but using the optimized C-ring cyclization conditions. However, only the bicyclo-[3.2.0]-heptanone product (**261**) and the starting material were returned, paralleling the result found earlier (section 4.3.2, page 82).



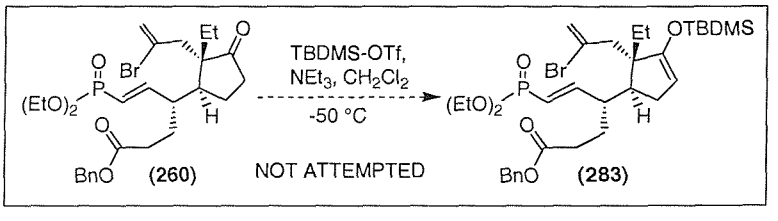
Scheme 98

The reaction was repeated using the aldehyde (**258**) as the domino precursor. It was hoped that this less complex substrate would simplify the domino process and enable further development of the reaction.



Scheme 99

This domino reaction also failed. On both attempts the products isolated could not be identified. This was a disappointing end to this series of work. It appears that the best way of proceeding from this point in the series is to obtain a compound with the benzyl ester already in place and with the C_{17}-keto group protected. A potential compound could be the silyl enol ether **(283)** (Scheme 100).

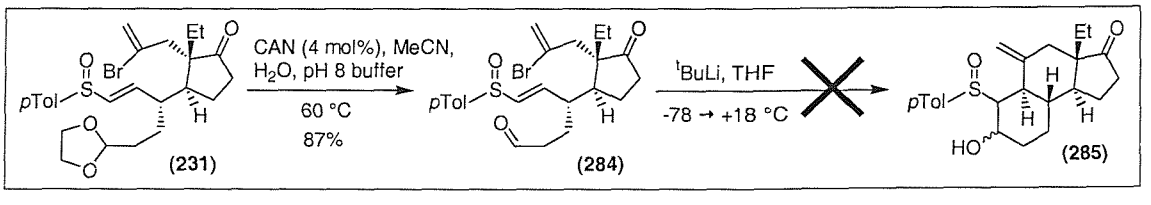


Scheme 100

The chemoselective protection of a ketone in the presence of an ester is precedented,[204] but this was not attempted for the domino precursor **(260)**.

4.7 Sulfoxide domino reaction

From the sulfoxide 1,4-addition compound **(231)**, the acetal was hydrolysed using Marko's conditions as described above.[169,170] The aldehyde **(284)** in the sulfoxide series was a suitable domino precursor because the residual 5-hydroxyl group would have been a sufficient handle for A-ring construction.



Scheme 101

The acetal cleavage with CAN worked extremely well, affording the aldehyde (**284**) in 87% yield. The domino reaction was attempted on the aldehyde, but once again, only non-identifiable products were isolated.

4.8 Summary

The three-step conversion of the 1,4-addition/alkylation product to the domino cyclization precursor was successfully achieved in high yield. The domino cyclization as described in the project plan was not realized. Whilst the exact reason is still unclear, it is clear that the unprotected C_{17}-ketone is detrimental for the reaction. The C-ring cyclization was investigated separately and again, the conclusion was that the C_{17}-ketone had to be protected. A suitable protecting group was found and conditions were found that led successfully to the C-ring cyclized product. An attempt to achieve the B-ring closure from the C-ring cyclized product was unsuccessful.

Chapter 5, Future directions of the research

5.1 Short term

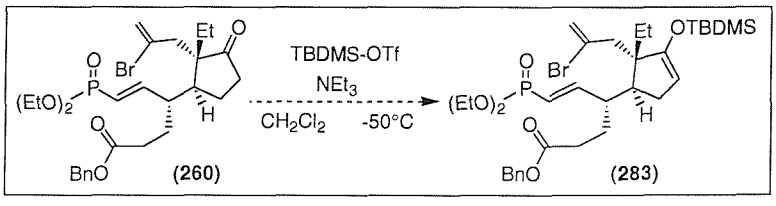
The primary objective for future work within this project is to complete the synthesis of racemic desogestrel. This comprises two key sections:

1. Completion of the domino investigation and
2. Construction of the A-ring.

5.1.1 Completion of the domino investigation

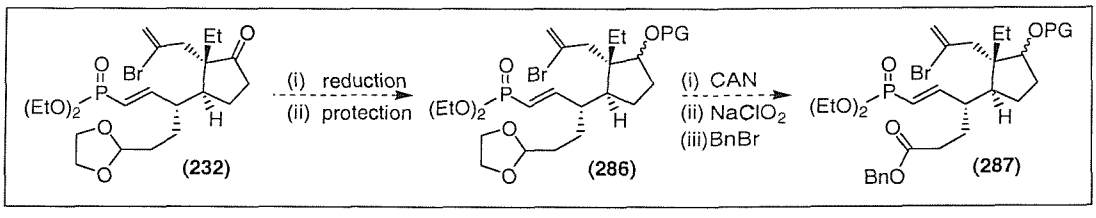
5.1.1.1 Phosphonate

As mentioned in chapter 4, the key compound required for future domino reactions is the C_{17}-protected domino precursor (**283**). Following the precedent of Mander and Sethi,[204] the chemoselective protection of the ketone in the presence of the ester should be straightforward (Scheme 102).



Scheme 102

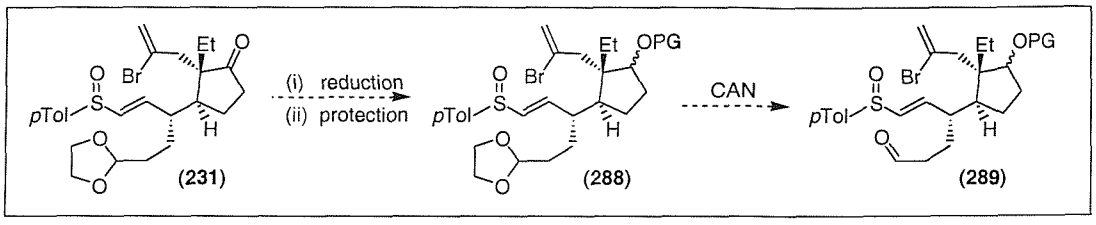
Should this reaction prove problematic, a more detailed investigation into the reduction of the C_{17}-carbonyl group should enable the synthesis of the C_{17}-alcohol. Subsequent protection of this group followed by the conversion of the acetal into the benzyl ester would lead to the domino precursor (**287**) (Scheme 103).



Scheme 103

5.1.1.2 Sulfoxide

The key compound for the domino reactions in the sulfoxide series would require the C_{17} group protected and have the aldehyde at C_5. Perhaps the simplest way to synthesise a compound of this type, and analogous to the scheme above, would be to reduce the C_{17}-carbonyl, protect the alcohol and then deprotect the aldehyde, affording **(289)** (Scheme 104).



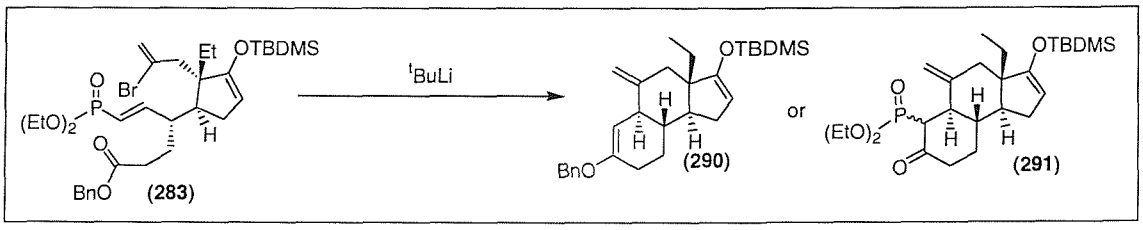
Scheme 104

Work would be required in order to optimize the reduction of C_{17}-carbonyl groups in both of the phosphonate and sulfoxide cases. The protection of the C_{17}-alcohol should be straightforward in both cases, as would the subsequent conversion of the acetals **(286)** and **(288)** into the corresponding domino precursors **(287)** and **(289)**.

5.1.2 Construction of the A-ring

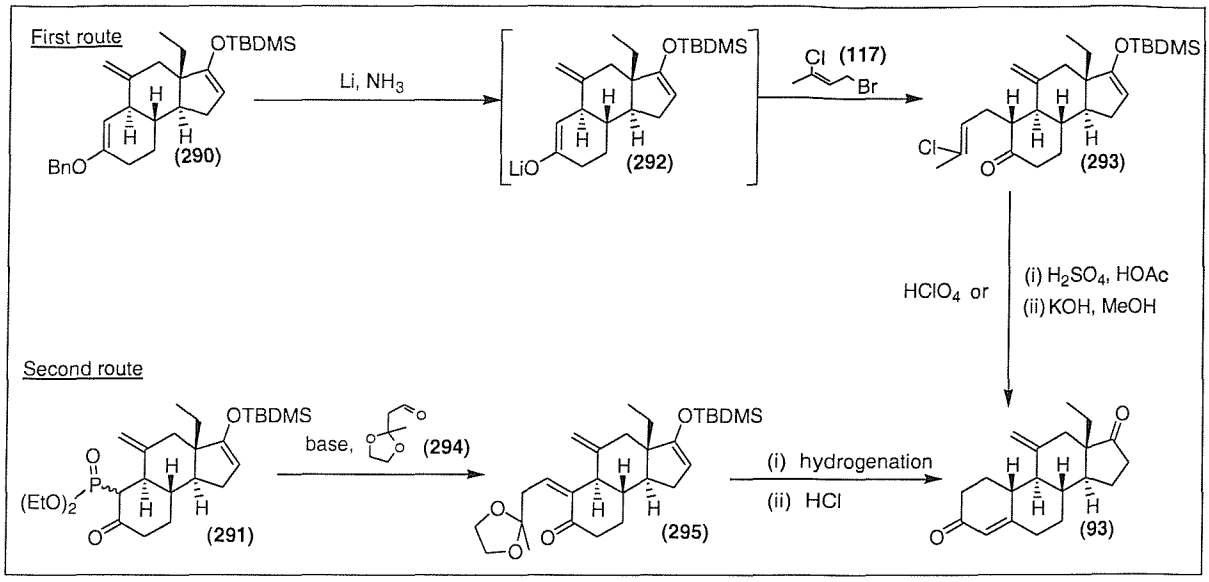
5.1.2.1 Phosphonate

As discussed in chapter 4, the Domino reaction could proceed via two different pathways, leading to either **(290)** or **(291)** or a mixture of both (Scheme 105).



Scheme 105

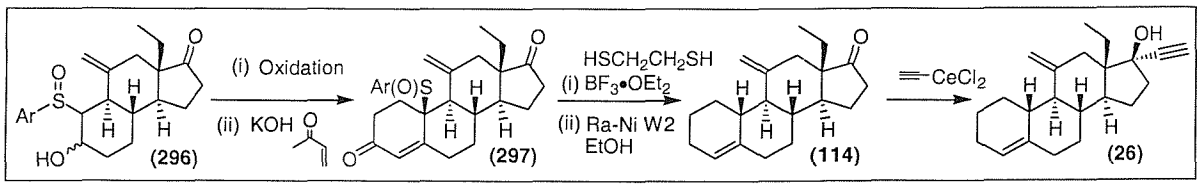
Both of the above potential domino products could lend themselves to the A-ring construction as shown in Scheme 106. The second route also has the advantage that any ester group including benzyl should be tolerated in the domino precursor.



Scheme 106

From the enolate (**292**), alkylation with 1-bromo-3-chlorobut-2-ene (**117**) is known to install the A-ring framework with the C_{10}-β-hydrogen.[61-63,207] The A-ring cyclization has been reported to proceed in one step using perchloric acid[208] but the alternative two-step procedure of acid hydrolysis followed by base-catalysed aldol/dehydration should also lead to the diketone (**93**).[209-211] Alternatively, the HWE reaction of (**291**) with the aldehyde (**294**) should lead to the enone (**295**). This route would not depend on the stereochemistry of the C_{10}-phosphonate group in (**291**). From (**295**), the hydrogenation of the enone followed by acid mediated aldol/dehydration should also lead to the diketone (**93**).[39] Completion of the desogestrel synthesis from (**93**) has been discussed in section 1.4.5, page 28.

5.1.2.2 Sulfoxide



Scheme 107

From the domino sulfoxide product (**296**), the C_5-hydroxyl group could be chemoselectively oxidized to the ketone[212,213] and subsequent Robinson annulation[214] with methyl vinyl ketone would lead to the steroid (**297**) with the 10β-sulfoxide configuration.[61-63,207] The enone could be selectively protected as the thioacetal. Subsequent treatment of this product with Raney nickel (W2) would remove the thioacetal group and it would also cleave the sulfoxide group with retention of configuration (**114**).[215] Desogestrel (**26**) would then be obtained by introducing the C_{17}-α-ethinyl group.[26,33,34,47]

5.2 Medium term

Once racemic desogestrel had been prepared via this methodology, the next aim would be to make the synthesis enantioselective using one of the known auxiliaries for the 1,4-addition reaction. Some examples are given in Figure 23.

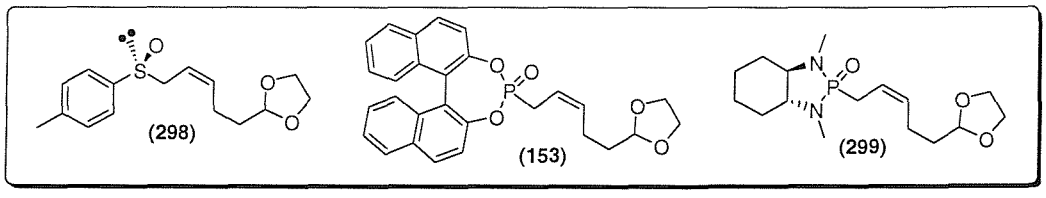


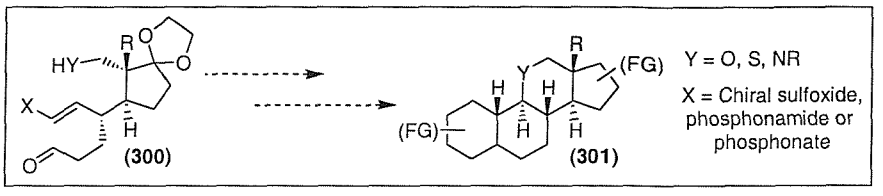
Figure 23

The sulfoxide (**298**) could be prepared via an enantioselective oxidation of the corresponding sulfide.[216,217] The synthesis of the phosphonate (**153**) has already been described in section 2.5, page 40. The synthesis of the homochiral version of this compound could be achieved using homochiral BINOL.[218-221] Hanessian and co-workers have devoted much of their time towards the synthesis and use of homochiral phosphonamides of the type illustrated by (**299**).[222-224]

5.3 Long term

Should this steroid synthesis methodology prove successful for the synthesis of desogestrel, it could be used to make other steroids, both known and new. Simple modifications include changing the ethyl group at C_{13} or changing the exocyclic methylene group at C_{11}. Both of these modifications are not simple transformations within existing steroidal syntheses.

Additionally, this methodology could also lend itself towards the synthesis of steroids containing a heteroatom at the 11 position. It is known that incorporation of heteroatoms at the 11 position leads to steroids with interesting biological properties and, to-date, all these steroids are made through hemi-syntheses via C-ring opening reactions.[225-227] Since heteroatom conjugate addition to α,β-unsaturated sulfoxides is known,[228,229] steroids such as **(301)** should be accessible via the proposed synthetic route (Scheme 108).



Scheme 108

Chapter 6, Overall summary

Despite not completing the synthesis towards desogestrel, many problems have been solved along the way and the stage is certainly set for the completion of this project. Successes include:

- The development of efficient syntheses of achiral phosphonate and sulfoxide 1,4-addition precursors.
- Utilization of a 1,4-addition/alkylation sequence to synthesise complex products with three controllable chiral centres.
- Prevention of an unwanted intramolecular cyclization through identification and resolution of the responsible factor.
- Optimization of an efficient route for the transformation of terminal acetal groups into the corresponding benzyl esters.
- The use of a silyl enol ether as a ketone protecting group.
- Optimization of the C-ring cyclization to afford products as single diastereoisomers in up to 92% yield.

As with any new research project, the background is always theoretically sound but problems do arise. Areas where there is scope for improvement within this project include:

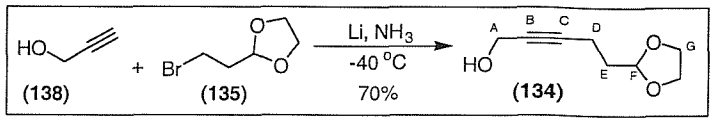
- The BINOL 1,4-addition reaction.
- The poor yield associated with the 1,4-addition reaction when using the ethyl cyclopentenone.
- Protection of the C_{17}-ketone as an acetal.
- Domino reactions.

Despite these problem areas, the project is still exciting and has good future prospects in both the shorter and longer terms.

Chapter 7, Experimental

Thin-layer chromatography was conducted on Macherey-Nagel 0.25 mm silica glass sheets, SIL G-25 UV_{254}. Melting points were carried out on a Gallenkamp melting point apparatus and are uncorrected. IR measurements were conducted on a Nicolet impact 400 ATR spectrometer using NaCl plates. ^{1}H NMR spectra, ^{13}C NMR spectra and ^{31}P spectra were recorded at 300, 75 and 121 MHz respectively in $CDCl_3$ at room temperature unless otherwise stated, on either a Bruker AM300 or Bruker AC300. Any 400 MHz ^{1}H or 100 MHz ^{13}C spectra were recorded on a Bruker DPX 400. ^{1}H spectra conducted in $CDCl_3$ are referenced to $CHCl_3$ as 7.27 ppm (or $(CH_3)_2CO$ as 2.17 ppm if $CHCl_3$ peak is not clear). ^{1}H spectra conducted in $(CD_3)_2CO$ are referenced to $(CH_3)_2CO$ as 2.05 ppm. ^{13}C spectra conducted in $CDCl_3$ are referenced to $CHCl_3$ as 77.00 ppm and ^{13}C spectra conducted in $(CD_3)_2CO$ are referenced to $(CH_3)_2CO$ as 206.26 ppm. ^{31}P spectra are externally referenced to 85% H_3PO_4. Where assignments of atoms have been made in the NMR data, this is determined by the use of $^{13}C^{1}H$ correlation (HMQC) and/or $^{1}H^{1}H$ correlation (COSY) NMR experiments. Q refers to a quaternary carbon centre. Mass spectrometry was performed using ES, EI or CI ionisation techniques. For dry solvents, pyridine was double distilled from calcium hydride and stored in a Schlenk flask. DMSO and HMPA were distilled from calcium hydride under reduced pressure and stored over molecular sieves. All other dry solvents for reactions were freshly distilled prior to use: THF and Et_2O were distilled from sodium with benzophenone as an internal indicator. Toluene was distilled from sodium. MeOH and EtOH were distilled from magnesium powder. CH_2Cl_2, NEt_3, DIPEA, hexane and 1,4-dioxane were distilled from calcium hydride. Preparative HPLC was performed using a Kontron pump PU38 set at 20 ml min^{-1} with a Kontron refractive index detector 475. The microwave reactions were conducted in a SmithSynthesiser operating at variable power (max 300 W) to maintain the pre-programmed temperature. All reaction vessels were oven dried overnight or flame dried under vacuum (<1 mmHg) and cooled under nitrogen prior to use. All column chromatography was conducted using Apollo silica gel (0.035–0.070 mm) as the solid phase unless otherwise stated.

5-(1,3-Dioxolan-2-yl)pent-2-yn-1-ol (134)



This is a known compound[73] but was synthesised here via a new procedure:
Into a 3 L, 3-neck flask equipped a large cold finger trap was condensed ammonia (1.5 L). An external cold bath (–78 °C) was used to aid the condensation, but throughout the reaction the temperature of this cold bath was maintained between –30 and –40 °C. To the ammonia was added granular lithium (~50 mg) and the reaction was stirred until a homogeneous blue solution was obtained (15 min). To this solution was added iron(III) nitrate nonahydrate (~200 mg), then lithium (3.03 g, 436 mmol, 3.2 equiv) was added portionwise over 30 min. The grey solution was stirred for 1 h at –40 °C. To this solution was added propargyl alcohol **(138)** (11.90 mL, 204 mmol, 1.5 equiv) dropwise over 15 min and stirring was continued for a further 2 h. The bromide **(135)** (16.0 ml, 136 mmol, 1.0 equiv) was dissolved in dry Et_2O (30 mL) and added to the reaction dropwise via cannula over 30 min. The mixture was stirred for 2 h then dry DMSO (30 mL) was added slowly. The cold bath was removed and the ammonia was allowed to evaporate overnight (atmospheric pressure). Water (500 mL) was added, cautiously at first, followed by CH_2Cl_2 (300 mL) and the biphasic mixture was stirred vigerously for 30 min. The biphasic solution was filtered directly into a 2 L separation funnel through celite, washing through with both water (250 mL) and CH_2Cl_2 (250 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/acetone 2 : 1). This yielded **(134)** as a yellow oil (14.9 g, 70%). On a small scale the product was purified by Kugelrohr distillation (210 °C/3 mmHg, Lit[73] = 85 °C/0.1 mmHg).

Mw = 156.184 ($C_8H_{12}O_3$).
$\mathbf{R_f}$ = 0.27 (Hexane/acetone 5 : 2).
IR (film): 3436 (br, w), 2950 (w), 2880 (w), 2207 (w), 1412 (m), 1139 (s), 1020 (s), 895 (m) cm^{-1}.

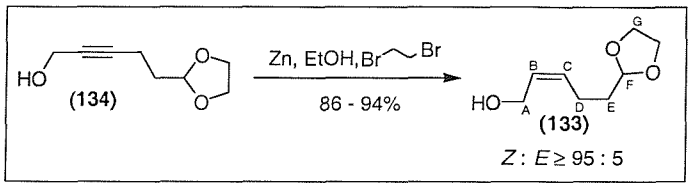
^{1}H NMR (400 MHz; $CDCl_3$): δ 4.97 (1H, t, J = 4.6 Hz, H_F); 4.24 (2H, t, J = 2.2 Hz, H_A); 3.99–3.85 (4H, m, H_G); 2.37 (2H, tt, J = 7.5, 2.2 Hz, H_D); 1.88 (2H, td, J = 7.5, 4.6 Hz, H_E) ppm.

^{13}C NMR + DEPT (75 MHz; $CDCl_3$): δ 103.1 (CH, C_F), 85.1 (Q, $C_{B/C}$), 78.6 (Q, $C_{C/B}$), 64.9 (CH_2, 2 × C_G), 51.1 (CH_2, C_A), 32.6 (CH_2, C_E), 13.5 (CH_2, C_D) ppm.

CIMS: *m/z* (%): 174 ($(M+NH_4)^+$, 75), 157 ($(M+H)^+$, 19), 139 (73), 112 (17), 73 (100).

The IR, ^{1}H NMR and MS spectra correspond to the reported data.[73]

5-(1,3-Dioxolan-2-yl)-2-(Z)-penten-1-ol (133)



This is a known compound[76] but was obtained via a procedure based on the method used by Aerssens and Brandsma:[85]

Into a 250 mL 2-neck flask equipped with a condenser was added Zinc (24.78 g, 379 mmol, 4.0 equiv) followed by EtOH (30 mL) and 1,2-dibromoethane (2.86 mL, 33.17 mmol, 0.35 equiv). The slurry was stirred and placed into a preheated oil bath at 100 °C until ethane evolution began. CAUTION, ethane evolves rapidly, ensure heat source is removed as soon as reaction begins and there is adequate pressure release. Once the ethane evolution was complete (~5 min), the alkyne **(134)** (14.8 g, 94.76 mmol, 1.0 equiv) was added neat, washing through with EtOH (5 mL). The reaction was then refluxed for 3 h (check by TLC in hexane/EtOAc 1 : 1), cooled and filtered through celite, washing with EtOH. The solvent was evaporated *in vacuo* and then CH_2Cl_2 (400 mL) was added. This solution was poured onto a room temperature, stirred solution of 7.5% (w/w) aqueous KOH and stirred for 5 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated. This yielded **(133)** as a light yellow oil (13.7 g, 91%). E : Z ratio = 5 : 95.

Mw = 158.200 ($C_8H_{14}O_3$).

R_f = 0.29 (Hexane/EtOAc 1 : 1).

IR (film): 3394 (br, m), 2956 (m), 2884 (m), 1649 (w), 1403 (m), 1134 (s), 1029 (s), 945 (m) cm^{-1}.

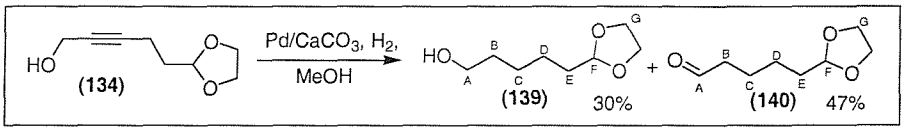
^{1}H NMR (300 MHz; $CDCl_3$): δ 5.74–5.52 (2H, m, H_B + H_C); 4.89 (1H, t, J = 4.9 Hz, H_F); 4.20 (2H, d, J = 6.8 Hz, H_A); 4.01–3.84 (4H, m, H_G); 2.26 (2H, q, J = 7.6 Hz, H_D); 1.75 (2H, td, J = 7.6, 4.9 Hz, H_E); 1.62 (1H, s, OH) ppm.

^{13}C NMR + DEPT (75 MHz; $CDCl_3$): δ 131.3 (CH, $C_{B/C}$), 129.1 (CH, $C_{B/C}$), 103.7 (CH, C_F), 64.7 (CH_2, 2 × C_G), 57.9 (CH_2, C_A), 33.2 (CH_2, C_E), 21.8 (CH_2, C_D) ppm.

CIMS: *m/z* (%): 159 ($(M+H)^+$, 6), 141 (100), 114 (70), 97 (89), 73 (88).

The IR, ^{1}H NMR, ^{13}C NMR and MS spectra correspond to the reported data.[76]

5-(1,3-Dioxolan-2-yl)pentan-1-ol (139) and **5-(1,3-Dioxolan-2-yl)pentanal (140)**



These are both known compounds but were obtained here via a new procedure:

Into a 2-neck 10 mL round bottom flask was placed Lindlar's catalyst (5% Pd on calcium carbonate) (68 mg, 0.03 mmol, 5 mol%). The atmosphere was reduced under vacuum and flushed with hydrogen twice. The alkyne **(134)** (100 mg, 0.64 mmol, 1 equiv) was then added as a THF solution (3 mL) via syringe and the atmosphere was flushed twice with hydrogen as above. The dark brown suspension was stirred under a hydrogen balloon at room temperature for 6.5 h before filtering through a small pad of Celite® filter aid, washing through with EtOAc. The filtrate was evaporated under reduced pressure and the crude product was purified by column chromatography (hexane/acetone 5 : 1). This yielded **(139)** (30 mg, 30%) and **(140)** (47 mg, 47%) as colourless oils.

Data for **(139)**:

Mw = 160.213 ($C_8H_{16}O_3$).

R_f = 0.10 (Hexane/acetone 5 : 1).

IR (neat): 3409 (br, w), 2926 (m), 2855 (m), 1455 (w), 1408 (m), 1140 (s), 1032 (s) cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 4.79 (1H, t, J = 4.8 Hz, H_F); 3.85 (4H, m, H_G); 3.56 (2H, t, J = 6.4 Hz, H_A); 2.15 (1H, br s, OH); 1.65–1.58 (2H, m, H_E); 1.52 (2H, quintet, J = 6.8 Hz, H_B); 1.44–1.34 (4H, m, H_C + H_D) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 104.4 (CH, C_F), 67.5 (CH_2, 2 × C_G), 62.4 (CH_2, C_A), 33.6 (CH_2, C_E), 32.5 (CH_2, C_B), 25.5 (CH_2, $C_{C/D}$), 23.7 (CH_2, $C_{C/D}$) ppm.

EIMS: *m/z* (%): 159 ($(M-H)^+$, 3), 99 (8), 73 (100).

The IR, and ^{1}H NMR spectra correspond to the reported data.[77]

Data for **(140)**:

Mw = 158.200 ($C_8H_{14}O_3$).

R_f = 0.26 (Hexane/acetone 5 : 1).

IR (neat): 2955 (w), 2874 (w), 1739 (s), 1701 (s), 1418 (m), 1361 (m), 1134 (s) cm^{-1}.

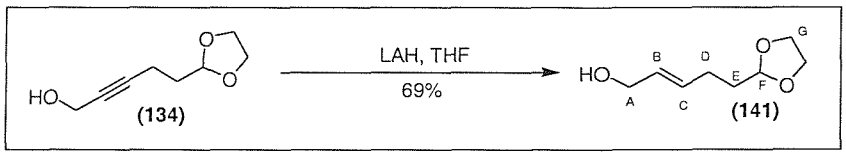
^{1}H NMR (300 MHz; $CDCl_3$): δ 9.76 (1H t, *J* = 1.7 Hz, H_A); 4.84 (1H, t, *J* = 4.8 Hz, H_F); 3.98–3.80 (4H, m, H_G); 2.44 (2H, td, *J* = 7.1, 1.7 Hz, H_B); 1.73–1.61 (4H, m, H_E + H_C); 1.51–1.39 (2H, m, H_D) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 202.5 (CH, C_A), 104.2 (CH, C_F), 64.8 (CH_2, 2 × C_G), 43.7 (CH_2, C_B), 33.5 (CH_2, C_C), 23.5 (CH_2, C_D), 21.9 (CH_2, C_E) ppm.

EIMS: *m/z* (%): 157 ($(M-H)^+$, 1), 99 (2), 73 (100).

The IR, and ^{1}H NMR spectra correspond to the reported data.[77]

5-(1,3-Dioxolan-2-yl)-2-(*E*)-penten-1-ol (141)



This is a known compound[137] but no experimental procedure or analytical data has been reported.

A solution of the alkyne **(134)** (1.15 g, 7.36 mmol, 1.0 equiv) in THF (10 mL) was added (dropwise) to a precooled (0 °C) suspension of LAH (1.68 g, 44.2 mmol, 6.0 equiv) in THF (30 mL). The dark grey suspension was refluxed for 75 min, and then slowly cooled to 0 °C. The reaction was quenched by dropwise addition of 0.5 M H_2SO_4 (3 mL). Dry THF (60 mL) was added to prevent the reaction from solidifying. Water (10 mL) was added slowly until a white suspension was obtained. This was filtered, the solids were washed with hot THF (30 mL), and the filtrate was evaporated *in vacuo*. The residue was partitioned between EtOAc/water (50 mL/30 mL), separated, and the aqueous phase was

extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/acetone 2 : 1). This yielded **(141)** as a pale yellow oil (0.80 g, 69%).

Mw = 158.200 ($C_8H_{14}O_3$).

$\mathbf{R_f}$ = 0.29 (Hexane/EtOAc 1 : 1).

IR (film): 3413 (br, m), 2950 (m), 2870 (m), 1664 (w), 1403 (m), 1138 (s), 1081 (m), 1034 (s), 964 (s) 902 (m) cm^{-1}.

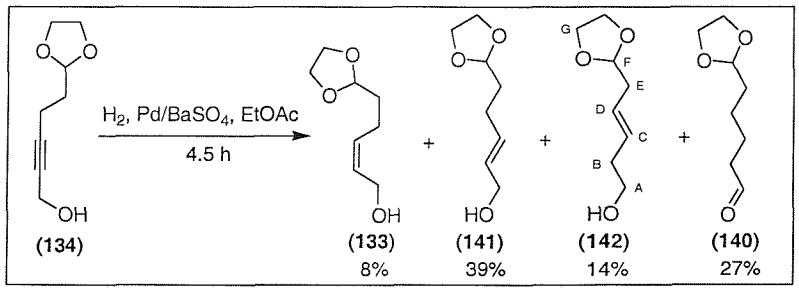
^{1}H NMR (300 MHz; $CDCl_3$): δ 5.76–5.62 (2H, m, H_B + H_C); 4.88 (1H, t, J = 4.7 Hz, H_F); 4.09 (2H, d, J = 4.7 Hz, H_A); 4.00–3.83 (4H, m, H_G); 2.19 (2H, m, H_D); 1.75 (2H, td, J = 8.0, 4.7 Hz, H_E); 1.60 (1H, s, OH) ppm.

^{13}C NMR + DEPT (75 MHz; $CDCl_3$): δ 132.0 (CH, $C_{B/C}$), 129.4 (CH, $C_{B/C}$), 103.9 (CH, C_F), 64.9 (CH_2, 2 × C_G), 63.6 (CH_2, C_A), 33.2 (CH_2, C_E), 26.6 (CH_2, C_D) ppm.

CIMS: *m/z* (%): 176 ($(M+NH_4)^+$, 43), 141 (100), 73 (6).

HREIMS: For $C_8H_{14}O_3$ $(M-H)^+$: calcd 157.0865, found 157.0865.

5-(1,3-Dioxolan-2-yl)-3-(*E*)-penten-1-ol (142)



The propargylic alcohol **(134)** (2.00 g, 12.8 mmol, 1.0 equiv) was weighed into a 50 mL 2-neck flask and dissolved in EtOAc (20 mL). To this solution was added $Pd/BaSO_4$ (5 wt%) (0.273 g, 1 mol%), and then the pressure was reduced using a water pump vacuum (~10 mmHg) and replaced with a hydrogen balloon. This was repeated twice before leaving the reaction stirring under a hydrogen atmosphere for 4.5 h. The light brown mixture was filtered through Celite® filter aid, washing with EtOAc. The filtrate was evaporated under reduced pressure and the crude product was purified by column chromatography (hexane/EtOAc 6 : 4). This yielded **(140)** as a colourless oil (0.554 g, 27%) and a mixture

of **(133)**, **(141)** and **(142)** (ratio = 14 : 63 : 23 respectively) as a colourless oil (1.222 g, 60%). An analytically pure sample of **(142)** was obtained after repeated preparative HPLC purification (EtOAc/hexane 6 : 4).

Data for **(133)**, **(141)** and **(140)**: see above.

Data for **(142)**:

Mw = 158.200 ($C_8H_{14}O_3$).

R_f = 0.23 (EtOAc/hexane 6 : 4).

IR (film): 3413 (br, m) 2884 (m), 1431 (m), 1399 (m), 1134 (s), 1039 (s), 977 (s) cm^{-1}.

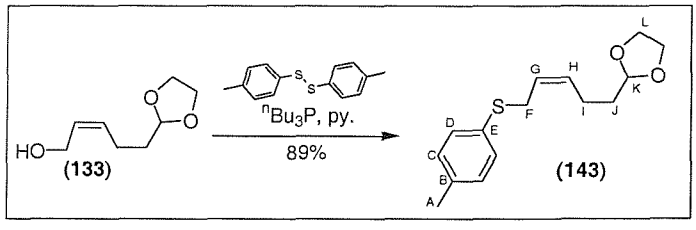
^{1}H NMR (400 MHz; $CDCl_3$): δ 5.63–5.51 (2H, m, H_C + H_D); 4.89 (1H, t, J = 4.7 Hz, H_F); 4.01–3.84 (4H, m, H_G); 3.65 (2H, t, J = 6.2 Hz, H_A); 2.43 (2H, m, H_E); 2.31 (2H, m, H_B); 1.56 (1H, s, OH) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 129.9 (CH, $C_{C/D}$), 127.1 (CH, $C_{C/D}$), 103.4 (CH, C_F), 65.0 (CH_2, 2 × C_G), 61.7 (CH_2, C_A), 37.5 (CH_2, $C_{B/E}$), 36.1 (CH_2, $C_{B/E}$) ppm.

CIMS: *m/z* (%): 176 ($(M+NH_4)^+$, 20), 159 ($(M+H)^+$, 22), 141 (2), 114 (6), 73 (100).

HREIMS: For $C_8H_{14}O_3$ $(M-H)^+$: calcd 157.0865, found 157.0857.

2-(5-*p*-Tolylsulfanylpent-3-(*Z*)-enyl)-[1,3]-dioxolane (143)



The allylic alcohol **(133)** (9 : 1 mixture of *Z* : *E* double bond isomers) (4.21 g, 26.6 mmol, 1.0 equiv) was placed in a dry 100 mL flask, followed by *p*-tolyl disulfide (9.84 g, 39.9 mmol, 1.5 equiv) and tri^{n}butylphosphine (9.95 mL, 39.9 mmol, 1.5 equiv). The mixture was stirred and cooled to 0 °C. Pyridine (21.5 mL, 266 mmol, 10.0 equiv) was added slowly, then the cold bath was removed and the reaction was stirred for 1 h. The pyridine was removed under high vacuum and crude product was purified by column chromatography (hexane/EtOAc 8 : 1). This yielded **(143)** as a colourless oil (6.31 g, 89%) (9 : 1 mixture of *Z* : *E* double bond isomers). The *E*-double bond isomer of **(143)** was synthesised from **(141)**

using the same procedure. The ^{1}H NMR values below for **(143)** are for the major product only.

Data for **(143)**:

Mw = 264.391 ($C_{15}H_{20}O_2S$).

R_f = 0.21 (Hexane/EtOAc 8 : 1).

IR (film): 2955 (m), 2916 (m), 2884 (m), 1489 (s), 1445 (w), 1399 (w), 1209 (w), 1139 (s), 1086 (m), 1039 (m), 807 (s) cm^{-1}.

^{1}H NMR (400 MHz; $(CD_3)_2CO$): δ 7.06–7.02 (2H, m, $H_{C/D}$); 6.91–6.84 (2H, m, $H_{C/D}$); 5.29–5.20 (2H, m, $H_G + H_H$); 4.50 (1H, t, J = 4.7 Hz, H_K); 3.68–3.49 (4H, m, H_L); 3.36 (2H, d, J = 6.5 Hz, H_F); 2.61 (3H, s, H_A); 1.84 (2H, m, H_I); 1.28 (2H, td, J = 7.8, 4.7 Hz, H_J) ppm.

^{13}C NMR + DEPT (100 MHz; $(CD_3)_2CO$): δ 137.1 (Q, $C_{B/E}$), 133.7 (Q, $C_{B/E}$), 133.1 (CH, $C_{G/H}$), 131.4 (CH, 2 × $C_{C/D}$), 130.5 (CH, 2 × $C_{C/D}$), 126.4 (CH, $C_{G/H}$), 104.5 (CH, C_K), 65.5 (CH_2, 2 × C_L), 34.5 (CH_2, C_F), 32.0 (CH_2, C_I), 22.6 (CH_2, C_J), 21.1 (CH_3, C_A) ppm.

EIMS: *m/z* (%): 264 ($(M)^+$, 8), 214 (5), 182 (10), 124 (56), 91 (83), 73 (100).

HREIMS: For $C_{15}H_{20}O_2S$ $(M)^+$: calcd 264.1184, found 264.1184.

Data for the *E*-double bond isomer of **(143)**:

Mw = 264.391 ($C_{15}H_{20}O_2S$).

R_f = 0.23 (Hexane/EtOAc 9 : 1).

IR (film): 2955 (m), 2879 (m), 1489 (s), 1445 (w), 1403 (m), 1214 (w), 1139 (s), 1091 (m), 1025 (s), 964 (s) 892 (m), 803 (s) cm^{-1}.

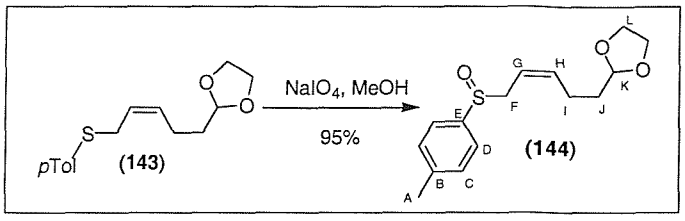
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.25 (2H, d, J = 8.1 Hz, $H_{C/D}$); 7.09 (2H, d, J = 8.3 Hz, $H_{C/D}$); 5.58–5.46 (2H, m, $H_G + H_H$); 4.78 (1H, t, J = 4.7 Hz, H_K); 3.99–3.78 (4H, m, H_L); 3.46 (2H, d, J = 5.3 Hz, H_F); 2.32 (3H, s, H_A); 2.12 (2H, m, H_I); 1.66 (2H, td, J = 7.8, 4.7 Hz, H_J) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 136.3 (Q, $C_{B/E}$), 132.9 (CH, $C_{G/H}$), 132.2 (Q, $C_{B/E}$), 130.9 (CH, 2 × $C_{C/D}$), 129.5 (CH, 2 × $C_{C/D}$), 125.8 (CH, $C_{G/H}$), 103.9 (CH, C_K), 64.8 (CH_2, 2 × C_L), 37.1 (CH_2, C_F), 33.3 (CH_2, C_I), 26.7 (CH_2, C_J), 21.0 (CH_3, C_A) ppm.

EIMS: *m/z* (%): 264 ($(M)^+$, 61), 141 (98), 123 (85), 99 (59), 91 (38), 73 (100).

HREIMS: For $C_{15}H_{20}O_2S$ $(M)^+$: calcd 264.1184, found 264.1186.

2-[5-(Toluene-4-sulfinyl)pent-3-(Z)-enyl]-[1,3]-dioxolane (144)



The sulfide **(143)** (1.46 g, 5.51 mmol, 1.0 equiv) (9 : 1 mixture of *Z* : *E* double bond isomers), and sodium periodate (1.30 g, 6.07 mmol, 1.1 equiv) were stirred in MeOH (20 mL) for 24 h. The solvent was evaporated under reduced pressure without heating and then EtOAc was added (30 mL). The suspension was filtered and washed with water (2 × 30 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane/acetone 2 : 1). This yielded **(144)** as a colourless oil (1.47 g, 95%) (9 : 1 mixture of *Z* : *E* double bond isomers). The NMR data below is for the major compound only.

Mw = 280.391 ($C_{15}H_{20}O_3S$).

R_f = 0.32 (Hexane/acetone 2 : 1).

IR (film): 2955 (m), 2884 (m), 1592 (w), 1488 (w), 1450 (w), 1403 (w), 1139 (s), 1086 (s), 1039 (s), 812 (m) cm^{-1}.

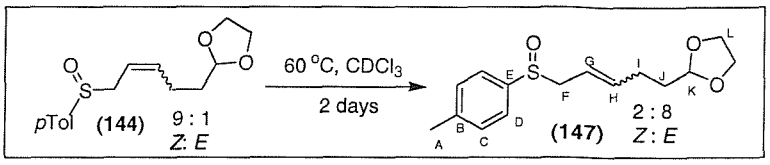
^{1}H NMR (400 MHz; $(CD_3)_2CO$): δ 7.19 (2H, d, *J* = 8.2 Hz, $H_{C/D}$); 7.02 (2H, d, *J* = 8.2 Hz, $H_{C/D}$); 5.39 (1H, m, $H_{G/H}$); 4.97 (1H, m, $H_{G/H}$); 4.37 (1H, t, *J* = 4.8 Hz, H_K); 3.58–3.38 (4H, m, H_L); 3.29 (1H, dd, *J* = 13.1, 7.8 Hz, H_F); 3.20 (1H, dd, *J* = 13.1, 7.8 Hz, $H_{F'}$); 2.46 (3H, s, H_A); 1.71–1.62 (2H, m, H_I); 1.18–1.11 (2H, m, H_J) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 142.5 (Q, $C_{B/E}$), 142.1 (Q, $C_{B/E}$), 138.0 (CH, $C_{G/H}$), 130.6 (CH, 2 × $C_{C/D}$), 125.3 (CH, 2 × $C_{C/D}$), 118.2 (CH, $C_{G/H}$), 104.4 (CH, C_K), 65.5 (CH_2, 2 × C_L), 55.8 (CH_2, C_F), 34.3 (CH_2, C_I), 23.1 (CH_2, C_J), 21.4 (CH_3, C_A) ppm.

ES$^+$MS: *m/z* (%): 303 ($(M+Na)^+$, 100), 281 ($(M+H)^+$, 13).

HRES$^+$MS: For $C_{15}H_{20}O_3S$ $(M+Na)^+$: calcd 303.1025, found 303.1028.

2-[5-(Toluene-4-sulfinyl)pent-3-(*E*)-enyl]-[1,3]-dioxolane (147)



The sulfoxide **(144)** (~30 mg) (9 : 1 mixture of *Z* : *E* double bond isomers) was dissolved in $CDCl_3$ (0.7 mL) and heated at 60 °C for 2 days. After cooling to room temperature, the sample was shown by NMR to have isomerized to a 2 : 8, *Z* : *E* mixture of double bond isomers. The NMR data below is for the major compound only.

Mw = 280.391 ($C_{15}H_{20}O_3S$).

R_f = 0.24 (Hexane/acetone 7 : 3).

IR (film): 2955 (w), 2879 (w), 1493 (w), 1398 (w), 1134 (m), 1086 (m), 1034 (s), 807 (m) cm^{-1}.

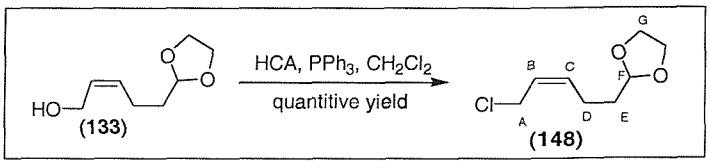
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.46 (2H, d, *J* = 8.2 Hz, $H_{C/D}$); 7.30 (2H, d, *J* = 8.0 Hz, $H_{C/D}$); 5.59 (1H, dt, *J* = 15.3, 6.7 Hz, $H_{G/H}$); 5.30 (1H, dtt, *J* = 15.3, 7.5, 1.4 Hz, $H_{G/H}$); 4.80 (1H, t, *J* = 4.7 Hz, H_K); 3.97–3.78 (4H, m, H_L); 3.46 (2H, d, *J* = 7.5 Hz, H_F); 2.41 (3H, s, H_A); 2.15 (2H, q, *J* = 7.5 Hz H_I); 1.69–1.63 (2H, m, H_J) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 141.4 (Q, $C_{B/E}$), 139.8 (Q, $C_{B/E}$), 139.4 (CH, $C_{G/H}$), 126.6 (CH, 2 × $C_{C/D}$), 124.4 (CH, 2 × $C_{C/D}$), 117.2 (CH, $C_{G/H}$), 103.7 (CH, C_K), 64.8 (CH_2, 2 × C_L), 60.2 (CH_2, C_F), 33.0 (CH_2, C_I), 27.0 (CH_2, C_J), 21.4 (CH_3, C_A) ppm.

ES$^+$MS: *m/z* (%): 863 ($(3M+Na)^+$, 20), 583 ($(2M+Na)^+$, 100), 561 ($(2M+H)^+$, 23), 344 ($(M+Na+MeCN)^+$, 24), 303 ($(M+Na)^+$, 13), 281 ($(M+H)^+$, 54).

HRES$^+$MS: For $C_{15}H_{20}O_3S$ $(M+Na)^+$: calcd 303.1025, found 303.1026.

2-(5-Chloropent-3-(Z)-enyl)-[1,3]-dioxolane (148)



The allylic alcohol **(133)** (450 mg, 2.84 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5 mL) and added via syringe to a solution of triphenylphosphine (821 mg, 3.13 mmol, 1.1 equiv) in

CH_2Cl_2 (10 mL). Upon complete dissolution, the mixture was cooled to 0 °C with stirring. To this mixture was added via syringe a solution of hexachloroacetone (479 μL, 3.13 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL) over 2 min. The cold bath was then removed and the reaction was stirred for 10 min. Silica (4.5 g) was added, the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (hexane/EtOAc 9 : 1). This yielded **(148)** as a colourless oil (519 mg, quantitative yield).

Mw = 176.643 ($C_8H_{13}O_2Cl$).

R_f = 0.30 (Hexane/EtOAc 9 : 1).

IR (film): 2950 (m), 2879 (w), 1730 (w), 1649 (w), 1436 (w), 1393 (w), 1252 (m), 1138 (s), 1053 (m), 1030 (m), 765 (m) cm^{-1}.

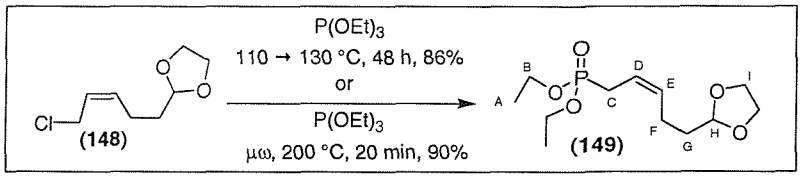
^{1}H NMR (300 MHz; $CDCl_3$): δ 5.68–5.63 (2H, m, $H_B + H_C$); 4.88 (1H, t, J = 4.9 Hz, H_F); 4.12 (2H, d, J = 6.8 Hz, H_A); 4.00–3.83 (4H, m, H_G); 2.28 (2H, m, H_D); 1.76 (2H, dt, J = 7.6, 4.9 Hz, H_E) ppm.

^{13}C NMR + DEPT (75 MHz; $CDCl_3$): δ 134.1 (CH, $C_{B/C}$), 126.0 (CH, $C_{B/C}$), 103.6 (CH, C_F), 64.9 (CH_2, 2 × C_G), 39.3 (CH_2, C_A), 33.1 (CH_2, C_E), 21.6 (CH_2, C_D) ppm.

CIMS: *m/z* (%): 177/179 (3 : 1, $(M+H)^+$, 5), 143 (28), 99 (11), 73 (100).

We have not obtained a HRMS or elemental analysis of this compound but copies of the ^{1}H and ^{13}C NMR are included in the appendix.

Diethyl-[5-(1,3-dioxolan-2-yl)-2-(Z)-pentenyl]phosphonate (149)



Thermal heating method:

The allylic chloride **(148)** (6.29 g, 35.62 mmol, 1.0 equiv) and triethyl phosphite (12.22 mL, 71.23 mmol, 2.0 equiv) were combined and heated between 110 and 130 °C for 48 h. The mixture was cooled and purified by vacuum distillation (0.15 mmHg). Excess triethyl phosphite was collected at 44 to 48 °C (oil bath = 110 °C) (colourless oil) and the

phosphonate **(149)** was collected at 144 to 150 °C (oil bath = 190 °C) as a colourless oil (8.54 g, 86% yield).

Microwave irradiation method:

The allylic chloride **(148)** (1.50 g, 8.49 mmol, 1.0 equiv) and triethyl phosphite (2.91 mL, 16.98 mmol, 2.0 equiv) were combined in a microwave tube and irradiated at various power to maintain a temperature of 200 °C (with stirring) for 20 min. After cooling, the crude reaction mixture was purified by column chromatography (eluting with EtOAc (neat) followed by hexane/acetone 1 : 1). This yielded **(149)** as a colourless oil (2.13 g, 90%).

Mw = 278.290 ($C_{12}H_{23}O_5P$).

R_f = 0.17 (Hexane/acetone 2 : 1).

IR (film): 2974 (m), 2884 (w), 1394 (w), 1252 (m), 1139 (m), 1053 (s), 1025 (s), 927 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.62 (1H, m, H_E); 5.44 (1H, m, H_D); 4.86 (1H, t, J = 4.7 Hz, H_H); 4.14–4.04 (4H, m, H_B); 3.97–3.81 (4H, m, H_I); 2.62 (2H, ddd, J = 22.1, 7.8, 0.8 Hz, H_C); 2.20 (2H, m, H_F); 1.72 (2H, td, J = 7.8, 4.7, H_G); 1.31 (6H, t, J = 7.0 Hz, H_A) ppm.

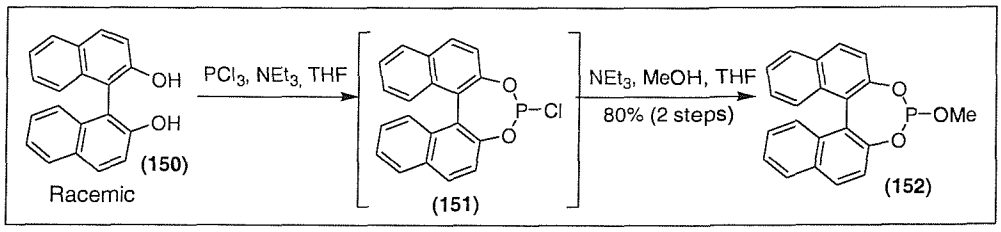
^{13}C NMR + DEPT (75 MHz; $CDCl_3$): δ 133.3 (d, J = 14.1 Hz, CH, C_E), 118.5 (d, J = 10.9 Hz, CH, C_D), 103.8 (CH, C_H), 64.8 (CH_2, 2 × C_I), 61.8 (d, J = 6.5 Hz, CH_2, 2 × C_B), 33.2 (d, J = 2.7 Hz, CH_2, C_G), 25.6 (d, J = 139.3 Hz, CH_2, C_C), 21.8 (d, J = 2.4 Hz, CH_2, C_F), 16.4 (d, J = 6.0 Hz, CH_3, 2 × C_A) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 28.60 ppm.

CIMS: *m/z* (%): 279 ($(M+H)^+$, 100), 235 (11), 206 (18), 156 (25), 140 (20), 99 (13), 73 (78).

HRES$^+$MS: For $C_{12}H_{23}O_5P$ $(M+Na)^+$: calcd 301.1175, found 301.1171.

4-Methoxy-3,5-dioxa-4-phosphacyclohepta-[2,1-a;3,4-a']-dinaphthalene (152)



This is a known compound[105] but no experimental procedure or analytical data has been reported.

BINOL (1 g, 3.49 mmol, 1.0 equiv) was azeotropically dried from toluene (3 × 20 mL) and then dissolved in dry THF (12 mL). This solution was then added dropwise via cannula to a stirred solution of NEt_3 (1070 μL, 7.68 mmol, 2.2 equiv) and PCl_3 (305 μL, 3.49 mmol, 1.0 equiv) in dry THF (5 mL) at 0 °C. After the addition, the cold bath was removed and the reaction was stirred for 2 h. The reaction was then cooled to 0 °C and a solution of MeOH (141 μL, 3.49 mmol, 1.0 equiv) and NEt_3 (487 μL, 3.49 mmol, 1.0 equiv) in THF (5 mL) was added dropwise. The white suspension was stirred at room temperature overnight and then filtered; washing with cold, dry THF. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (hexane/acetone 96 : 4). This yielded **(152)** as a white foam (0.97 g, 80%).

Mw = 346.325 ($C_{21}H_{15}O_3P$).

M.P. = 103–104 °C.

$\mathbf{R_f}$ = 0.40 (Hexane/acetone 95 : 5).

IR (film): 1589 (w), 1508 (w), 1463 (w), 1327 (w), 1231 (s), 1201 (m), 1072 (w), 1033 (s), 979 (w), 949 (s), 902 (w), 822 (s), 747 (s) cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.01–7.89 (4H, m); 7.52 (1H, dd, J = 8.8, 0.8 Hz); 7.48–7.33 (5H, m); 7.30–7.24 (2H, m); 3.55 (3H, d, J = 9.8 Hz) ppm.

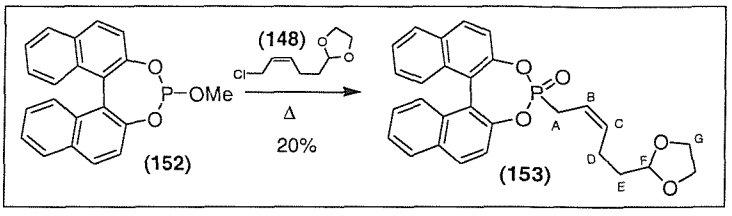
^{13}C NMR + DEPT (75 MHz; $CDCl_3$): δ 148.8 (d, J = 4.5 Hz, 2 × Q), 147.4 (d, J = 2.3 Hz, 2 × Q), 132.7 (d, J = 18.0 Hz, 2 × Q), 131.2 (d, J = 38.2 Hz, 2 × Q), 130.2 (d, J = 23.6 Hz, 2 × CH), 128.3 (d, J = 5.6 Hz, 2 × CH), 126.9 (2 × CH), 126.2 (2 × CH), 124.9 (d, J = 10.1 Hz, 2 × CH), 121.6 (d, J = 20.2 Hz, 2 × CH), 52.0 (d, J = 5.6 Hz, CH_3) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 140.64 ppm.

EIMS: (%): 346 ($(M)^+$, 79), 331 (76), 313 (45), 267 (100), 239 (67), 213 (16), 157 (39), 134 (18), 119 (66), 106 (11).

HRMS, Anal: Not thought necessary as discussed with supervisor.

4-(5-[1,3]-Dioxolan-2-ylpent-2-(Z)-enyl)-3,5-dioxa-4-phosphacyclohepta-[2,1-a;3,4-a']-dinaphthalene-4-oxide (153)



The phosphite **(152)** (897 mg, 2.59 mmol, 1.3 equiv) and the chloride **(148)** (354 mg, 2.00 mmol, 1.0 equiv) were combined and transferred into the reaction flask through a $MgSO_4$ pipette, followed by washing through with CH_2Cl_2. The solvent was removed using a N_2 flush for 1 h followed by 18 h under high vacuum. The viscous oil was then heated neat between 110 and 130 °C with slow stirring for 48 h. The crude mixture was purified by column chromatography (hexane/acetone 3 : 2) followed by preparative HPLC (hexane/acetone 3 : 2). This yielded **(153)** as a colourless oil (186 mg, 20%).

Mw = 472.484 ($C_{28}H_{25}O_5P$).

R_f = 0.38 (Hexane/acetone 3 : 2).

IR (film): 2950 (w), 2883 (w), 1588 (w), 1502 (w), 1460 (w), 1327 (w), 1285 (s), 1224 (s), 1143 (m), 1068 (m), 964 (s), 874 (m), 812 (m), 727 (m) cm^{-1}.

^{1}H NMR (400 MHz; $(CD_3)_2CO$): δ 8.02 (2H, d, *J* = 8.8 Hz); 7.95 (2H, t, *J* = 7.0 Hz); 7.60–7.25 (8H, m); 5.76-5.67 (1H, m, H_C); 5.60–5.49 (1H, m, H_B); 4.82 (1H, t, *J* = 4.8 Hz, H_F); 3.92–3.75 (4H, m, H_G); 2.87 (2H, dd, *J* = 21.4, 7.6 Hz, H_A); 2.22–2.11 (2H, m, H_D); 1.72 (2H, td, *J* = 7.7, 4.7 Hz, H_E) ppm.

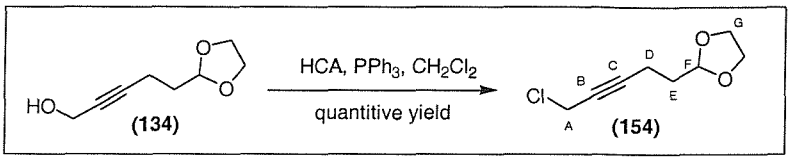
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 147.5 (d, *J* = 10.1 Hz, 2 × Q), 145.9 (d, *J* = 10.0 Hz, 2 × Q), 135.0 (d, *J* = 15.1 Hz, CH, C_C), 132.5 (d, *J* = 18.0 Hz, 2 × Q), 131.7 (d, *J* = 27.5 Hz, 2 × Q), 131.1 (d, *J* = 16.4 Hz, 2 × CH), 128.4 (d, *J* = 11.4 Hz, 2 × CH), 127.1 (d, *J* = 39.5 Hz, 2 × CH), 126.7 (d, *J* = 16.9 Hz, 2 × CH), 125.7 (d, *J* = 10.8 Hz, 2 × CH), 121.5 (d, *J* = 67.6 Hz, 2 × CH), 116.4 (d, *J* = 10.4 Hz, CH, C_B), 103.7 (CH, C_F), 64.8 (CH_2, 2 × C_G), 33.0 (d, *J* = 2.6 Hz, CH_2, C_E), 23.8 (d, *J* = 133.6 Hz, CH_2, C_A), 22.0 (d, *J* = 2.2 Hz, CH_2, C_D) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 38.57 ppm.

ES$^+$MS: *m/z* (%): 967 ($(2M+Na)^+$, 65), 536 ($(M+Na+MeCN)^+$, 100), 495 ($(M+Na)^+$, 22), 490 ($(M+NH_4)^+$, 43), 473 ($(M+H)^+$, 60).

HRES$^+$MS: For $C_{28}H_{25}O_5P$ $(M+H)^+$: calcd 473.1512, found 473.1517.

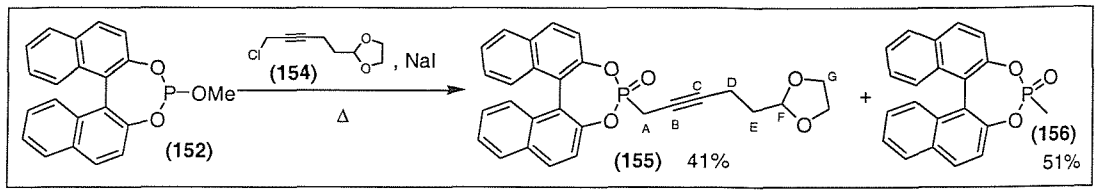
2-(5-Chloro-3-pentynyl)-1,3-dioxolane (154)



This is a known compound[73] but was synthesised here via a new procedure:
The propargylic alcohol **(134)** (100 mg, 0.64 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1 mL) and added via syringe to a solution of triphenylphosphine (185 mg, 0.70 mmol, 1.1 equiv) in CH_2Cl_2 (3 mL). Upon complete dissolution, the mixture was cooled to 0 °C and a solution of hexachloroacetone (107 µL, 0.70 mmol, 1.1 equiv) in CH_2Cl_2 (1 mL) was added via syringe over 1 min. The cold bath was then removed and the reaction was stirred for 10 min. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (hexane/EtOAc 7 : 1). This yielded **(154)** as a colourless oil (117 mg, quantitative yield).

Mw = 174.611 ($C_8H_{11}O_2Cl$).
R_f = 0.26 (Hexane/EtOAc 9 : 1).
IR (film): 2955 (m), 2889 (s), 2231 (w), 1441 (w), 1413 (w), 1261 (s), 1139 (s), 1068 (s), 1039 (s), 935 (m), 829 (m), 689 (s) cm^{-1}.
^{1}H NMR (300 MHz; $CDCl_3$): δ 4.96 (1H, t, J = 4.6 Hz, H_F); 4.13 (2H, t, J = 2.2 Hz, H_A); 4.00–3.84 (4H, m, H_G); 2.38 (2H, tt, J = 7.4, 2.2 Hz, H_D); 1.87 (2H, td, J = 7.4, 4.6 Hz, H_E) ppm.
^{13}C NMR + DEPT (75 MHz; $CDCl_3$): δ 103.0 (CH, C_F), 86.5 (Q, $C_{B/C}$), 75.1 (Q, $C_{C/B}$), 64.9 (CH_2, 2 × C_G), 32.5 (CH_2, C_E), 31.1 (CH_2, C_A), 13.6 (CH_2, C_D) ppm.
CIMS: *m/z* (%): 175/177 (3 : 1, $(M+H)^+$, 9), 14 (16), 73 (100).
The IR and ^{1}H NMR spectra correspond to the reported data.[73]

4-(5-[1,3]-Dioxolan-2-ylpent-2-ynyl)-3,5-dioxa-4-phosphacyclohepta-[2,1-a;3,4-a']-dinaphthalene-4-oxide (155) and **4-Methyl-3,5-dioxa-4-phosphacyclohepta-[2,1-a;3,4-a']-dinaphthalene-4-oxide (156)**



The phosphite **(152)** (4.12g, 11.89 mmol, 1.5 equiv) and the chloride **(154)** (1.39 g, 7.93 mmol, 1.0 equiv) were combined and heated between 110 and 130 °C for 18 h. The reaction was then cooled and sodium iodide was added (0.12 g, 0.79 mmol, 0.1 equiv). The reaction was then stirred and heated between 110 and 130 °C for a further 24 h. The reaction mixture was cooled and the residue was dissolved in CH_2Cl_2 (300 mL) (this required sonication). This solution was washed with water (200 mL) and brine (100 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 3 : 2) followed by preparative HPLC (hexane/acetone 1 : 1). This yielded **(155)** as a white foam (1.55 g, 41%) and **(156)** as a colourless oil (2.33 g, 51%).

Data for **(155)**:

Mw = 470.466 ($C_{28}H_{23}O_5P$).

$\mathbf{R_f}$ = 0.31 (Hexane/EtOAc 1 : 1).

IR (film): 3054 (w), 2959 (w), 2888 (w), 1592 (w), 1503 (m), 1460 (w), 1290 (s), 1223 (s), 1148 (m), 1072 (m), 963 (s), 868 (m), 817 (m), 727 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 8.04 (2H, d, *J* = 8.8 Hz); 7.95 (2H, d, *J* = 8.1 Hz); 7.60 (1H, dd, *J* = 9.8, 0.2 Hz); 7.57 (1H, d, *J* = 8.8 Hz); 7.52–7.45 (2H, m); 7.39–7.26 (4H, m); 4.89 (1H, t, *J* = 4.6 Hz, H_F); 3.96–3.80 (4H, m, H_G); 3.09–2.87 (2H, m, H_A); 2.20–2.13 (2H, m, H_D); 1.75–1.65 (2H, m, H_E); ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 147.8 (d, *J* = 10.6 Hz, 2 × Q), 145.8 (d, *J* = 9.7 Hz, 2 × Q), 132.4 (d, *J* = 9.7 Hz, 2 × Q), 131.7 (d, *J* = 21.3 Hz, 2 × Q), 131.2 (d, *J* = 24.7 Hz, 2 × CH), 128.4 (d, *J* = 15.5 Hz, 2 × CH), 127.0 (d, *J* = 32.8 Hz, 2 × CH), 126.8 (d, *J* = 11.6 Hz, 2 × CH), 125.8 (d, *J* = 7.4 Hz, 2 × CH), 121.6 (d, *J* = 27.0 Hz, 2 × CH), 103.1 (CH, C_F), 83.9 (d, *J* = 10.6 Hz, Q, $C_{B/C}$), 67.6 (d, *J* = 15.4 Hz, Q, $C_{B/C}$), 64.9 (CH_2, 2 × C_G), 32.5

(d, J = 2.9 Hz, CH_2, C_E), 16.4 (d, J = 140.0 Hz, CH_2, C_A), 13.5 (d, J = 2.9 Hz, CH_2, C_D) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 32.26 ppm.

ES$^+$MS: *m/z* (%): 963 ($(2M+Na)^+$, 49), 534 ($(M+Na+MeCN)^+$, 66), 493 ($(M+Na)^+$, 100), 471 ($(M+H)^+$, 61).

HRES$^+$MS: For $C_{28}H_{23}O_5P$ $(M+H)^+$: calcd 471.1356, found 471.1356.

Data for **(156)**:

Mw = 346.325 ($C_{21}H_{15}O_3P$).

R_f = 0.26 (Hexane/EtOAc 1 : 1).

IR (film): 3049 (w), 2987 (w), 2917 (w), 1621 (w), 1588 (m), 1512 (m), 1460 (m), 1432 (w), 1361 (w), 1323 (s), 1313 (s), 1276 (s), 1223 (s), 1157 (m), 1067 (s), 987 (s), 963 (s), 897 (s), 859 (s), 826 (s), 746 (s),

^{1}H NMR (400 MHz; $CDCl_3$): δ 8.04 (2H, dd, J = 8.9, 2.8 Hz); 7.96 (2H, dd, J = 8.3, 5.5 Hz); 7.60 (1H, dd, J = 8.9, 1.3 Hz); 7.53–7.39 (4H, m); 7.37–7.27 (3H, m); 1.73 (3H, d, J = 17.2 Hz, CH_3) ppm.

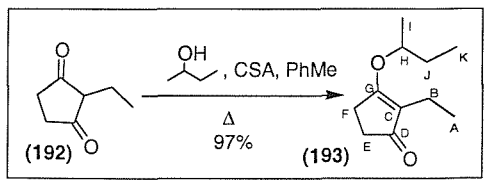
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 147.3 (d, J = 10.6 Hz, 2 × Q), 145.9 (d, J = 10.6 Hz, 2 × Q), 132.4 (d, J = 22.2 Hz, 2 × Q), 131.7 (d, J = 21.3 Hz, 2 × Q), 131.2 (2 × CH), 128.4 (d, J = 8.7 Hz, 2 × CH), 127.0 (d, J = 30.9 Hz, 2 × CH), 126.7 (d, J = 14.5 Hz, 2 × CH), 125.7 (d, J = 14.5 Hz, 2 × CH), 121.9 (d, J = 24.2 Hz, 2 × CH), 9.3 (d, J = 138.1 Hz, CH_3) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 41.05 ppm.

ES$^+$MS: *m/z* (%): 715 ($(2M+Na)^+$, 48), 693 ($(2M+H)^+$, 15), 410 ($(M+Na+MeCN)^+$, 100), 369 ($(M+Na)^+$, 15), 347 ($(M+H)^+$, 11).

HRES$^+$MS: For $C_{21}H_{15}O_3P$ $(M+Na+MeCN)^+$: calcd 410.0916, found 410.0927.

3-*sec*-Butoxy-2-ethylcyclopent-2-enone (193)



This compound has been previously synthesised by Organon N. V., (Oss) but no procedure or analytical data had been published:[64]

2-Ethyl-1,3-cyclopentanedione (50.43 g, 369 mmol, 1.0 equiv), *sec*-butyl alcohol (256 mL, 2770 mmol, 7.0 equiv), CSA (2.76 g, 11.9 mmol, 0.03 equiv) and toluene (680 mL) were refluxed for 23 days, separating water from the reaction in a Dean Stark trap. The reaction was then cooled and the toluene was evaporated under reduced pressure. The crude product was purified by vacuum distillation (105 °C/0.6 mmHg). This yielded a yellow oil (70.3 g, 97%).

Mw = 182.265 ($C_{11}H_{18}O_2$).

R_f = 0.53 (hexane/acetone 3 : 2).

IR (film): 2974 (s), 2931 (m), 2869 (w), 1687 (s), 1626 (s), 1464 (m), 1380 (s), 1342 (s), 1266 (s), 1233 (m), 1124 (s), 987 (m), 878 (m) cm^{-1}.

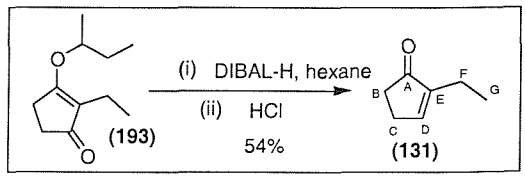
^{1}H NMR (400 MHz; $CDCl_3$): δ 4.37 (1H, sextet, J = 6.1 Hz, H_H); 2.60–2.56 (2H, m, $H_{F/E}$); 2.40–2.36 (2H, m, $H_{F/E}$); 2.10 (2H, q, J = 7.5 Hz, H_B); 1.75–1.55 (2H, m, H_J); 1.28 (3H, d, J = 6.1 Hz, H_I); 0.94 (3H, t, J = 7.5 Hz, H_A); 0.93 (3H, t, J = 7.4 Hz, H_K) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 204.6 (Q, C_D), 183.4 (Q, C_G), 122.3 (Q, C_C), 77.1 (CH, C_H), 33.3 (CH_2, $C_{F/E}$), 29.6 (CH_3, C_I), 24.8 (CH_2, $C_{F/E}$), 20.5 (CH_2, C_J), 14.3 (CH_2, C_B), 12.3 (CH_3, C_A), 9.4 (CH_3, C_K) ppm.

CIMS: *m/z* (%): 183 ($(M+H)^+$, 100), 127 (16), 57 (8).

We have not obtained a HRMS or elemental analysis but copies of the ^{1}H and ^{13}C NMR are included in the appendix.

2-Ethylcyclopent-2-en-1-one (131)



This is a known compound[125,126] but was synthesised here via an adaptation of an unpublished procedure devised by Organon N. V., (Oss):[64]

To a stirred solution of the enol ether **(193)** (34.06 g, 187 mmol, 1.0 equiv) in hexane (257 mL) at 0 °C was added DIBAL-H (1M in hexanes, 299 mL, 299 mmol, 1.6 equiv) via cannula. The cold bath was removed and the solution was stirred at room temperature for 24 h. The reaction was then cooled to 0 °C, a water condenser was fitted and 1M HCl (400 mL) (precooled to 0 °C) was poured in, followed by the addition of c. HCl (37 mL). The biphasic mixture was stirred vigorously for 2 h and then separated, washing the organic phase with water (2 × 50 mL). The combined aqueous phases were extracted with Et_2O (3 × 50 mL) then the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/acetone 12 : 1) followed by vacuum distillation (47 – 49 °C/5 mmHg (75 °C oil bath)). This yielded **(131)** as a light yellow oil (11.19 g, 54%).

Mw = 110.157 ($C_7H_{10}O$).

$\mathbf{R_f}$ = 0.31 (Hexane/acetone 9 : 1).

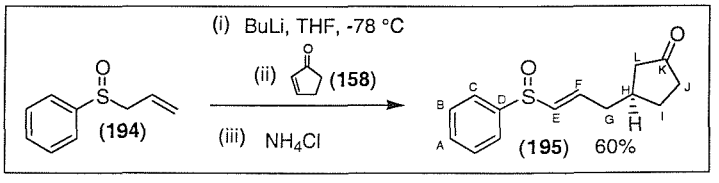
IR (neat): 2967 (w), 2925 (w), 1703 (s), 1662 (w), 1444 (w), 1348 (w), 1249 (w), 1002 (w), 947 (w), 791 (w).

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.29–7.23 (1H, m, H_D); 2.55–2.50 (2H, m, $H_{B/C}$); 2.38–2.34 (2H, m, $H_{B/C}$); 2.20–2.12 (2H, m, H_F); 1.06 (3H, t, J = 7.5 Hz, H_G) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 209.9 (Q, C_A), 156.5 (CH, C_D), 147.9 (Q, C_E), 34.7 (CH_2, $C_{B/C}$), 26.3 (CH_2, $C_{B/C}$), 18.0 (CH_2, C_F), 12.0 (CH_3, C_G) ppm.

The IR and ^{1}H spectra correspond to the reported data.[125,126]

3-(3-Benzenesulfinyl-(*E*)-allyl)cyclopentanone (195)



To a cooled (−78 °C) solution of phenylallylsulfoxide **(194)** (100 mg, 0.60 mmol, 1.0 equiv) in THF (2 mL) was added ^{n}BuLi (2.5 M in hexanes) (265 µl, 0.66 mmol, 1.1 equiv) dropwise over 2 min and the dark orange solution was stirred at −78 °C for 1 h. The enone **(158)** (50 µl, 0.60 mmol, 1.0 equiv) was added dropwise to this solution and then the reaction was stirred for 5 min. A solution of acetic acid (83 µl, 1.44 mmol, 2.4 equiv) in

Et_2O (0.2 mL) was then added and the light yellow mixture was warmed to room temperature over 1 h. The reaction mixture was then poured onto saturated aqueous NH_4Cl (3 mL) and extracted with Et_2O (3 × 3 mL). The combined organic phases were washed with brine (2 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/acetone 3 : 2) followed by preparative HPLC (hexane/acetone 3 : 2). This yielded (**195**) as a colourless oil (90 mg, 60%).

Mw = 248.348 ($C_{14}H_{16}O_2S$).

R_f = 0.17 (Hexane/acetone 55 : 45).

IR (film): 1734 (s), 1441 (w), 1157 (w), 1082 (m), 1039 (s), 741 (m) cm^{-1}.

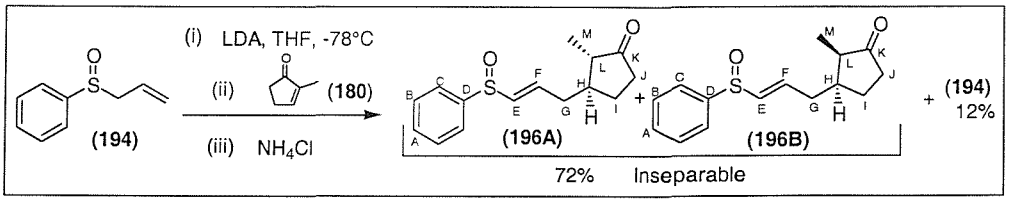
^1H NMR (400 MHz; $CDCl_3$): δ 7.63–7.59 (2H, m, $H_{A/B/C}$); 7.55–7.47 (3H, m, $H_{A/B/C}$); 6.59 (1H, dt, J = 15.1, 7.3 Hz, H_F); 6.30 (1H, d, J = 15.1 Hz, H_E); 2.44–2.26 (5H, m); 2.24–2.12 (2H, m); 1.84 (1H, dd, J = 16.5, 7.3 Hz, H_G); 1.63–1.51 (1H, m, H_I) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 218.0 (Q, C_K), 144.0 (Q, C_D), 137.2 (CH, C_F), 136.8 (CH, C_E), 131.1 (Q, C_A), 129.4 (CH, 2 × $C_{B/C}$), 124.4 (CH, 2 × $C_{B/C}$), 44.4 (CH_2, C_G), 38.1 (CH_2, $C_{J/L}$), 37.6 (CH_2, $C_{J/L}$), 36.1 (CH, C_H), 29.0 (CH_2, C_I) ppm.

CIMS: *m/z* (%): 249 ($(M+H)^+$, 12), 232 (61), 149 (100), 123 (42).

HRES$^+$MS: For $C_{14}H_{16}O_2S$ $(M+Na)^+$: calcd 249.0944, found 249.0942.

3-(3-Benzenesulfinyl-(*E*)-allyl)-2-methylcyclopentanone (196)



A LDA solution was freshly prepared by adding ^{n}BuLi (2.5 M in hexanes) (400 µl, 1.00 mmol, 1.0 equiv) to a cooled (–78 °C) solution of diisopropylamine (155 µL, 1.1 mmol, 1.1 equiv) in THF (20 mL). After allowing the LDA solution to stir at –78 °C for 30 min, phenylallylsulfoxide (**194**) (166 mg, 1.00 mmol, 1.0 equiv) was added as a THF (1 mL) solution via syringe. The resultant yellow solution was stirred for 5 min and then a THF (2 mL) solution of the enone (**180**) (98 µL, 1.00 mmol, 1.0 equiv) was added via syringe. After this addition the reaction was stirred at –78 °C for 2 min before quenching the

reaction with a saturated NH_4Cl solution (1 mL). The reaction was then warmed to room temperature, poured onto NH_4Cl (sat., aq.) (15 mL) and extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by gradient column chromatography, eluting with sequential 100 mL portions of 0%, 1%, 3%, 6%, 10% and 20% acetone in Et_2O. This yielded **(194)** (33 mg, 12%) and **(196)** (188 mg, 72%) as a light yellow oil and a colourless oil respectively. The vinyl sulfoxide **(196)** was isolated as a 75 : 25 **(196A)** : **(196B)** mixture of diastereoisomers, which could not be separated.

Data for **(196A)**

Mw = 262.375 ($C_{15}H_{18}O_2S$).

R_f = 0.29 (Neat Et_2O).

IR (film): 1734 (s), 1441 (w), 1162 (w), 1082 (m), 1044 (s), 959 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.63–7.58 (2H, m, $H_{A/B/C}$); 7.54–7.45 (3H, m, $H_{A/B/C}$); 6.62 (1H, dt, J = 15.0, 7.5 Hz, H_F); 6.32 (1H, d, J = 15.0 Hz, H_E); 2.60 (1H, dddd, J = 14.2, 7.0, 4.5, 1.3 Hz); 2.47–1.95 (4H, m); 1.87–1.65 (2H, m); 1.49–1.39 (1H, m); 1.06 (3H, d, J = 6.7 Hz, H_M) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 219.5 (Q, C_K), 143.9 (Q, C_D), 136.9 (CH, C_F) 136.8 (CH, C_E), 131.0 (CH, C_A), 129.3 (CH, 2 × $C_{B/C}$), 124.4 (CH, 2 × $C_{B/C}$), 49.6 (CH, C_L), 43.9 (CH, C_H), 37.0 (CH_2, C_G), 36.4 (CH_2, C_J), 26.8 (CH_2, C_I), 12.5 (CH_3, C_M) ppm.

EIMS: *m/z* (%): 246 ((M-16)$^+$, 38), 149 (100), 134 (26), 116 (62), 97 (29), 77 (42).

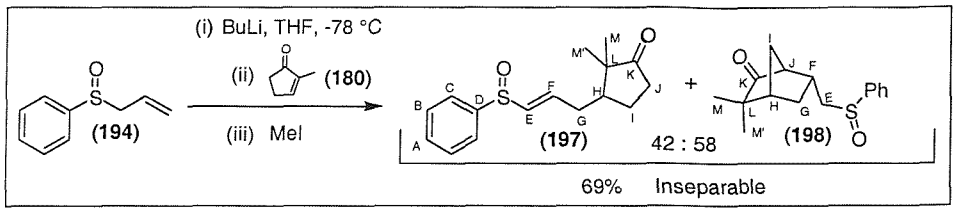
HRES$^+$MS: For $C_{15}H_{18}O_2S$ $(M+Na)^+$: calcd 263.1101, found 263.1100.

Significant data for **(196B)**:

^{1}H NMR (400 MHz; $CDCl_3$): δ 0.97 (3H, d, J = 7.3 Hz, H_M) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 222.3 (Q, C_K), 143.9 (Q, C_D), 137.9 (CH, C_F) 136.6 (CH, C_E), 131.0 (CH, C_A), 129.3 (CH, 2 × $C_{B/C}$), 124.4 (CH, 2 × $C_{B/C}$), 46.6 (CH, $C_{L/H}$), 39.1 (CH, $C_{L/H}$), 35.6 (CH_2, $C_{G/I/J}$), 31.9 (CH_2, $C_{G/I/J}$), 25.2 (CH_2, $C_{G/I/J}$), 9.7 (CH_3, C_M) ppm.

3-(3-Benzenesulfinyl-(*E*)-allyl)-2,2-dimethylcyclopentanone (197) and **6-benzenesulfinylmethyl-3,3-dimethylbicyclo-[2.2.1]-heptan-2-one (198)**



A LDA solution was freshly prepared by adding ^{n}BuLi (2.5 M in hexanes) (531 µl, 1.38 mmol, 1.0 equiv) to a cooled (–78 °C) solution of diisopropylamine (205 µL, 1.46 mmol, 1.1 equiv) in THF (2.8 mL). After allowing the LDA solution to stir at –78 °C for 30 min, phenylallylsulfoxide **(194)** (221 mg, 1.38 mmol, 1.0 equiv) was added neat via syringe. The resultant yellow solution was stirred for 30 min and then a THF (370 µL) solution of the enone **(180)** (130 µL, 1.38 mmol, 1.0 equiv) was added via syringe. Immediately after this addition the reaction was placed in a 0 °C ice/water bath and stirred for 10 min. Methyl iodide (248 µL, 3.98 mmol, 3.0 equiv) was then added and then the cold bath was removed. The reaction was stirred for 1 h and then poured onto NH_4Cl (sat., aq.) (15 mL) and extracted with EtOAc (4 × 6 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/acetone 2 : 1) followed by preparative HPLC (hexane/acetone 2 : 1) to yield an inseparable mixture of **(197)** and **(198)** as a colourless oil (252 mg, 69%), found to be a 42 : 58 mixture of **(197)** : **(198)** by NMR.

Data for **(197)**

Mw = 276.120 ($C_{16}H_{20}O_2S$).

R_f = 0.43 (Hexane/acetone 2 : 1).

IR (film): 2954 (m), 1734 (s), 1469 (w), 1446 (m), 1382 (m), 1086 (m), 1044 (s), 755 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.63–7.57 (2H, m, $H_{A/B/C}$); 7.54–7.46 (3H, m, $H_{A/B/C}$); 6.61 (1H, ddd, J = 15.0, 7.6, 7.0 Hz, H_F); 6.12 (1H, dt, J = 15.0, 1.3 Hz, H_E); 2.48–2.33 (2H, m, $H_J + H_G$); 2.22–2.03 (3H, m, $H_{G'} + H_{J'} + H_I$); 1.96–1.87 (1H, m, H_H); 1.53–1.42 (1H, m, $H_{I'}$); 1.04 (3H, s, H_M); 0.83 (3H, s, $H_{M'}$) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 222.2 (Q, C_K), 144.0 (Q, C_D), 138.0 (CH, C_F) 136.5 (CH, C_E), 131.0 (CH, C_A), 129.4 (CH_2, 2 × $C_{B/C}$), 124.4 (CH_2, 2 × $C_{B/C}$), 47.7 (Q, C_L),

46.6 (CH, C_H), 36.0 (CH_2, C_G), 32.7 (CH_2, C_J), 24.8 (CH_2, C_I), 22.8 (CH_3, C_M), 18.0 (CH_3, $C_{M'}$) ppm.

ES$^+$MS: *m/z* (%): 575 ($(2M+Na)^+$, 95), 340 ($(M+Na+MeCN)^+$, 45), 299 ($(M+Na)^+$, 34), 277 ($(M+H)^+$, 100).

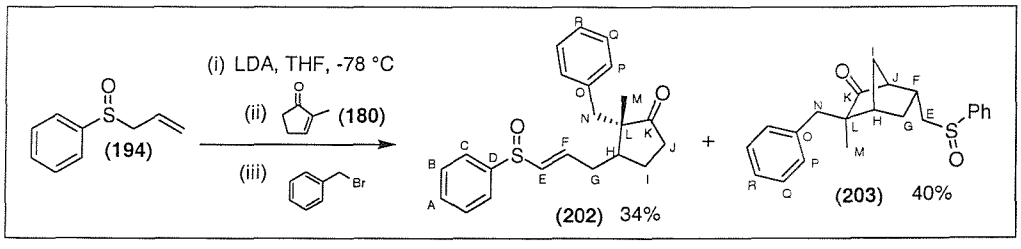
HRES$^+$MS: For $C_{16}H_{20}O_2S$ $(M+Na)^+$: calcd 299.1076, found 299.1077.

Significant data for **(198)**:

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.60–7.53 (2H, m, $H_{A/B/C}$); 7.51–7.42 (3H, m, $H_{A/B/C}$); 2.85 (1H, dd, *J* = 13.2, 4.4 Hz, H_E); 2.73–2.62 (1H, m, H_F); 2.39 (1H, dd, *J* = 13.2, 10.9 Hz, $H_{E'}$); 2.34–2.30 (1H, m, H_J); 2.25–2.20 (1H, m, H_H); 2.15–2.00 (2H, m, H_G + H_I); 1.64 (1H, ddd, *J* = 13.4, 4.4, 2.8 Hz, $H_{G'}$); 1.57 (1H, d, *J* = 10.8 Hz, $H_{I'}$); 1.03 (3H, s, H_M); 0.97 (3H, s, $H_{M'}$) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 220.8 (Q, C_K), 143.5 (Q, C_D), 131.1 (CH, C_A), 129.3 (CH_2, 2 × $C_{B/C}$), 123.9 (CH_2, 2 × $C_{B/C}$), 61.0 (CH_2, C_E), 54.9 (CH, C_J), 48.0 (Q, C_L), 46.4 (CH, C_H), 35.8 (CH_2, C_I), 32.7 (CH, C_F), 28.7 (CH_2, C_G), 23.6 (CH_3, C_M), 20.3 (CH_3, $C_{M'}$) ppm.

3-(3-Benzenesulfinyl-(*E*)-allyl)-2-benzyl-2-methylcyclopentanone (202) and 6-benzenesulfinylmethyl-3-benzyl-3-methylbicyclo-[2.2.1]-heptan-2-one (203)



A LDA solution was freshly prepared by adding ^{n}BuLi (2.5 M in hexanes) (240 μL, 0.60 mmol, 1.0 equiv) to a cooled (−78 °C) solution of diisopropylamine (93 μL, 0.66 mmol, 1.1 equiv) in THF (12 mL). After allowing the LDA solution to stir at −78 °C for 30 min, phenylallylsulfoxide **(194)** (100 mg, 0.60 mmol, 1.0 equiv) was added as a THF (1 mL) solution via syringe. The resultant yellow solution was stirred for 5 min and then a THF (1 mL) solution of the enone **(180)** (59 μL, 0.60 mmol, 1.0 equiv) was added via syringe. After 5 min at −78 °C, benzyl bromide (358 μL, 3.01 mmol, 5.0 equiv) was added. The reaction was removed from the cold bath to warm to room temperature over 1 h. Once at

room temperature, NH_4Cl (sat., aq.) (15 mL) was added and the reaction mixture was extracted with Et_2O (4 × 5 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/acetone 2 : 1) followed by preparative HPLC (hexane/EtOAc 55 : 45) to yield **(202)** (84 mg, 36%) and **(203)** (85 mg, 40%) as colourless oils. The 1,4-addition compound **(202)** could not be completely separated from the allylic sulfoxide starting material, the best purity achieved was 85 : 15, **(202)** : **(194)**.

Data for **(202)**:

Mw = 352.500 ($C_{22}H_{24}O_2S$).

R_f = 0.40 (Hexane/acetone 2 : 1).

IR (film): 1730 (s), 1441 (m), 1081 (m), 1037 (s), 958 (m), 747 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.60–7.55 (2H, m, Ar-H); 7.52–7.45 (3H, m, Ar-H); 7.20–7.14 (3H, m, Ar-H); 7.01 (2H, dd, J = 7.6, 2.3 Hz, Ar-H); 6.52 (1H, dt, J = 14.7, 6.8 Hz, H_F); 6.22 (1H, d, J = 14.7 Hz, H_E); 3.05 (1H, d, J = 13.6 Hz, H_N); 2.51 (1H, d, J = 13.6 Hz, $H_{N'}$); 2.33–2.25 (2H, m); 2.08–1.90 (3H, m); 1.82 (1H, td, J = 9.8, 2.6 Hz); 1.42–1.29 (1H, m); 0.92 (3H, s, H_M) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 221.8 (Q, C_K), 143.9 (Q, C_D), 137.5 (CH, C_F), 137.5 (Q, C_O), 136.1 (CH, C_E), 130.9 (CH, C_A), 129.9 (CH, 2 × $C_{P/Q}$), 129.2 (CH, 2 × $C_{B/C}$), 128.2 (CH, 2 × $C_{P/Q}$), 126.4 (CH, C_R), 124.3 (CH, 2 × $C_{B/C}$), 55.5 (Q, C_L), 41.6 (CH_2, C_N), 40.8 (CH, C_H), 37.3 (CH_2, C_J), 32.6 (CH_2, C_G), 24.7 (CH_2, C_I), 18.0 (CH_3, C_M) ppm.

ES$^+$MS: *m/z* (%): 416 ($(M+Na+MeCN)^+$, 15), 370 (30), 353 ($(M+H)^+$, 35), 128 (100).

HRES$^+$MS: For $C_{22}H_{24}O_2S$ $(M+H)^+$: calcd 353.1570, found 353.1562.

Data for **(203)**:

Mw = 352.500 ($C_{22}H_{24}O_2S$).

R_f = 0.33 (Hexane/acetone 2 : 1).

IR (film): 2964 (w), 1729 (s), 1488 (w), 1446 (m), 1086 (w), 1039 (s), 736 (m), 699 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.64–7.57 (2H, m, Ar-H); 7.55–7.48 (3H, m, Ar-H); 7.33–7.22 (3H, m, $H_{P/Q}$ + Ar-H); 7.16–7.12 (2H, m, $H_{P/Q}$); 2.91 (1H, dd, J = 13.3, 4.4 Hz, H_E); 2.82 (1H, d, J = 13.6 Hz, H_N); 2.81–2.71 (1H, m, H_F); 2.54 (1H, d, J = 13.6 Hz, $H_{N'}$); 2.46 (1H, dd, J = 13.3, 10.7 Hz, $H_{E'}$); 2.47–2.41 (2H, m, H_J + H_H); 2.30 (1H, br d, J = 10.8

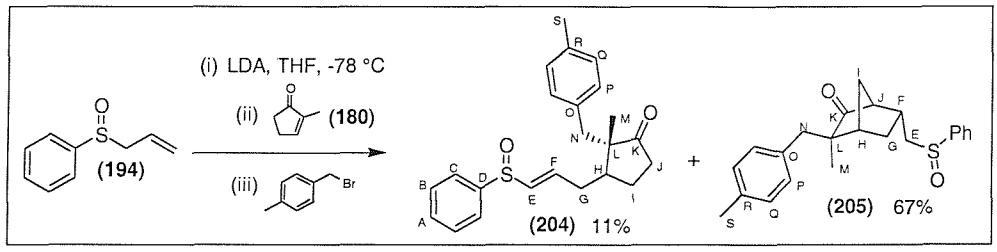
Hz, H_I); 2.08 (1H, ddd, J = 13.5, 11.4, 4.5 Hz, H_G); 1.69 (1H, br d, J = 10.8 Hz, $H_{I'}$); 1.54 (1H, ddd, J = 13.5, 4.3, 2.9 Hz); 0.96 (3H, s, H_M) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 219.8 (Q, C_K), 143.6 (Q, C_D), 136.8 (Q, C_O), 131.1 (CH, C_A), 130.5 (CH, 2 × $C_{P/Q}$), 129.3 (CH, 2 × $C_{B/C}$), 128.1 (CH, 2 × $C_{P/Q}$), 126.6 (CH, C_R), 123.9 (CH, 2 × $C_{B/C}$), 60.8 (CH_2, C_E), 55.3 (CH, C_J), 51.9 (Q, C_L), 42.8 (CH, C_H), 40.5 (CH_2, C_N), 35.6 (CH_2, C_I), 33.0 (CH, C_F), 28.6 (CH_2, C_G), 17.7 (CH_3, C_M) ppm.

ES$^+$MS: *m/z* (%): 727 ($(2M+Na)^+$, 100), 416 ($(M+Na+MeCN)^+$, 52), 353 ($(M+H)^+$, 97).

HRES$^+$MS: For $C_{22}H_{24}O_2S$ $(2M+Na)^+$: calcd 727.2886, found 727.2890.

3-(3-Benzenesulfinyl-(*E*)-allyl)-2-methyl-2-(4-methylbenzyl)cyclopentanone (204) and **6-benzenesulfinylmethyl-3-methyl-3-(4-methylbenzyl)bicyclo-[2.2.1]-heptan-2-one (205)**



A LDA solution was freshly prepared by adding ^{n}BuLi (2.5 M in hexanes) (480 µL, 1.20 mmol, 1.0 equiv) to a cooled (−78 °C) solution of diisopropylamine (186 µL, 1.32 mmol, 1.1 equiv) in THF (25 mL). After allowing the LDA solution to stir at −78 °C for 30 min, phenylallylsulfoxide **(194)** (200 mg, 1.20 mmol, 1.0 equiv) was added as a THF (1 mL) solution via syringe. The resultant yellow solution was stirred for 5 min and then a THF (1 mL) solution of the enone **(180)** (118 µL, 1.20 mmol, 1.0 equiv) was added via syringe. After 2 min at −78 °C, a solution of 4-methylbenzyl bromide (1.113 g, 6.01 mmol, 5 equiv) in THF (1 mL) was added. The reaction was left in the cold bath to warm to room temperature slowly. Once at room temperature, NH_4Cl (sat., aq.) (15 mL) was added and the reaction mixture was extracted with Et_2O (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/acetone 2 : 1) followed by preparative HPLC (hexane/acetone 2 : 1) to yield **(204)** (43 mg, 11%) and **(205)** (298 mg, 67%) as colourless oils.

Data for **(204)**:

Mw = 366.527 ($C_{23}H_{26}O_2S$).

R_f = 0.46 (Neat Et_2O).

IR (film): 2960 (m), 1734 (s), 1512 (m), 1441 (s), 1086 (s), 1044 (s), 954 (m), 812 (m), 746 (s) cm^{-1}.

^1H NMR (400 MHz; $CDCl_3$): δ 7.63–7.59 (2H, m, $H_{A/B/C}$); 7.55–7.46 (3H, m, $H_{A/B/C}$); 7.00 (2H, d, J = 7.8 Hz, $H_{P/Q}$); 6.91 (2H, d, J = 7.8 Hz, $H_{P/Q}$); 6.54 (1H, dt, J = 15.0, 7.0 Hz, H_F); 6.24 (1H, d, J = 15.0 Hz, H_E); 3.04 (1H, d, J = 13.8 Hz, H_N); 2.49 (1H, d, J = 13.8 Hz, H_N); 2.37–2.25 (2H, m, $H_G + H_J$); 2.29 (3H, s, H_S); 2.10–1.75 (4H, m, $H_G + H_H + H_I + H_J$); 1.38 (1H, m, H_I); 0.93 (3H, s, H_M) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 220.0 (Q, C_K), 144.0 (Q, C_D), 137.8 (CH, C_F), 136.1 (CH, C_E), 136.0 (Q, $C_{O/R}$), 134.4 (Q, $C_{O/R}$), 131.0 (CH, C_A), 129.9 (CH, 2 × $C_{P/Q}$), 129.3 (CH, 2 × $C_{B/C}$), 129.0 (CH, 2 × $C_{P/Q}$), 124.4 (CH, 2 × $C_{B/C}$), 52.7 (Q, C_L), 41.3 (CH_2, C_N), 40.9 (CH, C_H), 37.5 (CH_2, C_J), 32.7 (CH_2, C_G), 24.9 (CH_2, C_I), 20.9 (CH_3, C_S), 18.1 (CH_3, C_M) ppm.

HRES$^+$MS: For $C_{23}H_{26}O_2S$ $(M+H)^+$: calcd 367.1727, found 367.1728.

Data for **(205)**:

Mw = 366.527 ($C_{23}H_{26}O_2S$).

R_f = 0.32 (Hexane/acetone 2 : 1).

IR (film): 2978 (m), 1734 (s), 1507 (w), 1446 (m), 1082 (w), 1043 (s), 826 (w), 746 (m), 727 (m) cm^{-1}.

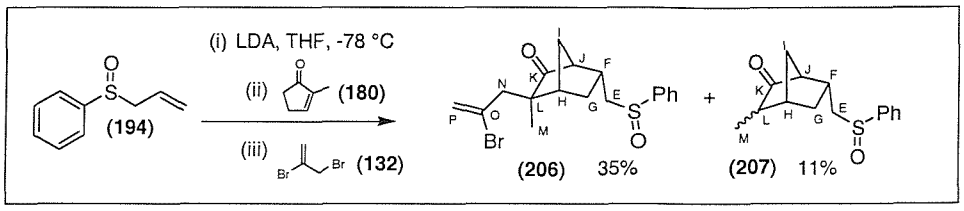
^1H NMR (400 MHz; $CDCl_3$): δ 7.56–7.48 (2H, m, $H_{A/B/C}$); 7.44–7.35 (3H, m, $H_{A/B/C}$); 7.00 (2H, d, J = 7.9 Hz, $H_{P/Q}$); 6.93 (2H, d, J = 7.9 Hz, $H_{P/Q}$); 2.81 (1H, dd, J = 13.3, 4.5 Hz, H_E); 2.75–2.55 (2H, m); 2.44–2.28 (4H, m); 2.23 (3H, s, H_S); 2.24–2.17 (1H, m); 1.95 (1H, ddd, J = 13.6, 11.5, 4.3 Hz); 1.56 (1H, d, J = 10.8 Hz); 1.43 (1H, ddd, J = 13.6, 4.3, 2.8 Hz); 0.87 (3H, s, H_M) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 219.3 (Q, C_K), 143.3 (Q, C_D), 135.7 (Q, $C_{O/R}$), 133.3 (Q, $C_{O/R}$), 130.7 (CH, C_A), 130.0 (CH, 2 × $C_{P/Q}$), 128.9 (CH, 2 × $C_{B/C}$), 128.4 (CH, 2 × $C_{P/Q}$), 123.5 (CH, 2 × $C_{B/C}$), 60.3 (CH_2, C_E), 54.9 (CH, C_J), 51.5 (Q, C_L), 42.4 (CH, C_H), 39.6 (CH_2, C_N), 35.2 (CH_2, C_I), 32.7 (CH, C_F), 28.2 (CH_2, C_G), 20.6 (CH_3, C_S), 17.3 (CH_3, C_M) ppm.

ES$^+$MS: *m/z* (%): 755 ($(2M+Na)^+$, 29), 430 ($(M+Na+MeCN)^+$, 33), 367 ($(M+H)^+$, 20), 225 (100).

HRES$^+$MS: For $C_{23}H_{26}O_2S$ $(2M+Na)^+$: calcd 755.3200, found 755.3216.

6-Benzenesulfinylmethyl-3-(2-bromoallyl)-3-methylbicyclo-[2.2.1]-heptan-2-one (206) and **6-benzenesulfinylmethyl-3-methylbicyclo-[2.2.1]-heptan-2-one (207)**



A LDA solution was freshly prepared by adding ^{n}BuLi (2.5 M in hexanes) (480 µL, 1.20 mmol, 1.0 equiv) to a cooled (−78 °C) solution of diisopropylamine (186 µL, 1.32 mmol, 1.1 equiv) in THF (25 mL). After allowing the LDA solution to stir at −78 °C for 30 min, phenylallylsulfoxide **(194)** (200 mg, 1.20 mmol, 1.0 equiv) was added as a THF (1 mL) solution via syringe. The resultant yellow solution was stirred for 5 min and then a THF (1 mL) solution of the enone **(180)** (118 µL, 1.20 mmol, 1.0 equiv) was added via syringe. After 2 min at −78 °C, a solution of 2,3-dibromopropene **(132)** (588 µL, 6.01 mmol, 5.0 equiv) in THF (1 mL) was added. The reaction was left in the cold bath to warm to room temperature slowly. Once at room temperature, NH_4Cl (sat., aq.) (15 mL) was added and the reaction mixture was extracted with Et_2O (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/acetone 2 : 1) followed by preparative HPLC (hexane/EtOAc 2 : 1) to yield **(206)** as a colourless oil (160 mg, 35%) and **(207)** as a white solid (54 mg, 11%) and as a single diastereoisomer, relative stereochemistry unknown. **(207)** could be further purified by recrystallisation from hot EtOH to afford white crystals.

Data for **(206)**:

Mw = 381.336 ($C_{18}H_{21}BrO_2S$).

R_f = 0.36 (Hexane/acetone 2 : 1).

IR (film): 2964 (w), 1734 (s), 1621 (w), 1441 (w), 1086 (m), 1048 (s), 745 (w), 694 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.65–7.57 (2H, m, $H_{A/B/C}$); 7.56–7.48 (3H, m, $H_{A/B/C}$); 5.64–5.57 (2H, m, H_P); 2.99–2.86 (1H, m); 2.89 (1H, dd, J = 13.3, 4.6 Hz, H_E); 2.82–2.70 (1H, m, H_F); 2.65 (1H, d, J = 14.9 Hz, H_N); 2.48 (1H, d, J = 14.9 Hz, $H_{N'}$); 2.47 (1H, dd, J = 13.2, 10.5 Hz, $H_{E'}$); 2.41–2.37 (1H, m); 2.17 (1H, ddd, J = 13.5, 11.4, 4.6 Hz, H_G); 2.14–2.07 (1H, m); 1.71–1.61 (2H, m); 1.10 (3H, s, H_M) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 219.2 (Q, C_K), 143.6 (Q, C_D), 131.2 (CH, C_A), 129.4 (CH, 2 × $C_{B/C}$), 127.8 (Q, C_O), 123.9 (CH, 2 × $C_{B/C}$), 121.8 (CH_2, C_P), 60.7 (CH_2, C_E), 54.8 (CH, C_J), 51.2 (Q, C_L), 45.2 (CH_2, C_N), 42.9 (CH, C_H), 35.6 (CH_2, C_I), 33.0 (CH, C_F), 28.7 (CH_2, C_G), 17.7 (CH_3, C_M) ppm.

ES$^+$MS: *m/z* (%): 783/785/787 (1 : 2 : 1, $(2M+Na)^+$, 27), 444/446 (1 : 1, $(M+Na+MeCN)^+$, 31), 381/383 (1 : 1, $(M+H)^+$, 15), 225 (100).

HRES$^+$MS: For $C_{18}H_{21}BrO_2S$ $(2M+Na)^+$: calcd 785.0784, found 783.0786.

Data for (**207**):

Mw = 262.375 ($C_{15}H_{18}O_2S$).

M.P. = 145–146 °C.

R_f = 0.35 (Neat Et_2O).

IR (film): 2965 (m), 1725 (s), 1442 (m), 1311 (m), 1130 (w), 1088 (m), 1037 (s), 920 (m), 745 (s) cm^{-1}.

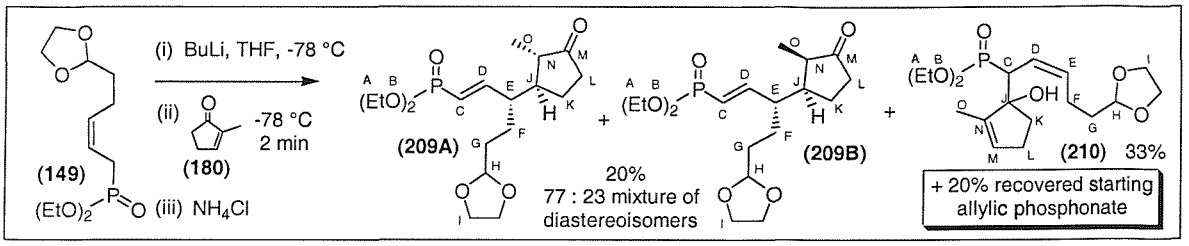
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.60–7.54 (2H, m, $H_{A/B/C}$); 7.52–7.45 (3H, m, $H_{A/B/C}$); 2.88 (1H, dd, J = 13.1, 3.8 Hz, H_E); 2.74–2.64 (1H, m, H_F); 2.39–2.28 (4H, m, H_J + H_G + H_H + $H_{E'}$); 1.91 (1H, m, H_I); 1.78 (1H, qd, J = 7.5, 3.8 Hz, H_L); 1.62 (1H, m, $H_{I'}$); 1.32–1.25 (1H, m, $H_{G'}$); 1.04 (3H, d, J = 7.5 Hz, H_M) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 218.9 (Q, C_K), 143.7 (Q, C_D), 131.1 (CH, C_A), 129.3 (CH, 2 × $C_{B/C}$), 123.8 (CH, 2 × $C_{B/C}$), 61.8 (CH_2, C_E), 54.4 (CH, C_J), 49.5 (CH, C_L), 41.6 (CH, C_H), 35.1 (CH_2, C_I), 34.7 (CH_2, C_G), 31.6 (CH, C_F), 14.1 (CH_3, C_M) ppm.

ES$^+$MS: *m/z* (%): 547 ($(2M+Na)^+$, 100), 326 ($(M+Na+MeCN)^+$, 57), 285 ($(M+Na)^+$, 21), 263 ($(M+H)^+$, 24).

HRES$^+$MS: For $C_{15}H_{18}O_2S$ $(M+H)^+$: calcd 263.1101, found 263.1099.

[5-[1,3]-Dioxolan-2-yl-3-(*S*)-(2-(*S*)-methyl-3-oxocyclopentyl)pent-1-(*E*)-enyl]phosphonic acid diethyl ester (209A) and **[5-[1,3]-dioxolan-2-yl-3-(*S*)-(2-(*R*)-methyl-3-oxocyclopentyl)pent-1-(*E*)-enyl]phosphonic acid diethyl ester (209B)** and **[5-[1,3]-dioxolan-2-yl-1-(1-hydroxy-2-methylcyclopent-2-enyl)pent-2-(*Z*)-enyl]phosphonic acid diethyl ester (210)**



To a cooled (−78 °C) solution of the phosphonate **(149)** (100 mg, 0.36 mmol, 1.0 equiv) in THF (8 mL)was added ^{n}BuLi (2.5 M in hexanes) (149 μL, 0.36 mmol, 1.0 equiv) over 2 min. The yellow solution was stirred for 5 min at −78 °C and then a THF (1 mL) solution of the enone **(180)** (35 μL, 0.36 mmol, 1.0 equiv) was added via syringe. After 2 min at −78 °C, NH_4Cl (sat., aq.) (1 mL) was added and the reaction mixture was warmed to room temperature over 1 h. Extra NH_4Cl was added (15 mL) and the reaction was extracted with EtOAc (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/acetone 2 : 1) to yield **(149)** (20 mg, 20%), **(209A)** and **(209B)** (27 mg, 20%) and **(210)** (43 mg, 33%) as colourless oils. The mixture of **(209A)** and **(209B)** was found to be a 77 : 23 ratio and these diastereoisomers could be separated by repeated preparative HPLC (hexane/acetone 2 : 1).

Data for **(209A)**:

Mw = 374.420 ($C_{18}H_{31}O_6P$).

R_f = 0.10 (Hexane/acetone 2 : 1).

IR (film): 2974 (m), 2869 (m), 1734 (s), 1630 (w), 1247 (m), 1129 (m), 1053 (s), 1020 (s) 959 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.63 (1H, ddd, J = 21.6, 17.1, 9.3 Hz, H_D); 5.72 (1H, dd, J = 20.6, 17.1 Hz, H_C); 4.84 (1H, t, J =4.3 Hz, H_H); 4.13–4.04 (4H, m, H_B); 3.99–3.82 (4H, m, H_I); 2.40–2.26 (2H, m); 2.19–2.08 (2H, m); 1.91–1.68 (4H, m); 1.60–1.44 (3H, m); 1.33 (6H, t, J = 7.0 Hz, H_A); 1.11 (3H, d, J = 6.8 Hz, H_O) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 220.1 (Q, C_M), 154.7 (d, J = 3.9 Hz, CH, C_D), 119.0 (d, J = 186.6 Hz, CH, C_C), 104.1 (CH, C_H), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.6 (d, J = 4.9 Hz, CH_2, 2 × C_B), 48.6 (CH), 48.4 (CH), 47.5 (CH), 37.0 (CH_2), 31.5 (CH_2), 25.0 (CH_2), 24.4 (CH_2), 16.4 (d, J = 5.8 Hz, CH_3, 2 × C_A), 14.5 (CH_3, C_O) ppm.

CIMS: *m/z* (%): 375 ($(M+H)^+$, 100), 329 (9), 278 (17), 233 (12), 191 (9), 159 (13), 97 (77), 73 (72).

HRES$^+$MS: For $C_{18}H_{31}O_6P$ $(M+H)^+$: calcd 375.1931, found 375.1928.

Data for **(209B)**:

Mw = 374.420 ($C_{18}H_{31}O_6P$).

R_f = 0.10 (Hexane/acetone 2 : 1).

IR (film): 2974 (m), 2869 (m), 1734 (s), 1630 (w), 1247 (m), 1129 (m), 1053 (s), 1020 (s) 959 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.54 (1H, ddd, J = 21.6, 17.1, 9.3 Hz, H_D); 5.70 (1H, dd, J = 20.6, 17.1 Hz, H_C); 4.84 (1H, t, J =4.3 Hz, H_H); 4.12–4.02 (4H, m, H_B); 3.98–3.81 (4H, m, H_I); 2.42–2.12 (6H, m); 1.83–1.50 (5H, m); 1.33 (6H, t, J = 7.0, H_A); 0.97 (3H, d, J = 6.8 Hz, H_O) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 221.1 (Q, C_M), 154.7 (d, J = 3.9 Hz, CH, C_D), 118.7 (d, J = 186.6 Hz, CH, C_C), 104.1 (CH, C_H), 65.0 (CH_2, C_I), 64.9 (CH_2, $C_{I'}$), 61.7 (d, J = 4.9 Hz, CH_2, 2 × C_B), 45.2 (CH), 44.8 (CH), 43.9 (CH), 37.1 (CH_2), 31.0 (CH_2), 25.4 (CH_2), 24.0 (CH_2), 16.4 (d, J = 6.8 Hz, CH_3, 2 × C_A), 8.4 (CH_3, C_O) ppm.

CIMS: *m/z* (%): 375 ($(M+H)^+$, 40), 278 (9), 233 (6), 207 (13), 191 (5), 156 (8), 97 (100), 73 (51).

HRES$^+$MS: For $C_{18}H_{31}O_6P$ $(M+H)^+$: calcd 375.1931, found 375.1929.

Data for **(210)**:

Mw = 374.420 ($C_{18}H_{31}O_6P$).

R_f = 0.24 (Hexane/acetone 2 : 1).

IR (film): 3399 (br, m), 2974 (m), 2851 (m), 1446 (w), 1389 (w), 1228 (m), 1134 (m), 1053 (s), 1025 (s), 968 (s) 746 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.58–5.49 (2H, m, H_E + H_M); 5.06 (1H, tdt, J = 10.7, 4.0, 2.0 Hz, H_D); 4.91 (1H, s, OH); 4.86 (1H, t, J = 4.5 Hz, H_H); 4.22–4.09 (4H, m, H_B); 3.97–3.81 (4H, m, H_I); 3.34 (1H, dd, J = 21.1, 10.7 Hz, H_C); 2.50–2.38 (2H, m); 2.27–2.12

(3H, m); 2.06–1.98 (1H, m), 1.76–1.69 (2H, m); 1.60 (3H, d, J = 1.6 Hz, H_O); 1.34 (6H, t, J = 7.0 Hz, H_A) ppm.

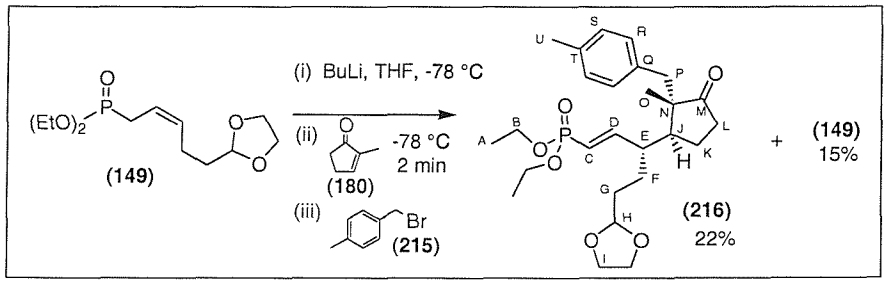
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 141.1 (d, J = 16.5 Hz, Q, C_N), 133.0 (d, J = 12.1 Hz, CH, C_E), 129.2 (CH, C_M), 121.2 (d, J = 10.7 Hz, CH, C_D), 103.8 (CH, C_H), 85.7 (d, J = 4.4 Hz, Q, C_J), 64.9 (CH_2, 2 × C_I), 62.3 (d, J = 6.3 Hz, CH_2, 2 × C_B), 44.5 (d, J = 132.7 Hz, CH, C_C), 34.9 (d, J = 2.9 Hz, CH_2, $C_{K/L}$), 33.4 (d, J = 2.9 Hz, CH_2, C_G), 29.8 (CH_2, $C_{K/L}$), 22.4 (d, J = 2.4 Hz, CH_2, C_F), 16.4 (d, J = 5.8 Hz, CH_3, C_A), 16.3 (d, J = 5.8 Hz, CH_3, $C_{A'}$), 11.2 (CH_3, C_O) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 29.98 ppm.

EIMS: *m/z* (%): 373 ($(M-H)^+$, 2), 356 (7), 276 (6), 218 (28), 129 (29), 115 (37), 91 (47), 73 (100).

HRES$^+$MS: For $C_{18}H_{31}O_6P$ $(M+Na)^+$: calcd 397.1750, found 397.1747.

{5-[1,3]-Dioxolan-2-yl-3-(*S*)-[2-methyl-2-(*S*)-(4-methylbenzyl)-3-oxocyclopentyl]pent-1-(*E*)-enyl}phosphonic acid diethyl ester (216)



To a cooled (−78 °C) solution of the phosphonate **(149)** (100 mg, 0.36 mmol, 1.0 equiv) in THF (8 mL) was added ^{n}BuLi (2.5 M in hexanes) (149 μL, 0.36 mmol, 1.0 equiv) over 2 min. The yellow solution was stirred for 5 min at −78 °C and then a THF (1 mL) solution of the enone **(180)** (35 μL, 0.36 mmol, 1.0 equiv) was added via syringe. After 2 min at −78 °C, a solution of 4-methylbenzyl bromide **(215)** (200 mg, 1.08 mmol, 3 equiv) in THF (1 mL) was added over 30 seconds and the reaction mixture was slowly warmed to room temperature overnight. NH_4Cl (sat., aq.) (15 mL) was added and the reaction was extracted with EtOAc (4 × 6 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/acetone 2 : 1) followed by preparative HPLC (hexane/acetone 2 : 1). This yielded **(216)** (39 mg, 22%) and **(149)** (15 mg, 15%) as colourless oils.

Mw = 478.572 ($C_{26}H_{39}O_6P$).

R_f = 0.31 (Hexane/acetone 1 : 1).

IR (film): 2974 (w), 1735 (s), 1629 (w), 1515 (w), 1243 (m), 1140 (m), 1050 (s), 1025 (s), 961 (m), 841 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.05 (2H, d, *J* = 8.0 Hz, $H_{S/R}$); 6.99 (2H, d, *J* = 8.0 Hz, $H_{S/R}$); 6.67 (1H, ddd, *J* = 21.6, 17.1, 10.0 Hz, H_D); 5.73 (1H, dd, *J* = 21.6, 17.1 Hz, H_C); 4.79 (1H, t, *J* = 4.5 Hz, H_H); 4.18–4.08 (4H, m, H_B); 3.94–3.78 (4H, m, H_I); 3.15 (1H, d, *J* = 13.9 Hz, H_P); 2.49 (1H, d, *J* = 13.9 Hz, $H_{P'}$); 2.36–2.24 (2H, m, $H_L + H_E$); 2.28 (3H, s, H_U); 2.07–1.93 (2H, m, $H_K + H_J$); 1.81–1.70 (2H, m, $H_{L'} + H_F$); 1.64 (1H, m, H_G); 1.52–1.20 (3H, m, $H_{G'} + H_{K'} + H_{F'}$); 1.35 (6H, t, *J* = 7.0 Hz, H_A); 1.01 (3H, s, H_O) ppm.

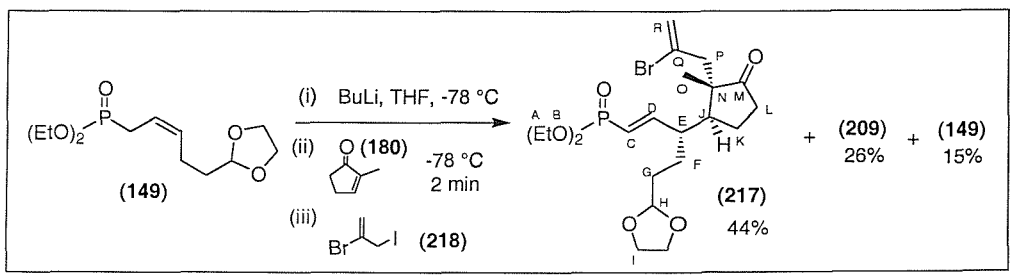
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 223.6 (Q, C_M), 155.6 (d, *J* = 3.9 Hz, CH, C_D), 135.8 (Q, $C_{T/Q}$), 134.8 (Q, $C_{T/Q}$), 130.1 (CH, $C_{S/R}$), 129.1 (CH, $C_{S/R}$), 118.8 (d, *J* = 186.6 Hz, CH, C_C), 104.1 (CH, C_H), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.7 (d, *J* = 5.4 Hz, CH_2, C_B), 61.6 (d, *J* = 5.4 Hz, CH_2, $C_{B'}$), 53.6 (Q, C_N), 46.7 (d, *J* = 21.3 Hz, CH, C_E), 43.5 (CH, C_J), 42.0 (CH_2, C_P), 38.2 (CH_2, C_L), 31.0 (CH_2, C_G), 25.5 (d, *J* = 1.9 Hz, CH_2, C_F), 23.8 (CH_2, C_K), 20.9 (CH_3, C_U), 19.2 (CH_3, C_O), 16.5 (d, *J* = 6.8 Hz, CH_3, C_A), 16.4 (d, *J* = 6.8 Hz, CH_3, $C_{A'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.08 ppm.

CIMS: *m/z* (%): 479 ($(M+H)^+$, 10), 377 (2), 295 (11), 278 (54), 233 (28), 206 (25), 191 (11), 178 (19), 156 (31), 138 (12), 105 (100), 91 (16), 73 (35).

HRES$^+$MS: For $C_{26}H_{39}O_6P$ $(M+H)^+$: calcd 479.2557, found 479.2551.

{3-(*S*)-[2-(2-(*S*)-Bromoallyl)-2-methyl-3-oxocyclopentyl]-5-[1,3]-dioxolan-2-ylpent-1-(*E*)-enyl}phosphonic acid diethyl ester (217)



To a cooled (−78 °C) solution of the phosphonate **(149)** (116 mg, 0.42 mmol, 1.0 equiv) in THF (8 mL)was added ^{n}BuLi (2.5 M in hexanes) (175 μL, 0.42 mmol, 1.0 equiv) over 2 min. The yellow solution was stirred for 5 min at −78 °C and then a THF (1 mL) solution of the enone **(180)** (41 μL, 0.42 mmol, 1.0 equiv) was added via syringe. After the addition, the flask was placed in a 0 °C cold bath. After 2 min, a solution of 2-bromo-3-iodopropene **(218)** (64 μL, 0.46 mmol, 1.1 equiv) in THF (1 mL) was added over 30 seconds and the reaction mixture was warmed to room temperature over 1 h. NH_4Cl (sat., aq.) (15 mL) was added and the reaction was extracted with EtOAc (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 3 : 2) followed by preparative HPLC (hexane/acetone 55 : 45). This yielded **(217)** (91 mg, 44%), **(209)** (35 mg, 26%) and **(149)** (18 mg, 15%) as colourless oils.

Mw = 493.381 ($C_{21}H_{34}BrO_6P$).

R_f = 0.39 (Hexane/acetone 3 : 2).

IR (film): 2950 (br m), 1739 (m), 1621 (w), 1451 (w), 1403 (w), 1361 (w), 1238 (m), 1134 (w), 1049 (s), 1025 (s), 963 (m), 841 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.61 (1H, ddd, J = 27.2, 17.1, 10.0 Hz, H_D); 6.02 (1H, t, J = 1.6 Hz, H_R); 5.69 (1H, dd, J = 20.8, 17.1 Hz, H_C); 5.56 (1H, br s, $H_{R'}$); 4.83 (1H, t, J = 4.6 Hz, H_H), 4.09 (4H, m, H_B); 3.90 (4H, m, H_I); 3.06 (1H, d, J = 14.9 Hz, H_P); 2.52 (1H, d, J = 14.9 Hz, $H_{P'}$); 2.44–2.20 (5H, m, H_K + $H_{K'}$ + H_L + H_J + H_E); 1.91–1.82 (1H, m, H_F); 1.73–1.63 (1H, m, H_G); 1.55–1.35 (3H, m, $H_{G'}$ + $H_{L'}$ + $H_{F'}$); 1.35 (6H, t, J = 7.0 Hz, H_A); 0.87 (3H, s, H_O) ppm.

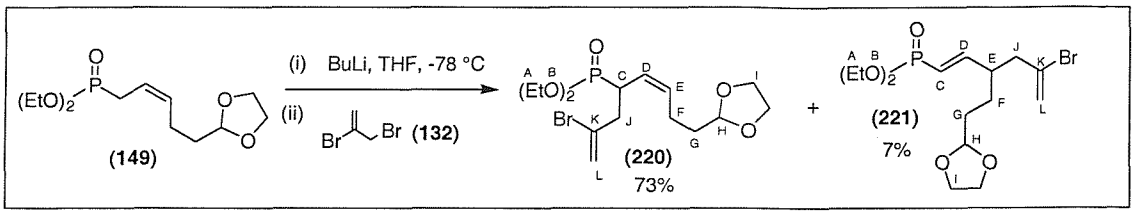
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 221.5 (Q, C_M), 155.3 (d, J = 3.9 Hz, CH, C_D), 129.9 (Q, C_Q), 122.6 (CH_2, C_R), 119.0 (d, J = 187.1 Hz, CH, C_C), 104.1 (CH, C_H), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.7 (d, J = 5.8 Hz, CH_2, C_B), 61.6 (d, J = 5.8 Hz, CH_2, $C_{B'}$), 51.6 (Q, C_N), 47.2 (d, J = 20.9 Hz, CH, C_E), 47.1 (CH_2, C_P), 43.7 (CH, C_J), 36.9 (CH_2, C_K), 30.9 (CH_2, C_G), 25.8 (d, J = 1.9 Hz, CH_2, C_F), 24.0 (CH_2, C_L), 18.7 (CH_3, C_O), 16.5 (d, J = 6.3 Hz, CH_3, C_A), 16.4 (d, J = 6.3 Hz, CH_3, $C_{A'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.88 ppm.

EIMS: (11.91 min) *m/z* (%): 493/495 (1 : 1, $(M+H)^+$, 9), 413 (4), 279 (4), 153 (15), 137 (9), 114 (8), 97 (100), 73 (10).

Anal: Calcd for $C_{21}H_{34}BrO_6P$: C, 51.12; H, 6.95. Found: C, 50.83; H, 7.11.

[1-(2-Bromoallyl)-5-[1,3]-dioxolan-2-ylpent-2-(*Z*)-enyl]phosphonic acid diethyl ester (220) and **[5-bromo-3-(2-[1,3]-dioxolan-2-ylethyl)hexa-1-(*E*)-5-dienyl]phosphonic acid diethyl ester (221)**



To a cooled (–78 °C) solution of the phosphonate **(149)** (100 mg, 0.36 mmol, 1.0 equiv) in THF (8 mL) was added ^{n}BuLi (2.4 M in hexanes) (150 μL, 0.36 mmol, 1.0 equiv) over 2 min. The solution was stirred for 5 min at –78 °C and then for 2 min at 0 °C before a THF (1 mL) solution of the bromide **(132)** (106 μL, 1.06 mmol, 3.0 equiv) in THF (1 mL) was added over 30 seconds. The reaction mixture was then warmed to room temperature over 1 h. NH_4Cl (sat., aq.) (15 mL) was added and the reaction was extracted with Et_2O (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 2 : 1) followed by preparative HPLC (hexane/acetone 2 : 1). This yielded **(220)** (84 mg, 73%) and **(221)** (5 mg, 7%) as colourless oils.

Data for **(220)**:

Mw = 397.251 ($C_{15}H_{26}BrO_5P$).

R_f = 0.33 (Hexane/acetone 2 : 1).

IR (film): 1626 (w), 1432 (w), 1394 (w), 1242 (s), 1141 (m), 1055 (s), 1027 (s), 966 (s), 727 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.65 (1H, m, H_E); 5.53 (1H, br s, H_L); 5.38 (1H, br s, $H_{L'}$); 5.11 (1H, tdt, J = 10.7, 5.0, 1.6 Hz, H_D); 4.85 (1H, t, J = 4.8 Hz, H_H); 4.07 (4H, m, H_B); 3.86 (4H, m, H_I); 3.25 (1H, dtd, J = 21.6, 11.0, 3.1 Hz, H_C); 2.86 (1H, m, H_J); 2.58 (1H, ddd, J = 18.8, 11.1, 7.6 Hz, $H_{J'}$); 2.31–2.13 (2H, m, H_F); 1.70 (2H, td, J = 7.9, 4.6 Hz, H_G); 1.28 (6H, d, J = 7.2 Hz, H_A) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 134.5 (d, J = 13.6 Hz, CH, C_E), 131.1 (d, J = 21.4 Hz, Q, C_K), 122.9 (d, J = 9.7 Hz, CH, C_D), 118.8 (CH_2, C_L), 103.9 (CH, C_H), 64.8 (CH_2, 2 ×

C_I), 62.3 (d, J = 6.8 Hz, CH_2, C_B), 61.9 (d, J = 6.8 Hz, CH_2, $C_{B'}$), 41.0 (d, J = 2.9 Hz, CH_2, C_J), 35.3 (d, J = 141.9 Hz, CH, C_C), 33.6 (d, J = 2.9 Hz, CH_2, C_G), 22.4 (d, J = 1.9 Hz, CH_2, C_F), 16.4 (d, J = 5.8 Hz, CH_3, C_A), 16.3 (d, J = 5.8 Hz, CH_3, $C_{A'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 28.46 ppm.

ES$^+$MS: *m/z* (%): 815/817/819 (1 : 2 : 1, $(2M+Na)^+$, 100), 460/462 (1 : 1, $(M+Na+MeCN)^+$, 49), 419/421 (1 : 1, $(M+Na)^+$, 57), 397/399 (1 : 1, $(M+H)^+$, 28).

HRES$^+$MS: For $C_{15}H_{26}BrO_5P$ $(M+H)^+$: calcd 397.0774, found 397.0771.

Data for **(221)**:

Mw = 397.251 ($C_{15}H_{26}BrO_5P$).

R_f = 0.26 (Hexane/acetone 2 : 1).

IR (film): 1630 (w), 1239 (m), 1143 (w), 1054 (m), 1027 (s), 946 (m), 911 (m), 731 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.51 (1H, ddd, J = 21.8, 17.1, 8.8 Hz, H_D); 5.53 (1H, dd, J = 20.2, 17.1 Hz, H_C); 5.57 (1H, br d, J = 1.2 Hz, H_L); 5.43 (1H, br d, J = 1.2 Hz, $H_{L'}$); 4.85 (1H, t, J = 4.1 Hz, H_H); 4.05 (4H, m, H_B); 3.90 (4H, m, H_I); 2.65 (1H, m, H_E); 2.53 (1H, dd, J = 14.3, 5.7 Hz, H_J); 2.44 (1H, dd, J = 14.3, 8.5 Hz, $H_{J'}$); 1.71–1.59 (3H, m, H_G + $H_{G'}$ + $H_{F'}$); 1.48 (1H, m, H_F); 1.32 (6H, d, J = 7.0 Hz, H_A) ppm.

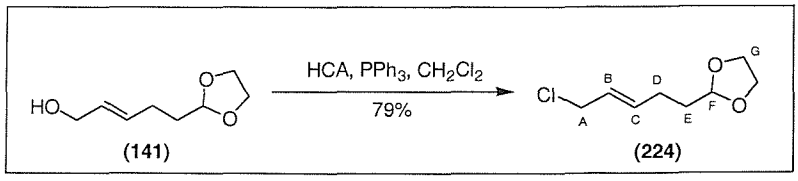
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 154.5 (d, J = 4.4 Hz, CH, C_D), 131.6 (Q, C_K), 118.8 (CH_2, C_L), 118.6 (d, J = 184.7 Hz, CH, C_C), 104.0 (CH, C_H), 64.9 (CH_2, 2 × C_I), 61.7 (d, J = 5.3 Hz, CH_2, C_B), 61.6 (d, J = 5.3 Hz, CH_2, $C_{B'}$), 45.9 (d, J = 1.5 Hz, CH_2, C_J), 42.3 (d, J = 21.4 Hz, CH, C_E), 31.3 (CH_2, C_G), 27.2 (d, J = 1.0 Hz, CH_2, C_F), 16.4 (d, J = 6.3 Hz, CH_3, 2 × C_A) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.63 ppm.

ES$^+$MS: *m/z* (%): 815/817/819 (1 : 2 : 1, $(2M+Na)^+$, 73), 460/462 (1 : 1, $(M+Na+MeCN)^+$, 100), 419/421 (1 : 1, $(M+Na)^+$, 58), 397/399 (1 : 1, $(M+H)^+$, 55).

HRES$^+$MS: For $C_{15}H_{26}BrO_5P$ $(M+H)^+$: calcd 397.0774, found 397.0771.

2-(5-Chloropent-3-(*E*)-enyl)-[1,3]-dioxolane (224)



To a solution of the allylic alcohol **(141)** (0.80 g, 5.05 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added a solution of triphenylphosphine (1.60 g, 5.56 mmol, 1.1 equiv) in CH_2Cl_2 (30 mL). Upon complete dissolution, the mixture was cooled to 0 °C and a solution of hexachloroacetone (850 µL, 5.56 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL) and added via syringe over 2 min. The cold bath was then removed and the reaction was stirred for 10 min. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (hexane/EtOAc 8 : 1) followed by preparative HPLC (hexane/acetone 96 : 4). This yielded **(224)** as a colourless oil (0.70 g, 79%).

Mw = 176.643 ($C_8H_{13}O_2Cl$).

R_f = 0.26 (Hexane/EtOAc 8 : 1).

IR (film): 2959 (s), 2889 (s), 1668 (w), 1441 (m), 1408 (m), 1252 (m), 1134 (s), 1039 (s), 963 (s), 902 (m) cm^{-1}.

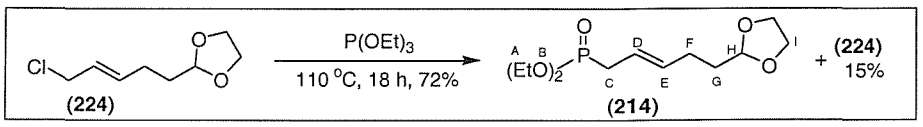
^{1}H NMR (400 MHz; $CDCl_3$): δ 5.81 (1H, dt, J = 15.1, 6.7 Hz, H_C); 5.65 (1H, dtt, J = 15.1, 7.0, 1.4 Hz, H_B); 4.88 (1H, t, J = 4.6 Hz, H_F); 4.03 (2H, dd, J = 7.0, 0.8 Hz, H_A); 3.99–3.81 (4H, m, H_G); 2.28 (2H, dt, J = 6.8, 6.8 Hz, H_D); 1.76 (2H, dt, J = 8.0, 4.6 Hz, H_E) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 135.0 (CH, C_C), 126.3 (CH, C_B), 103.8 (CH, C_F), 64.9 (CH_2, 2 × C_G), 45.3 (CH_2, C_A), 32.9 (CH_2, C_E), 26.4 (CH_2, C_D) ppm.

CIMS: *m/z* (%): 177 ($(M+H)^+$, 28), 141 (55), 99 (14), 73 (100).

HREIMS: For $C_8H_{13}O_2Cl$ $(M-H)^+$: calcd 175.0526, found 175.0520.

(5-[1,3]-Dioxolan-2-ylpent-2-(*E*)-enyl)phosphonic acid diethyl ester (214)



The allylic chloride **(224)** (689 mg, 3.90 mmol, 1.0 equiv) and triethyl phosphite (2.01 mL, 11.70 mmol, 3.0 equiv) were combined and heated between 110 and 130 °C for 18 h. The mixture was cooled and purified by column chromatography (hexane/EtOAc 8 : 1, followed by hexane/acetone 3 : 2). This yielded **(224)** (106 mg, 15%) and **(214)** (784 mg, 72%) as colourless oils.

Mw = 278.290 ($C_{12}H_{23}O_5P$).

R_f = 0.27 (Hexane/acetone 3 : 2).

IR (film): 2983 (m), 2907 (w), 1649 (w), 1484 (w), 1403 (w), 1238 (m), 1134 (m), 1044 (s), 1020 (s), 959 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.68–5.57 (1H, m, H_E); 5.49–5.38 (1H, m, H_C); 4.85 (1H, t, J = 4.7 Hz, H_H); 4.15–4.03 (4H, m, H_B); 4.00–3.79 (4H, m, H_I); 2.53 (2H, dd, J = 22.1, 6.9 Hz, H_C); 2.21–2.13 (2H, m, H_F); 1.76–1.69 (2H, m, H_G); 1.30 (6H, t, J = 7.1 Hz, H_A) ppm.

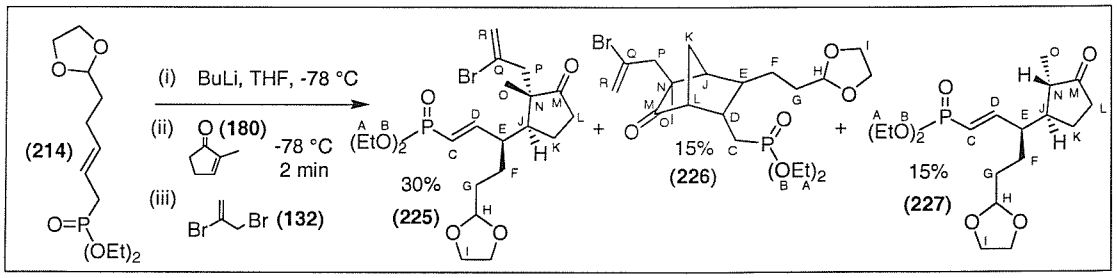
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 134.9 (d, J = 14.6 Hz, CH, C_E), 119.1 (d, J = 11.2 Hz, CH, C_D), 103.9 (CH, C_H), 64.8 (CH_2, 2 × C_I), 61.8 (d, J = 6.8 Hz, CH_2, 2 × C_B), 33.3 (d, J = 3.2 Hz, CH_2, C_G), 30.4 (d, J = 139.7 Hz, CH_2, C_C), 27.0 (d, J = 2.2 Hz, CH_2, C_F), 16.4 (d, J = 6.1 Hz, CH_3, 2 × C_A) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 28.50 ppm.

EIMS: *m/z* (%): 278 ($(M)^+$, 4), 235 (6), 206 (13), 156 (35), 127 (18), 99 (18), 73 (100).

Anal: Calcd for $C_{12}H_{23}O_5P$: C, 51.79; H, 8.33. Found: C, 51.49; H, 8.61.

{3-(*R*)-[2-(2-(*S*)-Bromoallyl)-2-methyl-3-oxocyclopentyl]-5-[1,3]-dioxolan-2-ylpent-1-(*E*)-enyl}phosphonic acid diethyl ester (225) and **[5-(2-bromoallyl)-3-(2-[1,3]-dioxolan-2-ylethyl)-5-methyl-6-oxobicyclo-[2.2.1]-hept-2-ylmethyl]phosphonic acid diethyl ester (226)** and **[5-[1,3]-dioxolan-2-yl-3-(2-(*S*)-methyl-3-(*R*)-oxocyclopentyl)pent-1-(*E*)-enyl]phosphonic acid diethyl ester (227)**



To a cooled (–78 °C) solution of the phosphonate (**214**) (124 mg, 0.45 mmol, 1.0 equiv) in THF (8 mL) was added ^{n}BuLi (2.4 M in hexanes) (204 μL, 0.49 mmol, 1.1 equiv) over 2 min. The yellow solution was stirred for 5 min at –78 °C and then a THF (1 mL) solution of the enone (**180**) (66 μL, 0.67 mmol, 1.0 equiv) was added via syringe. After the addition, the flask was placed in a 0 °C cold bath. After 2 min, a solution of 2,3-dibromopropene (**132**) (65 μL, 0.67 mmol, 1.5 equiv) in THF (1 mL) was added over 30 seconds and then the

reaction mixture was warmed to room temperature over 1 h. NH_4Cl (sat., aq.) (15 mL) was added and the reaction was extracted with EtOAc (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 3 : 2) followed by preparative HPLC (EtOAc/MeOH 98 : 2). This yielded **(227)** (25 mg, 15%), as a colourless oil and analytically pure samples of **(225)** (10 mg) and **(226)** (7 mg) as colourless oils. By extrapolation of the NMR of the initial mixture of **(225)** and **(226)**, the yields could be calculated as 30% and 15% respectively.

Data for **(225)**:

Mw = 493.381 ($C_{21}H_{34}BrO_6P$).

R_f = 0.34 (Hexane/acetone 3 : 2).

IR (film): 2974 (w), 2888 (w), 1734 (w), 1626 (w), 1389 (w), 1243 (m), 1129 (m), 1053 (s), 1020 (s), 959 (s), 850 (w), 789 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.54 (1H, ddd, J = 26.5, 17.1, 9.4 Hz, H_D); 5.68 (1H, dd, J = 20.6, 17.1 Hz, H_C); 5.61 (1H, t, J = 1.0 Hz, H_R); 5.54 (1H, t, J = 1.0 Hz, $H_{R'}$); 4.83 (1H, t, J = 4.4 Hz, H_H), 4.15–4.02 (4H, m, H_B); 3.90 (4H, m, H_I); 3.17 (1H, d, J = 14.9 Hz, H_P); 2.62 (1H, d, J = 14.9 Hz, $H_{P'}$); 2.43–2.26 (4H, m, $H_K + H_{K'} + H_J + H_E$); 2.06–1.98 (1H, m, H_L); 1.87–1.75 (1H, m, H_F); 1.73–1.62 (1H, m, H_G); 1.57–1.40 (3H, m, $H_{G'} + H_{L'} + H_{F'}$); 1.33 (6H, t, J = 7.0 Hz, H_A); 0.92 (3H, s, H_O) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 221.2 (Q, C_M), 155.7 (d, J = 4.1 Hz, CH, C_D), 129.7 (Q, C_Q), 121.7 (CH_2, C_R), 119.2 (d, J = 185.6 Hz, CH, C_C), 103.9 (CH, C_H), 65.0 (CH_2, C_I), 64.9 (CH_2, $C_{I'}$), 61.7 (d, J = 5.6 Hz, CH_2, C_B), 61.6 (d, J = 5.6 Hz, CH_2, $C_{B'}$), 51.8 (Q, C_N), 48.4 (CH_2, C_P), 46.8 (d, J = 20.9 Hz, CH, C_E), 44.1 (d, J = 1.2 Hz, CH, C_J), 37.4 (CH_2, C_K), 31.5 (CH_2, C_G), 26.5 (d, J = 1.7 Hz, CH_2, C_F), 24.2 (CH_2, C_L), 18.9 (CH_3, C_O), 16.4 (d, J = 6.8 Hz, CH_3, 2 × C_A) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.33 ppm.

EIMS: *m/z* (%): 493/495 (1 : 1, $(M+H)^+$, 7), 413 (5), 279 (4), 217 (6), 97 (100).

HRES$^+$MS: For $C_{21}H_{34}BrO_6P$ $(M+H)^+$: calcd 493.1349, found 493.1343.

Data for **(226)**:

Mw = 493.381 ($C_{21}H_{34}BrO_6P$).

R_f = 0.34 (Hexane/acetone 3 : 2).

IR (film): 2978 (w), 2912 (w), 1739 (w), 1616 (w), 1474 (w), 1403 (w), 1238 (m), 1162 (m), 1134 (m), 1025 (s), 959 (s), 821 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.63 (1H, br s, H_R); 5.59 (1H, d, J = 1.6 Hz, $H_{R'}$); 4.88 (1H, t, J = 4.3 Hz, H_H); 4.17–4.05 (4H, m, H_B); 4.00–3.84 (4H, m, H_I); 2.67 (1H, d, J = 14.8 Hz, H_P); 2.68–2.60 (1H, m); 2.50 (1H, d, J = 14.8 Hz, $H_{P'}$); 2.13–2.01 (1H, m); 2.00 (1H, d, J = 11.0 Hz, H_K); 1.80 (1H, d, J = 11.0 Hz, $H_{K'}$); 1.78–1.60 (7H, m); 1.56–1.45 (1H, m); 1.34 (6H, t, J = 7.0 Hz, H_A); 1.08 (3H, s, H_O) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 219.5 (Q, C_M), 128.1 (Q, C_Q), 121.6 (CH_2, C_R), 104.2 (CH, C_H), 64.9 (CH_2, 2 × C_I), 61.7 (d, J = 6.8 Hz, CH_2, C_B), 61.6 (d, J = 6.8 Hz, CH_2, $C_{B'}$), 55.5 (d, J = 8.7 Hz, CH, C_L), 50.8 (Q, C_N), 46.8 (CH, $C_{D/E}$), 45.9 (CH_2, C_P), 42.2 (d, J = 10.2 Hz, CH, C_J), 41.2 (d, J = 4.3 Hz, CH, $C_{D/E}$), 39.2 (CH_2, $C_{F/K/G}$), 32.7 (CH_2, $C_{F/K/G}$), 29.9 (CH_2, $C_{F/K/G}$), 28.4 (d, J = 140.4 Hz, CH_2, C_C), 17.4 (CH_3, C_O), 16.4 (d, J = 6.3 Hz, CH_3, 2 × C_A) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 30.14 ppm.

EIMS: *m/z* (%): 493/495 (1 : 1, $(M+H)^+$, 12), 413 (4), 375 (5), 341 (6), 279 (4), 97 (100), 73 (15).

HRES$^+$MS: For $C_{21}H_{34}BrO_6P$ $(M+H)^+$: calcd 493.1349, found 493.1335.

Data for **(227)**:

Mw = 374.420 ($C_{18}H_{31}O_6P$).

R_f = 0.26 (Hexane/acetone 3 : 2).

IR (film): 2988 (m), 2879 (m), 1730 (s), 1626 (w), 1455 (w), 1394 (w), 1238 (m), 1143 (m), 1053 (s), 1030 (s) 964 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.58 (1H, ddd, J = 26.8, 17.1, 9.7 Hz, H_D); 5.70 (1H, ddd, J = 20.6, 17.1, 0.6 Hz, H_C); 4.85 (1H, br s, H_H); 4.12–3.98 (4H, m, H_B); 3.98–3.79 (4H, m, H_I); 2.47–2.39 (1H, m, H_E); 2.34 (1H, dd, J = 18.8, 9.3 Hz, H_L); 2.14–1.96 (2H, m, $H_{L'}$ + H_K); 1.90–1.74 (2H, m, H_J + H_N); 1.73–1.47 (5H, m, H_F + $H_{F'}$ + H_G + $H_{G'}$ + $H_{K'}$); 1.31 (6H, t, J = 7.1 Hz, H_A); 1.05 (3H, d, J = 6.5 Hz, H_O) ppm.

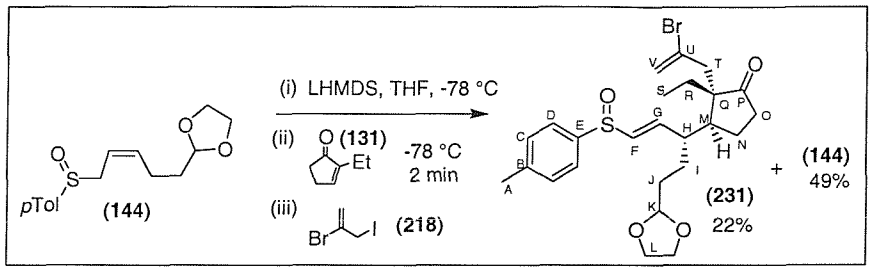
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 219.7 (Q, C_M), 152.4 (d, J = 3.9 Hz, CH, C_D), 120.6 (d, J = 185.6 Hz, CH, C_C), 104.0 (CH, C_H), 64.9 (CH_2, 2 × C_I), 61.7 (d, J = 5.4 Hz, CH_2, C_B), 61.6 (d, J = 5.4 Hz, CH_2, $C_{B'}$), 48.0 (CH, C_N), 47.4 (CH, C_J), 45.7 (d, J = 20.4 Hz, CH, C_E), 36.8 (CH_2, C_L), 31.8 (CH_2, $C_{F/G}$), 26.2 (CH_2, $C_{F/G}$), 22.1 (CH_2, C_K), 16.3 (d, J = 6.8 Hz, CH_3, 2 × C_A), 12.7 (CH_3, C_O) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.89 ppm.

EIMS: *m/z* (%): 375 ($(M+H)^+$, 1), 329 (3), 278 (5), 233 (7), 191 (7), 156 (20), 127 (10), 99 (14), 73 (100).

HRES$^+$MS: For $C_{18}H_{31}O_6P$ $(M+H)^+$: calcd 375.1931, found 375.1930.

2-(*S*)-(2-Bromoallyl)-3-[1-(*S*)-(2-[1,3]-dioxolan-2-(*E*)-ylethyl)-3-(toluene-4-sulfinyl)allyl]-2-ethylcyclopentanone (231)



To a cooled (−78 °C) solution of the sulfoxide **(144)** (9 : 1, *Z* : *E* mixture of double bond isomers) (525 mg, 1.87 mmol, 1.0 equiv) in THF (8 mL) was added LHMDS (1.06 M in THF) (1905 μL, 2.07 mmol, 1.1 equiv). The yellow solution was stirred for 5 min at −78 °C and then a THF (1 mL) solution of the enone **(131)** (259 μL, 2.20 mmol, 1.2 equiv) was added via syringe. After the addition, the flask was placed in a 0 °C cold bath. After 5 min, a solution of 2-bromo-3-iodopropene **(218)** (234 μL, 2.20 mmol, 1.2 equiv) in HMPA (959 μL, 5.51 mmol, 3.0 equiv) was added over 30 seconds and the reaction mixture was warmed to room temperature over 1 h. NH_4Cl (sat., aq.) (25 mL) was added and the reaction was extracted with EtOAc (4 × 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 2 : 1) followed by preparative HPLC (hexane/acetone 2 : 1). This yielded **(231)** (206 mg, 22%) as a yellow solid and **(144)** (253 mg, 49%) as a yellow oil. The sulfoxide **(231)** could be further purified by trituration with hexane/acetone (2 : 1) followed by filtration and recrystallisation from hot EtOH to afford a white solid.

Mw = 509.509 ($C_{25}H_{33}BrO_4S$).

M.P. = 107–108 °C.

R_f = 0.33 (Hexane/acetone 2 : 1).

IR (film): 2959 (w), 2884 (w), 1734 (s), 1616 (w), 1493 (w), 1403 (w), 1138 (m), 1120 (m), 1083 (m), 1045 (s), 982 (m), 812 (w) cm^{-1}.

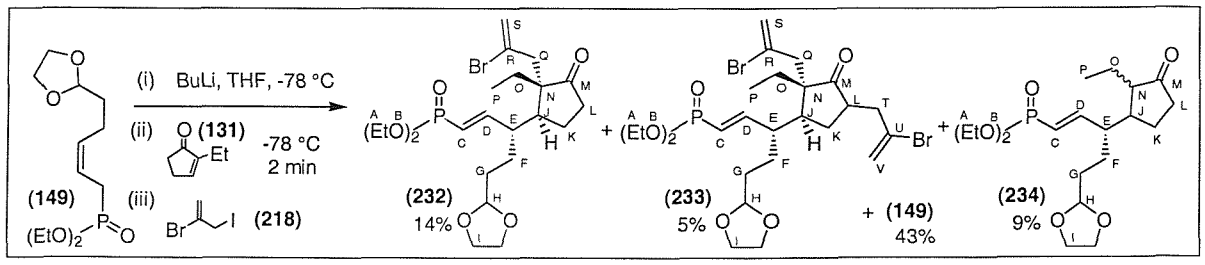
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.53 (2H, d, J = 8.0 Hz, H_D); 7.31 (2H, d, J = 8.0 Hz, H_C); 6.48 (1H, dd, J = 15.1, 10.2 Hz, H_G); 6.22 (1H, d, J = 15.1 Hz, H_F); 5.89 (1H, t, J = 1.6 Hz, H_V); 5.57 (1H, br s, $H_{V'}$); 4.81 (1H, t, J = 4.4 Hz, H_K); 3.93–3.80 (4H, m, H_L); 3.11 (1H, d, J = 14.7 Hz, H_T); 2.48–2.32 (4H, m); 2.41 (3H, s, H_A); 2.32–2.22 (1H, m); 2.27 (1H, d, J = 14.7 Hz, $H_{T'}$); 1.92–1.82 (1H, m, H_I); 1.69–1.61 (1H, m, H_J); 1.61–1.47 (1H, m); 1.47–1.32 (4H, m); 0.75 (3H, t, J = 7.5 Hz, H_S) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 220.2 (Q, C_P), 142.0 (Q, $C_{B/E}$), 140.9 (Q, $C_{B/E}$), 140.3 (CH, C_G), 135.8 (CH, C_F), 130.2 (Q, C_U), 130.2 (CH, 2 × C_C), 124.9 (CH, 2 × C_D), 122.6 (CH_2, C_V), 104.1 (CH, C_K), 64.9 (CH_2, C_L), 64.8 (CH_2, $C_{L'}$), 54.2 (Q, C_Q), 45.4 (CH_2, C_T), 44.4 (CH, $C_{H/M}$), 44.2 (CH, $C_{H/M}$), 37.1 (CH_2, C_O), 30.7 (CH_2, C_J), 26.4 (CH_2, C_I), 25.2 (CH_2, C_R), 24.2 (CH_2, C_N), 21.4 (CH_3, C_A), 8.3 (CH_3, C_S) ppm.

ES$^+$MS: *m/z* (%): 531/533 (1 : 1, $(M+Na)^+$, 14), 509/511 (1 : 1, $(M+H)^+$, 100).

Anal: Calcd for $C_{25}H_{33}BrO_4S$: C, 58.94; H, 6.53. Found: C, 58.87; H, 6.67.

{3-(*S*)-[2-(*S*)-(2-Bromoallyl)-2-ethyl-3-oxocyclopentyl]-5-[1,3]-dioxolan-2-ylpent-1-(*E*)-enyl}phosphonic acid diethyl ester (232) and **{3-(*S*)-[2-(*S*)-4-*bis*-(2-bromoallyl)-2-ethyl-3-oxocyclopentyl]-5-[1,3]-dioxolan-2-ylpent-1-(*E*)-enyl}phosphonic acid diethyl ester (233)** and **[5-[1,3]-dioxolan-2-yl-3-(*S*)-(2-(*S*)-ethyl-3-oxocyclopentyl)pent-1-(*E*)-enyl]phosphonic acid diethyl ester (234)**



To a cooled (−78 °C) solution of the phosphonate **(149)** (229 mg, 0.82 mmol, 1.0 equiv) in THF (5 mL) was added ^{n}BuLi (2.5 M in hexanes) (364 μL, 0.91 mmol, 1.1 equiv). The yellow solution was stirred for 15 min at −78 °C, and then a THF (1.5 mL) solution of the enone **(131)** (115 μL, 0.99 mmol, 1.2 equiv) was added via syringe. After the addition, the flask was placed in a 0 °C cold bath. After 15 min, a solution of 2-bromo-3-iodopropene

(218) (104 μL, 0.99 mmol, 1.2 equiv) in THF (1.5 mL) was added over 30 seconds and the reaction mixture was warmed to room temperature over 1 h. NH_4Cl (sat., aq.) (15 mL) was added and the reaction was extracted with EtOAc (4 × 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 3 : 2) followed by preparative HPLC (hexane/acetone 1 : 1). This yielded **(232)** (59 mg, 14%), **(233)** (27 mg, 5%), **(234)** (30 mg, 9%) and **(149)** (102 mg, 43%) as colourless oils.

Data for **(232)**:

Mw = 507.408 ($C_{22}H_{36}BrO_6P$).

R_f = 0.41 (Hexane/acetone 3 : 2).

IR (film): 2968 (m), 2884 (m), 1730 (s), 1630 (m), 1446 (w), 1403 (w), 1389 (w), 1252 (s), 1147 (m), 1053 (s), 1025 (s), 963 (s), 840 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.61 (1H, ddd, *J* = 21.8, 17.2, 10.0 Hz, H_D); 6.04 (1H, t, *J* = 1.5 Hz, H_S); 5.70 (1H, dd, *J* = 20.9, 17.2 Hz, H_C); 5.56 (1H, br s, $H_{S'}$); 4.84 (1H, t, *J* = 4.5 Hz, H_H), 4.15–4.04 (4H, m, H_B); 3.99–3.81 (4H, m, H_I); 3.13 (1H, d, *J* = 14.8 Hz, H_Q); 2.41 (1H, d, *J* = 14.9 Hz, $H_{Q'}$); 2.45–2.21 (5H, m); 1.93–1.82 (1H, m); 1.73–1.62 (1H, m); 1.61–1.40 (3H, m); 1.46 (2H, q, *J* = 7.5 Hz, H_O); 1.33 (6H, t, *J* = 7.1 Hz, H_A); 0.80 (3H, t, *J* = 7.5 Hz, H_P) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 220.4 (Q, C_M), 155.6 (d, *J* = 4.1 Hz, CH, C_D), 130.5 (Q, C_R), 122.7 (CH_2, C_S), 118.9 (d, *J* = 186.7 Hz, CH, C_C), 104.1 (CH, C_H), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.7 (d, *J* = 5.8 Hz, CH_2, C_B), 61.6 (d, *J* = 5.8 Hz, CH_2, $C_{B'}$), 54.0 (Q, C_N), 46.7 (d, *J* = 21.0 Hz, CH, C_E), 45.4 (CH_2, C_Q), 44.1 (CH, C_J), 37.0 (CH_2, $C_{K/L}$), 30.9 (CH_2, C_G), 25.9 (d, *J* = 2.0 Hz, CH_2, C_F), 25.4 (CH_2, C_O), 24.2 (CH_2, $C_{K/L}$), 16.5 (d, *J* = 6.3 Hz, CH_3, C_A), 16.4 (d, *J* = 6.3 Hz, CH_3, $C_{A'}$), 8.4 (CH_3, C_P) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.06 ppm.

ES$^+$MS: *m/z* (%): 507/509 (1 : 1, $(M+H)^+$, 100).

HRES$^+$MS: For $C_{22}H_{36}BrO_6P$ $(M+Na)^+$: calcd 525.1325, found 529.1329.

Data for **(233)**:

This compound was isolated as an inseparable mixture of diastereoisomers in approximately a 2 : 1 ratio.

Mw = 626.379 ($C_{25}H_{39}Br_2O_6P$).

R_f = 0.31 (Hexane/acetone 2 : 1).

IR (film): 2978 (m), 2874 (w), 1734 (s), 1621 (m), 1389 (w), 1243 (s), 1134 (m), 1053 (s), 1020 (s), 949 (s), 840 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.71–6.54 (1H, m, H_D); 6.05–6.01 (1H, m, H_S); 5.69 (1H, dd, *J* = 20.8, 17.3 Hz, H_C); 5.66–5.62 (1H, m, H_V); 5.59–5.55 (1H, m, $H_{s'}$); 5.50–5.46 (1H, m, $H_{V'}$); 5.46–5.42 (1H, m, $H_{V'(\text{minor only})}$); 4.85–4.80 (1H, m, H_H); 4.14–4.03 (4H, H_B); 3.98–3.80 (4H, m, H_I); 3.21 (1H, d, *J* = 14.8 Hz, H_Q); 3.14–3.04 (1H, m); 2.91–2.65 (2H, m); 2.49–2.27 (4H, m); 2.22 (1H, dd, *J* = 14.7, 10.2 Hz); 2.04–1.96 (1H, m); 1.93–1.60 (3H, m); 1.56–1.20 (8H, m, includes H_A); 0.80–0.72 (3H, m, H_P) ppm.

^{13}C NMR + DEPT Major (100 MHz; $CDCl_3$): δ 218.4 (Q, C_M), 155.2 (d, *J* = 4.2 Hz, CH, C_D), 132.6 (Q, C_U), 129.9 (Q, C_R), 123.1 (CH_2, C_S), 119.3 (d, *J* = 186.7 Hz, CH, C_C), 118.6 (CH_2, C_V), 104.1 (CH, C_H), 64.9 (CH_2, C_I), 64.8 (CH_2, $_{I'}$), 61.7 (d, *J* = 5.7 Hz, CH_2, C_B), 61.6 (d, *J* = 5.7 Hz, CH_2, $C_{B'}$), 55.8 (Q, C_N), 47.2 (d, *J* = 21.0 Hz, CH, C_E), 43.6 (CH, C_J), 43.6 (CH_2, C_Q), 42.0 (CH_2, C_T), 41.8 (CH, C_L), 30.9 (CH_2, C_G), 28.7 (CH_2, C_K), 25.9 (d, *J* = 21.0 Hz, CH_2, C_F), 24.8 (CH_2, C_O), 16.4 (d, *J* = 6.3 Hz, CH_3, C_A), 16.3 (d, *J* = 6.3 Hz, CH_3, $C_{A'}$), 7.9 (CH_3, C_P) ppm.

^{13}C NMR + DEPT Minor (100 MHz; $CDCl_3$): δ 219.4 (Q, C_M), 155.5 (d, *J* = 4.2 Hz, CH, C_D), 132.0 (Q, C_U), 130.2 (Q, C_R), 122.8 (CH_2, C_S), 119.2 (d, *J* = 186.7 Hz, CH, C_C), 118.2 (CH_2, C_V), 104.1 (CH, C_H), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.7 (d, *J* = 5.7 Hz, CH_2, C_B), 61.6 (d, *J* = 5.7 Hz, CH_2, $C_{B'}$), 54.5 (Q, C_N), 47.0 (CH, C_J), 46.3 (d, *J* = 21.0 Hz, CH, C_E), 46.0 (CH_2, C_Q), 44.1 (CH_2, C_T), 42.4 (CH, C_L), 31.0 (CH_2, C_G), 30.7 (CH_2, C_K), 26.0 (d, *J* = 2.0 Hz, CH_2, C_F), 25.7 (CH_2, C_O), 16.4 (d, *J* = 6.3 Hz, CH_3, C_A), 16.3 (d, *J* = 6.3 Hz, CH_3, $C_{A'}$), 8.7 (CH_3, C_P) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.92 ppm.

ES$^+$MS: *m/z* (%): 1274 ($(2M+Na)^+$, 6), 688/690/692 (1 : 2 : 1, $(M+Na+MeCN)^+$, 9), 647/649/651 (1 : 2 : 1, $(M+Na)^+$, 34), 625/627/629 (1 : 2 : 1, $(M + H)^+$, 100).

HRES$^+$MS: For $C_{25}H_{39}Br_2O_6P$ $(M+H)^+$: calcd 625.0924, found 625.0933.

Data for **(234)**:

Mw = 388.447 ($C_{19}H_{33}O_6P$).

R_f = 0.31 (Hexane/acetone 3 : 2).

IR (film): 2964 (m), 1729 (s), 1626 (m), 1455 (w), 1399 (w), 1223 (m), 1157 (m), 1049 (s), 1025 (s), 959 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.60 (1H, ddd, J = 21.1, 17.1, 9.4 Hz, H_D); 5.70 (1H, ddd, J = 21.6, 17.1, 0.7 Hz, H_C); 4.84 (1H, t, J = 4.3 Hz, H_H); 4.12–4.02 (4H, m, H_B); 3.98–3.80 (4H, m, H_I); 2.37–2.21 (2H, m); 2.14–1.98 (3H, m); 1.91–1.84 (1H, m); 1.80–1.65 (3H, m); 1.62–1.41 (4H, m); 1.32 (6H, t, J = 7.1 Hz, H_A); 0.86 (3H, t, J = 7.4 Hz, H_P) ppm.

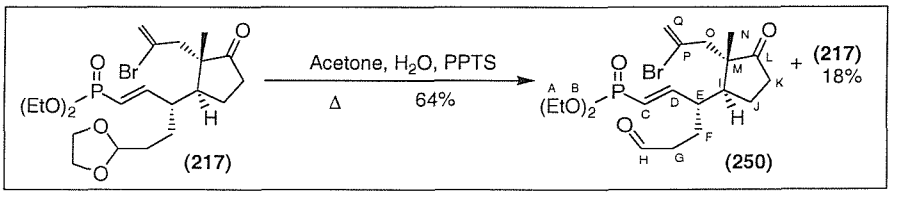
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 220.1 (Q, C_M), 154.6 (d, J = 4.1 Hz, CH, C_D), 119.0 (d, J = 186.4 Hz, CH, C_C), 104.0 (CH, C_H), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.7 (d, J = 5.6 Hz, CH_2, C_B), 61.6 (d, J = 5.6 Hz, CH_2, $C_{B'}$), 53.0 (CH, $C_{J/N}$), 48.5 (d, J = 20.6 Hz, CH, C_E), 43.9 (d, J = 1.4 Hz, CH, $C_{J/N}$), 37.9 (CH_2), 31.6 (CH_2), 24.3 (2 × CH_2), 21.7 (CH_2), 16.3 (d, J = 6.3 Hz, CH_3, 2 × C_A), 10.6 (CH_3, C_P) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.11 ppm.

ES$^+$MS: *m/z* (%): 799 ($(2M+Na)^+$, 100), 452 ($(M+Na+MeCN)^+$, 54), 411 ($(M+Na)^+$, 35), 389 ($(M+H)^+$, 32).

HRES$^+$MS: For $C_{19}H_{33}O_6P$ $(M+Na)^+$: calcd 411.1907, found 411.1910.

{3-(*S*)-[2-(2-(*S*)-Bromoallyl)-2-methyl-3-oxocyclopentyl]-6-oxohex-1-(*E*)-enyl}phosphonic acid diethyl ester (250)



To a solution of the acetal **(217)** (188 mg, 0.38 mmol, 1.0 equiv) in acetone (8 mL) was added PPTS (29 mg, 0.11 mmol, 0.3 equiv) and one drop of water. The mixture was refluxed for 23 h and then cooled to room temperature. The solvent was evaporated and the residue was partitioned between sat. aq. $NaHCO_3$ (5 mL) and EtOAc (10 mL). After separation, the aqueous phase was extracted with EtOAc (3 × 5 mL) and then the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 3 : 2) followed by preparative HPLC (hexane/acetone 3 : 2). This yielded **(250)**, (110 mg, 64%) and **(217)**, (34 mg, 18%) as colourless oils.

Mw = 449.327 ($C_{19}H_{30}BrO_5P$).

R_f = 0.16 (Neat Et_2O).

IR (film): 2983 (w), 2931 (w), 2912 (w), 1744 (s), 1626 (w), 1441 (w), 1394 (w), 1366 (w), 1238 (m), 1157 (m), 1049 (s), 1020 (s), 964 (m), 850 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 9.77 (1H, s, H_H); 6.57 (1H, ddd, J = 27.4, 17.2, 10.2 Hz, H_D); 5.98 (1H, t, J = 1.6 Hz, H_Q); 5.68 (1H, dd, J = 20.5, 17.3 Hz, H_C); 5.56 (1H, br s, $H_{Q'}$); 4.16–4.04 (4H, m, H_B); 3.08 (1H, d, J = 14.9 Hz, H_O); 2.50 (1H, d, J = 14.9 Hz, $H_{O'}$); 2.53–2.10 (8H, m); 1.59–1.45 (2H, m); 1.34 (6H, t, J = 7.0 Hz, H_A); 0.87 (3H, s, H_N) ppm.

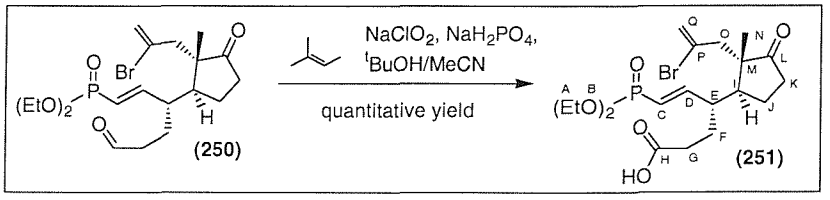
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 221.1 (Q, C_L), 201.2 (Q, C_H), 154.3 (d, J = 4.0 Hz, CH, C_D), 129.9 (Q, C_P), 122.6 (CH_2, C_Q), 119.9 (d, J = 187.5 Hz, CH, C_C), 61.9 (d, J = 5.9 Hz, CH_2, C_B), 61.8 (d, J = 5.9 Hz, CH_2, $C_{B'}$), 51.7 (Q, C_M), 47.0 (CH_2, C_O), 46.7 (d, J = 21.0 Hz, CH, C_E), 43.8 (CH, C_I), 40.9 (CH_2), 36.8 (CH_2), 23.9 (CH_2), 23.8 (d, J = 2.1 Hz, CH_2), 18.7 (CH_3, C_N), 16.4 (d, J = 6.1 Hz, CH_3, 2 × C_A) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.41 ppm.

ESMS: *m/z* (%): 901/899/897 (1 : 2 : 1, $(2M+H)^+$, 18), 449/451 (1 : 1, $(M+H)^+$, 100).

HRES$^+$MS: For $C_{19}H_{30}BrO_5P$ $(M+H)^+$: calcd 449.1087, found 449.1094.

4-(*S*)-[]-6-(diethoxyphosphoryl)hex-5-(*E*)-enoic acid (251)



To a stirred and cooled (0 °C) solution of the aldehyde **(250)** (341 mg, 0.76 mmol, 1.0 equiv) in 2-methyl-2-propanol (^{t}BuOH) (5.83 mL) and acetonitrile (3.50 mL) was added 2-methyl-2-butene (965 μL, 9.11 mmol, 12.0 equiv). Sodium chlorate (515 mg, 4.55 mmol, 6.0 equiv) and sodium dihydrogen phosphate (546 mg, 4.55 mmol, 6.0 equiv) were combined and dissolved in H_2O (9.3 mL) and then added dropwise to the cooled aldehyde solution. The reaction was stirred for 30 min before the addition of 5% (w/w) aq. sodium metabisulfate solution (7.43 mL). The pH was adjusted (pH 6) before extraction of the crude mixture with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. This yielded **(251)** as a colourless oil (366 mg, quantitative yield). Further purification by column chromatography (CH_2Cl_2/MeOH/AcOH 97 : 3 : 0.1) was possible but it did not seem necessary.

Mw = 465.327 ($C_{19}H_{30}BrO_6P$).

R_f = 0.24 (CH_2Cl_2/MeOH 95 : 5).

IR (film): 3423 (br, w), 2983 (w), 2931 (w), 2903 (w), 1734 (s), 1621 (w), 1399 (w), 1370 (w), 1214 (m), 1191 (m), 1162 (m), 1049 (s), 1030 (s), 968 (s), 850 (w) cm^{-1}.

^1H NMR (400 MHz; $CDCl_3$): δ 7.87 (1H, br hump, OH); 6.59 (1H, ddd, J = 27.2, 17.2, 10.0 Hz, H_D); 5.90 (1H, br s, H_Q); 5.71 (1H, dd, J = 21.1, 17.2 Hz, H_C); 5.53 (1H, br s, $H_{Q'}$); 4.16–4.04 (4H, m, H_B); 3.05 (1H, d, J = 14.9 Hz, H_O); 2.47 (1H, d, J = 14.9 Hz, $H_{O'}$); 2.43–2.04 (8H, m); 1.60–1.42 (2H, m); 1.33 (6H, t, J = 7.1 Hz, H_A); 0.85 (3H, s, H_N) ppm.

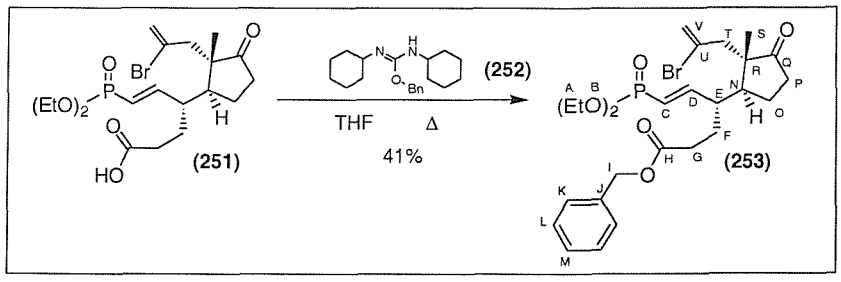
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 221.3 (Q, C_L), 176.4 (Q, C_H), 154.8 (d, J = 4.0 Hz, CH, C_D), 129.8 (Q, C_P), 122.4 (CH_2, C_Q), 119.2 (d, J = 188.0 Hz, CH, C_C), 62.1 (d, J = 5.9 Hz, CH_2, C_B), 62.0 (d, J = 5.9 Hz, CH_2, $C_{B'}$), 51.7 (Q, C_M), 47.0 (CH_2, C_O), 46.9 (d, J = 21.4 Hz, CH, C_E), 43.6 (CH, C_I), 36.8 (CH_2), 31.0 (CH_2), 26.5 (d, J = 2.0 Hz, CH_2), 23.9 (CH_2), 19.0 (CH_3, C_N), 16.3 (d, J = 6.2 Hz, CH_3, 2 × C_A) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.88 ppm.

ES^+MS: *m/z* (%): 933/931/929 (1 : 2 : 1, $(2M+H)^+$, 23), 465/467 (1 : 1, $(M+H)^+$, 100).

$HRES^+MS$: For $C_{19}H_{30}BrO_6P$ $(M+Na)^+$: calcd 487.0861, found 487.0875.

4-(*S*)-[2-(2-(*S*)-Bromoallyl)-2-methyl-3-oxocyclopentyl]-6-(diethoxyphosphoryl)hex-5-(*E*)-enoic acid benzyl ester (253)



To a solution of the acid **(251)** (322 mg, 0.69 mmol, 1.0 equiv) in dry THF (8 mL) was added the isourea **(252)**[152-154] (328 µL, 1.11 mmol, 1.6 equiv). The reaction was refluxed for 4 h and then cooled to room temperature. The solvent was evaporated *in vacuo* and hexane/acetone (2 : 1) (1 mL) was added. The suspension was filtered through a cotton wool pipette and washed through with hexane/acetone (2 : 1) (2 × 1 mL). This crude product was purified by column chromatography (hexane/acetone 2 : 1) followed by

preparative HPLC (hexane/acetone 2 : 1). This yielded **(253)** as a colourless oil (156 mg, 41%).

Mw = 555.452 ($C_{26}H_{36}BrO_6P$).

R_f = 0.28 (Hexane/acetone 2 : 1).

IR (film): 2978 (w), 2931 (w), 2903 (w), 1734 (s), 1621 (w), 1455 (w), 1389 (w), 1242 (m), 1157 (m), 1049 (s), 1020 (s), 959 (m), 845 (w), 741 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.38–7.32 (5H, m, H_K + H_L + H_M); 6.57 (1H, ddd, J = 27.6, 17.3, 10.5 Hz, H_D); 5.99 (1H, br s, H_V); 5.63 (1H, dd, J = 20.6, 17.3 Hz, H_C); 5.55 (1H, br s, $H_{V'}$); 5.13 (2H, s, H_I); 4.14–4.02 (4H, m, H_B); 3.06 (1H, d, J = 15.1 Hz, H_T); 2.48 (1H, d, J = 15.1 Hz, $H_{T'}$); 2.43–2.09 (8H, m); 1.58–1.37 (2H, m); 1.36–1.29 (6H, m, H_A); 0.82 (3H, s, H_S) ppm.

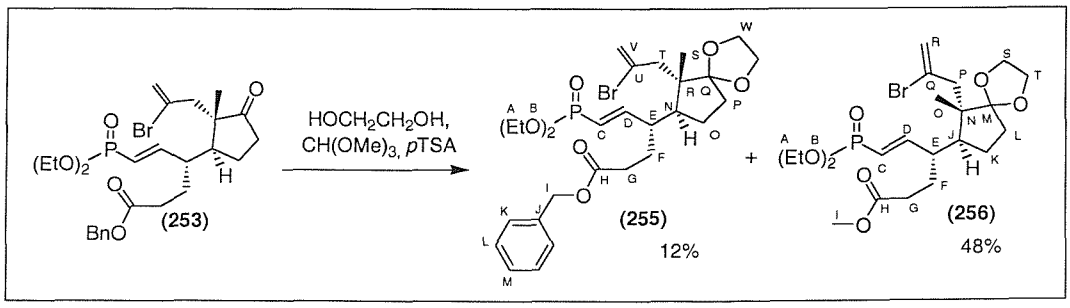
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 221.3 (Q, C_Q), 172.7 (Q, C_H), 154.3 (d, J = 4.2 Hz, CH, C_D), 135.8 (Q, C_J), 129.9 (Q, C_U), 128.6 (CH, 2 × $C_{K/L}$), 128.4 (CH, 2 × $C_{K/L}$), 128.3 (CH, C_M), 122.6 (CH_2, C_V), 119.8 (d, J = 186.5 Hz, CH, C_C), 66.4 (CH_2, C_I), 61.8 (d, J = 5.8 Hz, CH_2, C_B), 61.7 (d, J = 5.8 Hz, CH_2, $C_{B'}$), 51.7 (Q, C_R), 47.0 (CH_2, C_T), 46.7 (d, J = 21.0 Hz, CH, C_E), 43.6 (CH, C_N), 36.8 (CH_2), 31.3 (CH_2), 26.6 (d, J = 2.0 Hz, CH_2), 23.8 (CH_2), 18.7 (CH_3, C_S), 16.4 (d, J = 6.0 Hz, CH_3, 2 × C_A) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.54 ppm.

ES$^+$MS: *m/z* (%): 577/579 (1 : 1, $(M+Na)^+$, 31), 555/557 (1 : 1, $(M+H)^+$, 100).

HRES$^+$MS: For $C_{26}H_{36}BrO_6P$ $(M+H)^+$: calcd 557.1505, found 557.1490.

4-(*S*)-[6-(*S*)-(2-Bromoallyl)-6-methyl-1,4-dioxaspiro-[4.4]-non-7-yl]-6-(diethoxyphosphoryl)hex-5-(*E*)-enoic acid benzyl ester (255) and **4-(*S*)-[6-(*S*)-(2-bromoallyl)-6-methyl-1,4-dioxaspiro-[4.4]-non-7-yl]-6-(diethoxyphosphoryl)hex-5-(*E*)-enoic acid methyl ester (256)**



In a dry 5 mL pear shape flask were combined the ketone **(253)** (127 mg, 0.23 mmol, 1.0 equiv), ethylene glycol (64 μL, 1.14 mmol, 5.0 equiv), trimethyl orthoformate (125 μL, 1.14 mmol, 5.0 equiv) and *p*TSA (1.3 mg, 0.0068 mmol, 0.03 equiv). The reagents were stirred for 28 h, then EtOAc (10 mL) was added and the solution was washed with $NaHCO_3$ (sat. aq.) (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 3 : 2) followed by preparative HPLC (hexane/acetone 3 : 2). This yielded **(255)** (17 mg, 12%) and **(256)** (57 mg, 48%) as colourless oils.

Data for **(255)**:

Mw = 599.506 ($C_{28}H_{40}BrO_7P$).

R_f = 0.23 (Hexane/acetone 2 : 1).

IR (film): 2978 (w), 1735 (s), 1616 (w), 1455 (w), 1379 (w), 1245 (m), 1163 (m), 1052 (s), 1026 (s), 963 (s), 746 (w) 694 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.38–7.32 (5H, m, $H_K + H_L + H_M$); 6.47 (1H, ddd, J = 27.2, 17.1, 10.1 Hz, H_D); 5.61 (1H, dd, J = 20.6, 17.1 Hz, H_C); 5.53 (1H, br s, H_V); 5.44 (1H, br s, $H_{V'}$); 5.12 (2H, s, H_I); 4.14–4.01 (4H, m, H_B); 4.00–3.78 (4H, m, H_W); 2.77 (1H, d, J = 15.0 Hz, H_T); 2.54 (1H, d, J = 15.0 Hz, $H_{T'}$); 2.40–2.30 (1H, m); 2.26–2.15 (2H, m); 2.05–1.84 (3H, m); 1.72–1.62 (2H, m); 1.45–1.34 (2H, m); 1.35–1.27 (6H, m, H_A); 1.15 (3H, s, H_S) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 172.8 (Q, C_H), 155.7 (d, J = 3.8 Hz, CH, C_D), 135.9 (Q, C_J), 130.7 (Q, C_U), 128.6 (CH, 2 × $C_{K/L}$), 128.3 (CH, 2 × $C_{K/L}$), 128.3 (CH, C_M), 120.0 (CH_2, C_V), 119.1 (Q, C_Q), 118.9 (d, J = 185.7 Hz, CH, C_C), 66.3 (CH_2, C_I), 63.8 (CH_2, C_W), 63.3 (CH_2, $C_{W'}$), 61.8 (d, J = 5.5 Hz, CH_2, C_B), 61.6 (d, J = 5.5 Hz, CH_2, $C_{B'}$), 49.2 (Q, C_R), 49.1 (CH, C_N), 46.8 (CH_2, C_T), 46.7 (d, J = 20.8 Hz, CH, C_E), 31.4 (CH_2), 31.1 (CH_2), 26.7 (d, J = 2.1 Hz, CH_2), 24.1 (CH_2), 16.4 (CH_3, C_S), 16.4 (d, J = 6.0 Hz, CH_3, 2 × C_A) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.84 ppm.

ES$^+$MS: *m/z* (%): 621/623 (1 : 1, $(M+Na)^+$, 30), 599/601 (1 : 1, $(M+H)^+$, 100).

HRES$^+$MS: For $C_{28}H_{40}BrO_7P$ $(M+Na)^+$: calcd 621.1587, found 621.1583.

Data for **(256)**:

Mw = 523.408 ($C_{22}H_{36}BrO_7P$).

R_f = 0.23 (Hexane/acetone 2 : 1).

IR (film): 3248 (br, m), 2969 (w), 1734 (s), 1621 (w), 1432 (w), 1366 (w), 1233 (m), 1162 (m), 1053 (s), 1020 (s), 963 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.46 (1H, ddd, J = 27.2, 17.1, 10.0 Hz, H_D); 5.62 (1H, dd, J = 20.6, 17.1 Hz, H_C); 5.51 (1H, br s, H_R); 5.42 (1H, br s, $H_{R'}$); 4.12–4.00 (4H, m, H_B); 3.98–3.75 (4H, m, H_S); 3.64 (3H, s, H_I); 2.75 (1H, d, J = 14.4 Hz, H_P); 2.52 (1H, d, J = 14.4 Hz, $H_{P'}$); 2.31–2.09 (3H, m); 2.01–1.83 (3H, m); 1.72–1.65 (2H, m); 1.52–1.32 (2H, m); 1.31 (6H, t, J = 7.1 Hz, H_A); 1.16 (3H, s, H_S) ppm.

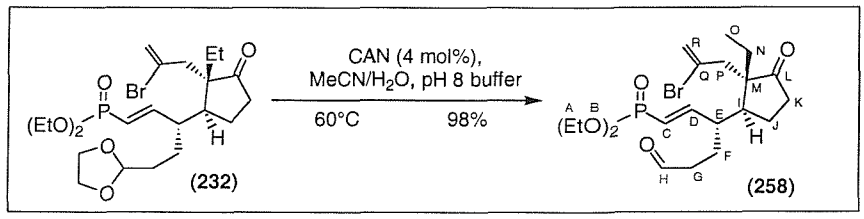
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 173.5 (Q, C_H), 155.7 (d, J = 3.8 Hz, CH, C_D), 130.6 (Q, C_Q), 119.9 (CH_2, C_R), 119.0 (Q, C_M), 118.6 (d, J = 186.0 Hz, CH, C_C), 63.7 (CH_2, C_S), 63.2 (CH_2, $C_{S'}$), 61.7 (d, J = 5.6 Hz, CH_2, C_B), 61.6 (d, J = 5.6 Hz, CH_2, $C_{B'}$), 51.5 (CH_3, C_I), 49.1 (CH, C_J), 49.0 (Q, C_N), 46.8 (CH_2, C_P), 46.8 (d, J = 20.8 Hz, CH, C_E), 31.1 (CH_2), 31.1 (CH_2), 26.6 (d, J = 2.1 Hz, CH_2), 24.0 (CH_2), 16.4 (CH_3, C_O), 16.4 (d, J = 6.0 Hz, CH_3, 2 × C_A) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.88 ppm.

ES$^+$MS: *m/z* (%): 545/547 (1 : 1, $(M+Na)^+$, 31), 523/525 (1 : 1, $(M+H)^+$, 100).

We have not obtained a HRMS or elemental analysis but copies of the ^{1}H and ^{13}C NMR are included in the appendix.

{3-(*S*)-[2-(2-(*S*)-Bromoallyl)-2-ethyl-3-oxocyclopentyl]-6-oxohex-1-(*E*)-enyl}phosphonic acid diethyl ester (258)



To a solution of the acetal **(232)** (1.0 g, 1.97 mmol, 1.0 equiv) in MeCN (6.1 mL) and a borate-HCl buffer (pH 8) (6.1 mL) was added CAN (43 mg, 0.079 mmol, 0.04 equiv) in one portion and the mixture was heated at 60 °C for 36 h. The reaction was cooled to room temperature, water (30 mL) and CH_2Cl_2 (10 mL) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 7 mL) and the combined organic phases

were dried over $MgSO_4$, filtered and evaporated *in vacuo*. This yielded **(258)** as a light yellow oil (0.89 g, 98%). The product could be purified by column chromatography (hexane/acetone 3 : 2) but this was not necessary.

Mw = 463.354 ($C_{20}H_{32}BrO_5P$).

R_f = 0.38 (Hexane/acetone 3 : 2).

IR (film): 3465 (br w), 2988 (m), 2935 (m), 2902 (m), 1730 (s), 1621 (m), 1446 (w), 1389 (m), 1243 (s), 1162 (m), 1096 (s), 1020 (s), 964 (s), 845 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 9.78 (1H, s, H_H); 6.57 (1H, ddd, J = 21.7, 17.2, 10.0 Hz, H_D); 6.01 (1H, t, J = 1.7 Hz, H_R); 5.69 (1H, dd, J = 20.6, 17.2 Hz, H_C); 5.57 (1H, br s, $H_{R'}$); 4.16–4.04 (4H, m, H_B); 3.15 (1H, d, J = 14.8 Hz, H_P); 2.54–2.25 (7H, m); 2.16 (1H, m); 1.75–1.57 (2H, m); 1.55–1.45 (1H, m); 1.45 (2H, q, J = 7.3 Hz, H_N); 1.34 (6H, t, J = 7.1 Hz, H_A); 0.81 (3H, t, J = 7.3 Hz, H_O) ppm.

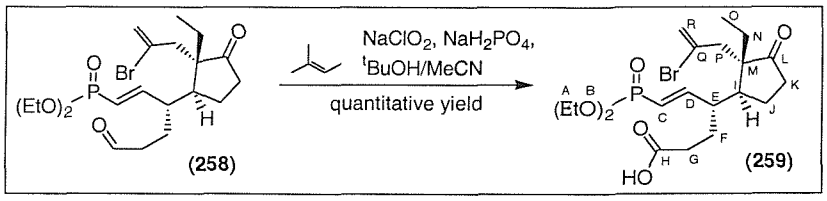
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 220.0 (Q, C_L), 201.3 (Q, C_H), 154.6 (d, J = 3.9 Hz, CH, C_D), 130.4 (Q, C_Q), 122.7 (CH_2, C_R), 119.8 (d, J = 187.4 Hz, CH, C_C), 61.9 (d, J = 5.9 Hz, CH_2, C_B), 61.8 (d, J = 5.9 Hz, CH_2, $C_{B'}$), 54.1 (Q, C_M), 46.1 (d, J = 21.0 Hz, CH, C_E), 45.3 (CH_2, C_P), 44.2 (CH, C_I), 40.9 (CH_2), 36.9 (CH_2), 25.4 (CH_2, C_N), 24.1 (CH_2), 23.9 (d, J = 2.0 Hz, CH_2), 16.5 (d, J = 6.1 Hz, CH_3, C_A), 16.4 (d, J = 6.1 Hz, CH_3, $C_{A'}$), 8.4 (CH_3, C_O) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.46 ppm.

ES$^+$MS: *m/z* (%): 947/949/951 (1 : 2 : 1, $(2M+Na)^+$, 14), 526/528 (1 : 1, $(M+Na+MeCN)^+$, 44), 485/487 (1 : 1, $(M+Na)^+$, 25), 463/465 (1 : 1, $(M+H)^+$, 100).

HRES$^+$MS: For $C_{20}H_{32}BrO_5P$ $(M+Na)^+$: calcd 485.1063, found 485.1073.

4-(*S*)-[2-(*S*)-(2-Bromoallyl)-2-ethyl-3-oxocyclopentyl]-6-(diethoxyphosphoryl)hex-5-(*E*)-enoic acid (259)



To a stirred and cooled (0 °C) solution of the aldehyde **(258)** (63 mg, 0.14 mmol, 1.0 equiv) in 2-methyl-2-propanol (^{t}BuOH) (1.1 mL) and acetonitrile (0.65 mL) was added 2-methyl-

2-butene (173 μL, 1.63 mmol, 12.0 equiv). Sodium chlorate (92 mg, 0.82 mmol, 6.0 equiv) and sodium dihydrogen phosphate (98 mg, 0.82 mmol, 6.0 equiv) were combined and dissolved in H_2O (1.7 mL) and then added dropwise to the cooled aldehyde solution. The reaction was stirred for 30 min before the addition of 5% (w/w) aq. sodium metabisulfate solution (1.4 mL). The pH was adjusted (pH 6) before extraction of the crude mixture with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. This yielded **(259)** as a colourless oil (75 mg, quantitative yield). Further purification by column chromatography (CH_2Cl_2/MeOH/AcOH 97 : 3 : 0.1) was possible but it did not seem necessary.

Mw = 479.354 ($C_{20}H_{32}BrO_6P$).

R_f = 0.28 (CH_2Cl_2/MeOH 9 : 1).

IR (film): 3385 (br, w), 2983 (m), 2940 (w), 2883 (w), 1730 (s), 1626 (w), 1550 (w), 1446 (w), 1370 (w), 1233 (m), 1157 (m), 1049 (s), 1025 (s), 968 (m) cm^{-1}.

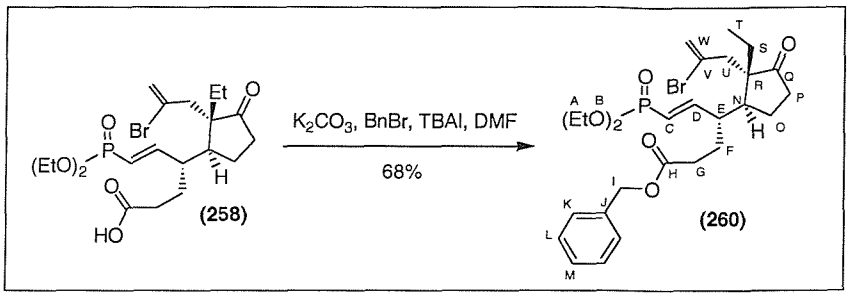
^{1}H NMR (400 MHz; $CDCl_3$): δ 8.5 (1H, br hump, OH); 6.59 (1H, ddd, J = 21.9, 17.2, 10.0 Hz, H_D); 5.92 (1H, t, J = 1.6 Hz, H_R); 5.71 (1H, dd, J = 21.0, 17.2 Hz, H_C); 5.54 (1H, br s, $H_{R'}$); 4.17–4.05 (4H, m, H_B); 3.13 (1H, d, J = 14.7 Hz, H_P); 2.42–2.05 (9H, m); 1.63–1.49 (2H, m); 1.44 (2H, q, J = 7.3 Hz, H_N); 1.33 (6H, t, J = 7.1 Hz, H_A); 0.80 (3H, t, J = 7.3 Hz H_O) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 220.2 (Q, C_L), 176.3 (Q, C_H), 155.1 (d, J = 4.0 Hz, CH, C_D), 130.4 (Q, C_Q), 122.5 (CH_2, C_R), 119.2 (d, J = 188.0 Hz, CH, C_C), 62.1 (d, J = 5.9 Hz, CH_2, C_B), 62.0 (d, J = 5.9 Hz, CH_2, $C_{B'}$), 54.1 (Q, C_M), 46.3 (d, J = 21.1 Hz, CH, C_E), 45.3 (CH_2, C_P), 44.0 (CH, C_I), 36.9 (CH_2), 31.0 (CH_2), 26.6 (d, J = 1.9 Hz, CH_2), 25.4 (CH_2, C_N), 24.0 (CH_2), 16.4 (d, J = 6.2 Hz, CH_3, C_A), 16.3 (d, J = 6.2 Hz, CH_3, $C_{A'}$) 8.3 (CH_3, C_O) ppm.

ES$^+$MS: *m/z* (%): 580/582 (1 : 1, $(M+NEt_3)^+$, 54), 479/481 (1 : 1, $(M+H)^+$, 100).

HRES$^+$MS: For $C_{20}H_{32}BrO_6P$ $(M+H)^+$: calcd 479.1193, found 479.1197.

4-(*S*)-[2-(2-(*S*)-Bromoallyl)-2-ethyl-3-oxocyclopentyl]-6-(diethoxyphosphoryl)hex-5-(*E*)-enoic acid benzyl ester (260)



To a solution of the acid **(259)** (85 mg, 0.18 mmol, 1.0 equiv) in DMF (1 mL) was added benzyl bromide (53 μL, 0.44 mmol, 2.5 equiv), K_2CO_3 (62 mg, 0.44 mmol, 2.5 equiv) and TBAI (10 mg, 0.03 mmol, 0.15 equiv). The suspension was stirred at room temperature for 3 days and then poured onto water (10 mL). The reaction was extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 2 : 1) and preparative HPLC (hexane/acetone 2 : 1). This yielded **(260)** as a colourless oil (69 mg, 68%).

Mw = 569.479 ($C_{27}H_{38}BrO_6P$).

R_f = 0.28 (Hexane/acetone 2 : 1).

IR (film): 2979 (m), 1729 (s), 1621 (m), 1455 (w), 1384 (w), 1247 (s), 1152 (m), 1020 (s), 949 (m), 840 (m), 741 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.38–7.33 (5H, m, H_K + H_L + H_M); 6.58 (1H, ddd, J = 27.6, 17.2, 9.9 Hz, H_D); 6.01 (1H, t, J = 1.6 Hz, H_W); 5.64 (1H, dd, J = 20.6, 17.2 Hz, H_C); 5.56 (1H, br s, $H_{W'}$); 5.13 (2H, s, H_I); 4.14–4.02 (4H, m, H_B); 3.14 (1H, d, J = 14.8 Hz, H_U); 2.45–2.30 (6H, m); 2.29–2.20 (2H, m); 2.19–2.10 (1H, m); 1.59–1.45 (2H, m); 1.40 (2H, q, J = 7.3 Hz, H_S); 1.32 (6H, d, J = 7.1 Hz, H_A); 0.78 (3H, t, J = 7.3 Hz, H_T) ppm.

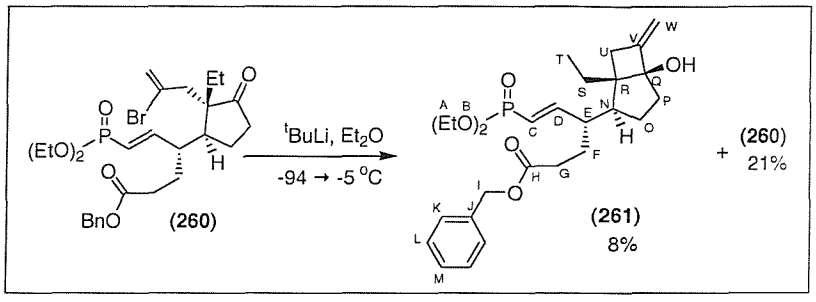
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 220.0 (Q, C_Q), 172.7 (Q, C_H), 154.6 (d, J = 4.1 Hz, CH, C_D), 135.8 (Q, C_J), 130.4 (Q, C_V), 128.6 (CH, 2 × $C_{K/L}$), 128.4 (CH, 2 × $C_{K/L}$), 128.3 (CH, C_M), 122.7 (CH_2, C_W), 119.8 (d, J = 187.5 Hz, CH, C_C), 66.4 (CH_2, C_I), 61.8 (d, J = 5.8 Hz, CH_2, C_B), 61.7 (d, J = 5.8 Hz, CH_2, $C_{B'}$), 54.1 (Q, C_R), 46.0 (d, J = 21.0 Hz, CH, C_E), 45.3 (CH_2, C_U), 44.1 (CH, C_N), 36.9 (CH_2, $C_{O/P}$), 31.3 (CH_2, $C_{F/G}$), 26.8 (d, J = 2.1 Hz, CH_2, C_S), 25.3 (CH_2, $C_{F/G}$), 24.0 (CH_2, $C_{O/P}$), 16.5 (d, J = 6.2 Hz, CH_3, C_A), 16.4 (d, J = 6.2 Hz, CH_3, $C_{A'}$), 8.3 (CH_3, C_T) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.57 ppm.

ES$^+$MS: *m/z* (%): 1159/1161/1163 (1 : 2 : 1, $(2M+Na)^+$, 12), 632/634 (1 : 1, $(M+Na+MeCN)^+$, 12), 591/593 (1 : 1, $(M+Na)^+$, 100), 569/571 (1 : 1, $(M+H)^+$, 69).

HRES$^+$MS: For $C_{27}H_{38}BrO_6P$ $(M+H)^+$: calcd 569.1662, found 569.1652.

6-(Diethoxyphosphoryl)-4-(*S*)-(1-(*S*)-ethyl-5-(*R*)-hydroxy-6-methylenebicyclo-[3.2.0]-hept-2-yl)hex-5-(*E*)-enoic acid benzyl ester (261)



To a stirred solution of the vinyl bromide **(260)** (140 mg, 0.25 mmol, 1.0 equiv) in dry deoxygenated Et_2O (2.5 mL), at –94 °C (MeOH/liquid N_2) was added ^{t}butyllithium (1.7 M in pentane) (294 μL, 0.49 mmol, 2.0 equiv) over 3 min. The reaction was stirred between –94 °C and –92 °C for 10 min and then placed in a –75 °C acetone/solid CO_2 cold bath and warmed slowly to –5 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (1 mL). Water and Et_2O (5 mL each) were added and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 3 : 1) and preparative HPLC (hexane/acetone 7 : 3). This yielded **(261)** (10 mg, 8%) and **(260)** (30 mg, 21%) as colourless oils.

Data for **(261)**:

Mw = 489.575 ($C_{27}H_{39}O_6P$).

R_f = 0.33 (Hexane/acetone 7 : 3).

IR (film): 3385 (br w), 2954 (br m), 1734 (s), 1668 (w), 1626 (w), 1460 (m), 1384 (m), 1238 (s), 1153 (s), 1058 (s), 1030 (s), 959 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.37–7.30 (5H, m, H_K + H_L + H_M); 6.66 (1H, ddd, J = 21.9, 17.2, 8.5 Hz, H_D); 5.62 (1H, ddd, J = 20.4, 17.2, 0.9 Hz, H_C); 5.13 (2H, s, H_I); 5.16–5.06

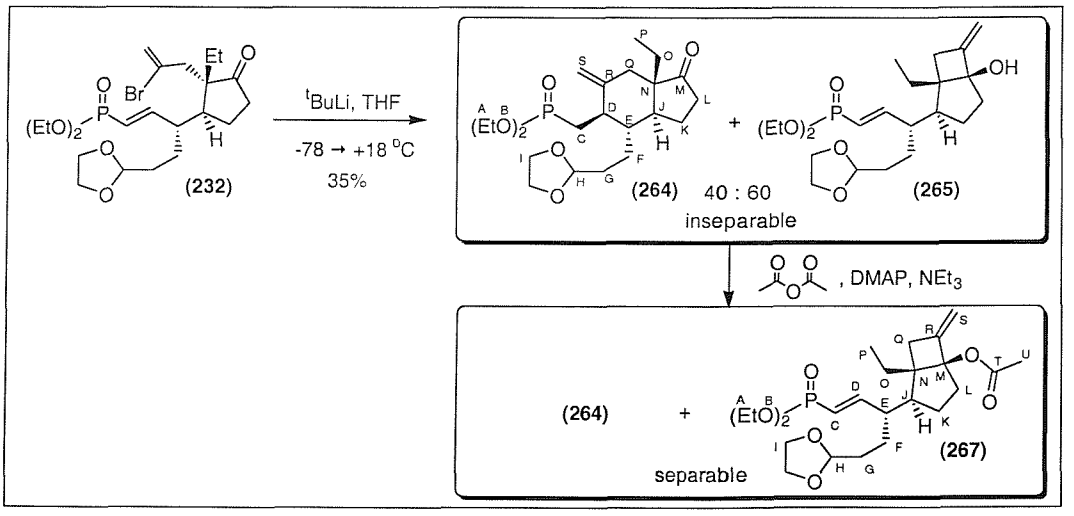
(1H, m); 4.80 (1H, t, J = 2.1 Hz), 4.12–4.01 (4H, m, H_B); 2.44–2.35 (2H, m); 3.32–2.18 (2H, m); 2.08–1.95 (3H, m); 1.94–1.78 (3H, m); 1.70–1.50 (3H, m); 1.32 (6H, t, J = 7.1 Hz, H_A); 0.92 (3H, t, J = 7.3 Hz, H_T) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 172.8 (Q, C_H), 155.9 (d, J = 4.1 Hz, CH, C_D), 155.2 (Q, C_V), 136.0 (Q, C_J), 128.5 (CH, 2 × $C_{K/L}$), 128.2 (CH, 2 × $C_{K/L}$), 128.2 (CH, C_M), 117.9 (d, J = 186.4 Hz, CH, C_C), 104.9 (CH_2, C_W), 87.5 (Q, C_Q), 66.2 (CH_2, C_I), 61.7 (d, J = 5.1 Hz, CH_2, C_B), 61.6 (d, J = 5.1 Hz, CH_2, $_{B'}$), 55.2 (Q, C_R), 49.5 (d, J = 1.7 Hz, CH, C_N), 43.5 (d, J = 20.3 Hz, CH, C_E), 39.1 (CH_2), 35.2 (CH_2), 32.6 (CH_2), 24.3 (CH_2), 24.0 (CH_2), 20.9 (CH_2), 16.4 (d, J = 6.3 Hz, CH_3, 2 × C_A), 9.2 (CH_3, C_T) ppm.

ES$^+$MS: *m/z* (%): 1003 ($(2M + Na)^+$, 42), 513 ($(M + Na)^+$, 100), 491 $(M + H)^+$, 9).

HRES$^+$MS: For $C_{27}H_{39}O_6P$ $(M+Na)^+$: calcd 513.2376, found 513.2368.

[4-(*S*)-(2-[1,3]-Dioxolan-2-ylethyl)-7a-(*S*)-ethyl-6-methylene-1-oxooctahydroinden-5-(*R*)-ylmethyl]phosphonic acid diethyl ester (264) and **acetic acid 4-[3-(diethoxyphosphoryl)-1-(*S*)-(2-[1,3]-dioxolan-2-ylethyl)-(*E*)-allyl]-5-(*S*)-ethyl-7-methylenebicyclo-[3.2.0]-hept-1-(*R*)-yl ester (267)**



A solution of the vinyl bromide (**232**) (163 mg, 0.32 mmol, 1.0 equiv) in THF was cooled to –78 °C and treated with ^{t}butyllithium (1.7 M in pentane) (415 μL, 0.71 mmol, 2.2 equiv). After the dropwise addition, the reaction was stirred for 5 min, then the cold bath was removed and the reaction was allowed to warm to room temperature over 1 h. NH_4Cl was added (5 mL) and the reaction was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated

in vacuo. The crude product was purified by column chromatography (hexane/acetone 4 : 1). This yielded an inseparable mixture of **(264)** and **(265)** as a colourless oil (48 mg, 35%). The ratio was shown to be 40 : 60 **(264)** : **(265)** by ^{1}H and ^{31}P NMR. To a mixture of **(264)** and **(265)** (169 mg, 0.39 mmol, 1.0 equiv) (ratio unknown) was added acetic anhydride (56 μL, 0.59 mmol, 1.5 equiv), DMAP (5 mg, 0.04 mmol, 0.1 equiv) and NEt_3 (82 μL, 0.59 mmol, 1.5 equiv). The mixture was stirred at room temperature for 48 h, then EtOAc (7 mL) was added and the solution was poured onto 1M HCl (10 mL). The aqueous phase was extracted with EtOAc (2 × 7 mL) then the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 4 : 1) followed by preparative HPLC (hexane/acetone 4 : 1). This yielded **(264)** (47 mg) and **(267)** (50 mg) as colourless oils.

Data for **(264)**:

Mw = 428.512 ($C_{22}H_{37}O_6P$).

R_f = 0.34 (Hexane/acetone 55 : 45).

IR (film): 2959 (m), 2884 (m), 1734 (s), 1645 (w), 1464 (w), 1436 (w), 1408 (w), 1384 (w), 1243 (m), 1143 (m), 1053 (s), 1025 (s), 959 (s), 727 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.53 (1H, s, H_S); 4.96 (1H, s, $H_{S'}$); 4.84 (1H, t, J = 4.3 Hz, H_H), 4.11–4.01 (4H, m, H_B); 3.97–3.80 (4H, m, H_I); 2.63 (1H, d, J = 13.5 Hz, H_Q); 2.40 (1H, dd, J = 18.9, 8.2 Hz); 2.24–2.04 (5H, m); 2.04–1.94 (1H, m); 1.86 (1H, d, J = 13.5 Hz, $H_{Q'}$); 1.79–1.51 (6H, m); 1.42 (1H, dq, J = 14.6, 7.3 Hz, H_O); 1.28 (6H, t, J = 7.1 Hz, H_A); 1.30–1.17 (1H, m, $H_{O'}$); 0.72 (3H, t, J = 7.2 Hz, H_P) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 218.5 (Q, C_M), 145.3 (d, J = 1.3 Hz, Q, C_R), 112.2 (CH_2, C_S), 104.4 (CH, C_H), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.5 (d, J = 6.7 Hz, CH_2, C_B), 61.4 (d, J = 6.7 Hz, CH_2, $C_{B'}$), 51.7 (Q, C_N), 49.4 (d, J = 1.4 Hz, CH, $C_{D/J}$), 40.4 (CH, $C_{D/J}$), 40.4 (d, J = 18.1 Hz, CH, C_E), 38.9 (CH_2, C_Q), 35.8 (CH_2), 28.3 (CH_2), 25.0 (d, J = 142.0 Hz, CH_2, C_C), 23.1 (CH_2), 21.8 (CH_2), 18.0 (CH_2, C_O), 16.3 (d, J = 6.2 Hz, CH_3, 2 × C_A), 6.8 (CH_3, C_P) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 31.83 ppm.

ES^{+}MS: *m/z* (%): 1308 ($(3M+Na)^+$, 4), 880 ($(2M+Na)^+$, 26), 492 ($(M+Na+MeCN)^+$, 62), 451 ($(M+Na)^+$, 25), 429 $(M+H)^+$, 100).

HRES^{+}MS: For $C_{22}H_{37}O_6P$ $(M+Na)^+$: calcd 451.2220, found 451.2228.

Data for **(267)**:

Mw = 470.550 ($C_{24}H_{39}O_7P$).

$\mathbf{R_f}$ = 0.41 (Hexane/acetone 55 : 45).

IR (film): 2959 (m), 2889 (m), 1734 (s), 1626 (w), 1470 (w), 1441 (w), 1365 (m), 1243 (s), 1143 (m), 1105 (m), 1058 (s), 1034 (s), 963 (s), 731 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.65 (1H, ddd, J = 22.1, 17.2, 8.2 Hz, H_D); 5.63 (1H, dd, J = 20.6, 17.2 Hz, H_C); 5.29 (1H, t, J = 2.4 Hz, H_S); 4.81 (1H, t, J = 2.4 Hz, $H_{S'}$); 4.77 (1H, t, J = 4.1 Hz, H_H); 4.10–4.00 (4H, m, H_B); 3.96–3.77 (4H, m, H_I); 2.62–2.54 (1H, m); 2.42–2.34 (1H, m, H_E); 2.37 (1H, dt, J = 16.0, 2.4 Hz, H_Q); 2.04 (1H, dd, J = 16.0, 2.4 Hz, $H_{Q'}$); 2.02 (3H, s, H_U); 1.96–1.84 (3H, m); 1.84–1.76 (1H, m); 1.71–1.55 (4H, m); 1.49–1.41 (1H, m); 1.30 (6H, t, J = 7.1 Hz, H_A); 1.30–1.26 (1H, m); 0.92 (3H, t, J = 7.5 Hz, H_P) ppm.

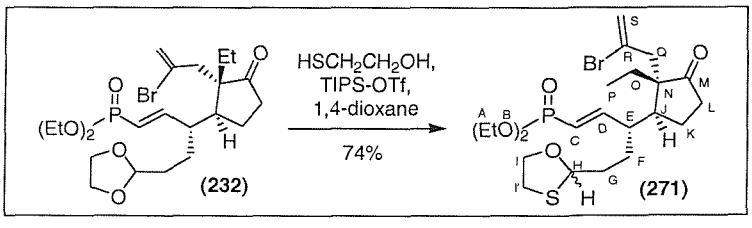
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 170.3 (Q, C_T), 156.4 (d, J = 4.3 Hz, CH, C_D), 149.0 (Q, C_R), 117.3 (d, J = 186.5 Hz, CH, C_C), 110.0 (CH_2, C_S), 104.2 (CH, C_H), 91.6 (Q, C_M), 64.8 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.6 (d, J = 5.5 Hz, CH_2, C_B), 61.5 (d, J = 5.5 Hz, CH_2, $C_{B'}$), 53.5 (Q, C_N), 48.9 (d, J = 1.7 Hz, CH, C_J), 43.9 (d, J = 20.2 Hz, CH, C_E), 38.9 (CH_2), 36.0 (CH_2, C_Q), 32.3 (CH_2), 25.4 (CH_2), 23.2 (d, J = 0.7 Hz, CH_2), 21.8 (CH_2, C_O), 21.2 (CH_3, C_U), 16.3 (d, J = 6.3 Hz, CH_3, 2 × C_A), 9.0 (CH_3, C_P) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 19.23 ppm.

ES$^+$MS: *m/z* (%): 963 ($(2M+Na)^+$, 12), 534 ($(M+Na+MeCN)^+$, 44), 493 ($(M+Na)^+$, 59), 471 $(M+H)^+$, 66), 128 (100).

HRES$^+$MS: For $C_{24}H_{39}O_7P$ $(M+Na)^+$: calcd 493.2325, found 493.2336.

{3-(*S*)-[2-(*S*)-(2-Bromoallyl)-2-ethyl-3-oxocyclopentyl]-5-[1,3]-oxathiolan-2-ylpent-1-(*E*)-enyl}phosphonic acid diethyl ester (271)



To a room temperature solution of TIPS-OTf (0.5 μL, 0.002 mmol, 0.01 equiv) in 1,4-dioxane (0.5 mL) was added a solution of the ketone **(232)** (93 mg, 0.18 mmol, 1.0 equiv)

and 2-mercaptoethanol (19 μL, 0.27 mmol, 1.5 equiv) in 1,4-dioxane (0.5 mL). The mixture was stirred and heated at 85 °C for 1 h. The solution was cooled to room temperature and NEt_3 (0.7 μL, 0.005 mmol, 0.03 equiv) was added. The reaction was poured onto sat. aq. $NaHCO_3$ (3 mL) and extracted with EtOAc (4 × 3 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 2 : 1). This yielded **(271)** as a colourless oil (71 mg, 74%), obtained as a 1 : 1 inseparable mixture of diastereoisomers.

Data for **(271)**:

Mw = 523.474 ($C_{22}H_{36}BrO_5PS$).

R_f = 0.48 (Hexane/acetone 3 : 2).

IR (film): 2974 (m), 2899 (m), 2874 (m), 1734 (s), 1626 (m), 1441 (w), 1389 (w), 1243 (s), 1157 (m), 1053 (s), 1025 (s), 958 (s), 845 (m), 731 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.61 (1H, ddd, *J* = 21.8, 17.3, 9.8 Hz, H_D); 6.03 (1H, s, H_S); 5.69 (1H, dd, *J* = 20.8, 17.3 Hz, H_C); 5.55 (1H, s, $H_{S'}$); 5.07–5.02 (1H, m, H_H), 4.32 (1H, ddd, *J* = 12.3, 6.0, 3.3 Hz, H_I); 4.14–4.03 (4H, m, H_B); 3.80–3.72 (1H, m, H_I); 3.13 (1H, d, *J* = 14.8 Hz, H_Q); 3.06–2.96 (2H, m, includes $H_{I'}$); 2.46–2.31 (4H, m); 2.30–2.22 (1H, m); 1.98–1.69 (4H, m); 1.68–1.40 (2H, m); 1.45 (2H, q, *J* = 7.5 Hz, H_O); 1.32 (6H, t, *J* = 7.0, H_A); 0.80 (3H, t, *J* = 7.5 Hz, H_P) ppm.

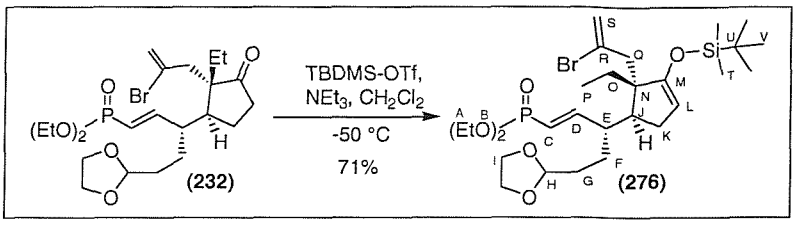
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 220.3 (Q, C_M), 155.5 (d, *J* = 4.4 Hz) and 155.4 (d, *J* = 4.4 Hz, CH, C_D), 130.4 (Q, C_R), 122.7 (CH_2, C_S), 119.0 (d, *J* = 186.7 Hz) and 118.9 (d, *J* = 186.7 Hz, CH, C_C), 86.5 and 86.3 (CH, C_H), 71.4 and 71.3 (CH_2, C_I), 61.7 (d, *J* = 5.8 Hz, CH_2, C_B), 61.6 (d, *J* = 5.8 Hz, CH_2, $C_{B'}$), 54.0 (Q, C_N), 46.7 (d, *J* = 21.0 Hz) and 46.6 (d, *J* = 21.0 Hz, CH, C_E), 45.4 (CH_2, C_Q), 44.0 (CH, C_J), 36.9 (CH_2, $C_{K/L}$), 33.3 and 33.2 (CH_2, $C_{G/I'}$), 32.8 and 32.6 (CH_2, $C_{G/I'}$), 28.4 (d, *J* = 2.0 Hz) and 28.1 (d, *J* = 2.0 Hz, CH_2, C_F), 25.3 (CH_2, C_O), 24.1 (CH_2, $C_{K/L}$), 16.5 (d, *J* = 6.3 Hz, CH_3, C_A), 16.4 (d, *J* = 6.3 Hz, CH_3, $C_{A'}$), 8.4 (CH_3, C_P) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.95 ppm.

ES$^+$MS: *m/z* (%): 540/542 (1 : 1, $(M+Na)^+$, 33), 523/525 (1 : 1, $(M+H)^+$, 100).

HRES$^+$MS: For $C_{22}H_{36}BrO_5PS$ $(M+H)^+$: calcd 523.1277, found 523.1291.

{3-(*S*)-[2-(*S*)-(2-Bromoallyl)-3-(*tert*-butyldimethylsilanyloxy)-2-ethylcyclopent-3-enyl]-5-[1,3]-dioxolan-2-ylpent-1-(*E*)-enyl}phosphonic acid diethyl ester (276)



To a cooled (–50 °C) solution of the ketone **(232)** (1.41 g, 2.77 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added NEt_3 (1.16 mL, 8.32 mmol, 3.0 equiv) and TBDMS-OTf (1.91 mL, 8.32 mmol, 3.0 equiv). The reaction was stirred for 2 h at –50 °C and then sat. aq. $NaHCO_3$ (20 mL), was added and the reaction was warmed to room temperature. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 5 : 1) whereby the silica was pre-neutralized by making the slurry in the said solvent system, containing ~1% of NEt_3. This yielded **(276)** as a colourless oil (1.23 g, 71%).

Mw = 621.672 ($C_{28}H_{50}BrO_6PSi$).

R_f = 0.42 (Hexane/acetone 2 : 1).

IR (film): 2959 (m), 2931 (m), 2855 (m), 1646 (m), 1616 (w), 1469 (w), 1389 (w), 1356 (w), 1252 (s), 1223 (s), 1138 (m), 1058, (s), 1025 (s), 963 (s), 868 (m), 840 (s), 789 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.66 (1H, ddd, J = 21.8, 17.2, 9.5 Hz, H_D); 5.86 (1H, t, J = 1.3 Hz, H_S); 5.69 (1H, dd, J = 21.8, 17.2 Hz, H_C); 5.58 (1H, br s, $H_{S'}$); 4.82 (1H, t, J = 4.5 Hz, H_H), 4.57 (1H, br s, H_L); 4.14–4.04 (4H, m, H_B); 3.97–3.80 (4H, m, H_I); 2.83 (1H, d, J = 15.2 Hz, H_Q); 2.44–2.32 (3H, m); 2.22 (1H, d, J = 15.2 Hz, $H_{Q'}$); 1.95–1.85 (1H, m, H_F); 1.81–1.62 (3H, m); 1.57–1.44 (2H, m); 1.34 (6H, t, J = 7.1 Hz, H_A); 1.30–1.17 (1H, m); 0.93 (9H, s, H_V); 0.84 (3H, t, J = 7.5 Hz, H_P); 0.20 (3H, s, H_T); 0.19 (3H, s, $H_{T'}$) ppm.

^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 157.0 (d, J = 3.6 Hz, CH, C_D), 155.3 (Q, C_M), 131.2 (Q, C_R), 120.9 (CH_2, C_S), 118.4 (d, J = 186.6 Hz, CH, C_C), 104.4 (CH, C_H), 98.4 (Q, C_L), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.6 (d, J = 5.6 Hz, CH_2, C_B), 61.5 (d, J = 5.6 Hz, CH_2, $C_{B'}$), 52.9 (Q, C_N), 46.5 (d, J = 20.7 Hz, CH, C_E), 45.7 (CH_2, C_Q), 43.2 (CH, C_J), 32.6 (CH_2, C_K), 31.0 (CH_2, C_G), 28.0 (CH_2, C_O), 26.3 (d, J = 2.1 Hz, CH_2, C_F), 25.6 (CH_3, 3 × C_V), 17.9

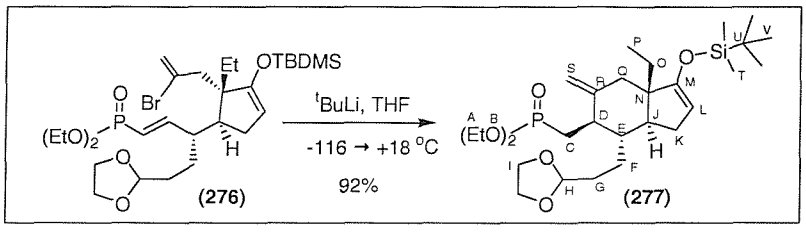
(Q, C_U), 16.5 (d, J = 6.3 Hz, CH_3, C_A), 16.4 (d, J = 6.3 Hz, CH_3, $C_{A'}$), 9.4 (CH_3, C_P), −4.9 (CH_3, C_T), −5.2 (CH_3, $C_{T'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.39 ppm.

ES$^+$MS: *m/z* (%): 1263/1265/1267 (1 : 2 : 1, $(2M+Na)^+$, 29), 684/686 (1 : 1, $(M+Na+MeCN)^+$, 100), 643/645 (1 : 1, (M+Na, 81).

HRES$^+$MS: For $C_{28}H_{50}BrO_6PSi$ $(M+Na)^+$: calcd 643.2190, found 643.2205.

[1-(*tert*-Butyldimethylsilanyloxy)-4-(*S*)-(2-[1,3]-dioxolan-2-ylethyl)-7a-(*S*)-ethyl-6-methylene-3a,4,5,6,7,7a-hexahydro-3H-inden-5-(*R*)-ylmethyl]phosphonic acid diethyl ester (277)



A solution of the vinyl bromide **(276)** (1.25 g, 2.00 mmol, 1.0 equiv) in THF was cooled to −116 °C in an EtOH/liquid N_2 cold bath and treated with ^{t}butyllithium (1.7 M in pentane) (2.59 mL, 4.41 mmol, 2.2 equiv). After the dropwise addition, the reaction was stirred for 5 min, then the cold bath was removed and the reaction was allowed to warm to room temperature over 1 h. Sat. aq. $NaHCO_3$ was added (10 mL) and the reaction was extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 4 : 1). This yielded **(277)** as a colourless oil (998 mg, 92%), as a single diastereoisomer.

Data for **(277)**:

Mw = 542.776 ($C_{28}H_{51}O_6PSi$).

R_f = 0.26 (Hexane/acetone 3 : 1).

IR (film): 2956 (m), 2922 (m), 2855 (m), 1621 (m), 1460 (m), 1393 (w), 1346 (m), 1252 (s), 1228 (s), 1138 (m), 1058, (s), 1025 (s), 954 (s), 902 (m), 850 (s), 779 (m) cm$^-$

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.00 (1H, s, H_S); 4.93 (1H, s, $H_{S'}$); 4.85 (1H, t, J = 4.1 Hz, H_H), 4.52 (1H, dd, J = 3.1, 1.4 Hz, H_L); 4.14–4.03 (4H, m, H_B); 4.00–3.80 (4H, m, H_I); 2.54

(1H, d, J = 13.1 Hz, H_Q); 2.23–1.90 (6H, m); 1.87–1.69 (2H, m); 1.65–1.49 (4H, m); 1.30 (6H, d, J = 7.0 Hz, H_A); 1.32–1.16 (2H, m, H_O); 0.92 (9H, s, H_V), 0.85 (3H, t, J = 7.5 Hz, H_P), 0.16 (3H, s, H_T), 0.14 (3H, s, $H_{T'}$) ppm.

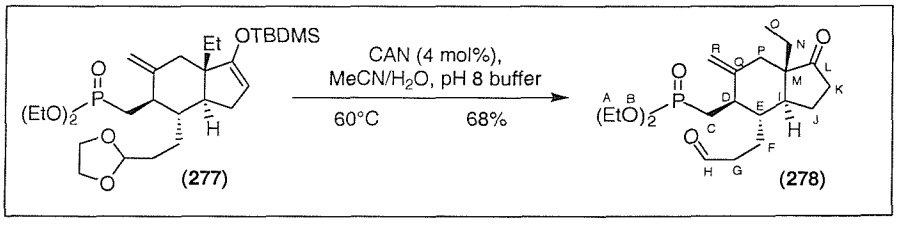
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 163.4 (Q, C_M), 147.3 (d, J = 1.3 Hz, Q, C_R), 111.7 (CH_2, C_S), 104.8 (CH, C_H), 99.2 (CH, C_L), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.5 (d, J = 6.6 Hz, CH_2, C_B), 61.4 (d, J = 6.6 Hz, CH_2, $C_{B'}$), 54.1 (d, J = 1.7 Hz, CH, C_D), 47.8 (Q, C_N), 42.1 (CH_2, C_Q), 41.1 (d, J = 4.9 Hz, CH, C_J), 39.9 (d, J = 12.9 Hz, CH, C_E), 29.0 (CH_2, $C_{G/K}$), 28.9 (CH_2, $C_{G/K}$), 25.6 (d, J = 141.2 Hz, CH_2, C_C), 25.6 (CH_3, 3 × C_V), 24.2 (CH_2, C_F), 22.4 (CH_2, C_O), 17.9 (Q, C_U), 16.4 (d, J = 6.2 Hz, CH_3, 2 × C_A), 8.3 (CH_3, C_P), –4.6 (CH_3, C_T), –5.1 (CH_3, $C_{T'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 32.56 ppm.

ES$^+$MS: *m/z* (%): 1108 ($(2M+Na)^+$, 67), 1086 ($(2M+H)^+$, 21), 607 ($(M+Na+MeCN)^+$, 100), 543 ((M+H, 54).

HRES$^+$MS: For $C_{28}H_{51}O_6PSi$ $(M+Na)^+$: calcd 565.3085, found 565.3088.

[7a-(*S*)-Ethyl-6-methylene-1-oxo-4-(*S*)-(3-oxopropyl)octahydroinden-5-(*R*)-ylmethyl]phosphonic acid diethyl ester (278)



To a solution of the acetal **(277)** (996 mg, 1.84 mmol, 1.0 equiv) in MeCN (9.2 mL) and a borate-HCl buffer (pH 8) (9.2 mL) was added CAN (30 mg, 0.055 mmol, 0.04 equiv) in one portion and the mixture was heated at 60 °C for 60 h. The reaction was cooled to room temperature, water (30 mL) and CH_2Cl_2 (10 mL) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 7 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 3 : 2). This yielded **(278)** as a light yellow oil (479 mg, 68%).

Mw = 384.458 ($C_{20}H_{33}O_5P$).

R_f = 0.21 (Hexane/acetone 2 : 1).

IR (film): 2973 (m), 2954 (m), 2889 (m), 1730 (s), 1635 (w), 1455 (w), 1441 (w), 1384 (w), 1228 (m), 1058 (s), 1025 (s), 959 (s), 741 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 9.82 (1H, br s, H_H); 5.04 (1H, s, H_R); 5.00 (1H, s, $H_{R'}$); 4.12–4.02 (4H, m, H_B); 2.66 (1H, d, J = 13.5 Hz, H_P); 2.70–5.59 (1H, m, H_G); 2.48–2.38 (2H, m, H_K + $H_{G'}$); 2.25–1.99 (4H, m, H_C + $H_{C'}$ + $H_{K'}$ + H_I); 1.96–1.83 (3H, m, H_F + $H_{F'}$ + $H_{P'}$); 1.73–1.60 (4H, m, H_J + $H_{J'}$ + H_E + H_D); 1.47–1.36 (1H, m, H_N); 1.30 (6H, t, J = 7.2, H_A); 1.31–1.19 (1H, m, $H_{N'}$); 0.74 (3H, t, J = 7.5 Hz, H_P) ppm.

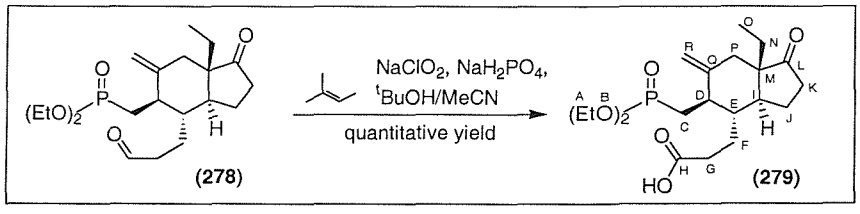
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 218.0 (Q, C_L), 201.6 (Q, C_H), 144.8 (d, J = 1.9 Hz, Q, C_Q), 112.5 (CH_2, C_R), 61.7 (d, J = 6.9 Hz, CH_2, C_B), 61.6 (d, J = 6.9 Hz, CH_2, $C_{B'}$), 51.7 (Q, C_M), 49.3 (d, J = 1.4 Hz, CH, $C_{D/I}$), 40.2 (d, J = 20.1 Hz, CH, C_E), 40.1 (d, J = 2.9 Hz, CH, $C_{D/I}$), 38.8 (CH_2, C_P), 36.6 (CH_2, $C_{G/K}$), 35.7 (CH_2, $C_{G/K}$), 25.0 (d, J = 142.4 Hz, CH_2, C_C), 21.9 (CH_2, $C_{F/J}$), 21.3 (CH_2, $C_{F/J}$), 18.2 (CH_2, C_N), 16.4 (d, J = 6.3 Hz, CH_3, 2 × C_A), 6.8 (CH_3, C_O) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 31.78 ppm.

ES$^+$MS: *m/z* (%): 439 ($(M+Na+MeOH)^+$, 100), 407 ($(M+Na)^+$, 13), 385 $(M+H)^+$, 2).

HRES$^+$MS: For $C_{20}H_{33}O_5P$ $(M+H)^+$: calcd 385.2139, found 385.2144.

3-[5-(*R*)-(Diethoxyphosphorylmethyl)-7a-(*S*)-ethyl-6-methylene-1-oxooctahydroinden-4-(*S*)-yl]propionic acid (279)



To a stirred and cooled (0 °C) solution of the aldehyde **(278)** (470 mg, 1.22 mmol, 1.0 equiv) in 2-methyl-2-propanol (^{t}BuOH) (9.8 mL) and acetonitrile (5.7 mL) was added 2-methyl-2-butene (1.55 mL, 14.67 mmol, 12.0 equiv). Sodium chlorate (829 mg, 7.34 mmol, 6.0 equiv) and sodium dihydrogen phosphate (880 mg, 7.34 mmol, 6.0 equiv) were combined and dissolved in H_2O (15.3 mL) and then added dropwise to the cooled aldehyde solution. The reaction was stirred for 30 min before the addition of 5% (w/w) aq. sodium metabisulfate solution (12.5 mL). The pH was adjusted (pH 6) before extraction of the

crude mixture with EtOAc (4 × 10 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. This yielded **(279)** as a colourless oil (693 mg, quantitative yield).

Mw = 400.458 ($C_{20}H_{33}O_6P$).

R_f = 0.30 (CH_2Cl_2/MeOH 9 : 1).

IR (film): 3446 (br w), 2974 (m), 2936 (m), 1734 (s), 1646 (w), 1460 (w), 1436 (w), 1399 (w), 1214 (m), 1118 (m), 1049 (s), 1025 (s), 959 (s), 902 (w), 816 (w), 727 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.40 (1H, br hump, OH); 5.00 (1H, br s, H_R); 4.98 (1H, br s, $H_{R'}$); 4.15–4.03 (4H, m, H_B); 2.66 (1H, d, J = 13.5 Hz, H_P); 2.53–2.38 (2H, m); 2.32–1.83 (9H, m); 1.73–1.57 (3H, m); 1.46–1.34 (1H, m, H_N); 1.31 (3H, t, J = 7.1, H_A); 1.29 (3H, t, J = 7.1, $H_{A'}$); 1.32–1.19 (1H, m, $H_{N'}$); 0.74 (3H, t, J = 7.4 Hz, H_P) ppm.

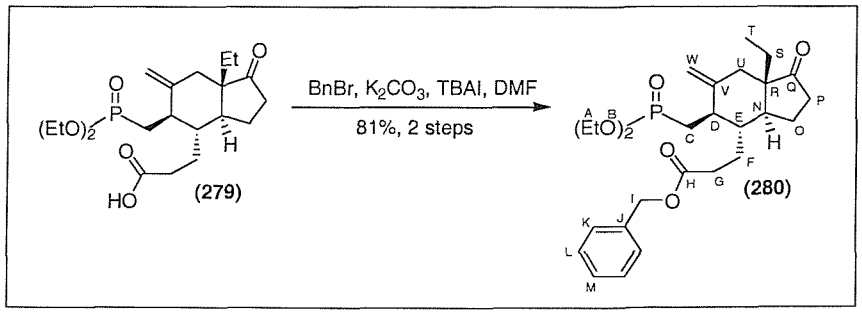
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 218.2 (Q, C_L), 176.2 (Q, C_H), 145.0 (d, J = 2.9 Hz, Q, C_Q), 112.2 (CH_2, C_R), 62.2 (d, J = 6.9 Hz, CH_2, C_B), 62.1 (d, J = 6.9 Hz, CH_2, $C_{B'}$), 51.6 (Q, C_M), 49.1 (d, J = 1.2 Hz, CH, $C_{D/I}$), 40.8 (d, J = 12.1 Hz, CH, C_E), 39.5 (d, J = 4.4 Hz, CH, $C_{D/I}$), 38.8 (CH_2, C_P), 35.8 (CH_2, $C_{G/K}$), 29.2 (CH_2, $C_{G/K}$), 25.0 (d, J = 142.4 Hz, CH_2, C_C), 24.6 (CH_2, $C_{F/J}$), 21.7 (CH_2, $C_{F/J}$), 18.1 (CH_2, C_N), 16.3 (d, J = 6.1 Hz, CH_3, 2 × C_A), 6.8 (CH_3, C_O) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 32.29 ppm.

ES$^+$MS: *m/z* (%): 1223 ($(3M+Na)^+$, 20), 823 ($(2M+Na)^+$, 71), 801 ($(2M+H)^+$, 72), 462 ($(M+Na+MeCN)^+$, 62), 423 ($(M+Na)^+$, 27), 401 $(M+H)^+$, 100).

HRES$^+$MS: For $C_{20}H_{33}O_6P$ $(M+H)^+$: calcd 401.2088, found 401.2088.

3-[5-(*R*)-(Diethoxyphosphorylmethyl)-7a-(*S*)-ethyl-6-methylene-1-oxooctahydroinden-4-(*S*)-yl]propionic acid benzyl ester (280)



To a solution of the acid **(279)** (1.22 mmol, 1.0 equiv) in DMF (1.2 mL) was added benzyl bromide (366 μL, 3.06 mmol, 2.5 equiv), K_2CO_3 (422 mg, 3.06 mmol, 2.5 equiv) and TBAI (68 mg, 0.18 mmol, 0.15 equiv). The suspension was stirred at room temperature for 3 days and then poured onto water (10 mL). The reaction was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 2 : 1). This yielded **(280)** as a colourless oil (484 mg, 81%).

Mw = 490.583 ($C_{27}H_{39}O_6P$).

R_f = 0.30 (Hexane/acetone 2 : 1).

IR (film): 2955 (m), 1730 (s), 1640 (w), 1455 (w), 1384 (w), 1233 (s), 1167 (s), 1053 (s), 1030 (s), 959 (m), 840 (m), 745 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.37–7.31 (5H, m, H_K + H_L + H_M); 5.14 (1H, d, J = 12.3 Hz, H_I); 5.10 (1H, d, J = 12.3 Hz, $H_{I'}$); 5.04 (1H, br s, H_W); 4.99 (1H, br s, $H_{W'}$); 4.10–4.01 (4H, m, H_B); 2.65 (1H, d, J = 13.6 Hz, H_U); 2.55–2.29 (3H, m); 2.20–2.06 (4H, m); 2.01–1.78 (4H, m); 1.75–1.55 (3H, m); 1.45–1.29 (1H, m, H_S); 1.27 (6H, t, J = 7.0, H_A); 1.28–1.17 (1H, m, $H_{S'}$); 0.73 (3H, t, J = 7.4 Hz, H_T) ppm.

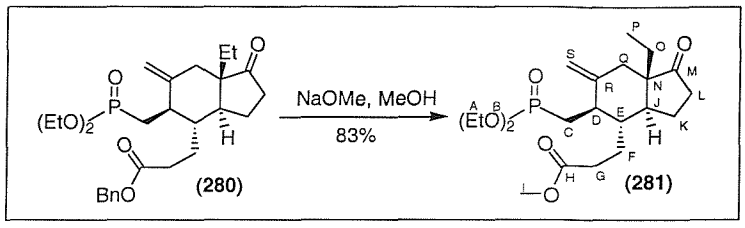
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 218.1 (Q, C_Q), 173.2 (Q, C_H), 144.9 (d, J = 1.4 Hz, Q, C_V), 135.8 (Q, C_J), 128.5 (CH, 2 × $C_{K/L}$), 128.3 (CH, 2 × $C_{K/L}$), 128.3 (CH, C_M), 112.5 (CH_2, C_W), 66.3 (CH_2, C_I), 61.6 (d, J = 6.8 Hz, CH_2, C_B), 61.5 (d, J = 6.8 Hz, CH_2, $C_{B'}$), 54.7 (Q, C_R), 49.6 (d, J = 1.4 Hz, CH, C_N), 40.4 (d, J = 12.6 Hz, CH, C_E), 40.4 (d, J = 4.4 Hz, CH, C_D), 38.8 (CH_2, C_U), 35.8 (CH_2, C_P), 29.5 (CH_2, $C_{F/G}$), 25.0 (d, J = 141.9 Hz, CH_2, C_C), 24.8 (CH_2, $C_{F/G}$), 21.9 (CH_2, C_O), 18.1 (CH_2, C_S), 16.4 (d, J = 6.3 Hz, CH_3, C_A), 16.3 (d, J = 6.3 Hz, CH_3, $C_{A'}$), 6.8 (CH_3, C_T) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 31.69 ppm.

ES$^+$MS: *m/z* (%): 1003 ($(2M+Na)^+$, 36), 513 ($(M+Na)^+$, 100), 491 ($(M+H)^+$, 44).

HRES$^+$MS: For $C_{27}H_{39}O_6P$ $(M+Na)^+$: calcd 513.2376, found 513.2380.

3-[5-(*R*)-(Diethoxyphosphorylmethyl)-7a-(*S*)-ethyl-6-methylene-1-oxooctahydroinden-4-(*S*)-yl]propionic acid methyl ester (281)



To a cooled (0 °C) suspension of sodium methoxide (16 mg, 0.30 mmol, 1.0 equiv) in MeOH (2.5 mL) was added a solution of the phosphonate (**280**) (147 mg, 0.30 mmol, 1.0 equiv) in MeOH (0.5 mL). The reaction was stirred for 1 h at 0 °C and than NH_4Cl (10 mL) was added and the reaction was extracted into EtOAc (3 × 7 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 3 : 2). This yielded (**281**) as a colourless oil (103 mg, 83%).

Mw = 414.485 ($C_{21}H_{35}O_6P$).

R_f = 0.23 (Hexane/acetone 2 : 1).

IR (film): 3407 (w), 2968 (m), 2879 (m), 1730 (s), 1644 (w), 1460 (w), 1451 (m), 1389 (w), 1237 (m), 1162 (m), 1058 (s), 1025 (s), 959 (s), 829 (m), 798 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.04 (1H, br s, H_S); 4.98 (1H, br s, $H_{S'}$); 4.12–4.02 (4H, m, H_B); 3.67 (3H, s, H_I); 2.64 (1H, d, J = 13.4 Hz, H_Q); 2.49–2.38 (2H, m, H_F + H_L); 2.32–2.22 (1H, m, $H_{F'}$); 2.21–2.07 (4H, m); 2.01–1.94 (1H, m, H_K); 1.91–1.83 (3H, m); 1.76–1.55 (3H, m); 1.47–1.36 (1H, m, H_O); 1.29 (6H, t, J = 7.1, H_A); 1.29–1.18 (1H, m, $H_{O'}$); 0.73 (3H, t, J = 7.5 Hz, H_P) ppm.

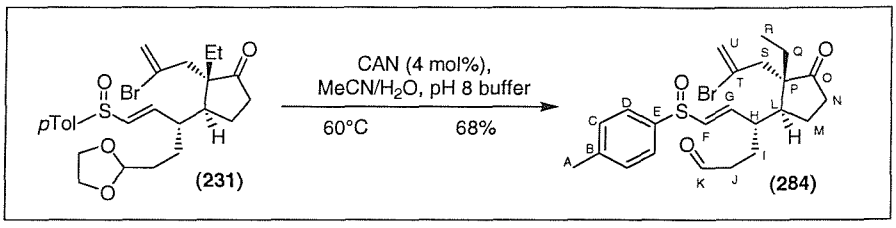
^{13}C NMR + DEPT (100 MHz; $CDCl_3$): δ 218.2 (Q, C_M), 173.8 (Q, C_H), 144.9 (d, J = 1.7 Hz, Q, C_R), 112.5 (CH_2, C_S), 61.6 (d, J = 6.8 Hz, CH_2, C_B), 61.5 (d, J = 6.8 Hz, CH_2, $C_{B'}$), 51.7 (Q, C_N), 51.6 (CH_3, C_I), 49.6 (d, J = 1.7 Hz, CH, C_J), 40.4 (d, J = 13.3 Hz, CH, C_E), 40.4 (d, J = 4.8 Hz, CH, C_D), 38.8 (CH_2, C_Q), 35.8 (CH_2, $C_{L/K}$), 29.1 (CH_2, $C_{F/G}$), 25.0 (d, J = 142.1 Hz, CH_2, C_C), 24.7 (CH_2, $C_{F/G}$), 21.9 (CH_2, $C_{L/K}$), 18.1 (CH_2, C_O), 16.4 (d, J = 6.1 Hz, CH_3, C_A), 16.3 (d, J = 6.1 Hz, CH_3, $C_{A'}$), 6.8 (CH_3, C_P) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 31.30 ppm.

ES$^+$MS: *m/z* (%): 851 ($(2M+Na)^+$, 12), 478 ($(M+Na+MeCN)^+$, 17), 437 ($(M+Na)^+$, 10), 415 ($(M+H)^+$, 100).

HRES^{+}MS: For $C_{21}H_{35}O_6P$ $(M+Na)^+$: calcd 437.2063, found 437.2065.

4-(*S*)-[2-(2-(*S*)-Bromoallyl)-2-ethyl-3-oxocyclopentyl]-6-(toluene-4-sulfinyl)hex-5-(*E*)-enal (284)



To a solution of the acetal **(231)** (92 mg, 0.18 mmol, 1.0 equiv) in MeCN (560 μL) and a borate-HCl buffer (pH 8) (560 μL) was added CAN (4 mg, 0.007 mmol, 0.04 equiv) in one portion and the mixture was heated at 60 °C for 17 h. The reaction was cooled to room temperature, water (15 mL) and CH_2Cl_2 (5 mL) were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (hexane/acetone 2 : 1). This yielded **(284)** as a light yellow oil (73 mg, 87%).

Mw = 465.455 ($C_{23}H_{29}BrO_3S$).

R_f = 0.29 (Hexane/acetone 2 : 1).

IR (film): 2968 (w), 1730 (s), 1612 (w), 1493 (w), 1445 (w), 1375 (w), 1214 (w), 1077 (m), 1048 (m), 1011 (w), 977 (w), 807 (w) cm^{-1}.

^{1}H NMR (400 MHz; $(CD_3)_2CO$): δ 9.23 (1H, br s, H_K); 7.23 (2H, d, J = 8.0 Hz, H_D); 7.05 (2H, d, J = 8.0 Hz, H_C); 6.25 (1H, d, J = 15.0 Hz, H_F); 6.02 (1H, dd, J = 15.0, 10.6 Hz, H_G); 5.70 (1H, br s, H_U); 5.21 (1H, br s, $H_{U'}$); 2.71 (1H, d, J = 14.8 Hz, H_S); 2.48 (3H, s, H_A); 2.49–2.40 (2H, m); 2.27–2.16 (1H, m); 2.10–1.85 (5H, m); 1.82–1.71 (1H, m); 1.36–1.24 (1H, m); 1.22–1.05 (3H, m); 0.39 (3H, t, J = 7.5 Hz, H_R) ppm.

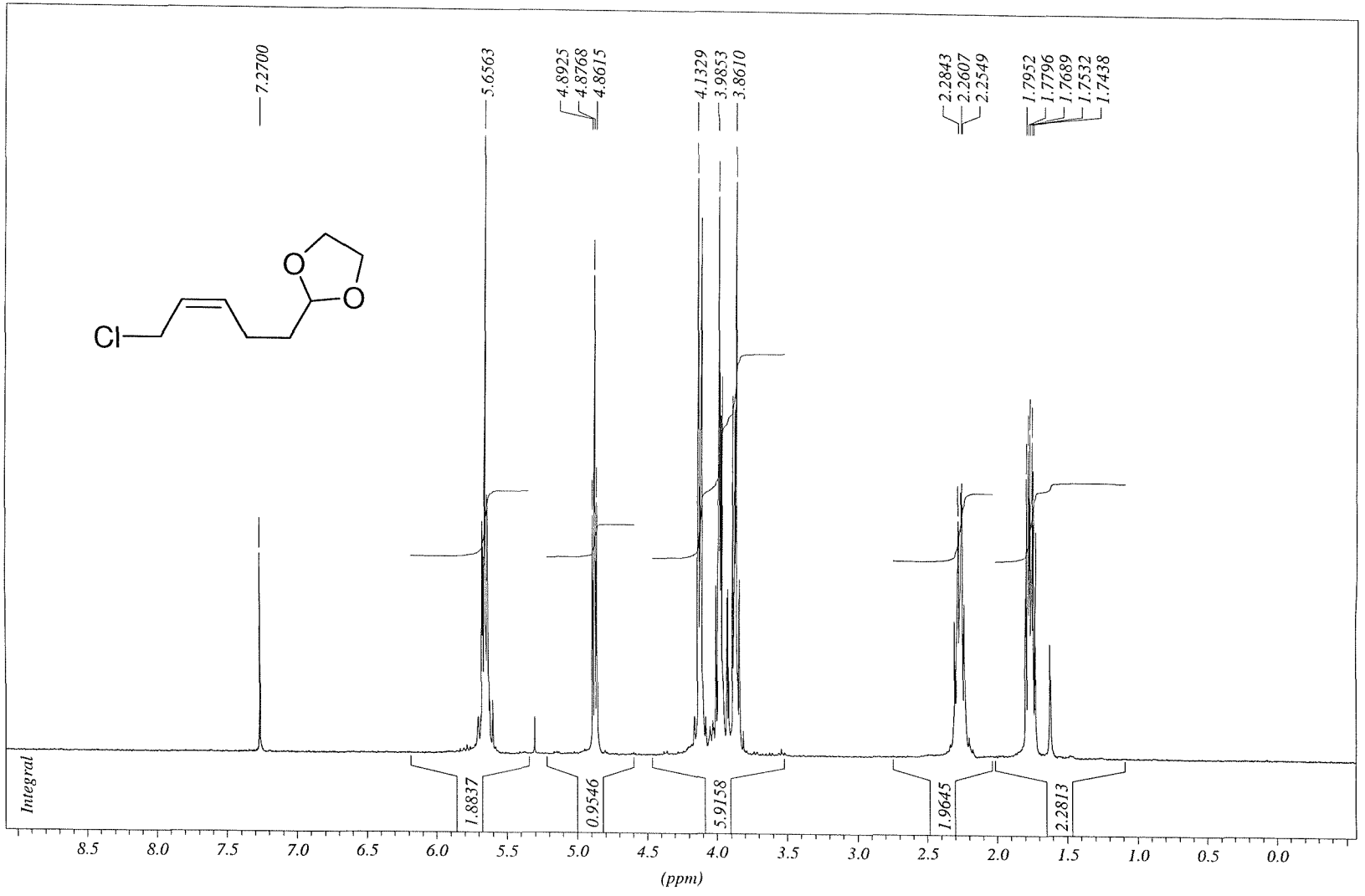
^{13}C NMR + DEPT (100 MHz; $(CD_3)_2CO$): δ 219.5 (Q, C_O), 202.2 (CH, C_H), 143.0 (Q, $C_{B/E}$), 142.5 (Q, $C_{B/E}$), 139.1 (CH, C_G), 138.0 (CH, C_F), 131.7 (Q, C_T), 131.0 (CH, 2 × C_C), 125.4 (CH, 2 × C_D), 123.4 (CH_2, C_U), 54.8 (Q, C_P), 46.2 (CH_2, C_S), 45.6 (CH, $C_{H/L}$), 44.1 (CH, $C_{H/L}$), 41.5 (CH_2), 37.5 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 21.4 (CH_3, C_A), 8.7 (CH_3, C_S) ppm.

ES$^+$MS: *m/z* (%): 465/467 (1 : 1, $(M+H)^+$, 42), 154 (100).

HRES$^+$MS: For $C_{23}H_{29}BrO_3S$ $(M+Na)^+$: calcd 487.0913, found 487.0922.

Appendix

RC/2964-99C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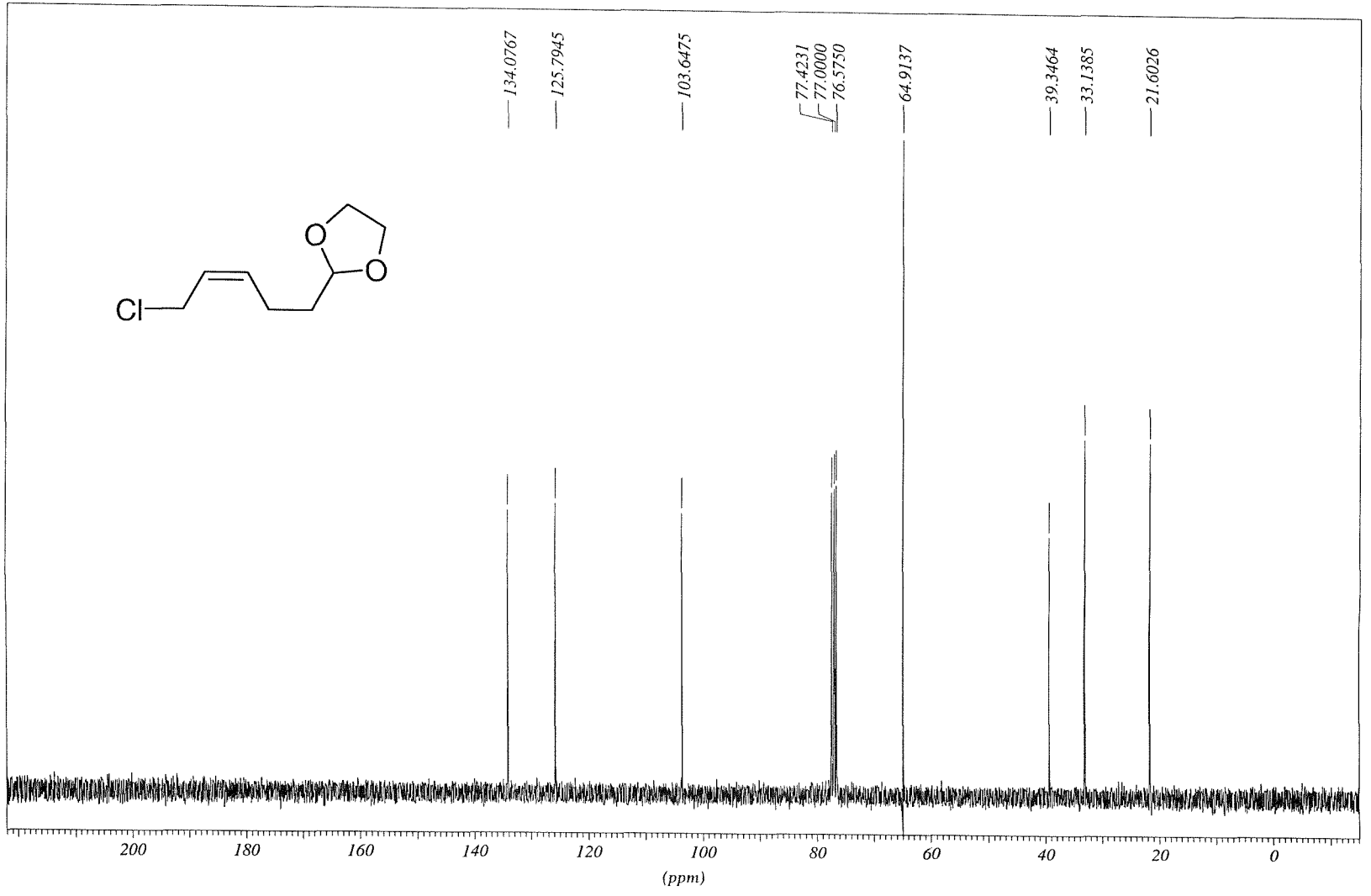
2.2549
1.7952
1.7796
1.7689
1.7532
1.7438
Cl
O
O
O
Integral
1.8837
0.9546
5.9158
1.9645
2.2813
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

RC/2964-99C


134.0767
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33.1385
21.6026
Cl
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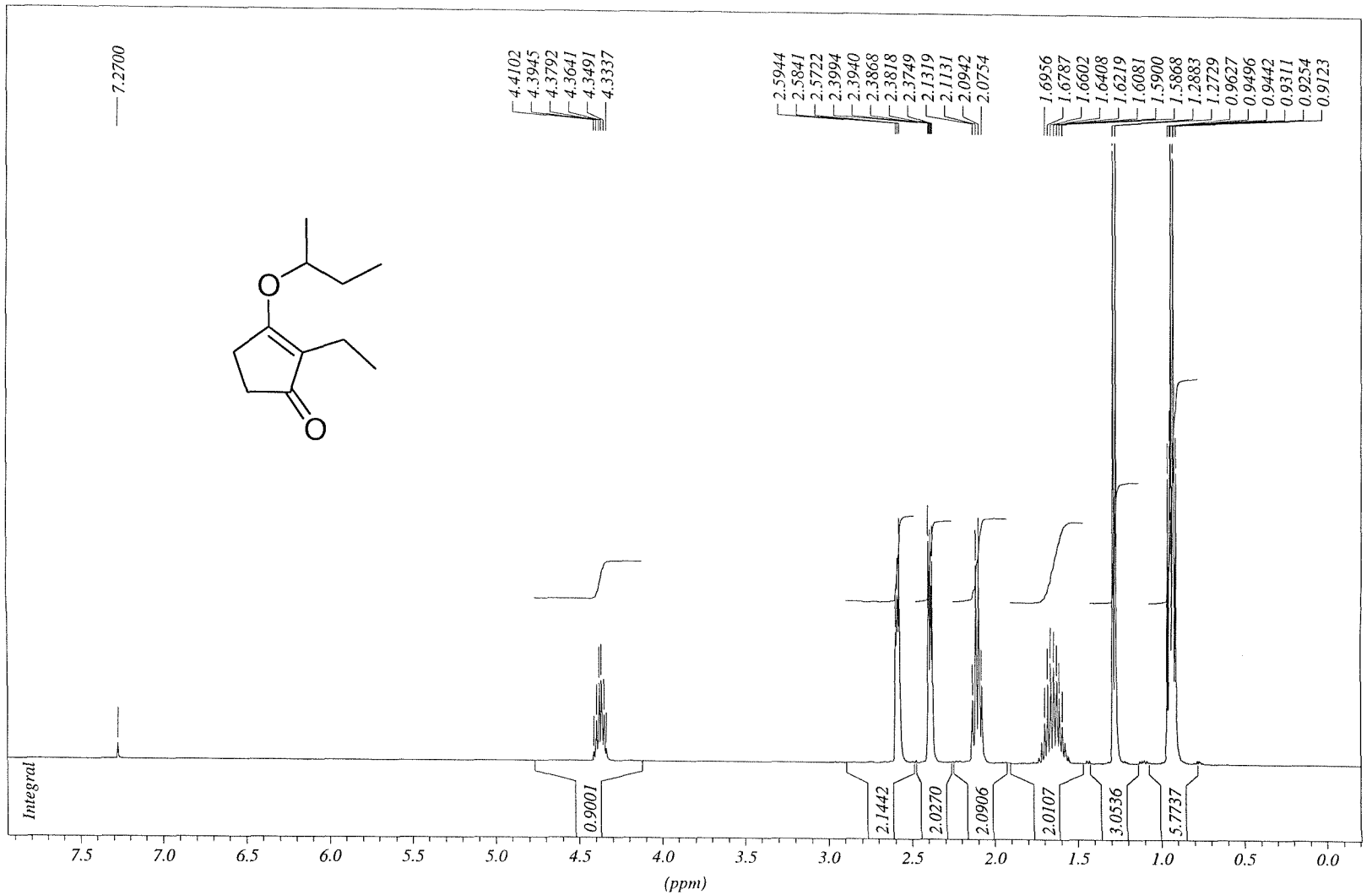
O
200
180
160
140
120
100
80
60
40
20
0
(ppm)

RC/3291-11C(1)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2.5841
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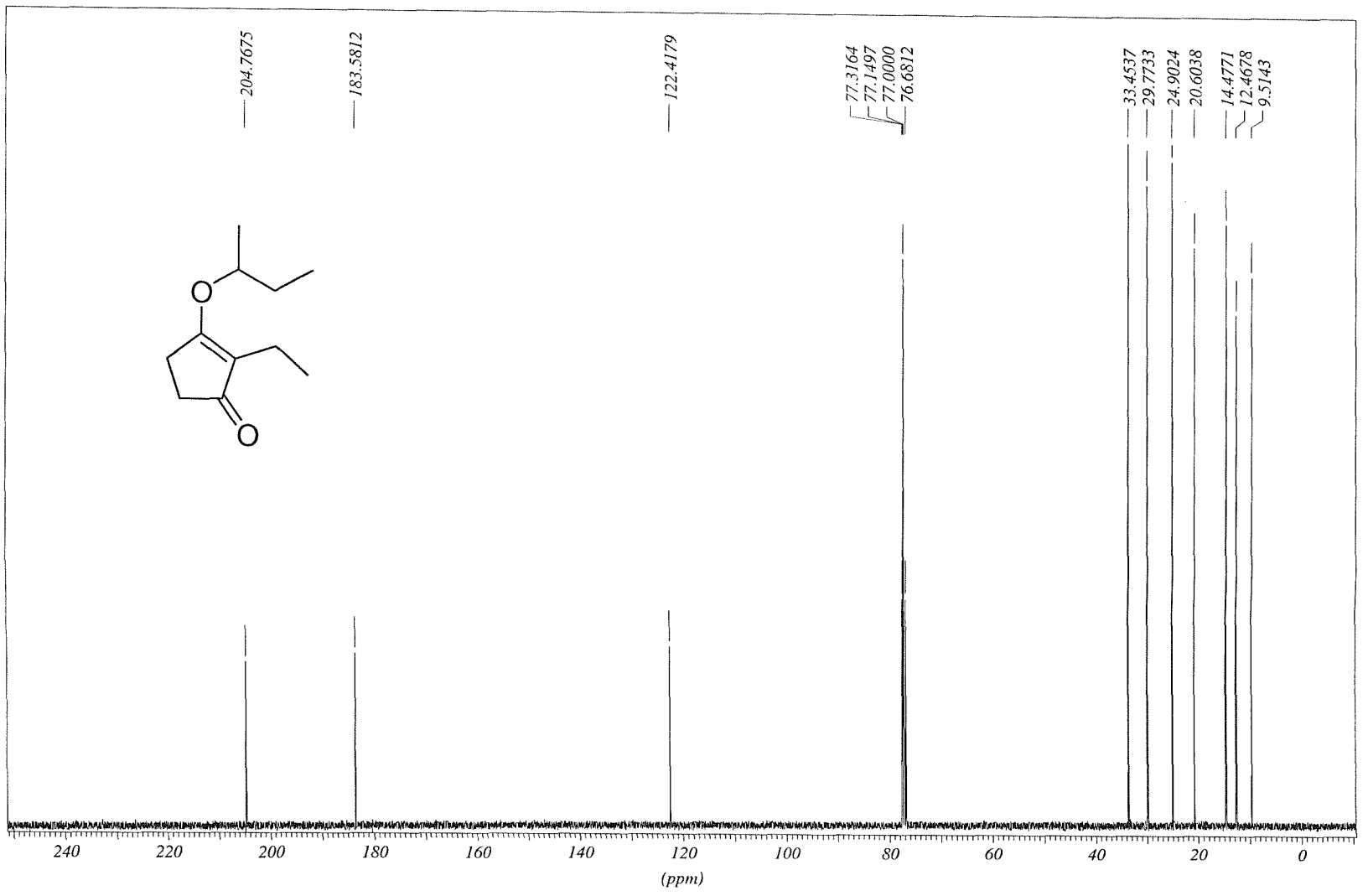
2.3994
2.3940
2.3868
2.3818
2.3749
2.1319
2.1131
2.0942
2.0754
1.6956
1.6787
1.6602
1.6408
1.6219
1.6081
1.5900
1.5868
1.2883
1.2729
0.9627
0.9496
0.9442
0.9311
0.9254
0.9123
O
O
Integral
0.9001
2.1442
2.0270
2.0906
2.0107
3.0536
5.7737
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

RC/3291-11C□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120
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40
20
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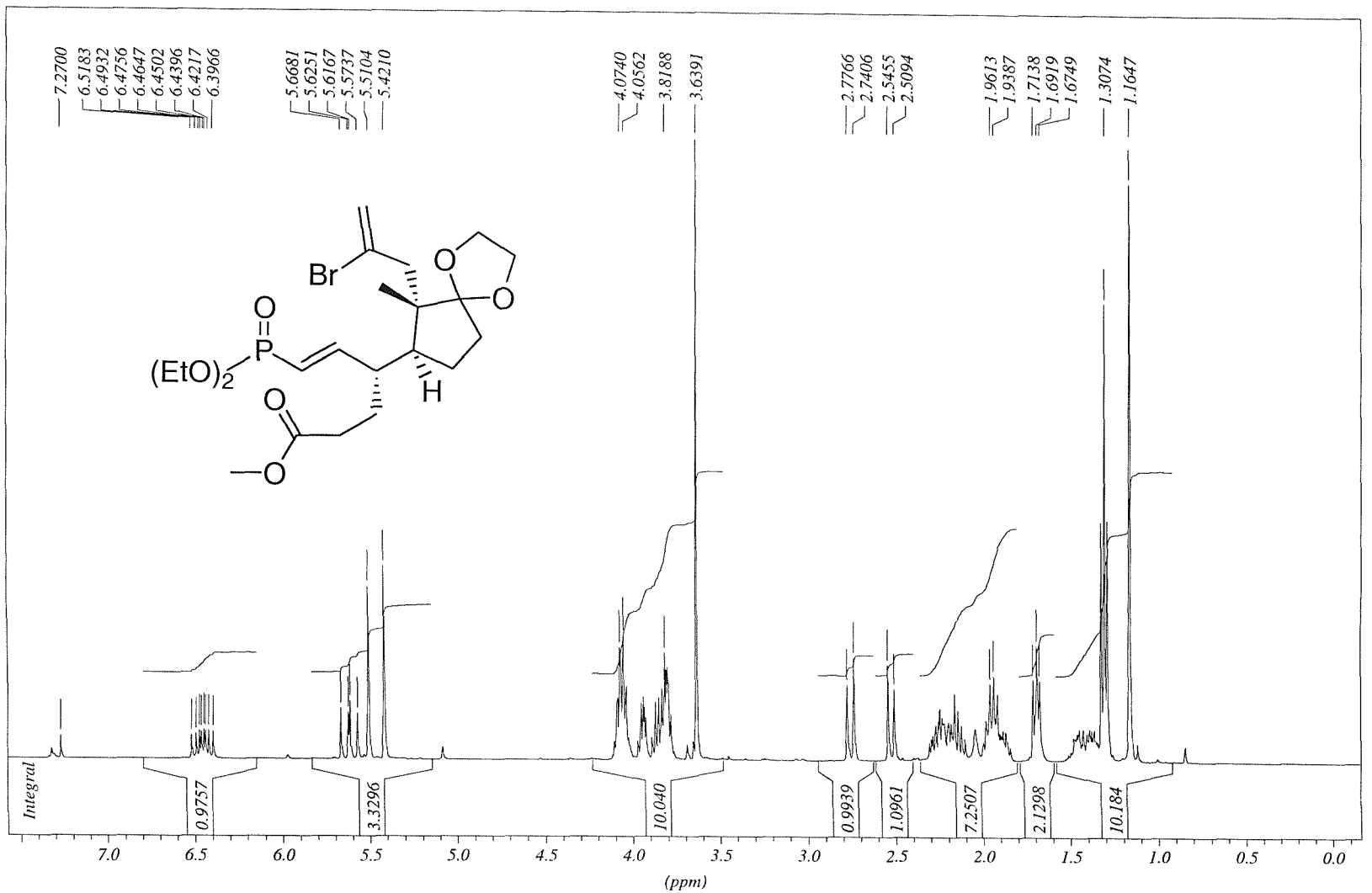
(ppm)

RC/3291-30I□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5.6167
5.5737
5.5104
5.4210
4.0740
4.0562
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3.6391
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2.5094
1.9613
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1.6919
1.6749
1.3074
1.1647
Br
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O
O
P
(EtO)2
O
H
O
Integral
0.9757
3.3296
10.040
0.9939
1.0961
7.2507
2.1298
10.184
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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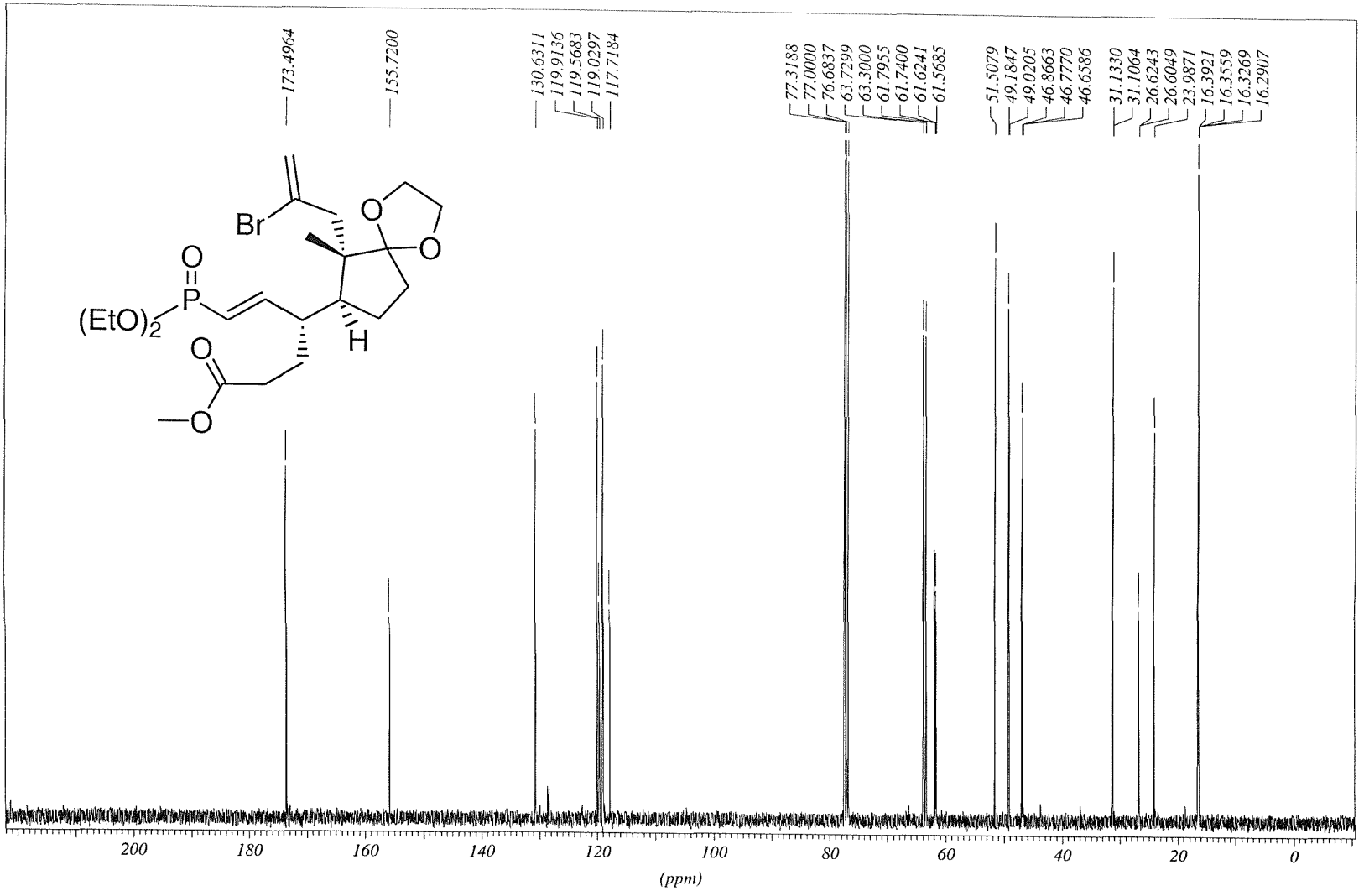
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

RC/3291-30I□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26.6049
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16.2907
Br
O
O
O
P
(EtO)2
O
H
O
200
180
160
140
120
100
80
60
40
20
0
(ppm)

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