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A Novel, Versatile D→BCD Steroid Construction Strategy, Illustrated by the Total Syntheses of Estrone and Desogestrel

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Doctor of Philosophy

Department of Chemistry

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UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHS

DEPARTMENT OF CHEMISTRY

Doctor of Philosophy

A Novel, Versatile D→BCD Steroid Construction Strategy, Illustrated by the Total Syntheses of Estrone and Desogestrel

By Vincent Foucher

Proposed are the total syntheses of the steroids desogestrel and estrone, utilizing a 1,4-addition/alkylation process to install the correct stereochemistry at C8, C13 and C14 in a single-pot operation. The racemic total synthesis of desogestrel includes a successful domino anionic cyclisation leading to the formation of the steroid C and B rings in a single operation with complete stereocontrol at C9. The β-keto phosphonates obtained were subsequently subjected to A-ring annelation via a multistep one-pot process.

The enantioselective synthesis as well as the racemic total synthesis of estrone include a sequential C and B-ring formation through ring closing metathesis and intramolecular Heck reaction.

DECLARATION OF AUTHORSHIP

I, Mr Vincent FOUCHER, declare that the thesis entitled:

A Novel, Versatile D→BCD Steroid Construction Strategy, Illustrated by the Total Syntheses of Estrone and Desogestrel.

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that: this work was done wholly or mainly while in candidature for a research degree at this University; where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated; where I have consulted the published work of others, this is always clearly attributed; where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work; I have acknowledged all main sources of help; where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself; parts of this work have been published as:

(1) Clarkson, R. A. *Towards the total synthesis of desogestrel*, PhD thesis, 2004.

(2) Guizzardi, B. *Total synthesis of 3-O-methyl-estrone*, PhD thesis, 2005.

Signed: ……..

Date:…….

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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 January 2006 and April 2009.

Acknowledgements

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Finally, all my friends met in Southampton, and all my friends from France for friendship and support.

Abbreviations

The following abbreviations have been used throughout this thesis:

b.p.	-	boiling point
br	-	broad
CAN	-	Cerium ammonium nitrate
CIMS	-	Chemical ionization mass spectrometry
CSA	-	DL-camphor-10-sulfonic acid
d	-	doublet
DCC	-	Dicyclohexylcarbodiimide
DCM	-	Dichloromethane
de	-	diastereomeric excess
DHA	-	Dehydroepiandrosterone acetate
DIBAL	-	Diisobutylaluminium hydride
DBU	-	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIC	-	Diisopropylcarbodiimide
DIPEA	-	Diisopropylethylamine
DMAP	-	Dimethylaminopyridine
DMF	-	Dimethylformamide
DMSO	-	Dimethylsulfoxide
ee	-	enantiomeric excess
EIMS	-	Electron ionization mass spectrometry
equiv	-	equivalent
FSH	-	Follicle stimulating hormone
g	-	gram
GnRH	-	Gonadotrophin releasing hormone

h	-	hour
HCA	-	Hexachloroacetone
HMPA	-	Hexamethylphosphoramide
HMPT	-	Hexamethyl phosphorus triamide
HPLC	-	High performance liquid chromatography
HRMS	-	High resolution mass spectrometry
HWE	-	Horner-Wadsworth-Emmons
IMHW	-	Intramolecular Horner-Wittig
L	-	Litre
LAH	-	Lithium aluminium hydride
LDA	-	Lithium diisopropylamide
LG	-	Leaving group
LH	-	Luteinizing hormone
min	-	minute
m.p.	-	melting point
NaHMDS	-	Sodium hexamethyldisilazide (sodium bis(trimethylsilyl)amide)
NBS	-	*N*-bromosuccinimide
NMO	-	*N*-Methylmorpholine-*N*-Oxide
NMR	-	Nuclear magnetic resonance
OTf	-	Triflate/trifluoromethanesulfonate
ox	-	oxidation
PG	-	Protecting group
PPTS	-	Pyridinium *p*-toluenesulfonate
*p*TSA	-	*para*-Toluenesulfonic acid
py	-	Pyridine
Q	-	Quaternary
q	-	quartet
RCM	-	Ring Closing Metathesis

rt	-	room temperature
s	-	singlet
t	-	triplet
TBS/TBDMS	-	*tert*-Butyldimethylsilyl
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
TLC	-	Thin layer chromatography
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 1.1. By convention, it is agreed that the rings are labeled 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.[1]

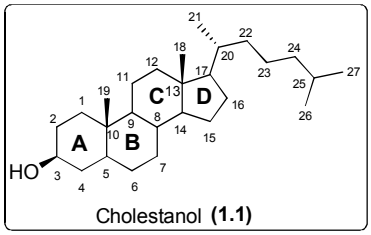


Figure 1.1

By convention, the upper and lower faces of the steroid are defined as the β-face and the α-face, as shown in Figure 1.2.

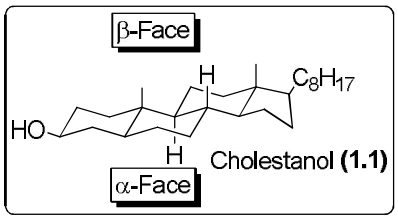


Figure 1.2

Another commonly used nomenclature within steroids is the nor-prefix which indicates the lack of a particular group.[1] As illustrated in Figure 1.3, 19-norcholesterol **(1.2)** is the analogue of cholesterol **(1.3)**, with a missing methyl group at C10 (the C19 methyl group).

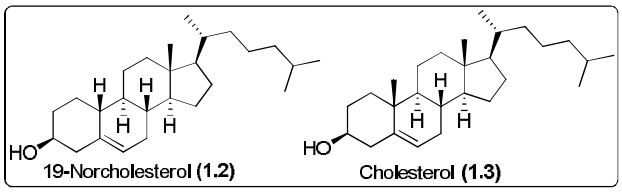


Figure 1.3

Hundreds of distinct steroids have been identified in plants and animals, where they play an essential role in many physiological functions.[1-8] For instance, they are particularly involved within the reproduction process and the regulation of growth.

1.1.2 Steroid hormones[9]

Within the human body, two classes of steroid hormones can be distinguished: the sex hormones which include androgens, progestogens and oestrogens; and the adrenal cortex hormones which include glucocorticoids and mineralocorticoids. There are many examples of individual steroids within each class, natural or synthetic steroids. Figure 1.4 presents some of the naturally occurring steroids.

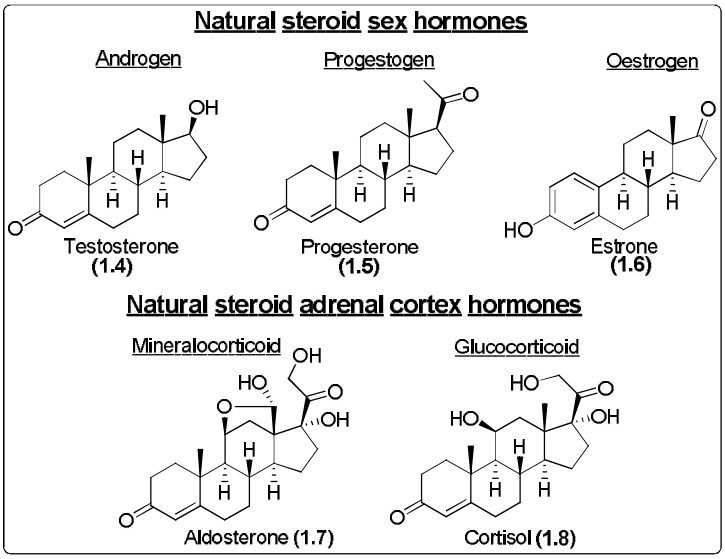


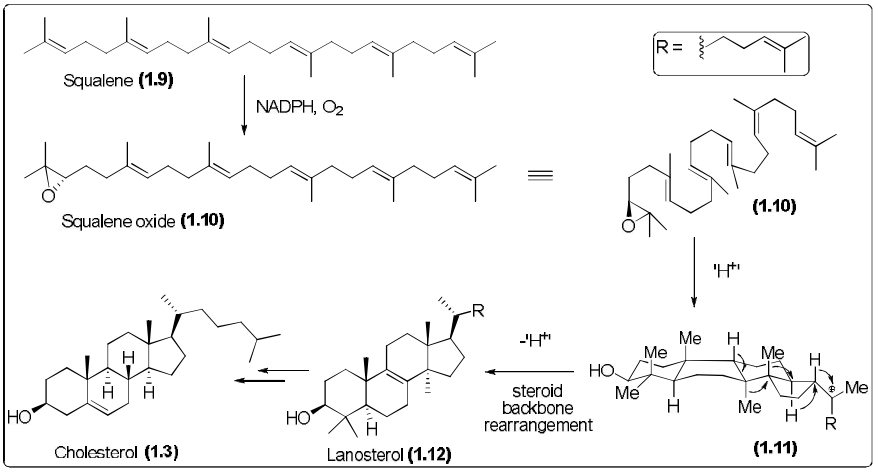
Figure 1.4

Androgens are mainly produced in the testes, though they are produced in small amounts in the adrenal cortex and ovaries, and are associated with the development and maintenance of male characteristics, fertility, muscle growth and mood effects. The most

well-known androgen is testosterone **(1.4)**. Progestogens, like progesterone **(1.5)** which is the only naturally occurring human one, are associated with the regulation of the menstrual cycle, the maintenance of pregnancy and the inhibition of ovulation. They are secreted by the ovaries and the placenta. Oestrogens are associated with the development and maintenance of female characteristics, fertility, muscle growth and mood effects. They are also involved in the control of the menstrual cycle and are mainly produced by the ovaries and the placenta. Estrone **(1.6)** is one of the three natural oestrogens that account for most of the estrogenic activity in humans. Mineralocorticoids and glucocorticoids are produced by the cortex of the adrenal gland. Mineralocorticoids, like aldosterone **(1.7)**, maintain the balance of sodium and potassium in the body and are therefore associated with blood volume and pressure. Glucocorticoids are involved in carbohydrate, protein and fat metabolism. They also have anti-inflammatory properties and cortisol **(1.8)**, also called hydrocortisone, is the most important human glucocorticoid.

1.1.3 Biosynthesis of steroid hormones

Any steroid hormone produced within nature has cholesterol **(1.3)** as the common precursor, which biosynthesis is shown in Scheme 1.1.[10]



Scheme 1.1

From squalene **(1.9)**, which has 30 carbon atoms (24 in the chain and 6 in the form of methyl-group branches), the first step is an enzymatic epoxidation that forms squalene oxide **(1.10)** as a single enantiomer, which then undergoes a complex cationic polycyclization leading to the tetracyclic cation intermediate **(1.11)**. Cation **(1.11)** then

undergoes a series of 1,2-shifts to form lanosterol **(1.12)**. Finally, lanosterol **(1.12)** is converted to cholesterol **(1.3)** by CO_2-elimination of the methyl groups at C4 and C14, transposition of the C8-9 to the C5-6 double bond and reduction of the side chain double bond.[10]

A key consequence of the use of squalene oxide **(1.10)** as steroid precursor is the resulting methyl group at the C13 position. Steroids with other groups than a methyl at C13 are synthetic steroids.

1.1.4 Hemi-synthesis of steroid hormones

Since steroids are such an important class of compounds, it is hardly surprising to discover that work concerning the synthesis of these compounds has been underway for many years. Beside the natural compounds, many synthetic steroids have been prepared in order to increase potency, limit side effects or improve other molecular characteristics (examples in Figure 1.5).

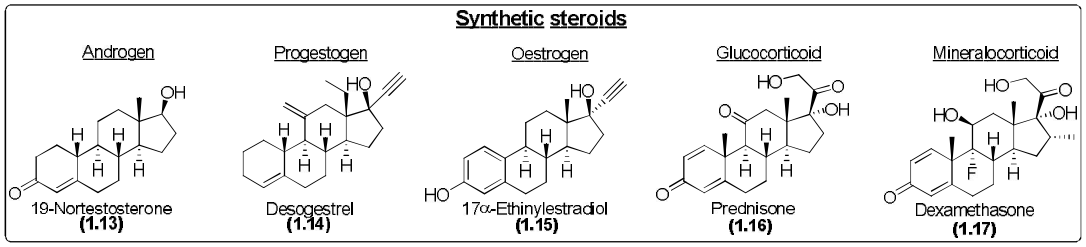


Figure 1.5

The industrial production of steroids, natural or synthetic, requires high yields and cheap and readily available starting materials. Although totally synthetic methods have been employed, these syntheses are not convenient as they often lead to isomeric mixtures of products. The steroid backbone itself often contains six asymmetric carbon centres, which means that up to 64 (2^6) stereoisomers are theoretically possible.[5] To avoid this problem, steroids are frequently obtained by hemi-synthesis from an abundant natural steroid. Natural steroid starting materials, a few examples are shown in Figure 1.6, are mainly extracted from plants: diosgenin **(1.18)** (*Dioscorea*), hecogenin **(1.19)** (*Agave Sisalana*), smilagenin **(1.20)** (*Smilax*), sitosterol **(1.21)** or stigmasterol **(1.22)** (soya seeds).

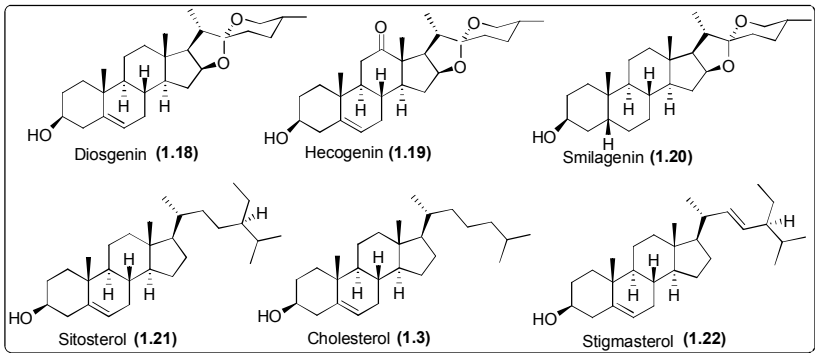
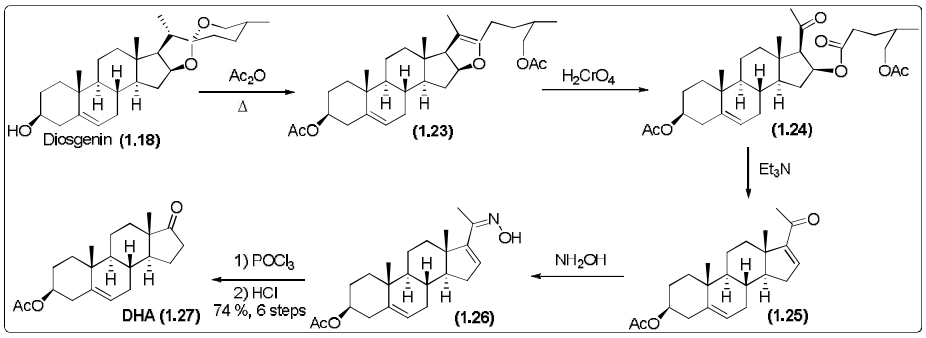


Figure 1.6

Diosgenin **(1.18)** and sitosterol **(1.21)** are the main sources of natural steroids for hemi-synthesis. For example, the commercial synthesis of desogestrel **(1.14)** is a hemi-synthesis starting from diosgenin **(1.18)** which is transformed to dehydroepiandrosterone acetate (DHA) **(1.27)** in six steps via the Marker process (Scheme 1.2).



Scheme 1.2

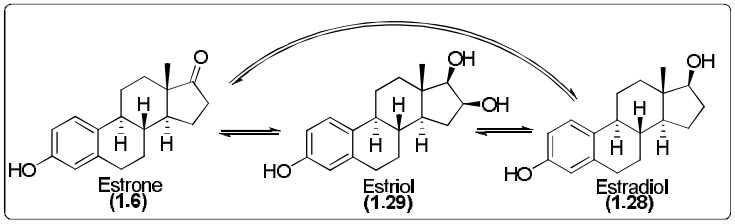
The first step of the Marker process is to cleave the F-ring in diosgenin by heating the compound at 200 °C with acetic anhydride. Chromic acid oxidation at the C20-22 double bond in **(1.23)** converts this compound into the keto ester diacetate **(1.24)** and immediate treatment of the keto ester diacetate with base eliminates the C16 side chain, forming the enone **(1.25)**. Treatment of **(1.25)** with hydroxylamine forms the C17-oxime **(1.26)**. $POCl_3$ is used to drive the Beckmann rearrangement of **(1.26)**, and DHA **(1.27)** is formed after acid hydrolysis. Overall, DHA can be prepared from diosgenin in 74% yield on an industrial scale.[1] The industrial desogestrel synthesis consists of 24 steps from diosgenin **(1.18)** but is not discussed in this thesis.

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

1.2.1 The menstrual cycle

The term menstrual cycle defines the periodic series of changes in the female reproductive system associated with the preparation of the uterus, key to which is the production and the release of an egg from the ovaries. The release of an egg is called ovulation and occurs every 28-35 days from non-pregnant women. The lining of the uterus, the endometrium, builds up in a synchronized fashion. If implantation of a foetus doesn't take place, the expanded endometrium is broken down and excreted which is known as the menstruation.

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 (Figure 1.6). GnRH is produced by the hypothalamus. FSH and LH are both gonadotrophin hormones and are secreted by the anterior pituitary gland (in the brain). Oestrogen and progesterone **(1.5)** are both steroid hormones and are mainly produced by the ovaries. As already mentioned in part 1.1.2, progesterone **(1.5)** is the only naturally occurring human steroid hormone that belongs to progestogens. Oestrogens, however, are represented by three naturally occurring steroids: estrone **(1.6)**, estradiol **(1.28)** and estriol **(1.29)** (Scheme 1.3).



Scheme 1.3

These are all produced in the body from androgens (like testosterone **(1.4)**) through enzyme action. Estradiol **(1.28)** is the primary oestrogen: it is 12 times more potent than estrone **(1.6)** and 80 times more potent than estriol **(1.29)**. Estradiol is converted to estrone in the blood. Estriol is produced in the liver by oxidation of the other two.

Figure 1.7 shows the change of blood levels for each hormone during the menstrual cycle.

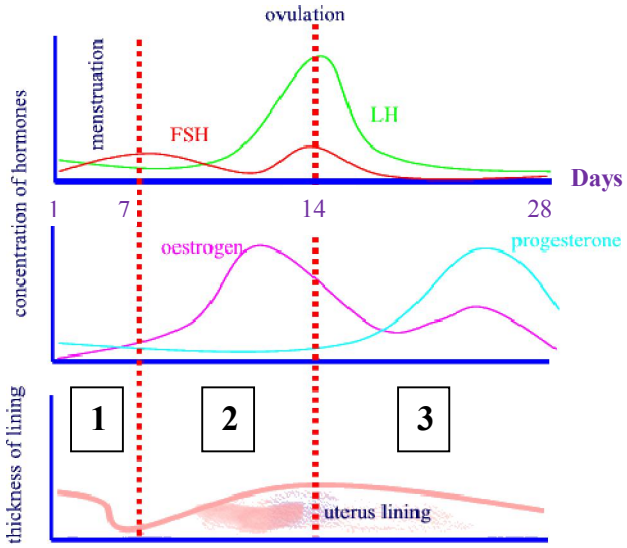


Figure 1.7

No units are displayed on the Y-axis as what is really important is the relative concentration of each hormone.

By convention, the "cycle day one" refers to the first day of menstrual bleeding. From day one, the hypothalamus releases GnRH, which causes the secretion of relatively low levels of LH and FSH from the pituitary gland (section 1, Figure 1.7). Under the influence of the FSH, a number of follicles in the ovary start to grow. The cells of these growing follicles release oestrogen (primarily estradiol) 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, and as a result increases gonadotrophin (LH and FSH) release. This in turn leads to a further increase in oestrogen production. The overall effect of this is to cause a surge in oestrogen, LH and FSH production, which in turn stimulates the release of an egg, and ovulation occurs (section 2, Figure 1.7).

After the ovulation, the residual follicle transforms into the *corpum luteum* under the effect of the LH. The *corpus luteum* will produce progesterone in addition to oestrogens for the next two weeks. 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. In the absence of pregnancy, the *corpus luteum* demises and oestrogen and progesterone levels fall. Progesterone withdrawal leads to menstrual shedding, while the falling oestrogen

levels allow FSH levels to rise resulting in the beginning of a new cycle (section 3, Figure 1.7).

1.2.2 Pregnancy

If fertilization of an egg has occurred, the *corpus luteum* does not degenerate but persists. This is the result of another hormone: the human chorionic gonadotrophin (hCG), secreted by the placenta. The *corpus luteum* is now able to continue to produce progesterone and low levels of oestrogen until the 3rd- 4th month of gestation, when the placenta replaces it.

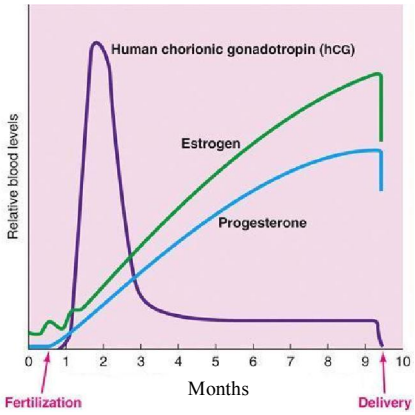


Figure 1.8

The placenta then secretes increasing amounts of oestrogen and progesterone until the end of pregnancy. The main oestrogen produced by the placenta is estriol. The high levels of oestrogen and progesterone during pregnancy maintain the development of the uterus, prevent menstruation and inhibit the production of FSH so that no further follicles can develop. They are also required by the mother's body to prepare for birth. For instance, they allow changes to the uterine musculature and also allow the development and the maintenance of the mammary glands for lactation. Variations in hormone levels during pregnancy are shown in Figure 1.8.

1.3 The contraceptive pill

1.3.1 Introduction to contraception

Contraceptives and other forms of fertility control have quite possibly always been employed in mankind history and the methods used have evolved alongside society.[13] The role of contraception is to reduce fertility in a reversible manner. There are many forms of contraception, which include diaphragms, caps, male or female condoms, the rhythm method, intrauterine contraceptive devices (IUCDs) and steroidal contraceptives.

1.3.2 Steroidal contraceptives

Steroidal oral contraceptives are one of the most innovative pharmacological products of the 20th century and no other pharmacological agents have been more widely studied.[14] They were introduced in the 1950s but they only became reliable and acceptably effective in the 1960s.

Two types or oral contraceptives can be distinguished: preparations that contain a combination of an oestrogen and a progestogen, and preparations that only contain a progestogen. The roles of these hormones in relation to contraception are explained in the next section.

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 gonadotrophin hormones FSH and LH. During pregnancy, the persistent production of progesterone also prevents further follicles from developing. The idea behind oral contraceptives was to supply a continuous source of a progestogen so as to inhibit the production of FSH and LH, and as a result ovulation could not occur. This is what the contraceptive pill does as it serves as an artificial source of a progestogen. The biggest weakness with this type of contraceptive is that the effects only last for 22-26 hours and therefore must be taken daily. Non-oral progestogen contraceptives do not have this problem. Injection is effective for 8 weeks and sub-dermal 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 in preventing the production of FSH and LH. The oestrogen is thought to promote the development of progesterone receptors, thus making the progestogens in the contraceptive pill more effective.

1.3.4 Side effects of the contraceptive pill

Oral contraceptives have a number of associated side-effects.[15,16] They may influence coagulation, increasing the risk of blood clots causing deep venous thrombosis, pulmonary embolism, stroke and myocardial infarction. This is especially true for women who already have some pre-existing vascular disease, for women who have a familial tendency to form blood clots, women with obesity or hypercholesterolaemia or smokers. The pill has also been linked to an increased risk of breast cancer, although this was mostly related to the high doses of oestrogen contained in the first pill type.[17] Minor side effects include weight gain, nausea, headaches, depression, libido changes or skin problems.

Not all of the side effects of taking oral contraceptives are negative however. Indeed, oral contraceptives users have a reduced risk of developing ovarian and endometrial cancers, and these effects can persist for up to ten years after discontinuation of oral contraceptive use.[14] Oral contraceptives also help women with menstrual disorders and have sometimes been found to reduce the incidences of acne amongst users.

1.3.5 The evolution of oral contraceptives[17-21]

The first steroid to be used as an oral contraceptive was norethisterone **(1.30)**, synthesised in 1951 (Figure 1.9). Norethisterone and all of the synthetic progestogens are derived from 19-nortestosterone **(1.13)**. 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 **(1.5)**.[18]

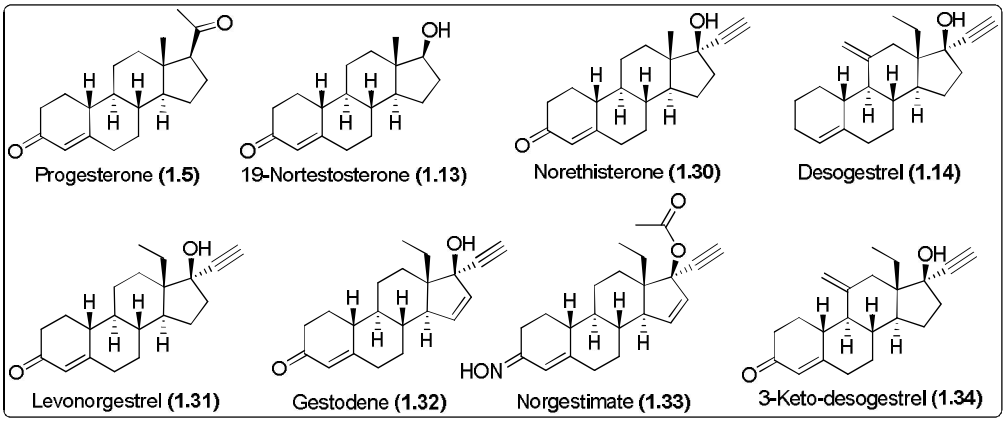


Figure 1.9

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 contraceptive 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 C18 (a C13 ethyl group) (Figure 1.9, levonorgestrel versus norethisterone). This group was believed responsible for the increased potency of the second generation compounds.[19] The different selectivity profile was not at 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, leading to bi or tri-phasic oral contraceptives. Meanwhile, further research was underway into the development of new progestogens. These became the third generation of oral contraceptives, of which desogestrel **(1.14)** was the first on the market; introduced in Europe in 1981. Several years later, two more third generation oral contraceptives were introduced: gestodene **(1.32)** and norgestimate **(1.33)** (Figure 1.9). 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 according to *in vivo* studies.[20] In terms of structure, gestodene is very similar to levonorgestrel, the only difference is an additional double bond between C15 and C16 in gestodene. Norgestimate and desogestrel both have two stuctural changes from levonorgestrel. Norgestimate has both the C17-β acetate and the C_3 oxime groups whereas desogestrel has no oxygenated C3 functional group, but it does have an exocyclic methylene group at C11. The C11 methylene group is responsible for the increased progestogenic but reduced androgenic activity of desogestrel.[20] The pharmacologically active form of desogestrel is its metabolite, 3-keto-desogestrel[17] **(1.34)** (Figure 1.9), which can be injected, implanted, or it can be formed in the liver from orally administered desogestrel **(1.14)**.

1.4 Previous syntheses of desogestrel

1.4.1 Synthetic challenges

Three main challenges can be identified for the synthesis of desogestrel **(1.14)** as shown in Figure 1.10:

- Construction of the A-ring with the double bond at the C4-C5 position
- Introduction of the exocyclic C11-methylene group
- Introduction of the angular C13-ethyl group, without contamination with the *cis*-fused C-D ring system

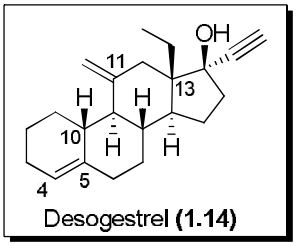


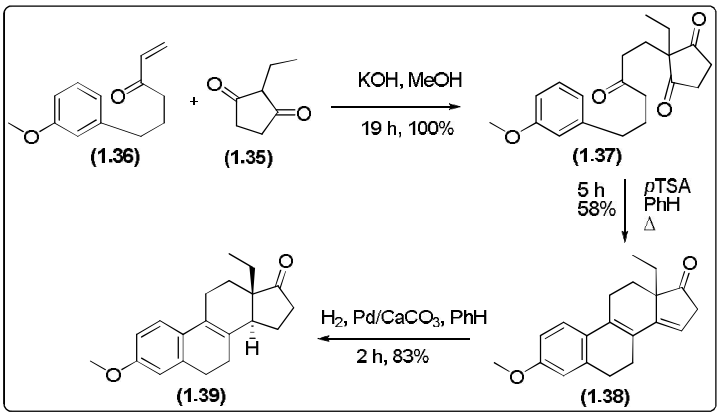
Figure 1.10

Each of these challenges is discussed below, as well as a discussion of selected examples of existing total syntheses of desogestrel. Hemi-synthesis approaches will not be discussed however.

1.4.2 Introduction of the C13-ethyl group

One of the most common method that enables the introduction of the C13-ethyl group involves the use of 2-ethyl-1,3-cyclopentanedione **(1.35)** as the D-ring precursor. Many groups including Smith,[22] Corey,[23] Saucy[24,25] or Tietze[26] have employed this precursor in related total syntheses of desogestrel.

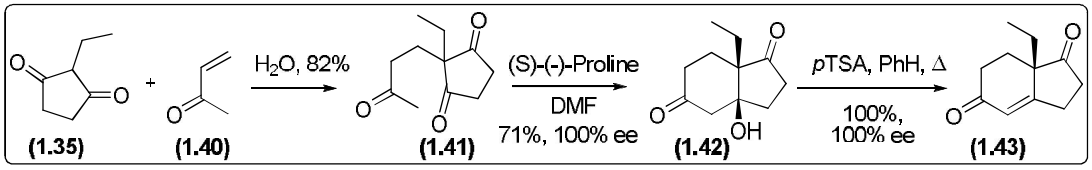
An example of the synthesis devised by Smith and co-workers[22] is shown in Scheme 1.4 where the triketone **(1.37)** is obtained by a Michael addition of the enolate of **(1.35)** onto the enone **(1.36)**.



Scheme 1.4

Acid mediated cyclisation led to the racemic tetracyclised steroid **(1.38)** which upon regio- and stereoselective hydrogenation afforded the desired *trans*-hydrindane ring system **(1.39)**. Due to the ease of the synthesis of steroid **(1.39)**, this starting material has frequently been used for C13-ethyl steroids.[27,28]

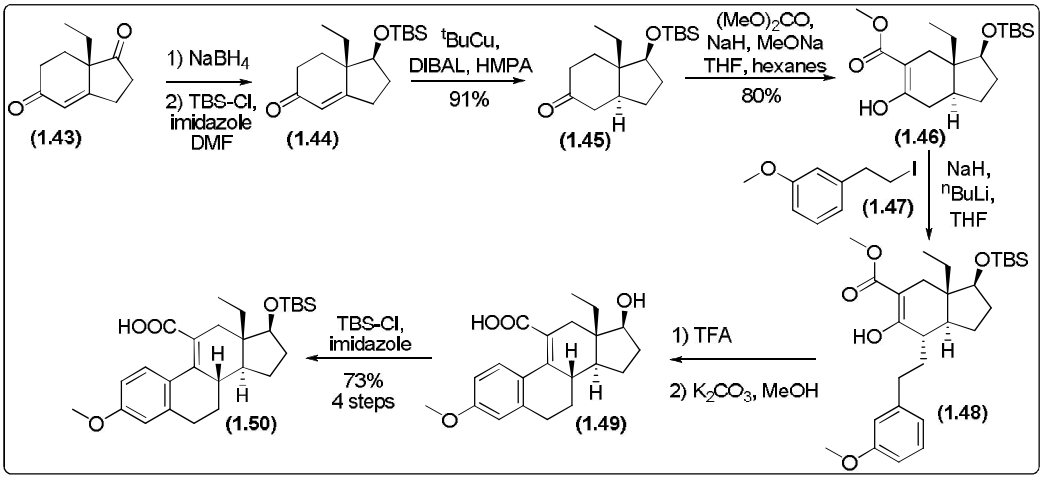
The Parrish-Hajos diketone[29,30] **(1.43)** has also been frequently employed for C13-ethyl steroids,[31-33] and can be synthesized enantioselectively by organocatalysis from **(1.35)** as shown in Scheme 1.5.



Scheme 1.5

A Michael addition conducted in aqueous media between diketone **(1.35)** and the enone **(1.40)** led to the triketone **(1.41)** in 82% yield. The next asymmetric aldol reaction, using a catalytic amount of (*S*)-(-)-proline, led to the optically pure *trans*-hydrindane **(1.42)** in 71% after recrystallization. The Parrish-Hajos diketone **(1.43)** was obtained by subsequent acid catalysed dehydration in quantitative yield.[31]

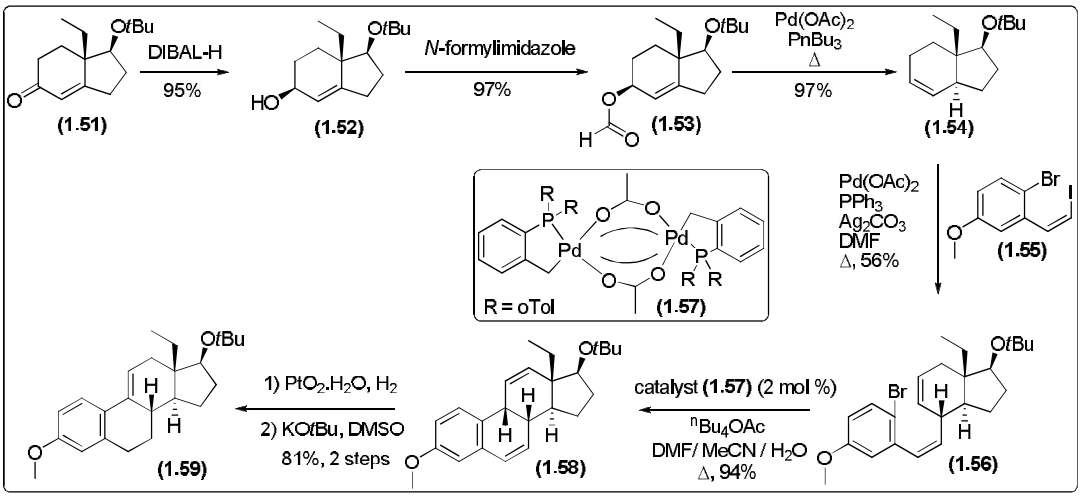
An example from Corey and Huang[23] is given below (Scheme 1.6) which illustrates the use of the Parrish-Hajos ketone **(1.43)** towards desogestrel synthesis.



Scheme 1.6

From the Parrish-Hajos ketone **(1.43)**, the ketone was selectively reduced in the presence of the enone using sodium borohydride and the intermediate alcohol was protected as a silyl ether **(1.44)**. Using a catalytic amount of ^{t}BuCu (0.3 equiv) in the presence of an excess of DIBAL-HMPA complex (2 equiv), the α,β-double bond in **(1.44)** was stereoselectively reduced. The *trans*-hydrindane compound **(1.45)** was obtained in 91% yield. The regioselectivity was problematic for the next α-methoxycarbonylation leading to **(1.46)** using dimethyl carbonate, sodium hydride and sodium methoxide in a 1 : 1 mixture of THF/hexane. The optimized conditions still led to a 6.3 : 1 mixture of regioisomers. The tricyclic β-keto ester **(1.48)** was then obtained by sequential double deprotonation with NaH followed by ^{n}BuLi and regio- and stereoselective alkylation with **(1.47)**. The cationic cyclization was achieved with 10% TFA in DCM that formed the tetracyclic steroid skeleton with the correct geometry at C8, C13 and C14. However, the use of TFA partially deprotected the C17-silyl ether, forming the C17-trifluoroacetate which was cleaved by methanolic base (also hydrolysing the C11-ester). The C17-silyl ether was reintroduced with TBS-Cl leading to **(1.50)** in 73% overall 4 steps. Details for the C11-methylene introduction are given below (part 1.4.3.4) and the final steps of the synthesis of desogestrel are discussed in part 1.4.4.

In a recent publication, Tietze and co-workers[26] also introduced the C13-ethyl group from a modification of the Parrish-Hajos ketone, where the steroid backbone was constructed via a double Heck reaction as illustrated in Scheme 1.7.

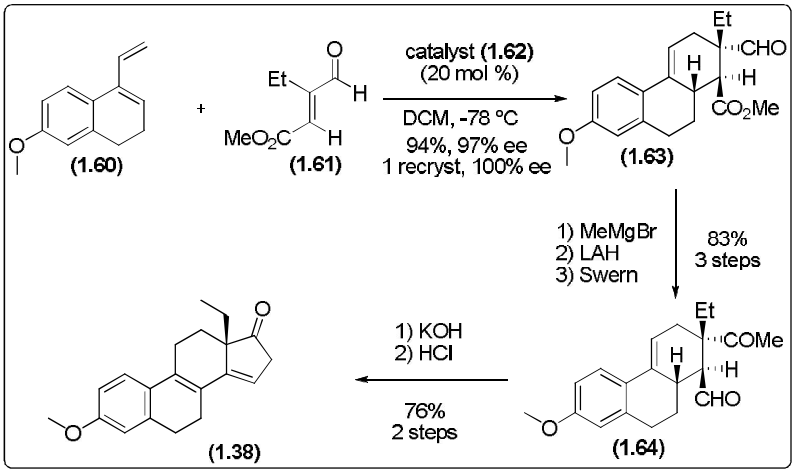


Scheme 1.7

Reduction of the carbonyl group in **(1.51)** was achieved with DIBAL-H in DCM with attack of the hydride taking place exclusively from the less hindered α-face to give alcohol **(1.52)**. Treatment of **(1.52)** with *N*-formylimidazole afforded allyl formate **(1.53)**, which was further transformed into the *trans*-hydrindane compound **(1.54)** by stereoselective Pd-catalysed rearrangement. For the first Heck reaction, coupling of **(1.54)** and **(1.55)**, the oxidative addition of the palladium catalyst exclusively took place at the more reactive vinyl iodide moiety in **(1.55)**. Although the reaction was very stereoselective, with exclusive insertion into the double bond in **(1.54)** from the α-face (the C13-ethyl group shielding the β-face), regioselectivity was not so great as a 7 : 1 mixture of regioisomers was obtained. The intramolecular Heck reaction, using Herrmann catalyst **(1.57)**, proceeded in a highly stereoselective fashion, leading exclusively to the unnatural *cis* junction of the B- and C-rings **(1.58)**. The less sterically hindered benzylic Δ6,7-double bond in **(1.58)** was then selectivily reduced with $PtO_2.H_2O$, and the remaining Δ11,12-double bond was isomerized to the Δ9,11-position **(1.59)**. Many total syntheses of desogestrel rely on this particular Δ9,11-double bond for the introduction of the exocyclic C11-methylene group, as discussed below (part 1.4.3). Tietze and co-workers have also employed this double Heck methodology in a related total synthesis of estrone **(1.6)**.[34]

Beside those examples that rely on 2-ethyl-1,3-cyclopentanedione **(1.35)** for the introduction of the C13-ethyl group, Corey and co-workers[35,36] have demonstrated it could be introduced via an enantioselective Diels-Alder reaction between Dane's diene[37,38]

(1.60) and the dienophile **(1.61)** in presence of an oxazoborilidine catalyst[36] **(1.62)** (Scheme 1.8, Figure 1.11).



Scheme 1.8

The ABC steroid precursor **(1.63)** was obtained in 94% and in 97% ee, which was improved to 100% ee after a single recrystallization. Such good enantioselectivity is explained by the diene **(1.60)** attacking the catalyst-dienophile complex **(1.65)** (Figure 1.11) from the sterically less shielded front face, directing the [4+2] cycloaddition to form **(1.63)**.

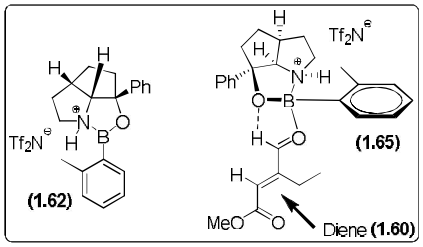


Figure 1.11

From **(1.63)**, the D-ring precursor **(1.64)** was obtained in 83% by addition of methyl magnesium bromide to the aldehyde followed by LAH reduction of the ester and Swern oxidation of the resulting two alcohols. Aldol reaction followed by acid mediated dehydration constructed the D-ring **(1.38)**, from which point literature methods were used to synthesise desogestrel.[23,39] Corey and co-workers have also employed this methodology in a related total synthesis of estrone **(1.6)**.[35]

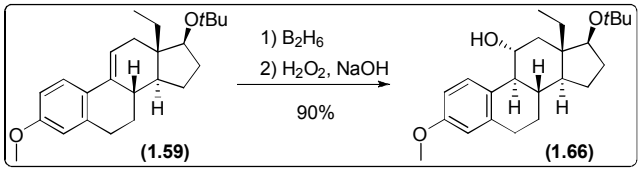
1.4.3 Introduction of the C11-methylene group

In the previous syntheses of desogestrel, the most frequently employed method for the introduction of the exocyclic methylene group has been via a C11-ketone introduced from a C11-hydroxyl group. Although several methods have been reported for the insertion of the C11-hydroxyl group,[40] only the methods used towards desogestrel synthesis shall be discussed in the following sections.

1.4.3.1 Introduction of the C11-hydroxyl group

1.4.3.1.1 Hydroboration/alkaline hydrogen peroxide

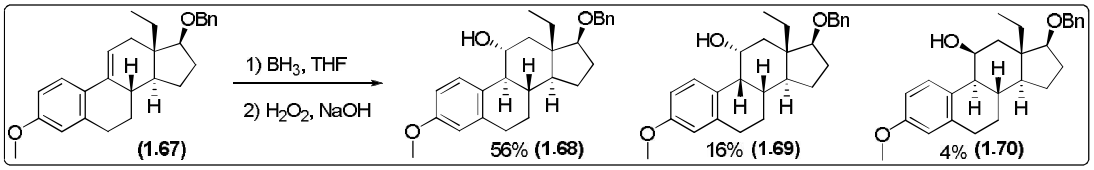
The most frequently employed method for the introduction of the C11-hydroxyl group has been the hydroboration of a C9-11 double bond followed by treatment with alkaline hydrogen peroxide. Many groups including Tietze[26] (Scheme 1.9), Corey,[35] Gao,[27] Schwarz[39] or Stéphan[41] have employed this methodology in related desogestrel syntheses.



Scheme 1.9

This hydroboration/alkaline hydrogen peroxide is particularly efficient (90% yield), but there are several limitations. The main limitation is the requirement of the C9-11 double bond and this could take several steps to install if not already present.

The other disadvantage is that the reaction seems not to be reliable. To illustrate this, Scheme 1.10 shows the results obtained by Gao and co-workers.[27]

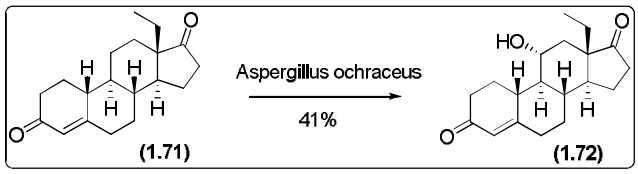


Scheme 1.10

Gao only reported a yield of 56% of desired 11α-OH product **(1.68)** along with 16% 9β-H product **(1.69)** and 4% of 11β-OH product **(1.70)**. The two side-products are not always obtained or mentioned in the literature examples when this hydroboration/alkaline hydrogen peroxide is employed.

1.4.3.1.2 Microbial oxidation

The other common method for the introduction of the C11-α-OH group has been a microbial oxidation[42] from the corresponding C11-hydrocarbon. For instance, the microbial oxidation is used in the industrial desogestrel synthesis, and Gao and co-workers[43] have also employed this procedure (Scheme 1.11).

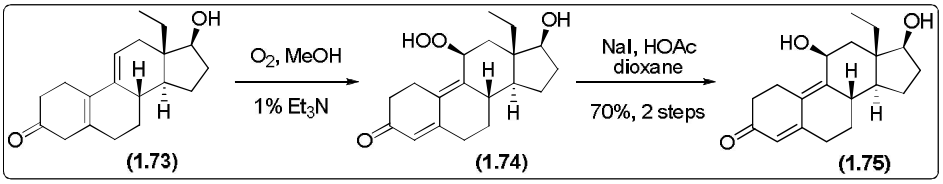


Scheme 1.11

Although this method is advantageous as it is a direct insertion of the hydroxyl group, which means no requirement of any functional group interconversion and so less steps, the yields are rarely excellent. This is in part due to the fact that by-products are often observed due to over-oxidation or non-selective oxidation.

1.4.3.1.3 Other methods

Other methods of insertion of the C11-hydroxyl group include oxygen-peroxidation[44,45] and epoxidation.[46] However, only the oxygen-peroxidation method has been successfully employed for the synthesis of desogestrel. This is illustrated in Scheme 1.12 which shows how Liu and co-workers have employed this methodology for the insertion of the 11β-OH group.



Scheme 1.12

Compared to the previously mentioned methods, this reaction is the only method that inserts the C11-hydroxyl group at the β-position. Upon exposure to oxygen, the diene **(1.73)** was peroxidized to the C11-β-hydroperoxide **(1.74)** which was reduced to the C11-β-alcohol **(1.75)** by reduction with sodium iodide.

1.4.3.2 Oxidation of the C11-hydroxyl group to the C11-ketone

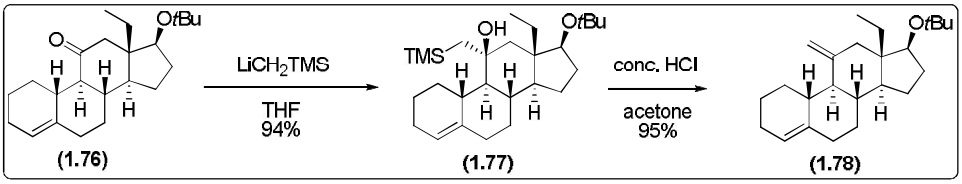
Many reagents have been successfully used for this transformation such as Jones's reagent,[43] PCC,[27] Dess-Martin periodinane[26] or activated DMSO methods.[39]

1.4.3.3 Conversion of the C11-ketone to the C11-methylene group

Conversion of the C11-ketone to the C11-methylene can be achieved by one of the three followings methods: Peterson olefination, Wittig reaction or nucleophilic addition of a methyl group followed by dehydration of the resulting tertiary alcohol.

1.4.3.3.1 Peterson olefination

Although the Peterson olefination has been used in the original synthesis of desogestrel,[47] it has not really been used since, apart from the recent desogestrel synthesis of Tietze[26] (Scheme 1.13).

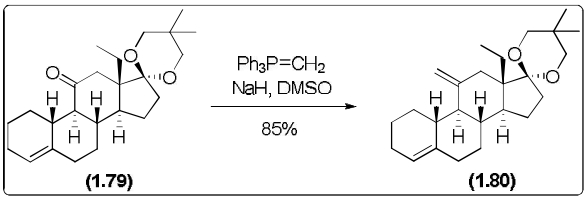


Scheme 1.13

Addition of $LiCH_2TMS$ to **(1.76)** in THF afforded the β-hydroxy intermediate **(1.77)** which upon acid-catalyzed Peterson olefination led to the C11-exo-methylene compound **(1.78)** in excellent yield.

1.4.3.3.2 Wittig reaction

The introduction of the C11-methylene has also been accomplished on separate occasions[39,48] by Wittig olefination with methylene triphenylphosphorane. An example is given in Scheme 1.14 from the group of Schwarz.[39]

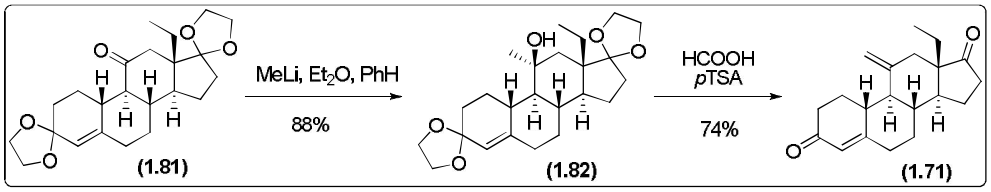


Scheme 1.14

Interestingly, the lack of functionality at C3 resulted in the reaction being very slow and with moderate yields. This was circumvented by running the reaction under sonication. Tietze has also reported this non-reactivity issue in his total synthesis of desogestrel.[26]

1.4.3.3.3 Nucleophilic addition of a methyl group/dehydration

The last method relies on the addition of methyl magnesium iodide or methyllithium followed by dehydration in formic acid. Gao and co-workers have used this method as illustrated in Scheme 1.15.[48]



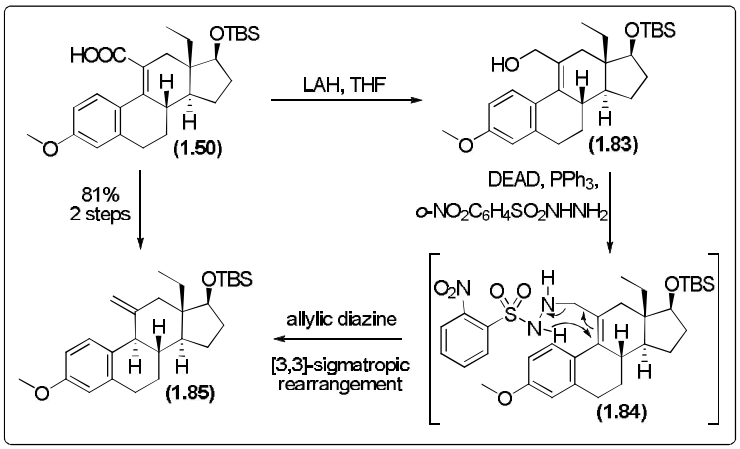
Scheme 1.15

Treatment of the C11-ketone **(1.81)** with methyllithium in Et_2O and benzene proceeded in good yield. The conditions required for the dehydration at the newly formed hydroxyl

group also removed the two acetal groups, and steroid **(1.71)** was obtained in 65% yield over both steps.

1.4.3.4 Other method

The only synthesis of desogestrel where the C11-methylene group is not inserted from the C11-ketone is the synthesis from Corey and Huang,[23] as shown in Scheme 1.16, via an allylic diazine-sigmatropic rearrangement.[49,50]

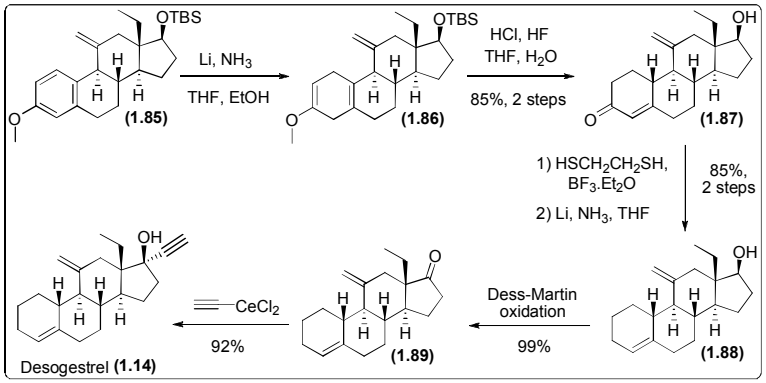


Scheme 1.16

The C11-acid **(1.50)** was reduced to the primary alcohol **(1.83)** with LAH. The C11-methylene group was then introduced via a Mitsunobu reaction leading to the sulphonamide intermediate **(1.84)**, which upon a [3,3]-sigmatropic rearrangement[49,50] stereoselectively introduced the C9-α proton as well as the exocyclic methylene group **(1.85)**.

1.4.4 Modification/Construction of the A-ring

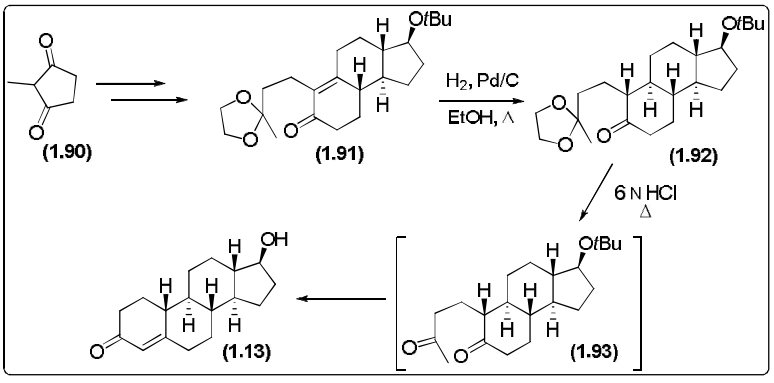
From a total synthesis point of view, only two methods exist for the formation of the A-ring for C19-norsteroids: Construction of the A-ring via a Robinson annulation or reduction of an aromatic A-ring. Towards the total synthesis of desogestrel, only the modification of an aromatic A-ring has been used. This methodology is illustrated in Scheme 1.17, for the final steps of the total synthesis of desogestrel from Corey and Huang.[23]



Scheme 1.17

A Birch reduction was employed for the de-aromatization of the A-ring in **(1.85)** using lithium in ammonia. Subsequent treatment of intermediate **(1.86)** with acid formed the α,β-unsaturated ketone **(1.87)** and also removed the TBS protecting group. From **(1.87)**, the C3-ketone was converted to a thioacetal which was reduced using lithium in ammonia in 85% over two steps. The final steps proceeded in high yields, where the C17-hydroxyl group in **(1.88)** was oxidized to the ketone **(1.89)** which allowed the introduction of the C17-α-ethinyl group in the final desogestrel product **(1.14)**.

The Robinson annulation is also a very common reaction in steroid chemistry and has been employed on separate occasions for the construction of the A, B and D rings.[51] As an example, the Robinson-type chemistry has successfully been employed for the construction of the A-ring in both natural steroids and C19-norsteroids. Scheme 1.18 shows how Parrish and Hajos have used this reaction to construct the A-ring in a total synthesis of 19-nortestosterone **(1.13)**.[32]



Scheme 1.18

Interestingly, 19-nortestosterone **(1.13)** was obtained from diketone **(1.90)** in 27% overall yield in 13 steps (or an average yield per chemical reaction of 93%) without any purification. The intermediate diketone **(1.93)** underwent an intramolecular aldol reaction/dehydration (which also deprotected the C17-O*t*Bu group) that completed the A-ring.

1.5 Previous syntheses of estrone

1.5.1 Introduction

Although (+)-estrone was the first steroid hormone ever isolated and one of the most synthesized, its synthesis still represents an appealing challenge in steroid methodology. The stereochemical complexity of the steroid backbone requires highly stereoselective steps to create new asymmetric centres with the desired geometry and in high yields.

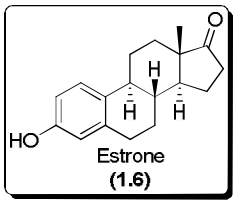
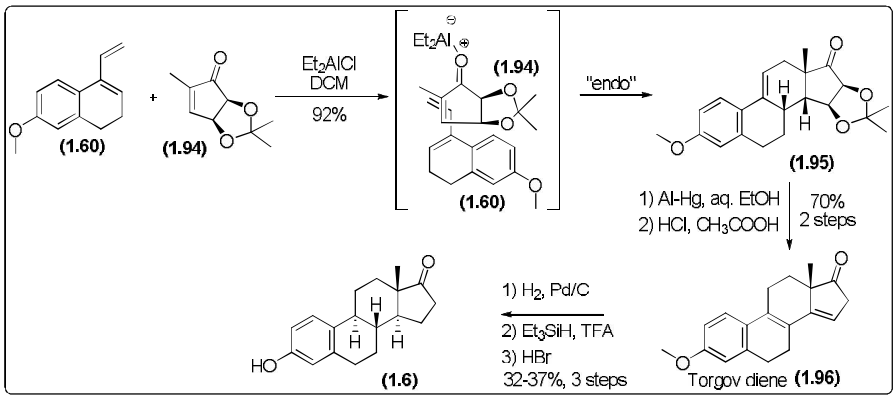


Figure 1.12

The enantiopure form of estrone, as shown in Figure 1.12, which is also the naturally occurring enantiomer, was first achieved in 1948 by Anner and Miescher.[52] Many syntheses of estrone have been described in the literature since, even very recently. Many ingenious methodologies have been developed, and as such only some of the most recent selected examples shall be discussed in the following sections.

1.5.2 Selected examples using Dane's diene

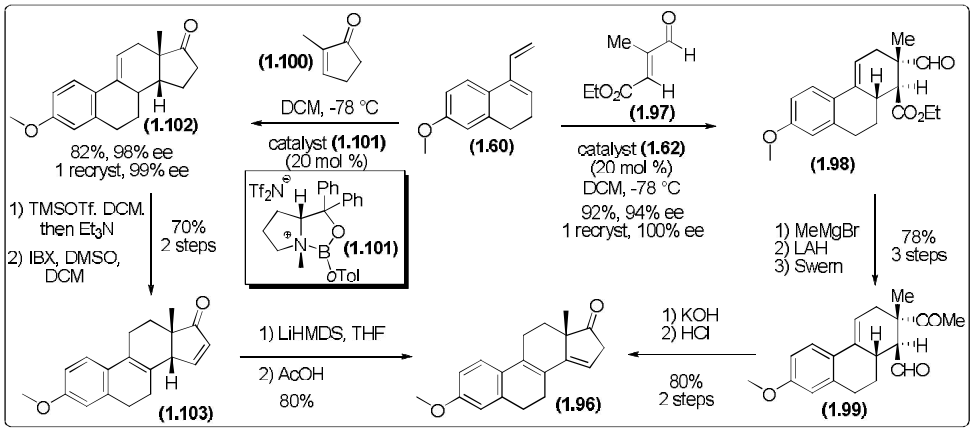
Among the most commonly used precursors for the synthesis of estrone is Dane's diene **(1.60)**.[37,38] This is illustrated in Scheme 1.19 for the synthesis of estrone by Ogasawara and co-workers[53] via a stereoselective Diels-Alder reaction between Dane's diene **(1.60)** and chiral dioxycyclopentenone **(1.94)**.



Scheme 1.19

The Diels-Alder reaction was conducted in presence of diethyl aluminum chloride which furnished the single steroid **(1.95)** diastereoselectively. Although the dioxolane moiety in enone **(1.94)** served as an excellent stereocontroling element, the reaction proceeded following the orbital-controlled *endo* rule as indicated by the *cis*-C9-C11 stereochemistry observed in **(1.95)**. Treatment of **(1.95)** with aluminum amalgam in aqueous ethanol gave the C15-β ketol which was converted to the Torgov diene[54] **(1.96)** with HCl/CH_3COOH in 70% over 2 steps. The conversion of the Torgov diene to estrone **(1.6)** was carried out in three steps following literature procedures.[55,56]

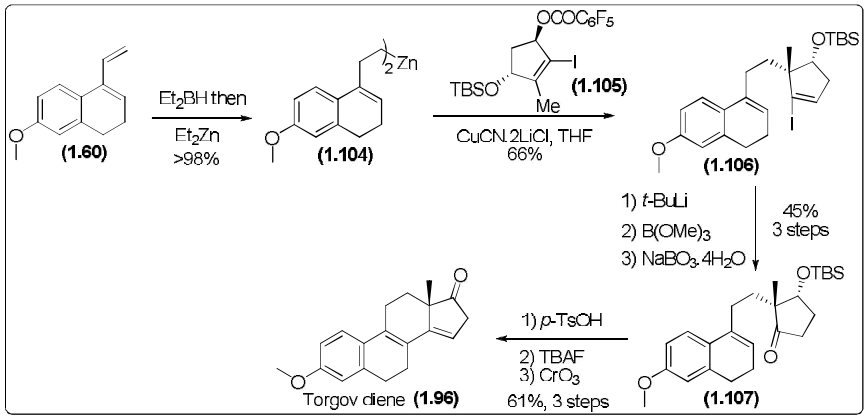
Corey and co-workers[35,36,57] have also conducted significant research in this area where the Dane's diene **(1.60)** is subjected to a Diels-Alder reaction using chiral oxazoborilidine catalysts (Scheme 1.20).



Scheme 1.20

From the Dane's diene **(1.60)**, they have developed two different synthetic pathways that both lead to the Torgov diene **(1.96)**. The first one, involving a stereoselective Diels-Alder reaction with the ester aldehyde **(1.98)** has already been touched upon for a similar total synthesis of desogestrel (part 1.4.2).[35,36] In this case, the Torgov diene could be obtained in 58% overall yield in six steps. More recently in 2008,[57] they reported a regio- and stereoselective Diels-Alder reaction between Dane's diene and cyclopentenone **(1.100)** using catalyst **(1.101)** which afforded *cis*-C13-C14 steroid **(1.102)** in 82% and 99% ee after a single recrystallization.

A final example involving Dane's diene is given below in Scheme 1.21, for the formal synthesis of estrone devised by Knochel and co-workers,[58] where the Torgov diene **(1.96)** is obtained via an asymmetric allylic substitution.

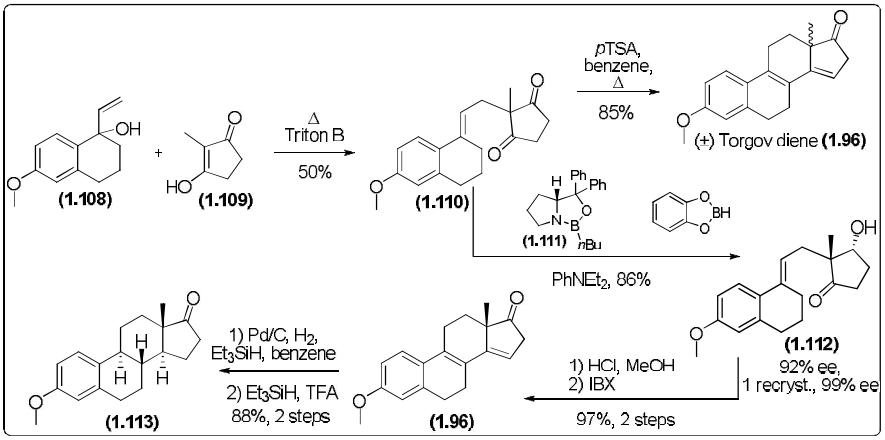


Scheme 1.21

Dane's diene **(1.60)** was converted to the zinc organometallic derivative **(1.104)** by hydroboration followed by a boron/zinc exchange sequence in excellent yield. The yield of the reaction was determined by GC analysis of hydrolyzed reaction aliquots. The chiral cycloalkenyl iodide **(1.106)** was then obtained by a copper(I)-mediated *anti*-S_N2'-allylic substitution of the dialkylzinc **(1.104)** with the allylic pentafluorobenzoate **(1.105)** in 66% yield. The cyclopentenyl iodide **(1.106)** was then converted to the corresponding ketone **(1.107)** by a one-pot sequence by treatment with *t*-BuLi followed by the addition of $B(OMe)_3$, and oxidation with sodium perborate. From the ketone **(1.107)**, acid-mediated ring closure followed by TBAF deprotection and subsequent oxidation of the C17-alcohol with CrO_3 led to the Torgov diene **(1.96)** in 61% overall yield in 3 steps.

1.5.3 Other selected methods

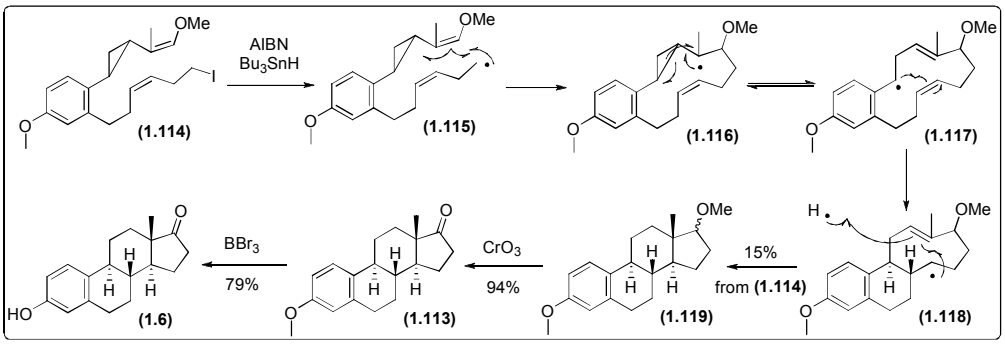
In 1963, Torgov and Anachenko disclosed a remarkably short synthesis of racemic Torgov diene **(1.96)** (from which the total synthesis of estrone has already been explained) which was based on the high yielding coupling of the readily available components **(1.108)** and **(1.109)** (Scheme 1.22).[54,59]



Scheme 1.22

Very recently, Corey and co-workers[60] have developed a new method for the enantioselective and diastereoselective reduction of the achiral Torgov diketone **(1.110)**. The key chirogenic step (Scheme 1.22), the reduction of **(1.110)** to **(1.112)** was successfully achieved by a slow addition of catecholborane (1.8 equiv) to a -50 °C solution of diketone **(1.110)** in presence of catalytic amounts of oxazoborilidine **(1.111)** and *N,N*-diethylaniline. The enantiopure C17-α-alcohol **(1.112)** was obtained in 86% with a 99% ee after recrystallization. The C-ring cyclization was achieved by treatment of **(1.112)** with methalonic HCl, and subsequent oxidation with IBX gave the enantiopure Torgov diene **(1.96)** in 97% overall yield in 2 steps. Enantiopure *O*-methyl-estrone **(1.113)** was then obtained in high yield by two successive hydrogenation steps.

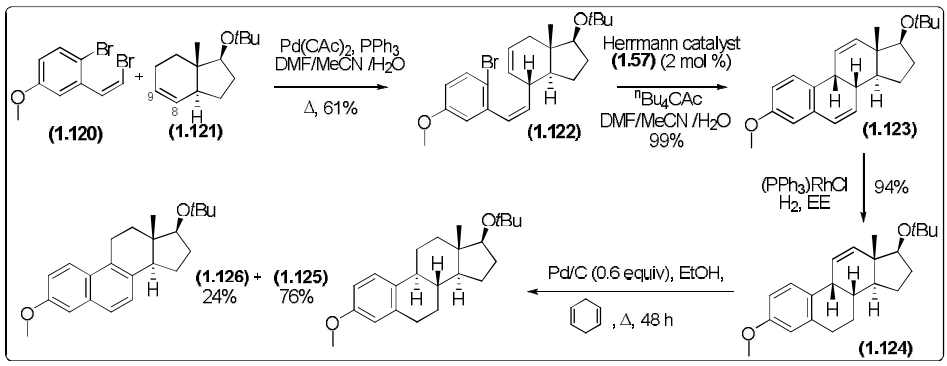
Another very interesting synthetic approach is the one devised by Pattenden and co-workers,[61,62] where the steroid B- C- and D-rings are constructed via a cascade radical-macrocyclisation and successive *trans*-annnulation reactions from a substituted aryl vinyl cyclopropane precursor **(1.114)** as shown in Scheme 1.23.



Scheme 1.23

The iodide **(1.114)** was refluxed with Bu_3SnH and AIBN in toluene, leading, through a regio- and stereoselective sequence of radical cyclizations, to a mixture of estradiol derivatives as a mixture of C17-OMe epimers **(1.119)** in 15% yield. The cascade of radical reactions from **(1.114)** to **(1.119)** involves 4 successive C-C bond formation reactions. First, a 12-*endo* trig macrocyclization of **(1.115)** to **(1.116)**. Then, a cyclopropenyl to but-2-enyl carbon equilibration of **(1.116)** to **(1.117)**. The two final reactions involve a 6-*exo* trig transannulation leading to **(1.118)** and finally a 5-*exo* trig transannulation and H-quench which led to **(1.119)**. Chromium trioxide oxidation afforded *O*-methyl-estrone **(1.113)** which was deprotected to estrone **(1.6)** with BBr_3.

Finally, Tietze and co-workers[34] have reported the total synthesis of estradiol derivative **(1.125)**, easily converted to estrone **(1.6)** via known reactions, by two successive Heck reactions between the doubly functionalized arene **(1.120)** and the chiral hydrindene **(1.121)** allowing the construction of the steroid skeleton (Scheme 1.24).



Scheme 1.24

Although the same methodology has already been described for a related total synthesis of desogestrel (Scheme 1.7, page 15), the final steps of our total synthesis of estrone mainly rely on this publication. The first Heck reaction, between **(1.120)** and **(1.121)**, proceeded in a very stereoselective fashion, with the only **(1.122)** reported. As already explained, it is believed that the angular C13-methyl group shielded the β-face of **(1.121)**. For the high regioselectivity in the C-C bond formation, it is believed that stereoelectronic effects force the attack of the palladium at C9 from the less hindered α-face in **(1.121)** to allow a chair-like transition state with subsequent *syn*-addition of the vinyl group in **(1.120)** at C8 (Figure 1.13).

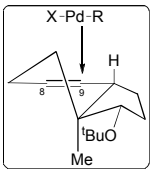
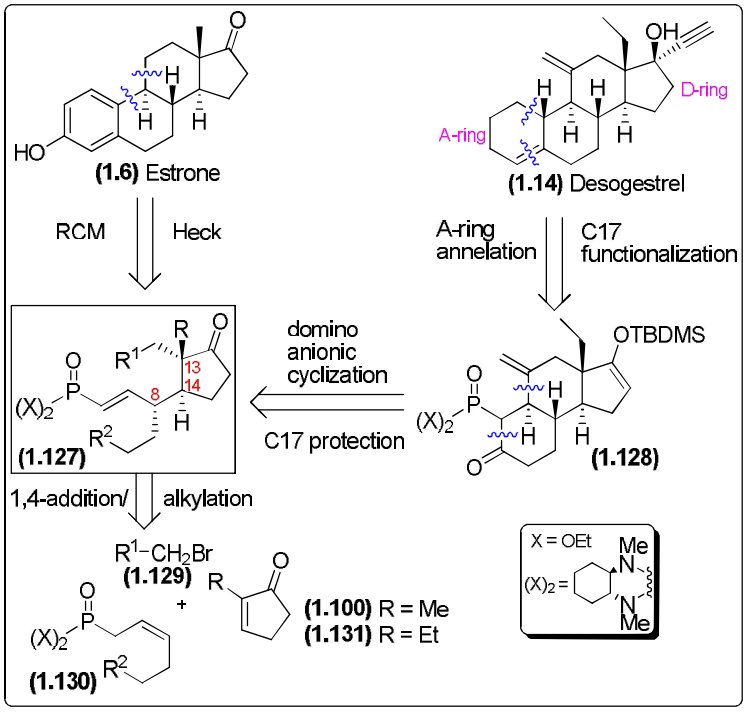


Figure 1.13

The next intramolecular Heck reaction using the Herrmann catalyst **(1.57)** proceeded in nearly quantitative yield, leading to **(1.123)** as a single diastereoisomer with the *cis*-ring junction between rings B and C. Selective hydrogenation of the more accessible Δ6,7-double bond with Wilkinson catalyst under homogeneous conditions led to intermediate **(1.124)** in 94% yield. The estradiol derivative **(1.125)** was then obtained in 76% yield by isomerisation of the remaining Δ11,12-double bond followed by hydrogenation using Pd/C with a large excess of 1,4-cyclohexadiene. However, the equilenin derivative **(1.126)** was also obtained in 24% yield.

1.6 Aim of the project

The aim of this project was to develop a new general steroid construction in which *three* stereocenters C8, C13 and C14 would be established prior to the actual formation of the steroid backbone. So as to demonstrate the versatility of the methodology, two very different steroid targets (estrone **(1.6)** and desogestrel **(1.14)**) have been envisioned, as shown in Scheme 1.25 below.



Scheme 1.25

The retrosynthetic analysis for both steroids via this approach involved a B- and C-ring disconnection in **(1.6)** and **(1.14)** leading to a key intermediate **(1.127)**, which possesses appropriate R, R^1 and R^2 groups. This intermediate was envisioned to be directly accessible by a one-pot process involving an allylic phosphonate/phosphonamide **(1.130)** to a 2-alkyl-2-cyclopentenone Michael acceptor **(1.100**, **1.131)**, followed by diastereoselective alkylation of the resulting enolate with alkyl-bromide **(1.129)**. Conjuguate addition reactions of allylic phosphonates are known to be very diastereoselective[63] with the allylic double bond configuration being translated into the relative configuration of the sp^3-centres of the formed C-C bond. The desired relative C8-C14 configuration requires a Z-configuration of the phosphonate double bond. By using a chiral phosphonamide auxiliary, an enantioselective synthesis would be possible. Introduction of the R, R^1 and R^2 groups as required for each steroid target would be easily achieved by appropriate choice of starting materials **(1.129)-(1.131)** and **(1.100)**.

Each of the key steps towards both steroid targets is described in more detail in the subsequent chapters:

chapter 2 discusses the synthesis of the various 1,4-addition precursors **(1.130)** used towards desogestrel/estrone total syntheses.

chapter 3 details the results of the Hanessian 1,4-addition reactions, leading to intermediates **(1.127)**, for both desogestrel and estrone projects.

chapter 4 emphasizes the tandem C-B ring cyclisation from **(1.127)** to **(1.128)** towards the total synthesis of desogestrel and its C13-methyl analogue.

chapter 5 discusses the A-ring annelation from **(1.128)** as well as the completion of the total synthesis of desogestrel and its C13-methyl analogue.

chapter 6 emphasizes the completion of the enantioselective and racemic total syntheses of estrone from **(1.127)**.

chapter 7 details future plans for the project.

chapter 8 gives an overall summary.

chapter 9 describes the experimental details.

Although both total syntheses of desogestrel and estrone have been achieved during this PhD, the estrone synthesis had already been achieved in our group by B. Guizzardi,[64] and was only repeated for optimization and data reasons. The desogestrel synthesis was first investigated by R. Clarkson,[21] though was not yet completed.

Results and Discussion

Chapter 2, Synthesis of the allylic phosphonates/ phosphonamide for the conjuguate addition reactions

2.1 Introduction

The synthesis of the phosphonate/phosphonamide substrates for the pivotal 1,4-addition reaction is relatively similar for both estrone and desogestrel synthesis (Figure 2.1). Hence, they are described together in this chapter. The desogestrel synthesis has only been achieved in racemic form, via a *Z*-allylic phosphonate. The synthesis of two phosphonates **(2.1)** and **(2.2)**, with a different protecting group for the required ester moiety was attempted.

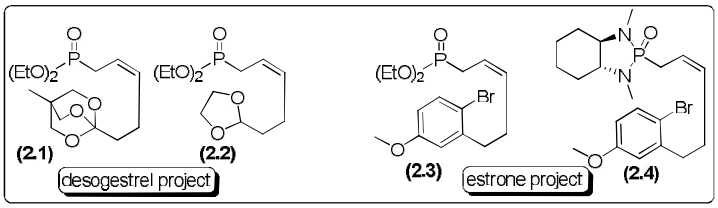


Figure 2.1

For the estrone synthesis, both the achiral phosphonate **(2.3)** and the homo chiral phosphonamide **(2.4)** have been synthesised.

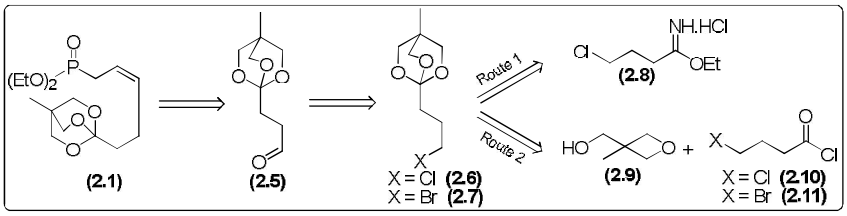
2.2 Desogestrel synthesis

The initial plan involved a trioxabicyclo-octane protecting group,[65,66] leading to **(2.1)** as the target. This synthesis was not successful and a revised plan involved the use of a dioxolane group, a well known aldehyde protecting group. The synthesis of **(2.2)** had already been achieved by R. Clarkson,[21] and was further optimised on large scale.

2.2.1 The attempted synthesis of orthoester (2.1)

2.2.1.1 Retrosynthetic analysis

The proposed retrosynthetic analysis towards the synthesis of the *Z*-allylic phosphonate **(2.1)** is shown in Scheme 2.1.

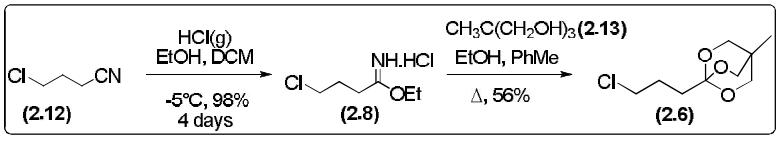


Scheme 2.1

The desired *Z*-allylic phosphonate **(2.1)** would be obtained via a *Z*-selective Wittig reaction from the aldehyde **(2.5)**, which would be synthesised from either the chloro orthoester **(2.6)** or the bromo orthoester **(2.7)**. Two routes were explored towards these orthoesters, the first one involving the imidate salt **(2.8)**, the second one involving the reaction between the oxetane **(2.9)** with the corresponding acid chlorides **(2.10**, **2.11)**.

2.2.1.2 Route 1: Synthesis of orthoester **(2.6)**

Ethyl-4-chloro-1-butanimidate hydrochloride **(2.8)** was synthesised using a Pinner reaction (Scheme 2.2).[67-71] This reaction involved the treatment of 4-chlorobutyronitrile **(2.12)** with gaseous HCl, prepared *in situ*, in a mixture of anhydrous DCM and anhydrous EtOH affording the desired imidate salt **(2.6)** in excellent yields (98%). Although this reaction was very efficient, it was necessary to keep the reaction mixture sealed, once the addition of HCl was complete, in the fridge for four days. The obtained salt could be stored for weeks when well protected from moisture. The gaseous HCl, generated by the addition of conc. H_2SO_4 onto conc. HCl, was bubbled through the reaction mixture by mean of a nitrogen gas steam.



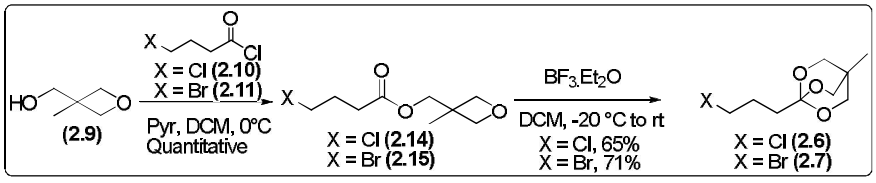
Scheme 2.2

Golding and co-workers[66] reported the synthesis of orthoester **(2.6)** derived from cheap and commercially available 1,1,1-tris(hydroxymethyl)ethane triol **(2.13)** and the tri-ethoxy orthoester derived from **(2.8)**. In order to save time, it was decided to apply their methodology by direct esterification of the imidate **(2.8)**.

The imidate salt **(2.8)** was refluxed overnight in toluene with triol **(2.13)** yielding the desired compound **(2.6)** in up to 37% yield. As the triol was not completely soluble in toluene, even while refluxing, EtOH (1.1 equiv) was added at the beginning of the reaction; leading to an improved yield of 56%. The purification by column chromatography led to the desired compound but an impurity was always remaining, necessitating an additional purification by distillation.

2.2.1.3 Route 2: Synthesis of orthoesters **(2.6)** and **(2.7)**

Although the desired product was obtained in acceptable yield, the long reaction time prompted us to investigate an alternative in which an acid chloride was reacted with an oxetane **(2.9)**, followed by acid-catalysed rearrangement (Scheme 2.3). [72-74]



Scheme 2.3

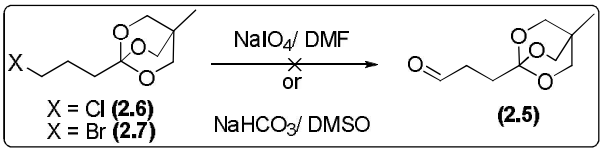
Treatment of commercially available 3-methyl-3(hydroxymethyl)oxetane **(2.9)** with the corresponding acid chloride in presence of pyridine in DCM quantitatively yielded upon simple work-up the intermediates **(2.14**, **2.15)** after 1 h of reaction. The desired trioxabicyclo-octane orthoesters **(2.6**, **2.7)** were then obtained by boron trifluoride-mediated rearrangement in good yields after column chromatography.

2.2.1.4 Oxidation to the aldehyde **(2.5)**

Oxidation of organic halides to the corresponding carbonyl compounds is a well known transformation in organic synthesis. Several methods have been developed to carry out this

conversion such as the Sommelet reaction[75] and the Kornblum reaction ($DMSO/NaHCO_3$).[76] More recently, Das and co-workers[77] reported the use of $NaIO_4$-DMF to oxidise various primary and secondary halides to the corresponding aldehydes or ketones under mild conditions (150 °C/40-60 min) in high yields (70-90%).

The $NaIO_4$ oxidation[77] was first explored (Scheme 2.4).

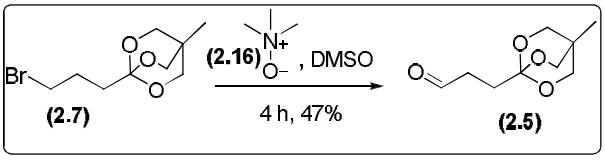


Scheme 2.4

Despite several attempts, only traces of aldehyde could be observed by ^1H NMR, present in a very complex mixture of compounds. The desired aldehyde **(2.5)** could not be isolated. It was believed that the orthoester group was not stable under the reaction conditions.

The Kornblum method ($NaHCO_3$/DMSO)[76] was also explored with both orthoesters **(2.6**, **2.7)**. However, again only traces of aldehyde could be observed (^1H NMR) and the protecting group was not stable under those conditions. This was quite surprising as the use of $NaHCO_3$ during the oxidation should have prevented the orthoester from being hydrolysed.

Finally, the oxidation was achieved using an amine-N-oxide as described by Ganem and co-workers (Scheme 2.5).[78]



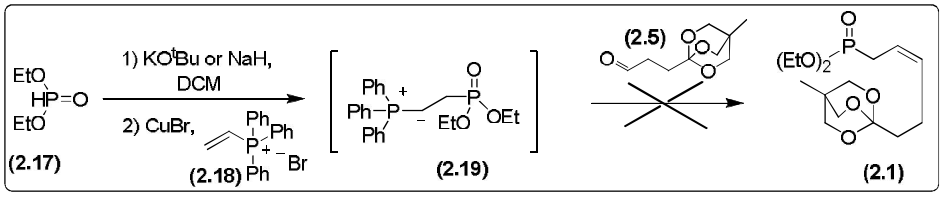
Scheme 2.5

They discovered that anhydrous trimethylamine-N-oxide (TMANO) **(2.16)** transforms nitrosamides to aldehydes under mild conditions. As DMSO enhances bimolecular nucleophilic displacements, the use of TMANO in DMSO could slowly oxidise aliphatic halides. Crystalline anhydrous TMANO, easily prepared with the method of Soderquist,[79] was only moderately soluble in DMSO, however the mixture reacted smoothly at room

temperature with the halide **(2.7)** to afford the desired aldehyde **(2.5)** in medium yields (47%). Enough material was at least obtained to explore the subsequent key *Z*-selective Wittig reaction.

2.2.1.5 *Z*-selective Wittig reaction[80,81]

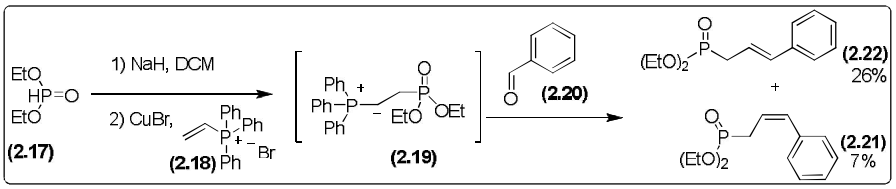
The *Z*-selective Wittig reaction with aldehyde **(2.5)**, that would lead to phosphonate **(2.1)**, was first investigated following the procedure of Shen and co-workers (Scheme 2.6).[80]



Scheme 2.6

They reported that the CuBr-catalysed reaction of vinyl triphenyl phosphonium bromide **(2.18)** with dialkyl potassium phosphite **(2.17)** resulted in phosphorane **(2.19)**, which can be reacted with aldehydes giving substituted allylphosphonates, in various yields, with the *Z*-isomer being formed exclusively in most cases. Because initial attempts with aldehyde **(2.5)** were unsuccessful, the reaction was also attempted with benzaldehyde **(2.20)**.

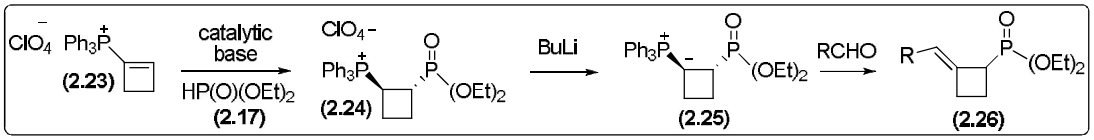
Carrying-out the reaction under the described conditions, with either the aldehyde **(2.5)** or benzaldehyde **(2.20)**, no reaction occurred, leading only to the recovery of the starting material. Interestingly, when the reaction was carried out with NaH as a base instead of KO^{t}Bu, the reactivity was completely different. In the case of benzaldehyde **(2.20)**, the desired *Z*-allylic phosphonate[82] **(2.21)** was obtained in 7% yield, but the *E*-isomer **(2.22)** was also isolated in 26 % yield; or a (*Z*/*E*) ratio of (21/79) (Scheme 2.7).



Scheme 2.7

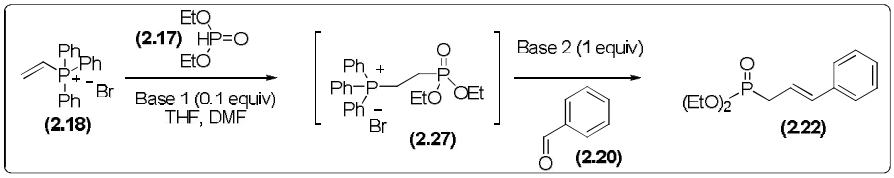
Unfortunately, under the same conditions (using NaH), the aldehyde **(2.5)** was almost fully consumed but no allylic phosphonate **(2.1**) was neither observed nor isolated. Given the lack of success, another route was explored.

Minami and co-workers[81] reported that when cyclobutenyltriphenylphosphonium salt **(2.23)** (Scheme 2.8) was treated with a catalytic amount of ^{n}BuLi in presence of diethylphosphite **(2.17)**, a phosphinyl-triphenylphosphonium salt **(2.24)** was generated *in situ*. This salt could then be deprotonated to generate the ylide **(2.25)**, which could react with aldehydes to undergo a Wittig reaction.



Scheme 2.8

This methodology was explored with benzaldehyde **(2.20)**, with a few changes however (Scheme 2.9). Instead of using ^{n}BuLi, NaH or NaHMDS were used, to avoid the competing elimination reaction transforming vinyl triphenyl phosphonium bromide **(2.18)** to triphenyl phosphine and acetylene.[83]



Scheme 2.9

Table 2.1 shows the results obtained with the different bases used. The use of NaH or NaHMDS gave almost the same results in terms of yield.

Base 1 (0.1 equiv)	Base 2 (1 equiv)	Yield of **(2.22)**
NaH	NaH	27%
NaH	NaHMDS	31%
NaHMDS	NaHMDS	25%

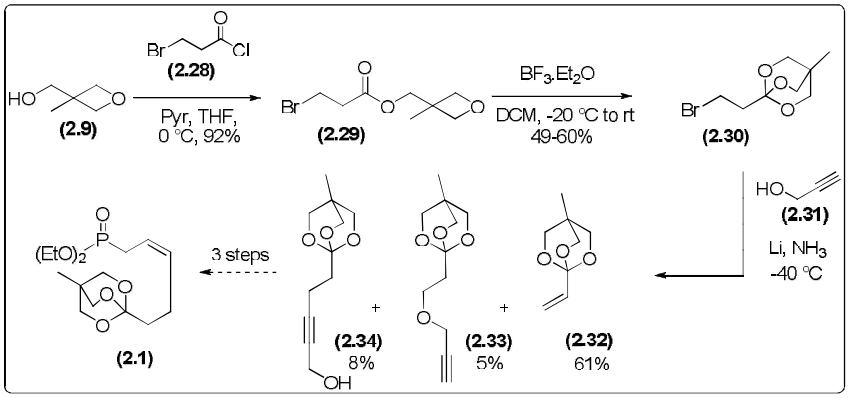
Table 2.1

Unfortunately, once again, the *E*-allylic phosphonate **(2.22)** was the isomer that was isolated. The *Z*-isomer was not observed. This methology was as efficient as the Shen method, but only gave the undesired isomer, so it was never attempted with aldehyde **(2.5)**.

Given the lack of success with the Z-selective Wittig reaction, an alternative route was investigated based on a propargylic triple bond.

2.2.1.6 Synthesis of the propargylic alcohol **(2.34)**

The final attempts towards the synthesis of *Z*-allylic phosphonate **(2.1)** involved the synthesis of propargylic alcohol **(2.34)** via alkylation of propargyl alcohol **(2.31)** with the known[84] bromide **(2.30)** (Scheme 2.10).



Scheme 2.10

The synthesis of **(2.30)** was achieved by treatment of commercially available 3-methyl-3(hydroxymethyl)oxetane **(2.9)** with 3-bromo propionic chloride **(2.28)** in the presence of pyridine in THF, which yielded after simple work-up the intermediate **(2.29)** in 92% after 3 h of reaction. The compound suffered HBr elimination to produce the corresponding alkene upon column chromatography so it was taken to the next step without further purification. Eventually, it could be purified by vacuum distillation, in which case the desired ester **(2.29)** was only isolated in 51% yield. Boron trifluoride-mediated rearrangement led to the desired trioxabicyclo-octane orthoester **(2.30)** in medium yields (49%), after direct recrystallization of the crude mixture. When the pure ester **(2.29)** was used for this rearrangement, the desired orthoester **(2.30)** was obtained in 60% yield.

By using lithium amide[85,86] to doubly deprotonate propargyl alcohol **(2.31)** and subsequent alkylation with the bromide **(2.30)**, the propargylic alcohol **(2.34)** was expected. This reaction led again to disappointing results. The desired propargylic alcohol **(2.34)** was obtained in very low yield, 8%, as the main compound isolated was the alkene **(2.32)** in 61% yield. Presumably, the orthoester group results in the adjacent protons to be sufficiently acidic, resulting in a competing E2 reaction. The unexpected propargylic ether **(2.33)** was also isolated in 5% yield.

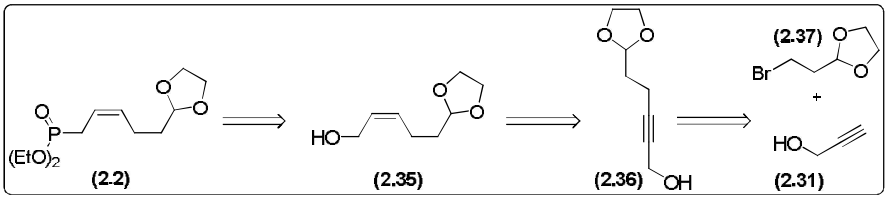
2.2.1.7 Conclusion

Further studies towards the synthesis of Z-allylic phosphonate orthoester **(2.1)** were discontinued because of lack of any positive results. The orthoester protecting group would have been beneficial compared to a dioxolane group in terms of number of steps needed to obtain the required ester group for the B-ring closure. It was decided to proceed with the synthesis using the latter protecting group.

2.2.2 The synthesis of the dioxolane containing *Z*-allylic phosphonate (2.2)

2.2.2.1 Retrosynthetic analysis

The proposed retrosynthetic analysis towards the synthesis of the Z-allylic phosphonate **(2.2)** is shown in Scheme 2.11.

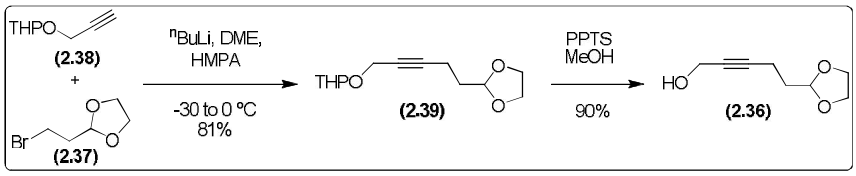


Scheme 2.11

Following this plan, phosphonate **(2.2)** would be obtained from allylic alcohol **(2.35)** which would be obtained via a key stereoselective reduction of propargylic alcohol **(2.36)**. This synthesis had already been achieved by R. Clarkson,[21] though optimisations were required to achieve a reproducible and reliable synthesis of **(2.2)**.

2.2.2.2 Synthesis of propargylic alcohol **(2.36)**

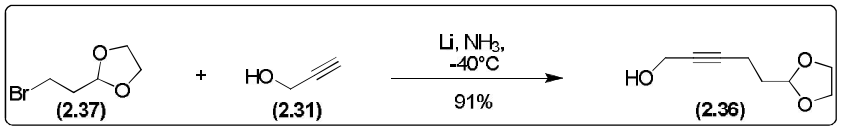
Propargyl alcohol **(2.36)** had previously been synthesised by Deslongchamps and Roy[87] via the following two-steps procedure (Scheme 2.12).



Scheme 2.12

Alkyne **(2.38)** was deprotonated with ^{n}Buli at -30 ^{o}C followed by alkylation with commercially available bromide **(2.37)**, affording THP protected propargylic alcohol **(2.39)** which was deprotected to alcohol **(2.36)** with PPTS in MeOH in 73% overall yield.

So as to avoid the use of large amounts of HMPA (3 equiv) on large scale, another route was explored where the desired propargylic alcohol **(2.36)** was obtained in a single-step process with excellent results (Scheme 2.13).

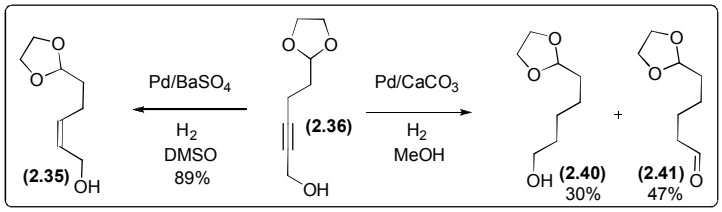


Scheme 2.13

By using lithium amide[85,86] to doubly deprotonate propargyl alcohol **(2.31)** and subsequent alkylation with the bromide **(2.37)**, the propargylic alcohol **(2.36)** could be reproducibly synthesised in 91% yield on a 15 g scale. It was also found that alcohol **(2.36)** could be easily purified by distillation which proved to be time- and cost-efficient compared to column chromatography, without decrease in yields. The 91% yield obtained represented a real improvement in the methodology towards the desired propargyl alcohol **(2.36)** as an efficient one-step synthesis was achieved, without the need for HMPA. On the other hand, this scale required the use of 1 L of liquid ammonia, which represented the upper limit of our technical abilities.

2.2.2.3 Z-selective reduction of the alkyne **(2.36)**

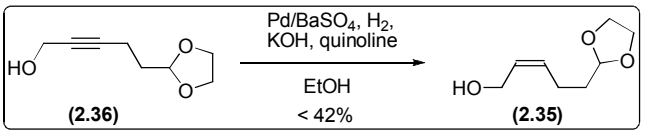
Typical hydrogenation conditions using either Lindlar catalyst ($Pd/CaCO_3$)[88] or Rosenmund catalyst ($Pd/BaSO_4$) were not explored as those conditions were previously found by R. Clarkson[21] to be difficult to reproduce, upon scaling-up (Scheme 2.14).



Scheme 2.14

Whatever the solvent used with Lindlar catalyst, the only products obtained were the fully reduced alcohol **(2.40)** along with the resulting aldehyde **(2.41)**. However, Clarkson had demonstrated that the use of Rosenmund catalyst in DMSO was very efficient and selective, but upon scaling-up (>10 g), the yields dropped to 55-76% and crucially the (*Z : E*) ratio varied from (97 : 3) to (87 : 13).

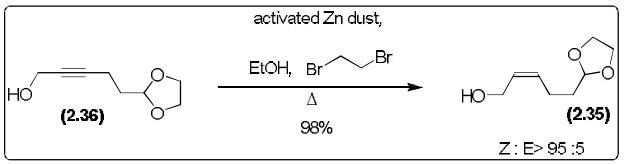
Actually, one reduction was attempted using KOH in conjunction with quinoline to poison the catalyst for the partial hydrogenation of the alkyne to give the Z-alkene.[89] This was subsequently investigated for the partial hydrogenation of the alkyne **(2.36)** using Rosenmund catalyst with very poor results (Scheme 2.15).



Scheme 2.15

After column chromatography, the desired alcohol **(2.35)** was obtained however contaminated with the fully reduced alcohol **(2.40)**. They could not be obtained pure, and the yield of desired alcohol **(2.35)** did not exceed 42% (^{1}H NMR).

Alternative reduction conditions were found which involved the use of activated zinc instead of hydrogenation conditions (Scheme 2.16, Table 2.2).[90-97]



Scheme 2.16

Table 2.2

Entry	Conditions	Solvent	Yield of **(2.35)**	(Z:E) ratio
1	Zn, CuBr, LiBr, $C_2H_4Br_2$, Δ	EtOH	72%	93:7
2	Zn, $Cu(OAc)_2$, $AgNO_3$	MeOH/H_2O	56%	95:5
3	Zn dust, $C_2H_4Br_2$, Δ	EtOH	no reaction	-
4	Zn powder, $C_2H_4Br_2$, Δ	EtOH	no reaction	-
5	Zn, $C_2H_4Br_2$, Δ	EtOH	86-94%	>95:5
6	activated Zn powder, $C_2H_4Br_2$, Δ	EtOH	10%	>95:5
7	**activated Zn dust, $C_2H_4Br_2$, Δ**	**EtOH**	**97-98%**	**>95:5**
8	activated Zn dust, Δ	EtOH	no reaction	-

Activation of the zinc with copper(I) bromide and lithium bromide[93,97] was first investigated (entry 1) and gave acceptable results. The desired *Z*-allylic alcohol was isolated in 72% yield with approximately 7% of the *E*-double bond isomer. The Zn(Cu/Ag) system in aqueous MeOH was also investigated (entry 2).[91] Despite 7 days of reaction and gradual increase in heating, the reaction never went to completion affording 56% of the *Z*-alkene **(2.35)** with a good selectivity. Because the reaction did not go to completion and the use of 25 equiv of Zn would have made scaling-up very difficult, no further optimisation was attempted with this procedure.

Activation of zinc with 1,2-dibromoethane[90] was then explored. This procedure had been previously used in our group but with irreproducible results (entry 5). Whatever the type of zinc used (powder or dust), as described in the literature, the reaction only led to the complete recovery of the starting alkyne **(2.36)**; even after overnight reflux (entries 3-4). Although the activation of the zinc with 1,2-dibromoethane was achieved as the ethane evolution was perfectly observed, the lack of reactivity observed was quite possibly due to the zinc. It was then decided to pre-activate the zinc so as to remove the zinc-oxide coating by using a HCl 0.1 M solution (entries 6,7).

Interestingly, the type of zinc used led to very different results. When zinc powder was employed, after 6 hours of reflux, 90% of the starting alkyne **(2.36)** was still remaining (entry 6). When zinc dust was employed, after 4 hours of reaction, total conversion was observed by TLC; and after simple work-up the desired allylic alcohol **(2.35)** was obtained in 98% yield with an excellent (*Z : E*) ratio of (96 : 4) (entry 7).

Upon scaling-up, the *Z*-alkene product **(2.35)** was always obtained in 97-98% yields, 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 coordinate to the metal, assisting the adsorption of the C≡C bond onto the metal surface.[90] 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.[92]

This new practical procedure for the *Z*-selective reduction of alkyne also shows the importance of the use of pre-activated zinc dust in conjunction with 1,2-dibromoethane. Indeed, when the reaction was conducted without the use of 1,2-dibromoethane (entry 8), the reduction did not occur leading only to the recovery of the starting alkyne **(2.36)**.

2.2.2.4 Determination of the E/Z ratio

Once the *Z*-alkene **(2.35)** was obtained, an analytical tool had to be found so as to precisely determine the *E/Z* ratio of the mixture of isomers. For this purpose, the corresponding *E*-isomer **(2.42)** was prepared via a LAH reduction of alkyne **(2.36)** in THF (Scheme 2.17).[21]

Scheme 2.17

Wang and co-workers[98] had previously reported this compound but no experimental conditions or analytical data were published. Using 6 equiv of LAH in refluxing THF, the propargyl alcohol **(2.36)** was reduced exclusively to the desired *E*-allylic alcohol **(2.42)** in 75% yield after column chromatography. This enabled a direct comparison of the two ^{1}H NMR spectra of the *E*- and *Z*-allylic alcohols. The ^{1}H NMR for each isomer is displayed in Figure 2.2.

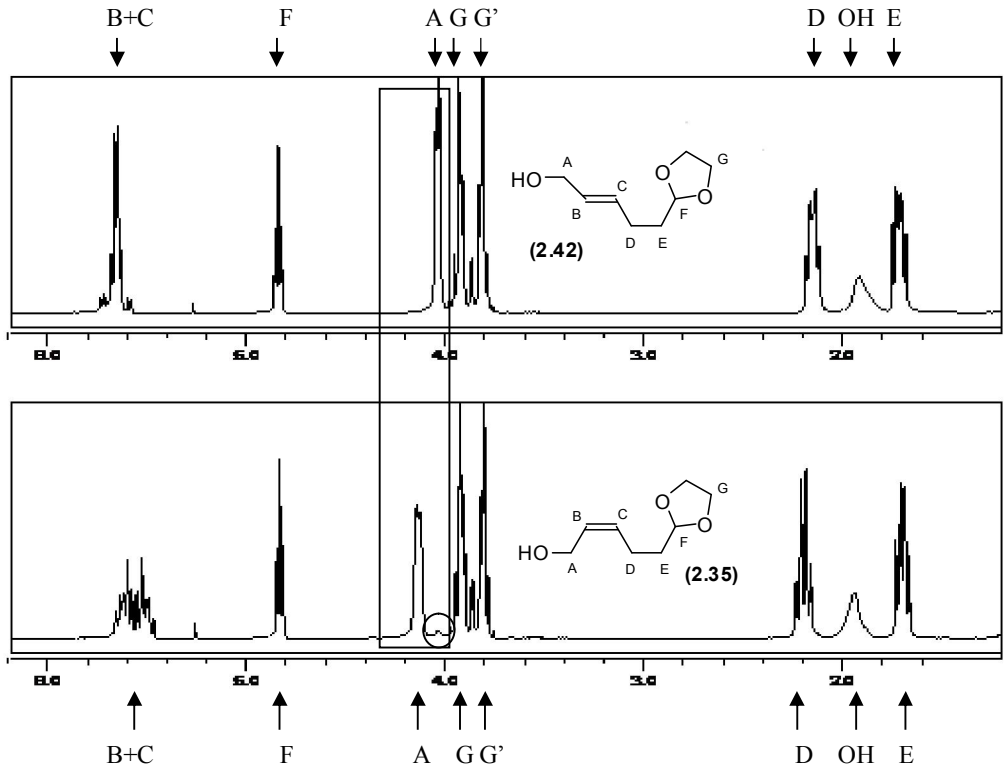
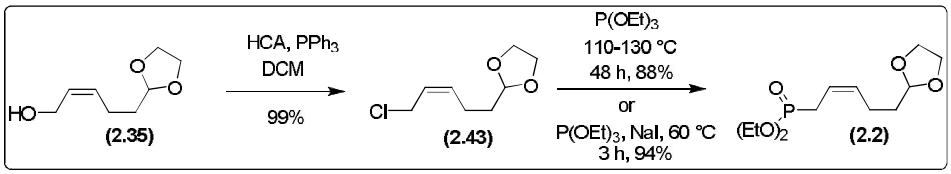


Figure 2.2

Unfortunately, the alkene protons completely overlapped. However, excellent resolution appeared in the medium-field region (δ 4.0-4.2 ppm) corresponding to the protons H_A in α-position to the alcohol group. The (*E:Z*) ratio was determined based on the integration of those signals.

2.2.2.5 Synthesis of the *Z*-allylic phosphonate **(2.2)**

The phosphonate **(2.2)** was synthesised from the alcohol **(2.35)** via the allylic chloride **(2.43)** (Scheme 2.18).



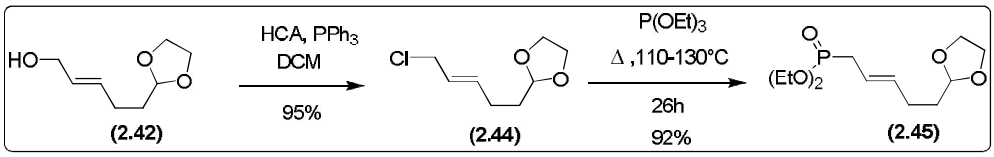
Scheme 2.18

The use of hexachloroacetone (HCA) with PPh_3[99-101] in DCM was explored and gave excellent results. The reaction was complete after 30 min of reaction but the purification was found much easier on a large scale than on a small scale. Indeed, on large scale, after removal of the resulting triphenylphosphine oxide by taking the crude in hot hexane followed by filtration, the resulting crude oil was distilled under reduced pressure affording the pure desired chloride **(2.43)** in excellent yield despite the distillation step.

Treatment of the *Z*-allylic chloride **(2.43)** with triethyl phosphite[102,103] at 110 to 130 °C gave good yields of the *Z*-allylic phosphonate **(2.2)**, which was also 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 a S_N2 displacement of the chloride by the nucleophilic phosphite.[102] 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 time of reaction.

2.2.2.6 Synthesis of the *E*-allylic phosponate **(2.45)**

This *E*-phosphonate **(2.45)** was not required for the total synthesis of desogestrel but it would allow access to isomers of the key 1,4-addition reaction products in order to fully investigate this reaction. The phosphonate **(2.45)** was synthesised from the precursor **(2.42)** via the allylic chloride **(2.45)** (Scheme 2.19).



Scheme 2.19

The procedures used were the same as for the synthesis of the *Z*-phosphonate **(2.2)**. The main noticeable difference was the reaction time from the allylic chloride **(2.44)** to the synthesis of the *E*-phosphonate **(2.45)** to go to completion. The reaction was complete in only 26 h, compared to 48 h for the *Z*-phosphonate **(2.2)**, in similar yields, confirming the slower S_N2 process in case of the *Z*-alkene.

2.2.2.7 Conclusion

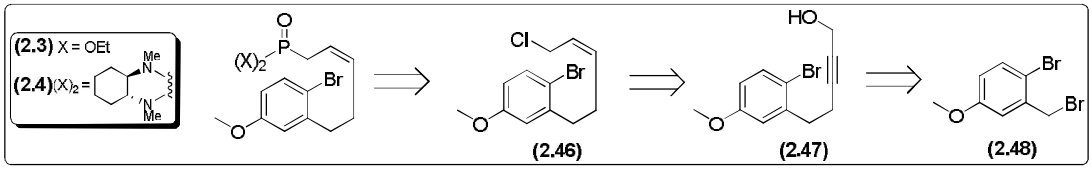
The *Z*-allylic phosphonate **(2.2)** was synthesised on large scale in four steps and in 83% overall yield. This synthesis could be completed in 5 days, finishing with 23 g of the *Z*-allylic phosphonate starting from bromide **(2.37)**. Importantly, all intermediates were isolated by vacuum distillation. The avoidance of chromatography (no silica, less solvents) represents an environmentally friendlier synthesis of the *Z*-allylic phosphonate **(2.2)** with still excellent yields.

2.3 Estrone synthesis

For the estrone total synthesis, two different substrates were synthesised: an achiral phosponate **(2.3)** that would enable a racemic total synthesis, and a chiral phosphonamide **(2.4)** that would enable an enantioselective total synthesis. Both compounds were previously synthesized by B. Guizzardi.[64]

2.3.1 Retrosynthetic analysis

The proposed retrosynthetic analysis towards the synthesis of the *Z*-allylic phosphonate **(2.3)** and phosphonamide **(2.4)** is shown in Scheme 2.20.



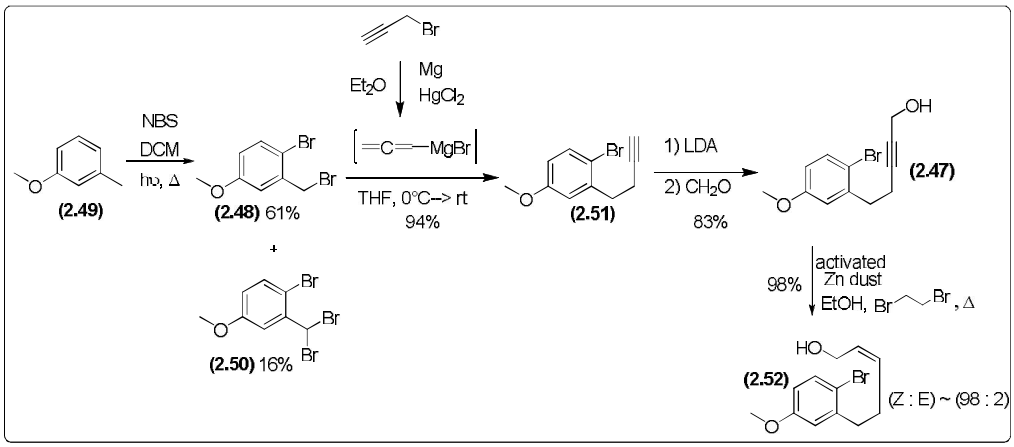
Scheme 2.20

This plan incorporated a degree of convergence as both phosphonate **(2.3)** and phosphonamide **(2.4)** would be obtained from the common precursor **(2.46)** through Arbuzov reactions. Allylic chloride **(2.46)** could be obtained in a few steps from the known dibromide **(2.48)**.[104] The Z-selective alkyne reduction of **(2.47)** was planned as the key step. Optimization of most of the steps had already been achieved by B. Guizzardi.[64]

2.3.2 Synthesis of the allylic chloride common precursor (2.46)

2.3.2.1 Synthesis of the *Z*-allylic alcohol (2.52)

The synthesis of the *Z*-allylic alcohol **(2.52)** started from the known dibromide **(2.48)**, which was prepared from 3-methylanisole following a literature procedure (Scheme 2.21).[104]



Scheme 2.21

The desired dibromide **(2.48)** was synthesized several times on large scale (15-20 g) but literature results could not be reproduced, yielding after recrystallisation the dibromide **(2.48)** in 61%, along with 16% of the tribromide **(2.50)**. In this process, the electrophilic aromatic substitution step is the slow process, leading to a double radical halogenation reaction. Optimisation of the yield was not successful.

Chain extension was achieved by treatment of **(2.48)** with a large excess of allenyl magnesium bromide[105,106] in Et_2O/THF, to give the desired alkyne **(2.51**) in excellent yield after distillation.

So as to introduce the propargyl alcohol, alkyne **(2.51)** was deprotonated with LDA (1.2 equiv),[106] followed by addition of gaseous formaldehyde in large excess,[107] yielding the desired alcohol **(2.47)** in a reproducible 83% yield. The formaldehyde was generated in a separate flask by heating paraformaldehyde to 400-500 °C with a heat gun and then bubbled into the solution by mean of a nitrogen stream.

The subsequent Z-selective reduction of the triple bond, using activated Zn/dibromoethane/EtOH[90] worked very well. The method had already been developed

during the desogestrel project, but the reaction time in this case was critical to avoid the formation of debrominated adduct **(2.53)** which cannot be separated from the desired alcohol **(2.52)** (Figure 2.3).

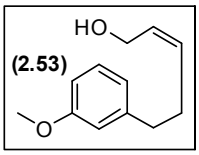


Figure 2.3

The reaction mixture was complete after 3 h, affording the desired alcohol **(2.52)** in excellent yield. Despite irradiation experiments, the (*Z/E*) ratio could not be determined by ^{1}H NMR as no clear signals corresponding to the *E*-isomer could be observed. Therefore, the (*Z/E*) ratio was estimated on the basis of the ^{13}C NMR spectrum (Figure 2.4).

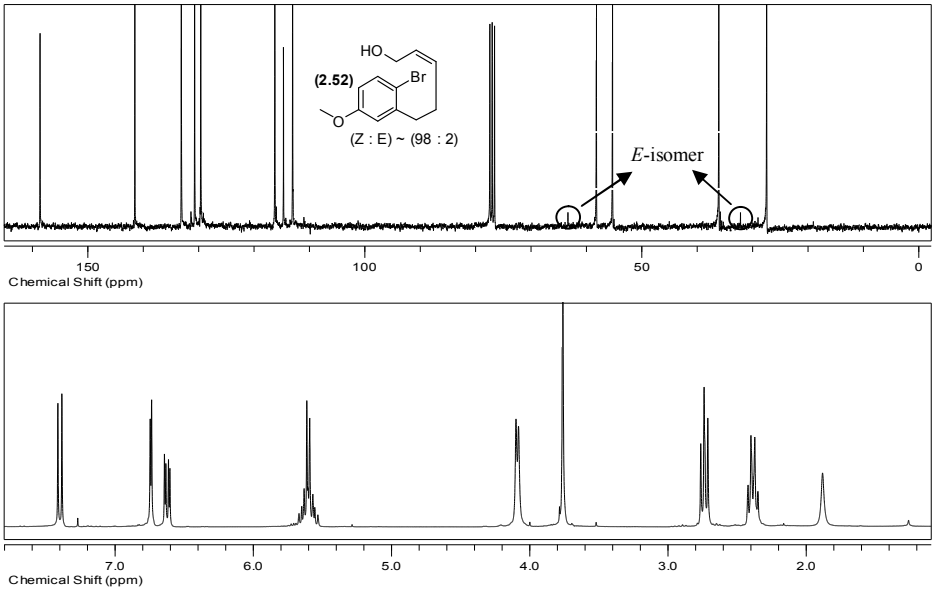
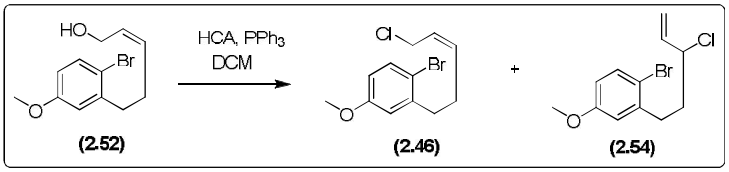


Figure 2.4

2.3.2.2 Conversion of the alcohol **(2.52)** to the chloride **(2.46)**

The next step, the conversion of the allylic alcohol **(2.52)** into the chloride **(2.46)** was achieved using hexachloroacetone and PPh_3 in nearly quantitative yield (Scheme 2.22).[99-101]



Scheme 2.22

Although this reaction had been successfully used several times during the desogestrel project, an unexpected rearrangement was observed once, leading to the formation of **(2.54)**, when purification by distillation was first attempted (Table 2.3).

Entry	Scale	Method of purification	Overall yield (%)	Ratio of products[a] (%)	
				(2.46)	**(2.54)**
1	41 mmol	Distillation	94%	75-70	25-30
2	53 mmol	Column chromatography	99%	100	0

[a] = ratio determined by ^{1}H NMR

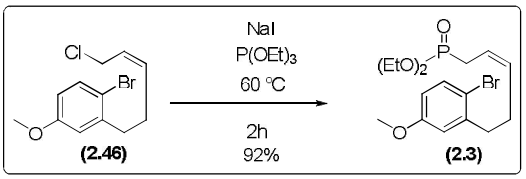
Table 2.3

Interestingly, allylic chlorides like **(2.46)** are not known to rearrange to allylic chlorides like **(2.54)**, and this could only be explained by the temperature required for the distillation (b.p. = 126 °C / 0.2 mmHg); resulting in an inseparable 12 g mixture of **(2.46)** and **(2.54)**.

2.3.3 Synthesis of the *Z*-allylic phosphonate (2.3)

2.3.3.1 Synthesis of the *Z*-allylic phosphonate **(2.3)**: Arbuzov reaction

The *Z*-allylic phosphonate **(2.3)** was synthesised through Arbuzov reaction of the chloride **(2.46)** with triethyl phosphite (Scheme 2.23).[102,103]



Scheme 2.23

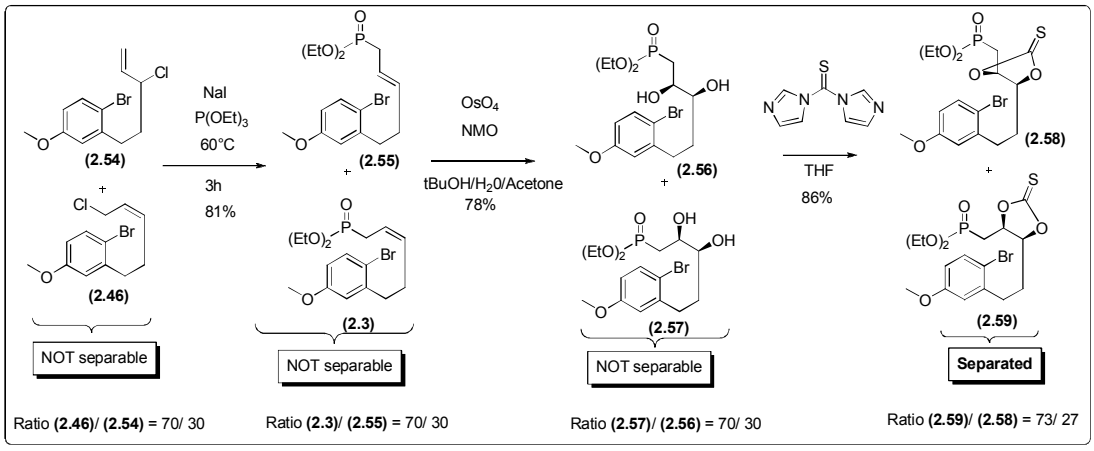
Conducting the reaction as described in the literature[102] didn't afford the desired *Z*-allylic phosphonate **(2.3)**.[64] Interestingly, conducting the reaction with 1 equiv NaI had a

dramatic effect on the time required for completion of the reaction as well as the temperature required (60 °C instead of 130 °C). After 2 h of reaction, excess $P(OEt)_3$ was removed by distillation and phosphonate **(2.3)** was isolated in excellent yield by column chromatography.

Without the use of NaI, procedure used for the desogestrel project, the reaction required 48 h to reach completion at 130 °C (part 2.2.2.5, synthesis of **(2.2)**).

2.3.3.2 Synthesis of the Z-allylic phosphonate **(2.3)**: Corey-Winter olefination[108]

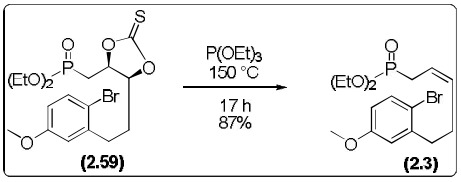
From a synthetic point of view, it was interesting to know whether the desired Z-allylic phosphonate **(2.3)** could be obtained from the 12 g mixture of allylic chlorides **(2.46)** and **(2.54)** obtained by distillation (Scheme 2.24).



Scheme 2.24

To do so, the mixture of allylic chlorides **(2.46)** and **(2.54)** was subjected to Arbuzov reaction, leading to a mixture of (*E/Z*) allylic phosphonates **(2.3)** and **(2.55)** which unfortunately couldn't be separated. Separation by derivatisation was attempted. OsO_4/NMO *cis*-dihydroxylation,[109] leading to inseparable racemic diols **(2.56)** and **(2.57)** (only one enantiomer of each is shown), followed by cyclic isothiocarbonate formation[110] using thiocarbonyldiimidazole led to adducts **(2.58**) and **(2.59)** which could be separated by column chromatography. None of the steps were optimized as the sequence was only attempted once on small scale.

The final *syn*-elimination[111] using a trialkylphosphite was only achieved with isothiocarbonate **(2.59)**, with good results (Scheme 2.25).



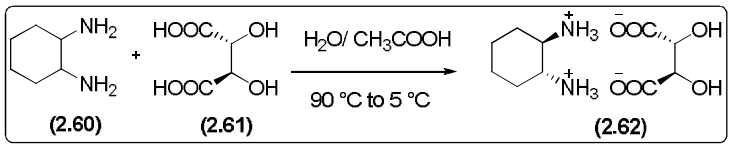
Scheme 2.25

Under the same conditions, isothiocarbonate **(2.58)** would lead exclusively to the *E*-phosphonate **(2.55)**, but this was not attempted.

2.3.4 Synthesis of the Z-allylic phosphonamide (2.4)

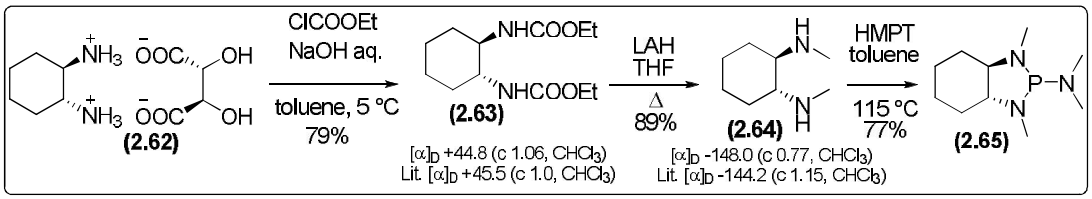
2.3.4.1 Synthesis of the chiral phospholidine precursor (2.65)

The synthesis of the key chiral phospholidine precursor **(2.65)** started with the preparation of *trans*-1,2-diaminocyclohexane **(2.62)** in enantiopure form, following Hanessian and co-workers procedure,[112,113] by treatment of commercially available racemic mixture of *cis* and *trans*-1,2-diaminocyclohexane **(2.60)** with L-(+)-tartaric acid **(2.61)** (Scheme 2.26).



Scheme 2.26

The precipated monotartrate salt **(2.62)** was easily obtained in high diastereoisomeric form by filtration followed by a series of MeOH washes to the filtered salt that effectively removed traces of the unwanted isomer.[114] The precise e.e. of the product was not actually determined since a good $[\alpha]_D$ correspondence with literature data[112] was found for the intermediates **(2.63)** and **(2.64)** (Scheme 2.27).

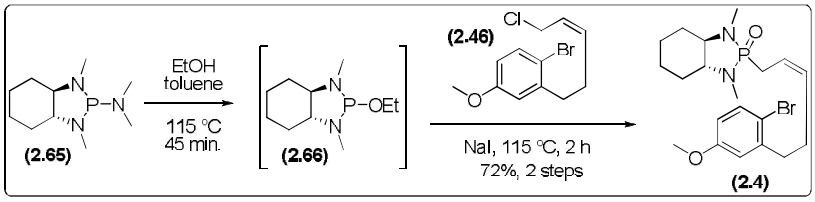


Scheme 2.27

(*R,R*)-1,2-diaminocyclohexane tartaric salt **(2.62)** was then treated with simultaneous addition of ethyl chloroformate and NaOH 4 M in toluene at 5 °C to afford enantiopure dicarbamate **(2.63)** in good yield. Reduction of the dicarbamate **(2.63)** to the *N,N*'-dimethyl-diaminocyclohexane **(2.64)** was achieved via a LAH reduction in refluxing THF in excellent yield. Finally, chiral phospholidine **(2.65)** was obtained by treatment of diamine **(2.64)** with HMPT in refluxing toluene overnight. Excess HMPT was successfully removed by Kugelröhr distillation to afford phospholidine **(2.65)** in 77% yield. The very low stability of phospholidine **(2.65)** that would have required its immediate use was circumvented as it was found it could be stored as a 0.2 M solution in toluene under nitrogen.[115]

2.3.4.2 Arbuzov reaction with homochiral phospholane **(2.66)**

From phospholidine **(2.65)**, the key intermediate required for the final Arbuzov reaction with the previously obtained allylic chloride **(2.46)** was phospholane **(2.66)** (Scheme 2.28).



Scheme 2.28

As described in the literature,[113,115] phospholane **(2.66)** showed very low stability and therefore had to be used in a one-pot sequence.

In practice, phospholidine **(2.65)** (1 equiv) was refluxed with EtOH (1.15 equiv) in toluene until exclusion of dimethylamine was complete. The phospholane **(2.66)** solution was then added to allylic chloride **(2.46)** (0.75 equiv) in presence of NaI (0.75 equiv). The Arbuzov reaction was complete after 2 h of reaction and up-to 3 g of Z-allylic phosphonamide **(2.4)** was obtained in good yield.

2.4 Summary

Although the synthesis of the orthoester phosphonate **(2.1)** has not been achieved, a very efficient procedure was developed for the synthesis of the dioxolane containing achiral phosphonate 1,4-addition precursor. The *Z*-allylic phosphonate **(2.2)** could be reliably synthesised in four steps and 83% overall yield from commercially available reagents. All intermediates were isolated by vacuum distillation and the synthesis could be completed in five days, finishing with 23 g of the *Z*-allylic phosphonate.

Towards estrone total synthesis, two different 1,4-addition precursors were prepared (a chiral phosphonamide and an achiral phosphonate) from a common precursor. From commercial reagents, *Z*-allylic phosphonate **(2.3)** was obtained in 42% overall yield in six steps that could be completed in five days finishing with 18 g of phosphonate. The *Z*-allylic phosphonamide **(2.4)** was also obtained, on 3 g scale in 10 overall steps.

Chapter 3, The Hanessian 1,4-addition reactions

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 syntheses of desogestrel and estrone. The expected products from this 1,4-addition/alkylation step, as shown in Figure 3.1, are relatively similar for both the estrone and desogestrel synthesis, although each steroid target requires specific functionalization for the later cyclisation reactions. Hence, they are described together in this chapter.

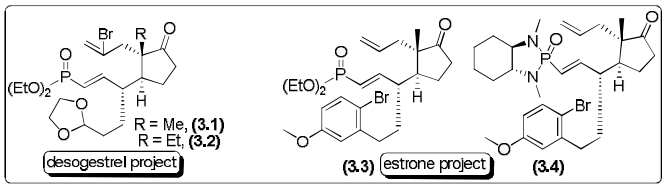
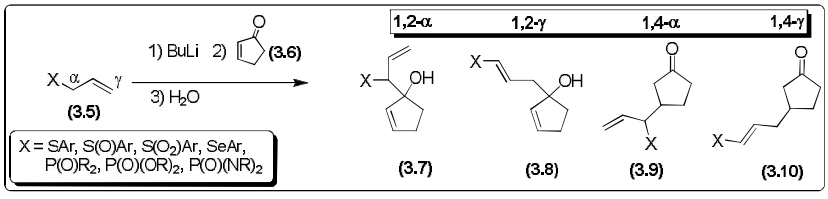


Figure 3.1

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 the stereoselectivity of the 1,4-addition reaction are discussed, followed by an overview of the expected 1,4-addition reactions for both projects.

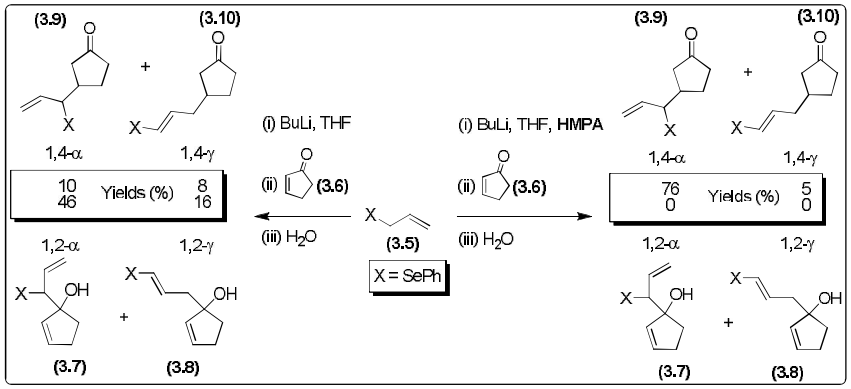
3.1.1 Regioselectivity of the 1,4-addition reaction

Regioselectivity can be a problem during the addition of heteroatom stabilized allyl anion to enones, as four products are possible: 1,2-α-addition, 1,2-γ-addition, 1,4-α-addition and 1,4-γ-addition. The four possible products are summarised in Scheme 3.1.



Scheme 3.1

Haynes and others have shown that the heteroatom 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 exclusively produced, with ~95 : 5, α : γ selectivity (Scheme 3.2).[116-118]

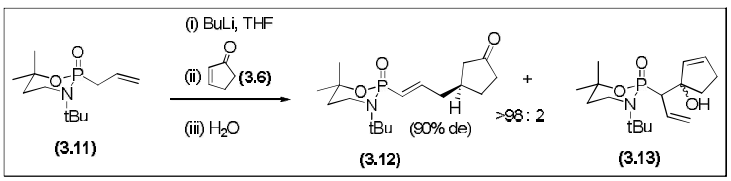


Scheme 3.2

Phosphine oxides and sulfoxides have been reported to undergo exclusive 1,4-γ-addition,[118-120] even at temperatures as low as -100 °C.[121] 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.[118,120] Additionally, conducting these reactions at temperatures as high as 0 °C had no detectable loss on diastereoselection.[118]

With phosphonamide systems, Hanessian and co-workers have also found that the addition of HMPA improves the ratio of 1,4- to 1,2-addition.[122,123]

During the investigation of the conjugate addition of allyl-1,3,2-oxazaphosphoriname-2-oxides **(3.11)**, Denmark and co-workers[124] 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 3.3).

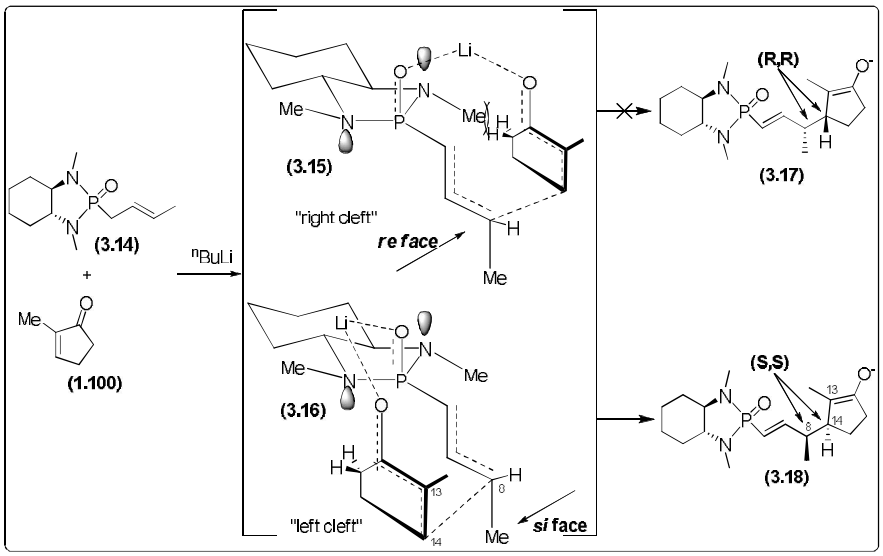


Scheme 3.3

Denmark's observations are consistent with the hard-soft, acid-base principle,[125] which states that hard nucleophiles would rather attack hard electrophiles and vice-versa. A hard nucleophile has no stabilizing effect (e.g. allyl$^-$) 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

Hanessian and co-workers proposed that this 1,4-addition proceeds via a *trans*-decalinoid Li-chelated transition state,[122,123,126,127] and that this accounts for the high levels of stereocontrol observed during the reaction. Scheme 3.4 shows an example of the 1,4-addition reaction from Hanessian's group and shows two transition states where the enone component has either approached from the "right cleft" or the "left cleft". Hanessian and co-workers proposed that the approach from the "right cleft" **(3.15)** is less favorable due to the steric interaction between the *N-Me* group of the phosphonamide and the α-CH_2 of the enone and that the reaction therefore proceeded via the "left cleft" **(3.16)**, resulting in a *si*-face attack.

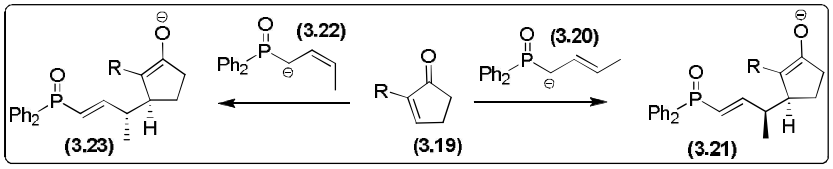


Scheme 3.4

The *trans*-decalinoid transition state is directly responsible for the stereocontrolled introduction of the relative stereochemistry of C8 and C14, whilst the chiral auxiliary defines the absolute stereochemistry of two centres. Transition state **(3.16)** leads to the (*S*)-

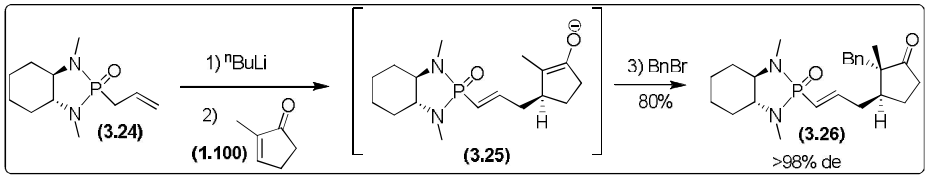
configuration at C8 and C14, whilst transition state **(3.15)** leads to the (*R*)-configuration at C8 and C14. Both of these examples make use of a (*R,R*)-phosphonamide **(3.14)**. Quite clearly, using an achiral phosphonate instead of a chiral phosphonamide like **(3.14)** would result in both "left cleft" and "right cleft" approaches to happen simultaneously and would lead to a racemic mixture of enolates like **(3.17**, **3.18)**. However, since a *trans*-decalinoid transition state would still be involved, the relative stereochemistry at C8 and C14 would still be stereocontrolled.

Importantly, the geometry of the double bond in the 1,4-addition precursor is translated into the particular C8 configuration in **(3.18)**, due to the closed *trans*-decalinoid transition state. Haynes and co-workers[118-121,128] have conducted significant research in this area, demonstrating the different stereochemical outcomes for *E* or *Z* crotyl phosphine oxides as shown in Scheme 3.5 (only one enantiomer of each enolate is shown).



Scheme 3.5

The chirality at the position which becomes C13 in the steroid products is controlled after the 1,4-addition reaction via a diastereoselective alkylation of the intermediate enolate.[129] Scheme 3.6 shows an example from Hanessian's group.

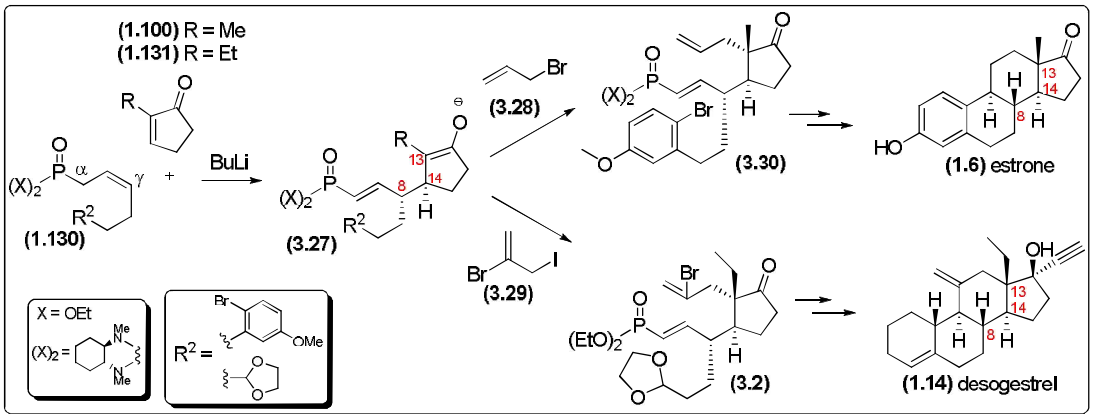


Scheme 3.6

In the enolate **(3.25)**, the adjacent C14 moiety directs the attack of the electrophile to the least hindered back face. Many groups including Hanessian,[122,123,130] Haynes,[131-133] Jones,[134,135] and Fuji[136] have employed this methodology in related 1,4-addition reactions.

3.1.3 Overview of the expected 1,4-addition/alkylation reactions

For both steroid targets, desogestrel **(1.14)** and estrone **(1.6)**, the diastereoselective 1,4-addition/alkylation process, as shown in Scheme 3.7, would introduce in a single-operation three contiguous stereogenic centers (C8, C13 and C14) of the final steroid products.



Scheme 3.7

Both projects rely on the same methodology, but the expected 1,4-γ-addition products **(3.30**, **3.2)** require specific functional groups: depending on the starting *Z*-allylic-phosphorus based products **(1.130)**, the choice of the Michael acceptor **(1.100**, **1.131)** would introduce the required C13-alkyl group (methyl for estrone, ethyl for desogestrel). The diastereoselective alkylation of enolates **(3.27)** with electrophiles **(3.28**, **3.29)** would also introduce the required C13 substituent for the later cyclisation reactions.

As described in chapter 2, three different 1,4-addition precursors **(1.130)** were prepared. Towards estrone **(1.6)**, the achiral phosphonate **(2.3)** and the chiral phosphonamide **(2.4)** will both lead, upon 1,4-addition with methyl-enone **(1.100)** and alkylation with allyl bromide **(3.28)**, to key intermediates **(3.30)**. The results obtained are discussed below in ***part 3.3***. Towards desogestrel **(1.14)**, only the achiral phosphonate **(2.2)** was synthesised. Although key intermediate **(3.2)** would be obtained via a 1,4-addition with ethyl-enone **(1.131)**/alkylation with iodide **(3.29)**, the reaction was also explored with commercially available methyl-enone **(1.100)**. The results obtained with both Michael acceptors are shown together in the section below.

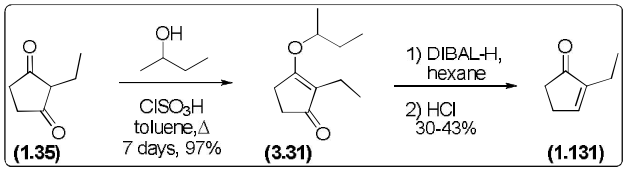
3.2 Desogestrel synthesis

R. Clarkson[21] had already achieved significant progress on this Hanessian 1,4-addition reaction. However, given the complexity of the reaction and despite taking advantage of his previous research, much optimization was required to achieve acceptable yields.

3.2.1 Synthesis of the Michael acceptor (1.131) and electrophile (3.27)

3.2.1.1 Synthesis of 2-ethylcyclopent-2-en-1-one **(1.131)**

For the desogestrel synthesis, the 2-ethylcyclopentenone **(1.131)** Michael acceptor was required and it was not commercially available, although several preparative procedures have been reported.[56,137] Eventually, **(1.131)** was synthesised using a variation of the Organon N. V. Procedure as previously achieved by R. Clarkson (Scheme 3.8).[21]

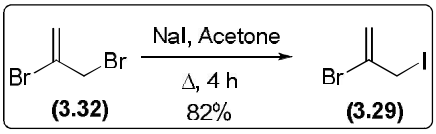


Scheme 3.8

Condensation of the diketone **(1.35)** with *sec*-butanol in refluxing toluene in the presence of an acid catalyst afforded the enol ether **(3.31)** in excellent yield after distillation. Reduction of the keto group followed by acid hydrolysis of the enol ether and subsequent elimination of the hydroxyl group gave the enone **(1.131)** in 30-43% yield after distillation. Although R. Clarkson successfully achieved the reaction on both 5 g and 20 g scale of diketone **(1.35)** in 52% overall yield, those results could not be reproduced. The condensation step leading to enol ether **(3.31)** was actually optimized by replacing CSA for $ClSO_3H$ as the acid catalyst. In which case, the reaction was complete after only 7 days instead of 23 days, in similar yields. Unfortunately, the DIBAL-H reduction/HCl hydrolysis reaction led to very different results depending on the scale of the reaction. Ethyl-cyclopentenone **(1.131)** could only be obtained in 30-43% yield by vacuum distillation. Moreover, it showed very low stability which did also complicate the 1,4-addition optimization process.

3.2.1.2 Synthesis of the electrophile **(3.29)**

From previous studies by R. Clarkson,[21] the iodide **(3.29)** was also required for the alkylation step, since the corresponding bromide was not reactive enough. It was successfully prepared from the bromide **(3.32)** via a Finkelstein exchange[138] as shown in Scheme 3.9.

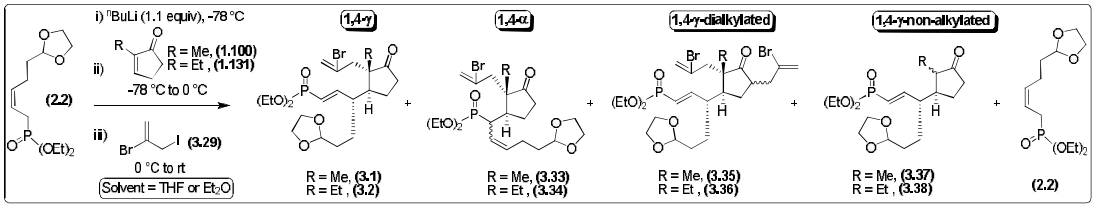


Scheme 3.9

An alternative purification of iodide **(3.29)** was developed in which column chromatography was avoided as it was successfully purified by vacuum distillation. This was easier to handle on large scale: 1) the iodide **(3.29)** was relatively volatile (b.p. = 68-72 °C/5 mmHg) and losses were being suffered as this compound partially co-evaporated on the rotary evaporator. 2) the thus obtained iodide was solvent-free, pure and could be stored for weeks over molecular sieves when well protected from light.

3.2.2 Attempted 1,4-additions

The 1,4-addition/alkylation reaction was conducted several times with both methyl-enone **(1.100)** and ethyl-enone **(1.131)** (Scheme 3.10, Table 3.1). Although ethyl-enone **(1.131)** was required for the completion of desogestrel total synthesis, initial experiments led to very poor results. The reaction was then optimized with methyl-enone **(1.100)**, as scaling-up the process was quickly required and it was commercially available. Interestingly, under the same conditions, very different results were obtained depending on the Michael acceptor. Characteristic results obtained during the optimization process are shown in Scheme 3.10 and Table 3.1 below.



Scheme 3.10

As a typical procedure, the phosphonate **(2.2)** was deprotonated with ^{n}BuLi at -78 °C for 15 min. in THF or Et_2O. Then a solution of the enone **(1.100)** or **(1.131)** in the reaction solvent was added at -78 °C and the reaction mixture was stirred for 1 h at 0 °C. The iodide **(3.29)** was then added neat and the reaction mixture warmed to room temperature.

Entry	R	Scale (mmol) of **(2.2)**	equiv of **(1.100)/ (1.131)**	equiv of **(3.29)**	Solvent	Yield of products (%)				
						1,4-γ	**1,4-α**	**1,4-γ dialkylated**	**1,4-γ non-alkylated**	**(2.2)**
1[a]	Et	2.23	1.2	1.2	THF	8	e	0	e	55
2	Et	1.80	1.2	1.2	THF	10	4	0	e	61
3[b,c]	Et	1.80	1.3	1.3	THF	11	7	0	e	59
4[c]	Et	1.80	1.3	1.3	Et_2O	13	8	0	e	63
5	Me	1.80	1.3	5	Et_2O	20	6	e	e	35
6	Me	1.80	1.2	1.2	Et_2O	24	5	e	14	26
7	Me	1.80	0.83	1.5	Et_2O	38	11	4	5	21
8	Me	12.48	0.83	1.5	Et_2O	42	13	7	8	24
9	**Me**	**30.24**	**0.83**	**1.5**	**Et_2O + HMPA[d]**	**54**	**6**	**4-5**	**3**	**17**
10	Me	13.78	0.83	1.5	THF	31	8	6	5	39
11	Et	12.52	0.83	1.5	Et_2O + HMPA[d]	21	23	traces	4	36
12	**Et**	**17.76**	**0.83**	**1.5**	**THF**	**43**	**8**	**5**	**7**	**24**

[a] = temperature raised to rt after enone addition; [b] = 1.3 equiv ^{n}BuLi; [c] = enone added at 0 °C; [d] = added after the electrophile addition; e = not isolated

Table 3.1

It was not possible to display 100% mass balance of the products because decomposition leading to base-line material was observed (TLC). Additionally, products were occasionally isolated by HPLC analysis that could not be assigned a structure. The ^{1}H NMR of these compounds was typically extremely messy-possibly the indication of a number of compounds despite eluting from the HPLC as a single peak.

When the enone **(1.131)** was employed (entries 1-4), only three compounds could be isolated and determined: the desired γ-1,4-addition product **(3.2)** as a single diastereoisomer, the α-1,4-addition product **(3.34)** as a single diastereoisomer and the starting phosphonate **(2.2)** with unchanged double bond geometry.

Varying the temperature of the reaction mixture before the enone addition did not seem to influence the course of the reaction (entries 1, 2 and 4 versus 3). The temperature of the reaction mixture after the enone addition seemed important however. Better yields in 1,4-addition products as well as starting material recovery were obtained when the reaction was kept at 0 °C instead of room temperature (entries 2-4 versus 1). The use of an excess of the reactants enone **(1.131)**, iodide **(3.29)** and ^{n}BuLi did not seem to give better results (entry 3 versus 1 and 2).

However, the solvent used during the 1,4-addition reaction seemed quite important (entry 4 versus 3). The use of Et_2O instead of THF didn't afford a significative improvement in the yield of desired γ-1,4-addition product, but really eased the purification, with less by-products observed than when THF was employed. When Et_2O was used, a precipitate was observed which was presumed to be intermediate enolate **(3.39)** (Figure 3.2).

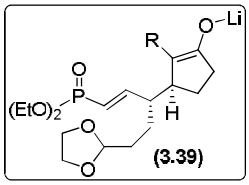
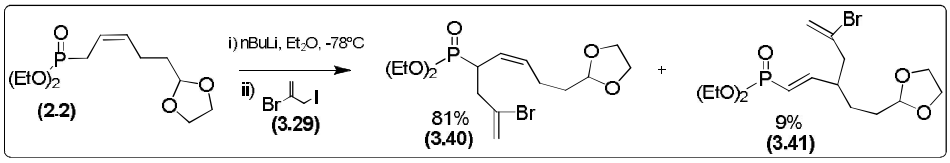


Figure 3.2

This observation, also noticed when the enone **(1.100)** was employed could have led us to modify the procedure of the alkylation.

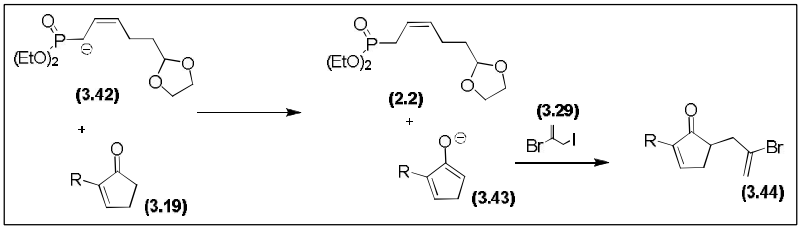
In a bid to identify the factor leading to the high recovery of starting material when the ethyl-cyclopentenone **(1.131)** was used, the deprotonated phosphonate was directly alkylated with iodide **(3.29)** (Scheme 3.11).



Scheme 3.11

This reaction afforded 81% of the α-addition product **(3.40)** and 9% of the γ-addition product **(3.41)**. None of the starting material **(2.2)** was recovered and no other products were detected other than base-line material. It became clear that from the 90% conversion of starting material into products that one equivalent of base and of the electrophile was sufficient for this reaction. Interestingly, the alkene geometry in **(3.40)** was found to be *Z* by ^{1}H NMR, which led us to assign the same alkene configuration for the α-1,4-addition products **(3.33)** and **(3.34)**. Also, since this was the first result where all of the starting material allylic phosphonate had been consumed, it led us to suspect that the 1,4-addition process itself was responsible for the high recovery of the allylic phosphonate material during the 1,4-addition reaction.

Alternatively, another possible explanation for the high recovery of the starting allylic phosphonate material during the 1,4-addition process (Table 3.1, entries 1-4) is shown in Scheme 3.12.



Scheme 3.12

Instead of undergoing a 1,4-addition, this route proposes that the enone **(3.19)** could be deprotonated by the phosphonium anion **(3.42)**. In this event, the allylic phosphonate **(2.2)** would be reformed and the enolate of the enone would be formed **(3.43)**. This anion should be rather unreactive and would most likely be quenched, returning to the enone **(3.19)**, but the possibility of alkylation with **(3.29)** also exists, leading to the enone **(3.44)**. Despite the significant amounts of apolar products that were separated from the 1,4-addition products after each reaction, the alkylated enone **(3.44)** was never isolated nor identified. Since the use of an excess of enone **(1.131)** led to high yields of recovered starting phosphonate **(2.2)** (Table 3.1, entries 1-4), one obvious option would be to use an excess of phosphonate **(2.2)** instead. This might favor 1,4-addition over the supposed deprotonation of the enone.

Returning to the 1,4-addition investigations, the reaction was also explored with the methyl-enone **(1.100)** to see if the ethyl group in the enone **(1.131)** could be a factor responsible for the poor yields obtained (Table 3.1, entries 5-10).

Under the same conditions (entry 6 versus 2), the desired γ-1,4-addition product was isolated in 24% yield with interestingly 14% of the non-alkylated product **(3.37)**. This showed that the 1,4-addition process proceeded better with the methyl-enone **(1.100)** than with the ethyl-enone **(1.131)**.

The use of an excess of the starting phosphonate **(2.2)** was then explored (entries 7-10). The results obtained were in this case quite promising, leading on a 12.48 mmol scale of **(2.2)** to 42% yield of isolated γ-1,4-addition product **(3.1)** (entry 8). However, a technical issue arose while scaling-up the reaction. Alkylation of the presumed precipitated enolate **(3.39)** led to the formation of a very sticky oil which hampered stirring of the reaction mixture. Adding more of the electrophile didn't solve the problem, but this was overcome by adding HMPA. This effectively solubilised the enolate and up to 54% of 1,4-γ-product **(3.1)** could be obtained on a 30 mmol scale (entry 9). Unfortunately, under the same conditions, the reaction with ethyl-enone **(1.131)** led to a (1:1) (1,4-γ:1,4-α) regioselectivity, in 44% overall yield (entry 11). However, conducting the reaction in THF (entry 12) afforded 1,4-γ-product **(3.2)** in 43% yield along with 8% of 1,4-α-product **(3.34)** on a 17 mmol scale.

Overall, the greatest yield obtained for the 1,4-γ-addition compound **(3.2)** using the ethyl-enone **(1.131)** was 43% compared with 54% achieved for the same 1,4-addition reaction using the methyl-enone **(1.100)**. It was thought that the larger ethyl group caused an increased steric interaction in the transition state and this was responsible for the poorer yield, as well as favouring the 1,4-α-addition (Figure 3.3).

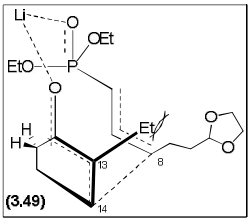
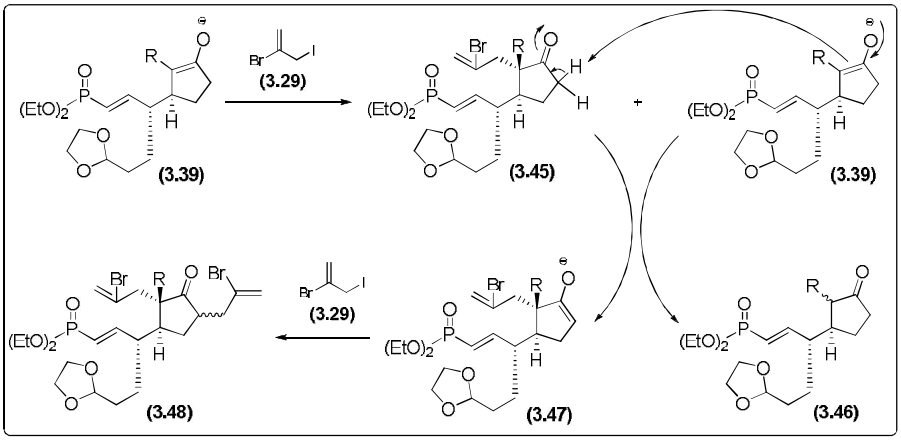


Figure 3.3

However, it still remains unclear why such differences of regioselectivity were observed depending on the solvent used and the use of HMPA.

During this 1,4-addition investigation, two side-products were often commonly observed: the *bis*-alkylated 1,4-γ-addition products **(3.35**, **3.36)** and the non-alkylated 1,4-γ-addition compounds **(3.37**, **3.38)**. Although they were not always isolated, it is believed that they both originate from the intermediate enolate **(3.39)** following the suggested process (Scheme 3.13).



Scheme 3.13

Assuming the alkylation of enolate **(3.39)** is a relatively slow process, **(3.39)** could exist at the same time as the 1,4-γ-addition product **(3.45)**. In this event it would be possible for the enolate **(3.39)** to abstract a hydrogen from **(3.45)**, leading to both enolate **(3.47)** and non-alkylated adduct **(3.46)**. Alkylation of enolate **(3.47)** would then lead to the *bis*-alkylated adduct **(3.48)**. This is still quite speculative, but since both side-products were also observed during the 1,4-addition/alkylation reactions towards estrone (part 3.3), this pathway remains quite reasonable.

Finally, quite possibly the most interesting but also troublesome was the formation of the 1,4-α-addition products **(3.33**, **3.34)**. Troublesome, as separation from the desired 1,4-γ-addition products **(3.1**, **3.2)** could only be achieved by HPLC, which also meant very lengthy separation on large scale. Interesting, as this regioselectivity is almost unprecedented with phosphorus-based Michael addition reactions. Although the 1,4-α regioselectivity is precedented with allyl-phosphonates and acyclic α,β-unsaturated

ketones,[63,139] only 1,4-γ, 1,2-α and 1,2-γ regioselectivities have been reported with cyclic α-β-unsaturated ketones.[119,122-123] It was also demonstrated that depending on the Michael acceptor, the solvent used was critical for the α/γ-regioselectivity.

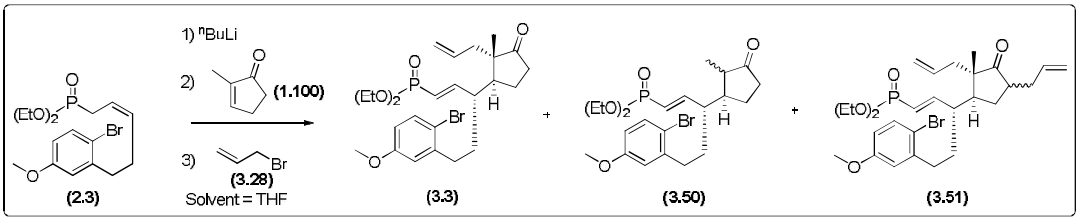
As a conclusion, the 1,4-γ-addition products **(3.1**, **3.2)** and the 1,4-α-addition products **(3.33**, **3.34)** were obtained as single diastereoisomers but they were all oils. This meant that X-ray analysis could not be used to ascertain the configuration of the newly established C8, C13 and C14 stereogenic centres at this point. The 1,4-γ-adducts relative stereochemistry was however unambiguously proven on separate occasions later on during the course of the project (Chapter 4).

3.3 Estrone synthesis

The estrone project was first investigated by B. Guizzardi[64] who also achieved significant research on this Hanessian 1,4-addition reaction. Nevertheless, the reaction had to be repeated with both phosphonate **(2.3)** and phosphonamide **(2.4)** in order to obtain clean characterisation data. Identification of possible side-products during the reaction was also required.

3.3.1 Racemic synthesis

With the Z-allylic phosphonate **(2.3)** in hand, the 1,4-addition/ alkylation process could be investigated (Scheme 3.14). Optimisation of the process was done by B. Guizzardi,[64] who reported an excellent 75% yield of 1,4-γ-addition product **(3.3)**, though no mention of side-products was made (Table 3.2, entry 1).



Scheme 3.14

Phosphonate **(2.3)** was treated with ^{n}BuLi at -78 °C for 15 min. Cyclopentenone **(1.100)** was then added at 0 °C, followed 1 h later by alkylation with **(3.28)**. The results obtained are shown in Table 3.2.

Entry	Scale of **(2.3)**	equiv of ^{n}BuLi	equiv of **(1.100)**	equiv of **(3.28)**	''Purification'' of **(3.28)**	Yield of products (%)		
						(3.3)	**(3.50)**	**(3.51)**
1[a]	*1.23 mmol*	*1.3*	*1.3*	*5*	*n.a.*	*75*	[c]	[c]
2	2.56 mmol	1.3	1.3	10	none	64[b]	13[b]	4-5[b]
3	2.58 mmol	1.1	1.3	10	over mol.sieves	63	15	4
4	*2.53 mmol*	*1.1*	*1.3*	*10*	*freshly distilled*	*69*	*11*	*5*

[a] = previous results by B. Guizzardi, [b] = contaminated with 10-15% debrominated product, [c] = yields not given.

Table 3.2

The desired 1,4-γ-adduct **(3.2)** was indeed isolated in good yield (69%) as a single diastereoisomer, with traces of diallylated adduct **(3.51)** and 11% yield of non-allylated adduct **(3.50)** when allyl bromide **(3.28)** used was freshly distilled (entry 3). The amount of ^{n}BuLi employed for the deprotonation of **(2.3)** was found quite important as the use of 1.3 equiv ^{n}BuLi led to the formation of 10-15% of debrominated adducts **(3.52)**, **(3.53)** and **(3.54)** (Figure 3.4) which could not be separated from the brominated ones (entry 2) (ratio determined by ^{1}H NMR).

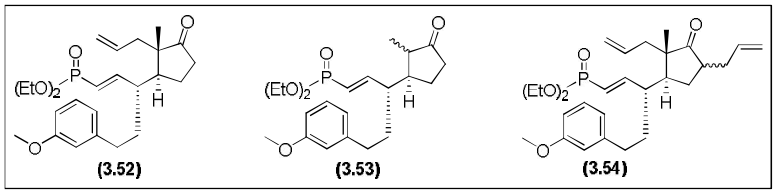


Figure 3.4

Delightfully, recrystallization of **(3.3)** in DCM/Hexane allowed access to X-ray crystallographic analysis, as shown in Figure 3.5.

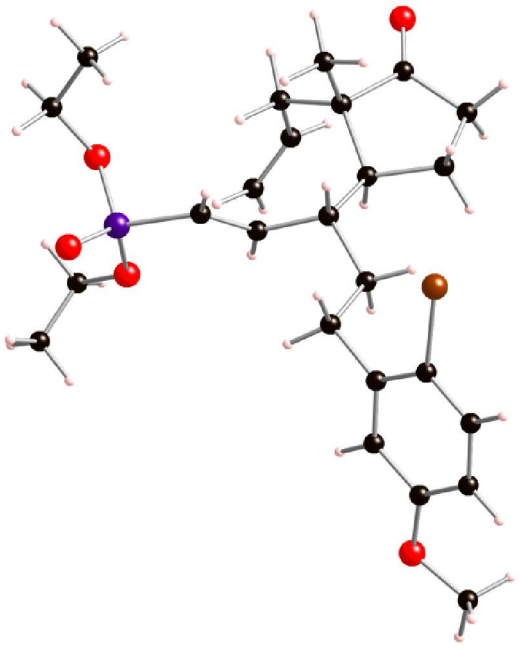


Figure 3.5: X-Ray structure of (3.3)

The expected relative stereochemistry at the newly established C8, C13 and C14 stereogenic centres was thus unambiguously proven, confirming that the 1,4-addition/alkylation process occurred as shown above (Scheme 3.7). This result was interesting, as the relative stereochemistry of none of the previously mentioned 1,4-addition products (desogestrel project) had been unambiguously proven so far.

Interestingly, despite the fact that the reaction had a very similar TLC profile compared with desogestrel project (part 3.2), no trace of 1,4-α-addition product **(3.55)** was ever observed (Figure 3.6).

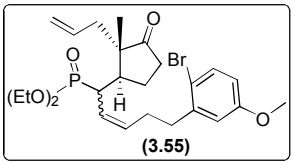
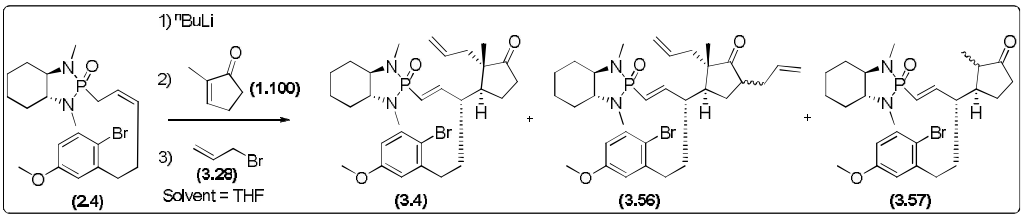


Figure 3.6

Also interesting, the *bis*-allylated product **(3.51)** and the non-allylated product **(3.50)** were once again obtained. This observation might be another hint that they could both originate from the intermediate 1,4-addition enolate, as depicted above in Scheme 3.13.

3.3.2 Enantioselective synthesis

The enantioselective 1,4-addition/alkylation reaction was only attempted at the very end of this PhD, and therefore remains not fully optimized (Scheme 3.15, Table 3.3). The reaction with phosphonamide **(2.4)** required very different conditions than when the phosphonate **(2.3)** was employed. Although B.Guizzardi reported a good 59% yield of desired 1,4-γ-addition product **(3.4)** on a 100 mg scale of starting phosphonamide **(2.4)** (entry 1), lower yields were obtained on bigger scale.



Scheme 3.15

Table 3.3

Entry	Scale of **(2.4)**	C (mol/L)	equiv of ^{n}BuLi	equiv of **(1.100)**	equiv of **(3.28)**	time of alkylation (h)	additive[b]	Yield of products (%)		
								(3.4)	**(3.56)**	**(3.57)**
1[a]	0.22 mmol	0.10	1.3	1.3	5	1	none	59	[c]	[c]
2	0.42 mmol	0.14	1.1	1.3	10	1	none	20	[c]	27
3	0.90 mmol	0.23	1.1	1.3	10	16	none	26	[c]	23
4	0.89 mmol	0.30	1.1	1.3	10	1	HMPA	52	7	9

[a] = previous results by B. Guizzardi; [b] = added after the electrophile addition; [c] = yields not given.

Quite clearly, the weak spot of the reaction was the alkylation step (entries 2-4). Despite the use of 10 equiv of allyl bromide **(3.28)** (entry 2), a 27% yield of non-allylated product **(3.57)** was obtained after 1 h of alkylation at room temperature. Even by increasing the concentration of the reaction as well as allowing 16 h for the alkylation step to take place (entry 3), 23% of undesired non-allylated adduct was isolated. This was circumvented, in a final attempt, by adding HMPA after the electrophile addition (entry 4). The desired 1,4-γ-product **(3.4)** was then obtained in 52% yield, along with only 9% of non-allylated adduct **(3.57)** and 7% of *bis*-allylated **(3.56)**. Even if those results were not as good as the results obtained with phosphonate **(2.3)**, enough material was obtained so as to complete the enantiospecific total synthesis of estrone.

3.4 Summary

The 1,4-addition reaction has been investigated on a number of phosponate and phosphonamide substrates. Towards desogestrel total synthesis, with a *Z*-allylic phosphonate, the 1,4-addition/alkylation process was successfully achieved on large scale with two different Michael acceptors. Considering the complexity of the 1,4-γ-addition products obtained (as single diastereoisomers), the medium 54% yield obtained with a methyl-enone and the 43% yield with the required ethyl-enone were considered good results.

Towards estrone synthesis, the same 1,4-addition/alkylation process was successfully achieved in a racemic and more importantly in an enantioselective fashion. Using an achiral phosphonate, an excellent 85% overall yield of 1,4-addition products was obtained. Although the 75% yield of desired 1,4-γ-product obtained by B. Guizzardi could not be reproduced, the 69% yield obtained was an excellent result. Moreover, an X-Ray of the 1,4-γ-product was obtained. Not only did this proved the relative stereochemistry of the specific product, this also validated the entire methodology for both projects. The enantioselective version of the reaction however, with the *Z*-allylic phosphonamide proceeded in slightly lower yields.

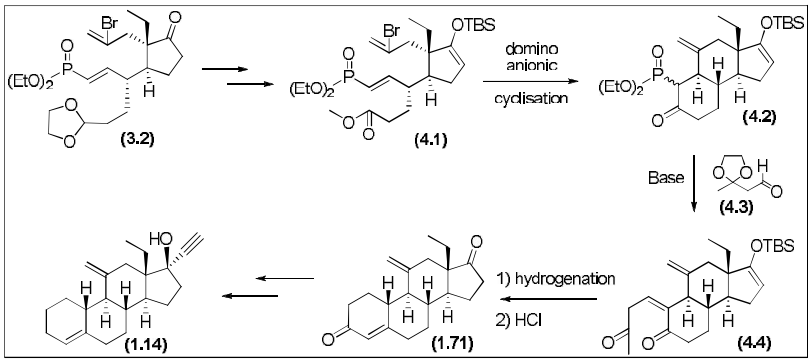
Finally, the determination of the diastereoselectivity for the desired 1,4-γ-Michael addition manifold was beyond the limits of NMR. Careful examination of the ^{1}H and ^{31}P NMR spectra showed a single set of resonances and single peak, respectively. The ^{13}C NMR, though complicated due to extensive phosphorus couplings, indicated single diastereoisomers as well.

Those results are, to date, also believed to be the first examples that the 1,4-addition process is stereoselective on more complex allylic phosphonates and phosphonamides than the crotyl examples used by Haynes and co-workers or Hanessian and co-workers.

Chapter 4, Desogestrel: the tandem C-B ring cyclisation

4.1 Introduction

With the key C_8, C_{13} and C_{14} stereogenic centres introduced by the phosphonate conjuguate addition, the next key operation concerned the C and B ring closure. This was planned via a tandem process, made possible by the particular functionality introduced in the 1,4-addition/alkylation step (Scheme 4.1).



Scheme 4.1

The next key step of the synthesis was a domino anionic cyclisation from **(4.1)**, prepared in four steps from the 1,4-addition product **(3.2)**, that would diastereoselectively construct the steroid C and B-rings, in a single operation. From β-keto-phosphonate **(4.2)**, the A-ring would be achieved through a Horner-Wadsworth-Emmons reaction with aldehyde[140] **(4.3)**, subsequent hydrogenation of the enone **(4.4)** followed by acid mediated aldol/dehydration,[31] that would lead to the known diketone **(1.71)**.[31,48] Completion of desogestrel synthesis from **(1.71)** would be achieved via known reactions.

4.2 Steroid C and B ring formation

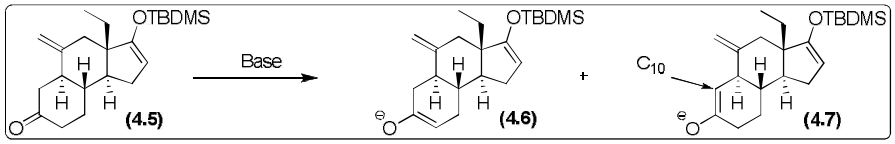
4.2.1 Introduction to the domino reaction

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."[141] The benefits of using domino reactions are both economic and ecological (reduced amounts of solvents, reagents, adsorbents and consequently waste).

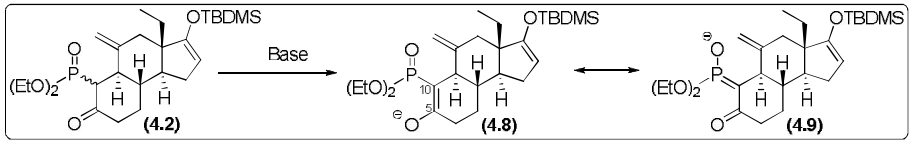
4.2.2 Overview of the expected domino C-B reaction

So as to enable the construction of the A-ring, the enolate **(4.7)** was the crucial intermediate required, as this would lead exclusively to C10-alkylated products. Clearly this enolate could not be synthesised cleanly from the ketone **(4.5)** since a mixture of the enolates **(4.6)** and **(4.7)** would be expected as shown in Scheme 4.2.[142]



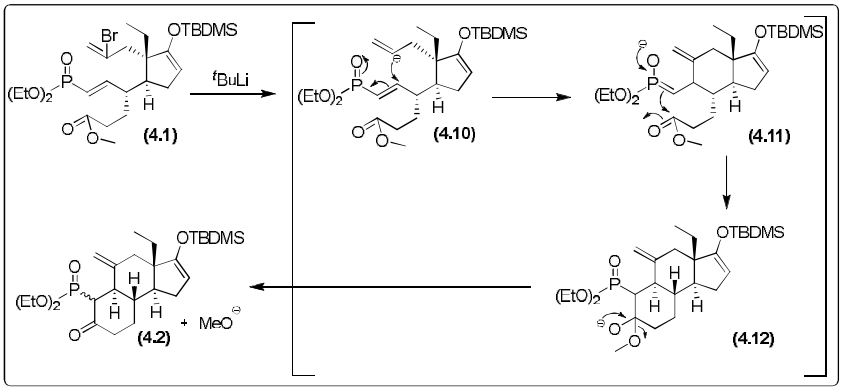
Scheme 4.2

A synthetic equivalent of enolate **(4.7)** was therefore required to circumvent this problem. It was envisioned that the β-keto phosphonate **(4.2)** which would be obtained by the cyclisation process, as shown in Scheme 4.3, would be an ideal precursor to selectively afford the desired C5-C10 enolate-type anion **(4.8)** which upon HWE chemistry would allow access to suitable C10-alkylated precursors for A-ring closure.



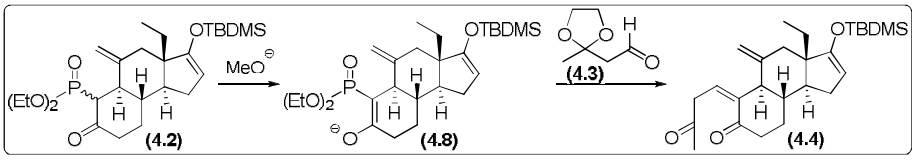
Scheme 4.3

The envisioned domino route to the expected β-keto phosphonate **(4.2)**, starting from a specifically functionalized precursor **(4.1)** is shown in Scheme 4.4 below.



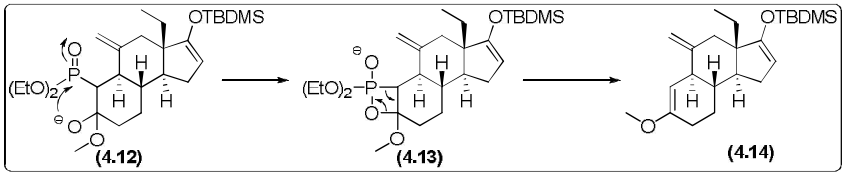
Scheme 4.4

Bromine-lithium exchange of the vinyl bromide **(4.1)** with ^{t}BuLi was expected to induce the intramolecular addition onto the α,β-unsaturated phosphonate **(4.10)**, forming the C-ring. The anion **(4.11)** would then attack the carbonyl of the ester, forming the B-ring **(4.12)**. Finally, oxyanion **(4.12)** would reform the carbonyl by eliminating methoxide, a synthetic pathway which was precedented.[143-146] It was also envisioned that the methoxide species could eventually deprotonate β-keto phosphonate **(4.2)** to *in situ* generate key enolate **(4.8)** (Scheme 4.5) that would allow a one-pot C-B-ring formation and C10-alkylation sequence.



Scheme 4.5

An alternative synthetic pathway could also be expected from oxyanion **(4.12)** as shown in Scheme 4.6.



Scheme 4.6

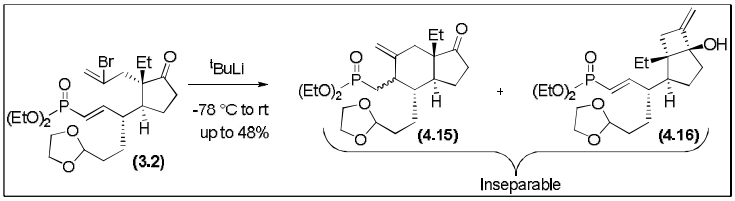
Instead of eliminating methoxide, oxyanion **(4.12)** could undergo an IntraMolecular Horner-Wittig (IMHW) reaction that would lead to enol ether **(4.14)**. IMHW reactions on esters leading to enol ethers were precedented,[147-149] but from the outset it was not clear which pathway would be adopted by the planned domino C-B reaction.

4.2.3 Lessons learned from previous studies by R. Clarkson[21]

As already mentioned several times, this project was first investigated by R. Clarkson[21] who did extensive research towards achieving this domino C-B reaction. For clarity reasons, only the key lessons learned from his previous work are summarized in the following sections.

4.2.3.1 Lesson 1: C17-ketone protection requirement prior to cyclisation/ Choice of the base for the halogen/metal exchange.

The first key lesson learned was that if the cylisation was conducted on a non C17-protected ketone **(3.2)**, the desired *trans*-hydrindane compound **(4.15)** was formed together with the undesired bicyclo-[3.2.0]-heptane **(4.16)** (Scheme 4.7).



Scheme 4.7

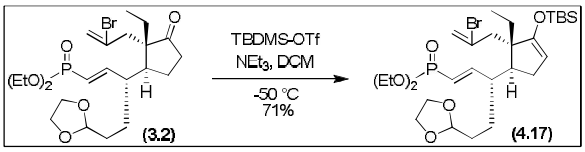
Initial investigations also looked at the choice of base and the effect of additives known to be beneficial in halogen/metal exchange-intramolecular cyclisations.[150-158] Interestingly, ^{n}BuLi or lithium-2-thienylcyanocuprate were not strong enough to initiate any reaction and the starting material was recovered in high yields. In contrast, ^{t}BuLi was able to promote this reaction and depending on the additives, various ratios of **(4.15)** and **(4.16)** were obtained.

4.2.3.2 Lesson 2: Protection of the C17-ketone

Having established that ^{t}Buli was the base of choice for the halogen/metal exchange, the second key lesson learned was that the protection of the C17-ketone in **(3.2)** was not an easy task. Protection of the ketone as either a hydrazone[159] or as a cyanohydrin[160] were both irrelevant as they would be suitable electrophiles for cyclization to take place.

Many other protecting groups were explored: the O,O-acetal formation,[161] the hemithioacetal formation,[162] or protection as an enamine.[163] In each cases, either no reaction took place, side-reactions were observed or very low yields were obtained.

However, success came when protection of the ketone **(3.2)** as a silyl enol ether **(4.17)** was attempted (Scheme 4.8).[164]



Scheme 4.8

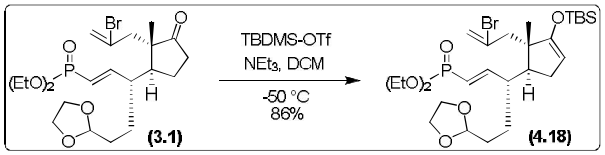
Taking advantage of those results, the C-ring formation was first explored.

4.2.4 Preamble to a successful domino C-B reaction: C-ring formation

As it was suspected that the C-ring cyclisation would be a more difficult process than the B-ring formation, it was decided to investigate the first step of the domino cyclisation. The 1,4-addition/alkylation product **(3.1)** was chosen as it was directly available in considerable quantities.

4.2.4.1 C17-ketone protection

Given the high lability of TMS enol ethers,[163] the C17-ketone protection was achieved as a TBDMS enol ether using TBDMS-OTf (Scheme 4.9).[21,164]

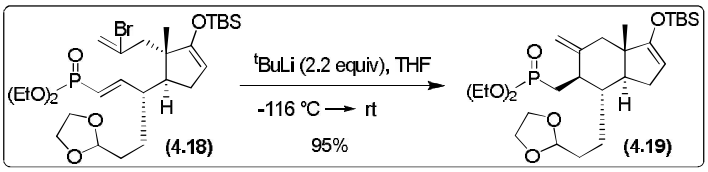


Scheme 4.9

Using 3.0 equiv of TBDMS-OTf at -50 °C afforded the desired silyl enol ether (**4.18**) in very good yield. After 3 hours the reaction was worked-up and purified by column chromatography using pre-neutralized silica gel; affording the enol ether **(4.18)** in 86% yield. Having obtained the C17-protected compound **(4.18)**, the C-ring cyclisation could be investigated.

4.2.4.2 C-ring formation

Following previous studies,[21] the best conditions for this C-ring formation were found to be the use of ^{t}BuLi as a base. The temperature was also found to be extremely important so as to achieve control on the highly reactive ^{t}BuLi; meaning the lower the temperature the better the results were (Scheme 4.10).



Scheme 4.10

In practice, the reaction was conducted at -116 °C, by forming an EtOH/N_2 slurry.[165] Occasionally the reaction mixture became 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 cold bath and the ^{t}BuLi addition continued. This procedure could be used without incurring any problems or even loss in the yield of product obtained.

This result was obviously of great importance: the anion **(4.20)** (Figure 4.1) must have been formed which should then enable a successful domino process, as B-ring cyclisation could occur if an appropriate electrophile was also present in the molecule (for instance, a methyl ester like (**4.21**)). .

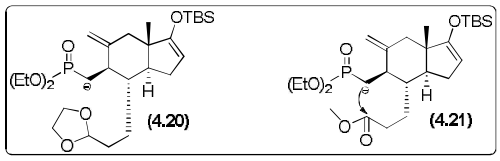
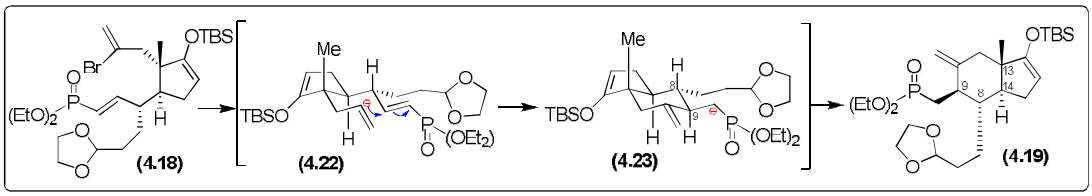


Figure 4.1

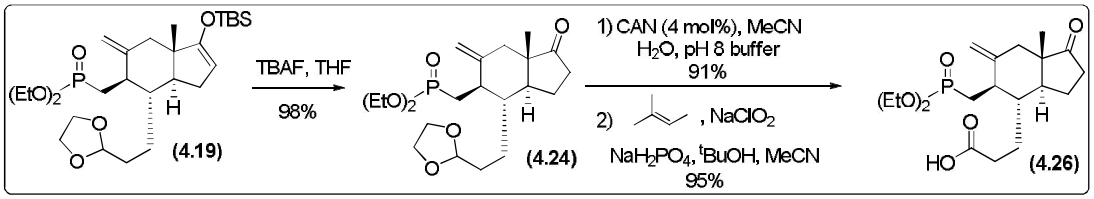
The above compound was obtained as a single diastereoisomer as determined by NMR. Although the stereochemistry of **(4.19)** couldn't be proven at this point, it was expected that the hydrogen on C9 adopts the α-position. This configuration was expected because it would be obtained through the lowest energy reactive conformation. Scheme 4.11 shows a three dimensional projection of this cyclization including the expected reactive conformation. The ^{1}H NMR spectrum shows a $^{3}J_{H8\text{-}H9}$ of 10.0 Hz, which indicates that H_8 and H_9 adopt an anti conformation as shown in **(4.23)**.



Scheme 4.11

4.2.4.3 Establishing the C-ring formation stereochemistry

In parallel to the main project (part **4.2.5**), further studies on the C-ring cyclised adduct **(4.19)** were conducted in an attempt to prove the stereochemistry involved, by preparing the acid derivative **(4.26)** which was hoped to be crystalline (Scheme 4.12).



Scheme 4.12

The C-ring product **(4.19)** was treated with TBAF[166] in THF to afford the deprotected ketone **(4.24)** in excellent yield. The acetal **(4.24)** was then hydrolysed using cerium ammonium nitrate (CAN) as reported by Markó and co-workers.[167,168] Finally, the intermediate aldehyde **(4.25)** (not shown) was smoothly oxidized to the corresponding acid using sodium chlorite[169,170] with excellent yields. As expected, the desired acid **(4.26)** could be recrystallised from DCM/hexane to afford fine white crystals in excellent yield.

X-ray crystallographic analysis (Figure 4.2) allowed determination of the relative stereochemistry, which confirmed that the cyclisation occurred as shown above (Scheme 4.11).

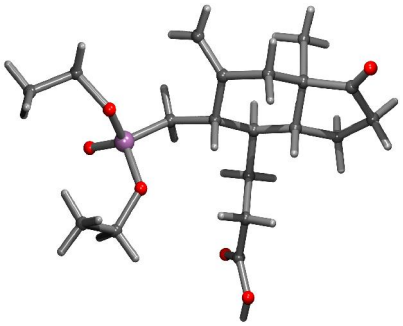


Figure 4.2: X-Ray structure of **(4.26)**

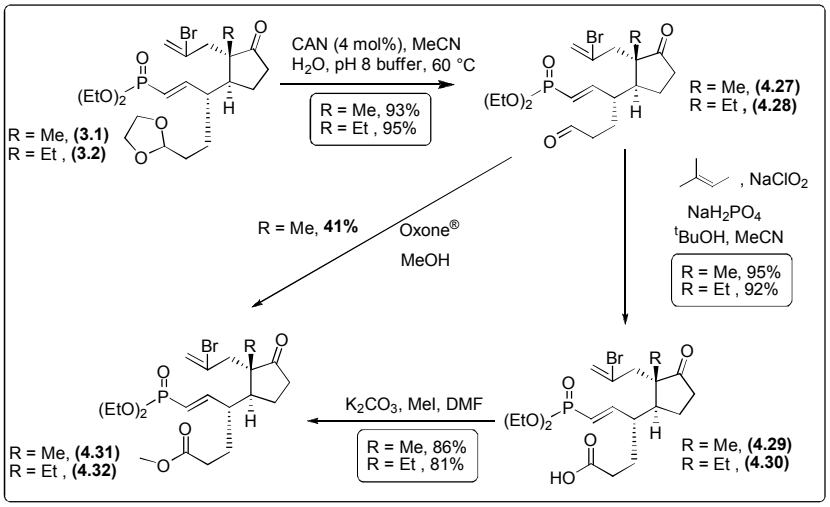
The expected C9-stereochemistry was thus clearly demonstrated.

4.2.5 Synthesis of the methyl ester domino C-B precursors (4.1) and (4.33)

To achieve the tandem cyclisation, the acetal group was converted to a methyl ester. From the 1,4-addition products **(3.1)** and **(3.2)**, a number of functional group transformations were required to prepare the domino precursors **(4.1)** and **(4.33)**.

4.2.5.1 Acetal to methyl ester transformations

As shown in Scheme 4.13, the methyl esters **(4.31)** and **(4.32)** were formed by cleavage of the acetal group and subsequent ester formation of the intermediate aldehyde or acid.



Scheme 4.13

It was found[21] that the best conditions for the acetal hydrolysis involved using cerium ammonium nitrate (CAN) as reported by Markó and co-workers.[167,168] The acetals **(3.1)** and **(3.2)** were stirred in a buffer suspension (pH 8) of CAN in an acetonitrile/water solvent system at 60 °C until the reaction had gone to completion to afford the desired aldehydes **(4.27)** and **(4.28)** in very good yields. The only drawback was that the reaction would appear to have gone to completion as judged by TLC, but still have up to 10% of the acetal remaining, in which case the reaction was repeated on the crude mixture without loss in yield.

The next step, the direct oxidation of the aldehyde to the methyl ester **(4.31)**, was not optimised and was only attempted with the aldehyde **(4.27)**. Usually, this esterification is accomplished via a two-step procedure where the aldehyde is oxidized to the acid which is then esterified.

Unfortunately, the use of Oxone® ($KHSO_5$) in MeOH only afforded the desired methyl ester **(4.31)** in 41% yield.[171] This was quite disappointing as the starting material was fully consumed (TLC analysis). Actually, the main spot observed was an intermediate which decomposed during the work-up to partially recover the starting aldehyde **(4.27)** in 23% yield. The process was not optimised as the two-step preparation via the carboxylic acid was preferred.

Indeed, the aldehydes **(4.27)** and **(4.28)** were smoothly oxidized to the corresponding acids using sodium chlorite[169,170] with excellent yields. Despite similar results for both compounds, only the C13-methyl acid **(4.29)** could be recrystallized from Et_2O which allowed access to crystallographic analysis as shown in Figure 4.3.

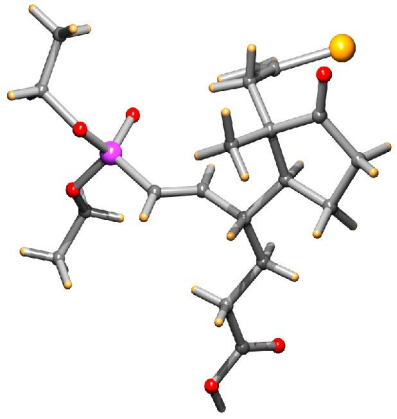


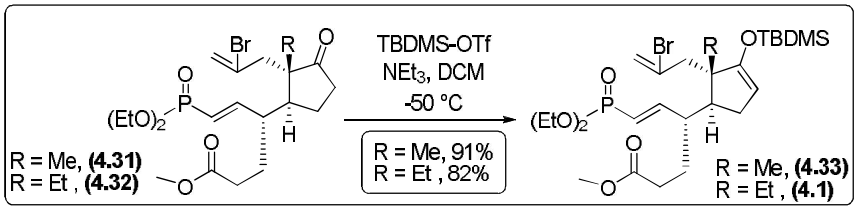
Figure 4.3: X-Ray structure of **(4.29)**

On the time-scale of this PhD, this was the very first X-Ray obtained which proved the relative stereochemistry at C8, C13 and C14 involved during the 1,4-addition/alkylation process (Chapter 3), as well as the *trans*-configuration of the unsaturated phosphonate.

The final esterification reaction leading to **(4.31)** and **(4.32)** using MeI in presence of K_2CO_3 in DMF gave good results.[172,173] After 2 h of reaction, the desired esters could be isolated by column chromatography. Obviously, the use of diazomethane would have been advantageous for this type of reaction, but this was not possible for safety reasons.

4.2.5.2 C17-ketone protection

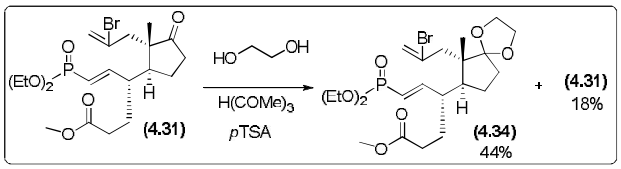
Chemoselective protection of a ketone as a silyl enol ether in the presence of an ester was precedented[163,164,174,175] by using 1-2 equiv of TBDMSOTf at room temperature. Following these procedures, the methology used to prepare the silyl enol ether **(4.18)** (part 4.2.4.1) was employed (Scheme 4.14).



Scheme 4.14

Using 3 equiv of Et_3N/TBDMSOTf at -50 °C, the desired silyl enol ethers (**4.33**) and **(4.1)** were obtained in excellent yields. After 2 h, the reaction was worked-up and purified by column chromatography using pre-neutralized silica gel; affording the enol ether **(4.33)** in 91% yield. However, the yield was dependent on the concentration of the reaction. When a concentration of 0.05 M was used, only 13% of the ketone **(4.31)** had reacted. By increasing the concentration to 0.25 M, the reaction was complete after 2-3 h at -50 °C. The silyl enol ether protection was found more difficult with the crucial ketone **(4.32)**. Under the same conditions, the reaction required 9 h to reach completion to afford **(4.1)** in 75% yield. By increasing the concentration to 0.5 M, the reaction was complete after 2 h affording **(4.1)** in 82% yield. The temperature was also found critical. Above -30/-20 °C, only baseline material was observed by TLC.

Although the silyl enol ether protection was very efficient, the protection of the C17-ketone was also attempted as an O,O-acetal, which would have been more stable and easier to handle for the reactions to follow (Scheme 4.15).



Scheme 4.15

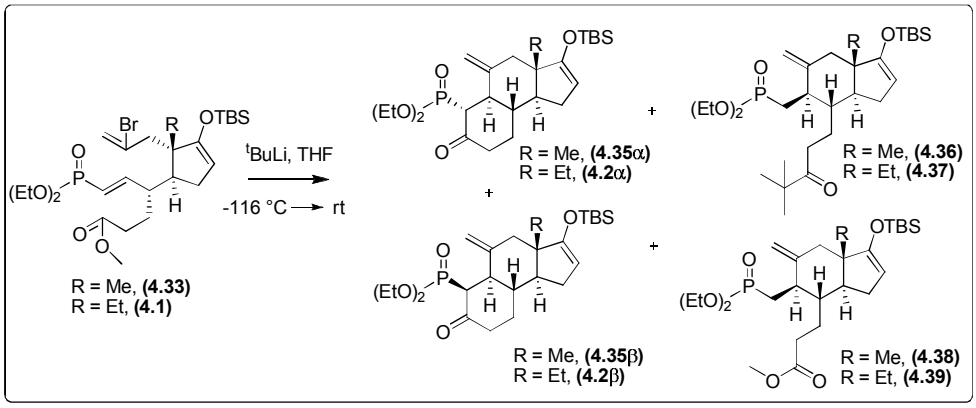
The use of trimethyl orthoformate[161] as an internal drying agent only afforded, after 24 h of reaction, the desired acetal **(4.34)** in 44% yield, with only 18 % of recovered starting material **(4.31)**. The O,O-acetal protection was not further optimised as those results were in accord with previous studies by R. Clarkson.[21]

To conclude, the desired methyl ester domino precursors **(4.1)** and **(4.34)** were synthesised in 4 steps from the 1,4-addition products **(3.1)** and **(3.2)**, which were amenable to scale-up.

4.2.6 Attempted domino C-B reactions

4.2.6.1 Main domino C-B reactions

The domino C-B cyclisation was conducted under the same conditions used previously for the C-ring formation (Scheme 4.16).



Scheme 4.16

The silyl enol ethers **(4.1)** and **(4.33)** were treated with ^{t}BuLi at -116 °C in THF for 15 min and then allowed to warm to room temperature. The desired β-keto phosphonates **(4.2α**, **4.35α)** and **(4.2β**, **4.35β)** were isolated along with the monocyclised esters **(4.38**, **4.39)** and the products resulting from the nucleophilic attack on the ester by ^{t}BuLi **(4.36**, **4.37)**. Table 4.1 presents characteristic results obtained for the methyl and ethyl series. Optimisation of the reaction was achieved with the C13-methyl series showing that a few parameters drove the effectiveness of the process.

Entry	R =	[C] (mol/L)	Equiv of ^{t}BuLi / Method of addition	Yield of Products (%)				
				(4.2α) / (4.35α)	**(4.2β) / (4.35β)**	**(4.36) / (4.37)**	**(4.38) / (4.39)**	**(4.33) / (4.1)**
1[a]	Me	0.14	2.2 / dropwise	42	0	18	6	12
2[a]	Me	0.08	2.2 / dropwise	36	0	21	[c]	16
3[b]	Me	0.2	2.4 / dropwise	27	10	22	9	10
4[b]	Me	0.2	2.4 / very fast	**46**	**5**	14	11	6
5[b]	Me	0.12	2.4 / very fast	21	15	28	13	8
6[b]	Et	0.2	2.4 / very fast	**39**	**11**	15	10	7

[a] = scale of 0.4 mmol, [b] = scale > 2 mmol, [c] = not isolated.

Table 4.1

While conducting initial experiments on small scale (entries 1-2), the C10-β-epimer **(4.35β)** was never observed. It also appeared that the use of 2.2 equiv of ^{t}BuLi was not enough to fully initiate the reaction as the starting material was recovered in 12% yield (entry 1). The biggest issue at this point was the formation of the undesired monocyclised ketone **(4.36)** as separation of compounds **(4.35α)** and **(4.36)**, due to the need of neutralized silica, was particularly complex. Despite several attempts, separation by preparative HPLC or using alumina was unsuccessful. Conducting the reaction under more diluted conditions, in order to disfavor the intermolecular side-reaction of ^{t}BuLi towards the ester actually had the opposite effect (entry 1 versus 2), and decreased yields of **(4.35α)** were observed. Other experiments looked at the use of activated molecular sieves, without change in the outcome of the reaction. Conducting the reaction in Et_2O instead of THF was a complete failure as none of the previously mentioned products were observed.

While scaling-up the reaction, the concentration was increased as well as the amount of ^{t}BuLi (entry 3), in an attempt to avoid any recovery of starting material **(4.33)**. Clearly, adding 2.4 equiv of ^{t}BuLi dropwise had the same effect as decreasing the concentration.

This led to an increased yield of undesired monocyclised ketone **(4.36)**. The breakthrough came when instead of adding ^{t}BuLi dropwise, it was added very quickly (entry 4). The desired β-keto phosphonates **(4.35α)** and **(4.35β)** were isolated in 51% combined yield. The procedure was successfully repeated with the precious C13-ethyl precursor **(4.1)** in which case the main isomer **(4.2α)** was obtained in 39% and minor isomer **(4.2β)** in 11% yield (entry 6).

Although it is still unclear why such different ratios of the C10-β-epimers and C10-α-epimers were obtained, one of the reasons was the purification using pre-neutralized silica gel. Indeed, on large scale which also meant a lengthy separation, epimerisation of **(4.35α)** and **(4.2α)** was clearly observed during the column chromatography which led to increased yields of **(4.35β)** and **(4.2β)**.

The stereochemistry at the newly established C10-epimeric centre was first determined by ^{1}H NMR as shown in Figure 4.4 below for the C13-ethyl products **(4.2α, 4.2β)**.

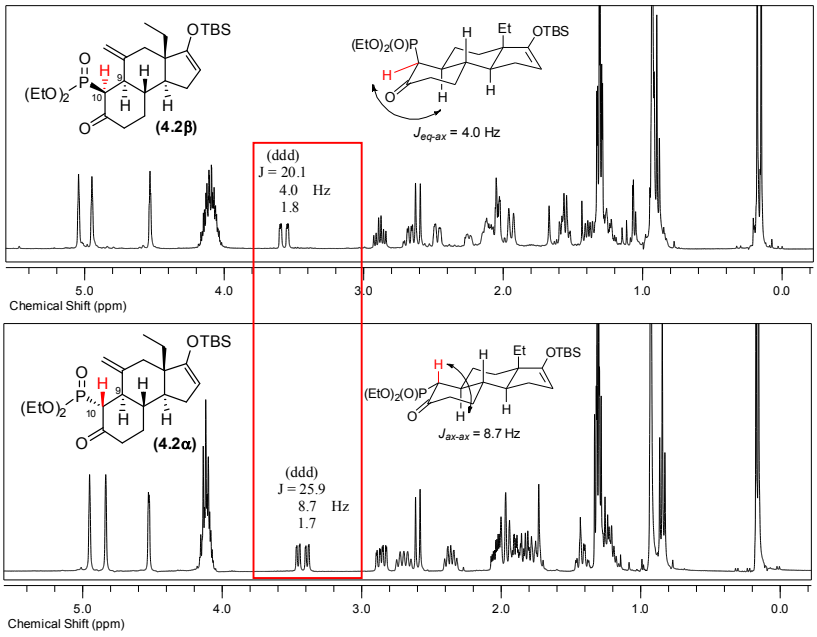


Figure 4.4

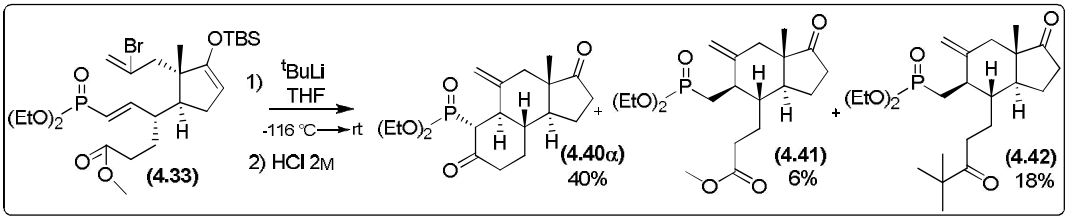
Significant differences are displayed in the medium-field region (δ = 3.3 to 3.6 ppm) corresponding to the protons on C10. As expected, main isomer **(4.2α)** displayed a higher $J_{ax\text{-}ax}$ coupling constant, between H on C10 and H on C9, of *8.7 Hz* whereas minor isomer

(4.2β) displayed a $J_{eq\text{-}ax}$ coupling constant of *4.0 Hz*. The stereochemistry was later unambiguously proven by X-Ray of the deprotected derivatives (part 4.2.6.3).

As a conclusion, the domino C-B reaction was successfully achieved for both C13-methyl and C13-ethyl series, in good yields (50-51%) for a challenging reaction. By increasing the concentration and very fast addition of ^{t}BuLi, the formation of the undesired monocyclised ketones **(4.36**, **4.37)** could be limited, but the monocyclised esters **(4.38, 4.39)** were unfortunately always present. Avoiding the formation of the monocyclised side-products was clearly desired and other substrates were envisioned that could also undergo a domino C-B cyclisation (*part 4.2.7 and 4.2.8*). Finally, the β-keto phosphonates were quite unstable and could not be stored for a long time despite storage in the freezer even flushed with N_2.

4.2.6.2 Alternative domino C-B reaction

Initial investigations on the domino C-B reaction also looked at a direct deprotection of the C17-silyl enol ether by quenching the reaction with HCl 2M (Scheme 4.17)



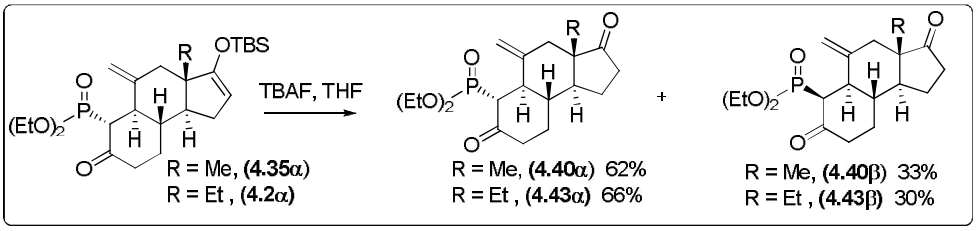
Scheme 4.17

In this case, despite no increase in the yield of desired tricyclic product **(4.40α)**, the separation with the undesired monocyclised ketone **(4.42)** could easily be achieved. This was obviously of great importance for identification purposes. However, this sequence was only attempted once, as the C17-protection was required for the construction of the A-ring.

4.2.6.3 Derivatisation of the domino C-B products

Because adducts obtained from the domino C-B reaction were quite unstable, deprotection of the C17-ketone was achieved for characterisation purposes, also allowing access to crystallographic determination of the relative stereochemistry. Scheme 4.18 shows the

deprotection of the main isomers **(4.35α)** and **(4.2α)** obtained during the domino C-B reaction.



Scheme 4.18

Upon TBAF deprotection (2 equiv),[166] a mixture of the two deprotected phosphonate epimers was obtained. Although completion was observed after 2 min of reaction, in which case only the C10-α-epimers **(4.40α**, **4.43α)** were observed, the reaction was deliberately conducted for over 1 h, allowing for epimerisation at the C10-centre to also afford the **(4.40β**, **4.43β)** epimers.

Depending on the C13-series, recrystallisation in DCM/hexane gave crystals for **(4.40α)** and **(4.43β)** (Figures 4.5, 4.6).

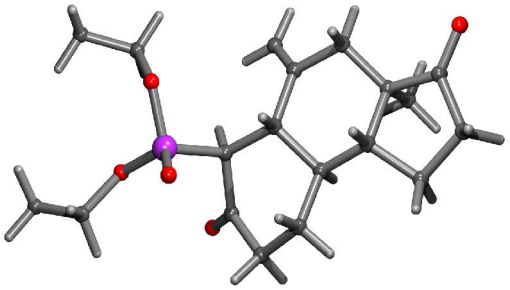


Figure 4.5: X-Ray structure of (4.40α)

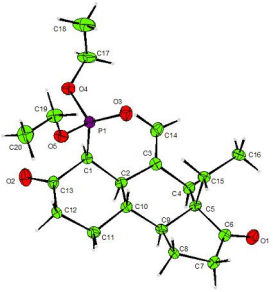
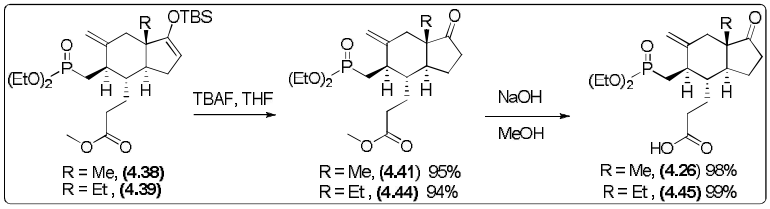


Figure 4.6: X-Ray structure of (4.43β)

Derivatisation was also achieved on the monocyclised esters **(4.38**, **4.39)** (Scheme 4.19).



Scheme 4.19

Deprotection with TBAF proceeded smoothly, affording **(4.41)** and **(4.44)** in excellent yields. Saponification[176] with NaOH in MeOH afforded carboxylic acids **(4.26)** and **(4.45)**. Recrystallisation of **(4.45)** in DCM/hexane gave access to the X-Ray shown in Figure 4.7. An X-Ray of **(4.26)** had previously been obtained (Figure 4.2), and the NMR data following this path were consistent with the previously obtained NMRs.

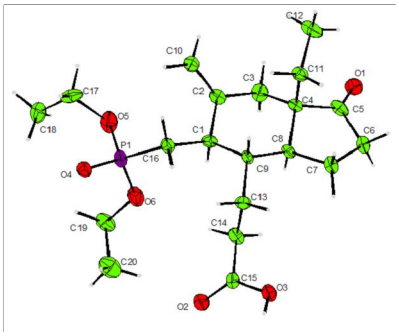
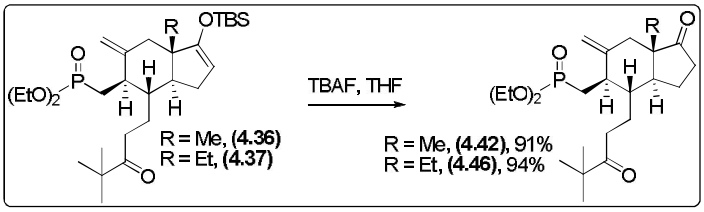


Figure 4.7: X-Ray structure of **(4.45)**

Obviously, monocyclised ketones **(4.36**, **4.37)** were also deprotected (Scheme 4.20).

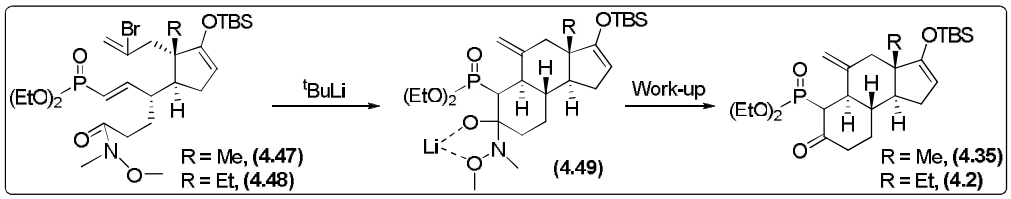


Scheme 4.20

Despite many attempts, none of the diketones **(4.42**, **4.46)** could be recrystallised. The C9-stereochemistry involved during the domino C-B reaction having already been proven several times, an unambiguous proof of the stereochemistry of those diketones wasn't really required.

4.2.7 Domino C-B reactions with Weinreb amides

In order to avoid/limit the formation of the monocyclised esters during the domino C-B reaction, the Weinreb amides **(4.47)** and **(4.48)** were also envisioned (Scheme 4.21).

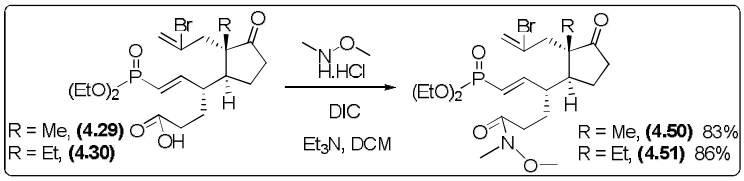


Scheme 4.21

For instance, employing a Weinreb amide **(4.48)** would lead, upon domino C-B cyclisation, to a tetrahedral intermediate **(4.49)** by chelating the counter-cation Li, which upon work-up would lead to the desired β-keto phosphonate **(4.2)** (Scheme 4.21). Formation of the tetrahedral intermediate **(4.49)** was hoped would favor the B-ring cyclisation.

4.2.7.1 Synthesis of the domino C-B precursors **(4.47)** and **(4.48)**

The desired Weinreb amides were easily prepared from the carboxylic acids **(4.29**, **4.30)** (Scheme 4.22).



Scheme 4.22

Initial experiments to prepare **(4.50)** following literature examples[177] using 1 equiv of DCC in combination with 1 equiv of Et_3N and 1 equiv of amine was a very slow process, needing the addition of an extra 0.5 equiv of all the reagents to reach completion. The desired Weinreb amide **(4.50)** was then isolated in 56% yield along with 21% of the undesired urea **(4.52)** (Figure 4.8).

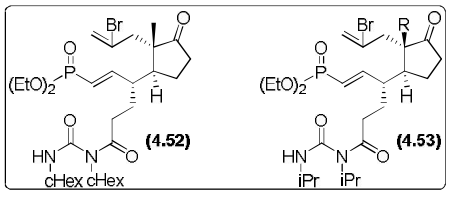
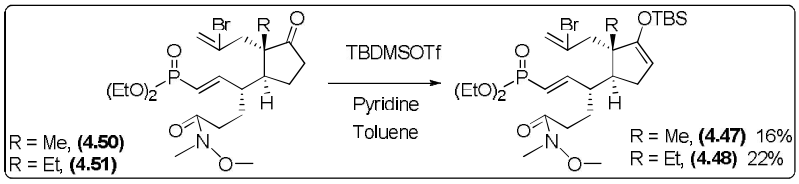


Figure 4.8

The procedure was then modified, using DIC instead of DCC; and directly adding to the acids **(4.29)** and **(4.30)** 1.5 equiv of all the reagents. This procedure afforded the desired Weinreb amides **(4.50)** and **(4.51)** in 83% and 86 % yield respectively, after 2 h of reaction and with only traces of undesired rearranged ureas like **(4.53)** (TLC).

Protection of a ketone in the presence of an amide as a silyl enol ether is quite well documented[178-184] and is reported to be usually quite high yielding (Scheme 4.23).



Scheme 4.23

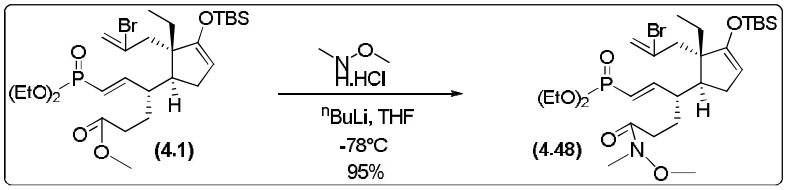
However, using our standard procedure[164] with 3 equiv Et_3N/TBDMSOTf at -50 °C, the expected profile by TLC monitoring was not observed, since silylation at the C17-ketone induces a great decrease in polarity. Warming to room temperature was not efficient either and adding more TBDMSOTf/Et_3N only led to decomposition.

The combination of collidine/TBDMSOTf was then explored.[183] Using 10 equiv of collidine with 6 equiv of TBDMSOTf, the desired TLC profile was observed. However, after 24 h of reaction, only a small part of the starting material had reacted and a competitive decomposition reaction could be observed. Adding more TBDMSOTf led to decomposition and removal of the collidine from the desired product was problematic.

Collidine was replaced by pyridine, and after many attempts, the best conditions found were the use of 10 equiv of pyridine with successive additions of 3 equiv TBDMSOTf in very diluted conditions, so as to avoid complete decomposition. In the best cases, the desired silyl enol ethers **(4.47)** and **(4.48)** were isolated in 16% and 22% respectively along with 25-30% of starting material.

Pre-mixing LDA with TBDMSOTf at -78 °C prior to the addition of the Weinreb amide **(4.51)**, known as the in situ quench technique,[185,186] only led to the recovery of the starting material.

The strategy needed to be modified, in which case the C17-ketone had to be protected prior to the introduction of the Weinreb amide (Scheme 4.24).[187]

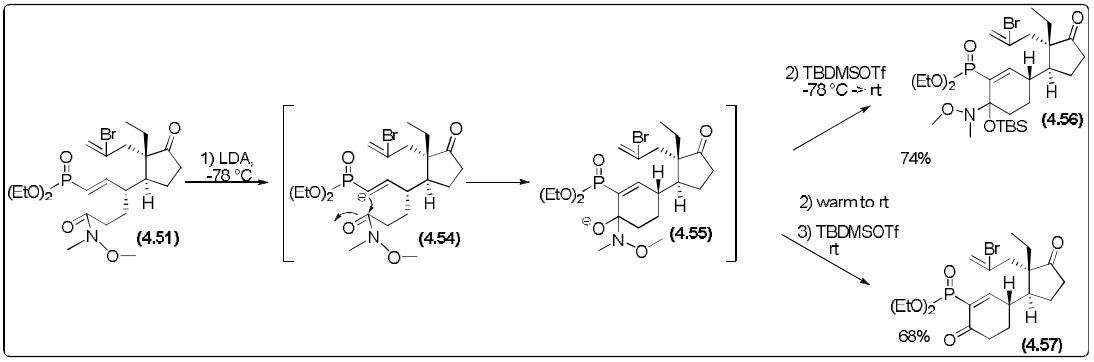


Scheme 4.24

In practice, the amine (6 equiv) in THF was treated with ^{n}BuLi (9 equiv) from -78 °C to room temperature until complete dissolution of the salt. A solution of the ester **(4.1)** in THF was then added at -78 °C. The reaction was complete after 1 h leading to the desired Weinreb amide **(4.48)** in excellent yield.

4.2.7.2 C17-ketone protection with LDA/TBDMSOTf: B-ring cyclisation

While examining protection of the Weinreb amide **(4.51)** with LDA/TBDMSOTf, some very interesting side reactions were observed, which are described in this section (Scheme 4.25).[188,189]



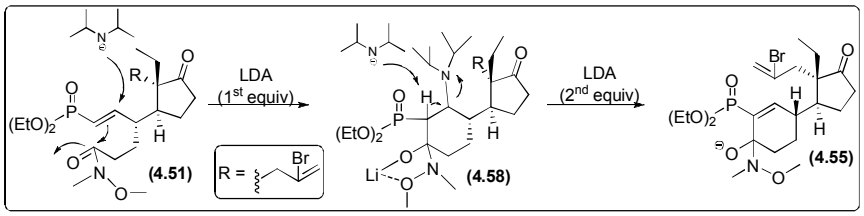
Scheme 4.25

Treatment of the Weinreb amide **(4.51)** with LDA at -78 °C for 2 h followed by quenching with TBDMSOTf (2.5 equiv) led to the unexpected B-ring cyclised adduct **(4.56)** in good yield as a (4/1) mixture of diastereoisomers. The use of 2.5 equiv of LDA was necessary for the reaction to go to completion, or only starting material was recovered with **(4.56)** in lower yields. Interestingly, no traces of C17-silyl enol ether were observed despite the large excess of LDA.

Also interesting, the intermediate oxyanion **(4.55)**, readily trapped at -78 °C, could also undergo elimination at room temperature leading to the β-keto phosphonate **(4.57)**.

Indeed, when Weinreb amide **(4.51)** was treated with 2.5 equiv of LDA at -78 °C for 15 min, then warmed to room temperature, quenching with TBDMSOTf didn't trap the oxyanion as the unsaturated β-keto phosphonate **(4.57)** was already formed in good yield (Scheme 4.25). Those results were very interesting, since alternative C-ring cyclisation pathways could now be envisaged from either **(4.56)** or **(4.57)**.

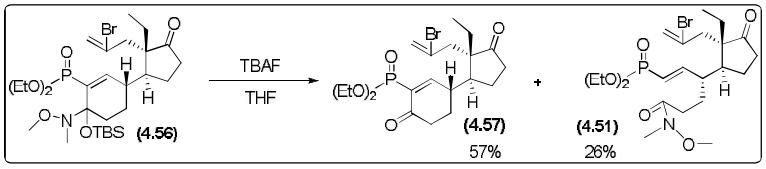
Although the presence of oxyanion **(4.55)** had been demonstrated, its origin still remains unclear. As an alternative to the direct deprotonation of the unsaturated-phosphonate **(4.51)** as shown in Scheme 4.25, the possibility of a Michael Initiated – Condensation – Elimination (MICE) sequence also exists (Scheme 4.26).[188]



Scheme 4.26

Following this pathway, LDA would add onto the α,β-unsaturated phosphonate **(4.51)**, initiating the B-ring cyclisation leading to intermediate **(4.58)**. A second equivalent of LDA would then re-establish the alkene via elimination of the amine, leading to oxyanion **(4.55)**.

Conversion of **(4.56)** to the corresponding β-keto unsaturated phosphonate **(4.57)** was also attempted, with some unexpected results (Scheme 4.27).

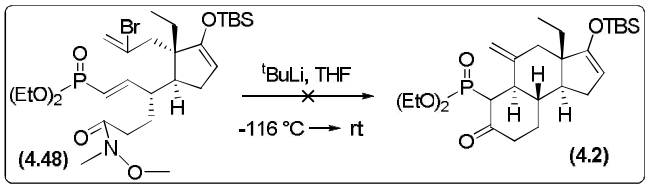


Scheme 4.27

Very surprisingly, treatment of **(4.56)** with TBAF led to the desired β-keto phosphonate **(4.57)** in 57% but also gave rise to a B-ring opening side reaction. Indeed, the Weinreb amide **(4.51)** was also obtained in 26%. To the best of our knowledge, this is unprecedented in the literature, and suggests that the reaction of **(4.54)** to **(4.55)** can be reversed. The strong red colour observed upon addition of TBAF also suggests the presence of phosphonium anion **(4.54)**.

4.2.7.3 Attempted domino C-B reactions

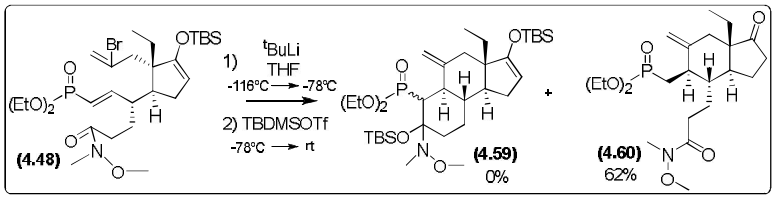
The domino C-B cyclisation was conducted under the same conditions successfully used previously for the methyl esters (part 4.2.6) (Scheme 4.28).



Scheme 4.28

The Weinreb amide **(4.48)** was treated with ^{t}BuLi (2.4 equiv) at -116 °C in THF for 15 min and then allowed to warm to room temperature. Unfortunately, the reaction was a complete failure and no trace of the desired β-keto phosphonate **(4.2)** was observed. Three products could clearly be observed by TLC but separation was unsuccessful and none were identified. Assuming the conditions were too harsh, the reaction was repeated with gradual temperature increase from -116 °C to room temperature and careful monitoring of the reaction. Above -78 °C, a very complex mixture was observed, and **(4.2)** was not isolated.

As a single product was observed at -78 °C, the reaction was repeated one last time with TBDMSOTf quenching (2.5 equiv) so as to trap any oxyanion intermediate as previously achieved when the B-ring cyclisation was observed (Scheme 4.29).



Scheme 4.29

Unfortunately, under those conditions, tricyclic phosphonate **(4.59)** was not isolated. Instead, the monocyclised C17-ketone **(4.60)** was obtained in 62% yield. Quite clearly, B-ring cyclisation didn't occur at -78 °C, and using an excess of TBDMSOTf under those conditions possibly introduced enough TfOH leading to deprotection of the C17-silyl enol ether.

Clearly, the Weinreb amide was not electrophilic enough to undergo a B-ring cyclisation, which is in apparent contrast with the cyclisation of **(4.51)** to give **(4.57)** in excellent yield.

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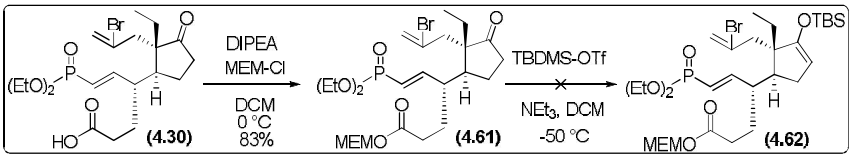
4.2.8 Domino C-B reactions with other substrates

Two other substrates were envisioned in order to obtain better results during the domino C-B reaction: a MEM-ester that could also chelate the counter cation Li, and a phenyl ester.

4.2.8.1 The attempted synthesis of a MEM-ester domino C-B precursor

The attempted synthesis of a MEM-ester domino C-B precursor **(4.62)** is shown in Scheme 4.30.



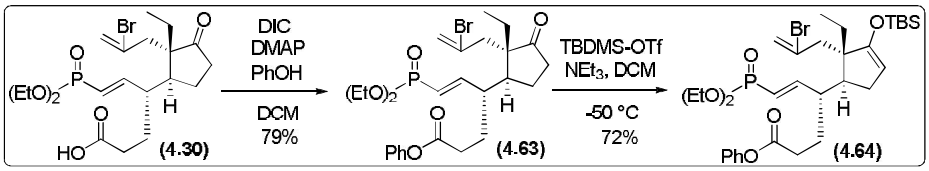
Scheme 4.30

The carboxylic acid **(4.30)** was treated with DIPEA (1.1 equiv) in presence of MEM-Cl (1.2 equiv) in DCM at 0 °C for 2 h.[190] The desired MEM-ester **(4.61)** was isolated in good

yield. Protection of the C17-ketone was attempted following the procedure used several times during the project.[164] Unfortunately, only decomposition was observed, even at -50 °C, so no further experiments were attempted.

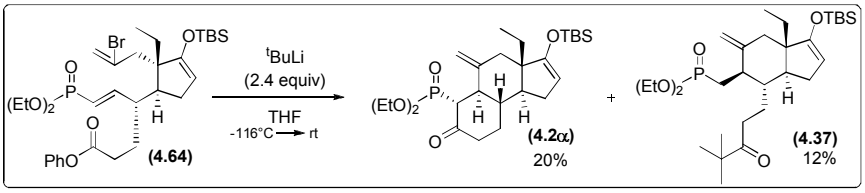
4.2.8.2 Domino C-B reaction with a phenyl ester **(4.64)**

The synthesis of a phenyl-ester domino C-B precursor **(4.64)** is shown in Scheme 4.31.



Scheme 4.31

The phenyl ester **(4.63)** was easily prepared from the carboxylic acid **(4.30)** following a literature procedure in good yield.[191] Protection of the C17-ketone using 3 equiv of Et_3N/TBDMS-OTf at -50 °C afforded the desired silyl enol ether (**4.64**) in good yield after 2 h of reaction. None of the steps were optimized and were conducted on small scale. Enough material was obtained to attempt the domino C-B cyclisation reaction (Scheme 4.32).



Scheme 4.32

Surprisingly, the results were once again disappointing. The behaviour of the reaction was completely different than when a methyl ester was employed. Only the desired β-keto phosphonate **(4.2α)** and the monocyclised ketone **(4.37)** were isolated respectively in 20 and 12% yields. Lots of baseline material was observed however. This was obviously a very disappointing conclusion to the attempted optimizations of the domino C-B reaction.

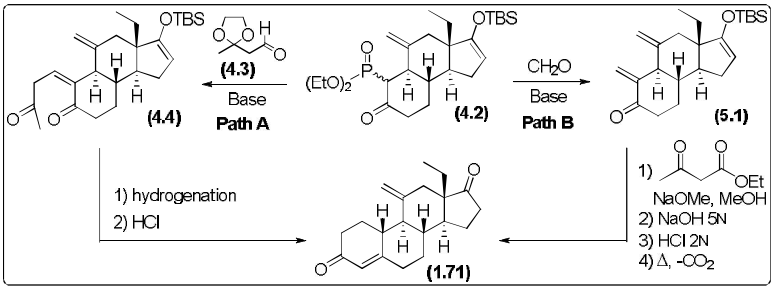
4.2.9 Conclusion

The domino C-B cyclisation reaction was successfully achieved for the C13-methyl and the C13-ethyl series on a methyl ester precursor. The stereochemistry involved during the process was unambiguously proven on separate occasions. Attempts to optimize this complex reaction with other substrates were however all equally unsuccessful.

Chapter 5, Desogestrel: A-ring annelation and synthesis conclusion.

5.1 Introduction

As mentioned in the retrosynthetic analysis, the last key step of the synthesis from β-keto phosphonate **(4.2)** was planned to be an A-ring annelation via a Horner-Wadsworth-Emmons (HWE) reaction with aldehyde **(4.3)**,[140] hydrogenation of the enone **(4.4)** followed by acid mediated aldol/dehydration,[31] that would lead to the known diketone[31,48] **(1.71) (**Path A**,** Scheme 5.1).



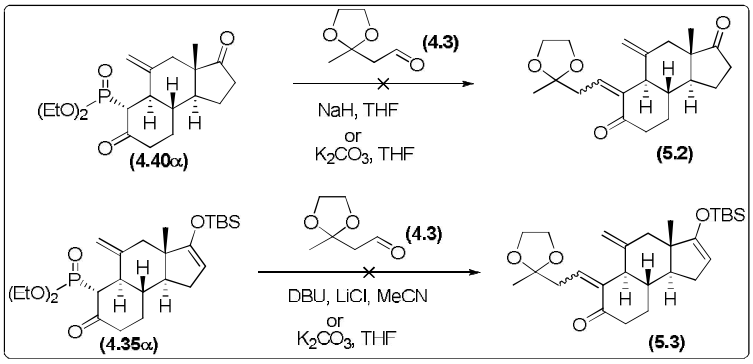
Scheme 5.1

However, as the HWE reaction with aldehyde **(4.3)** could not be achieved, the plan was modified. HWE reaction with formaldehyde would lead to the enone **(5.1)** that would undergo a complex Michael addition/cyclization/dehydration/decarboxylation process that would also construct the A-ring (Path B).[31,192]

5.2 The Horner-Wadsworth-Emmons reactions

5.2.1 Initial experiments with aldehyde (4.3)

HWE reactions with β-keto phosphonates are well documented. They usually involve K_2CO_3 in THF,[193] dioxane[194] or EtOH.[195] Other examples involve NaH in THF.[196,197] The HWE reaction was first investigated with the two β-keto phosphonates **(4.35α)** and **(4.40α)** obtained previously with similar results when the aldehyde[140] **(4.3)** was employed (Scheme 5.2).



Scheme 5.2

In both cases, the use of aqueous K_2CO_3 in THF[193] never afforded the desired products. The starting material was in each case recovered or partially recovered in the case of **(4.35α)** as the silyl enol ether partially decomposed. Using NaH[196,197] on the deprotected β-keto phosphonate **(4.40α)** gave a very complex mixture of compounds where the desired HWE adduct **(5.2)** was not observed but what seemed to be the result of an aldol reaction. Unfortunately, the aldol adduct could not be separated from the starting phosphonate **(4.40α)**. NaH conditions were not attempted with the protected β-keto phosphonate **(4.35α)** as a promising procedure using DBU/LiCl/MeCN[198] was preferred. Once again, no HWE product **(5.3)** was observed but the result of a competitve aldol reaction **(5.4)** in 36% yield (Figure 5.1).

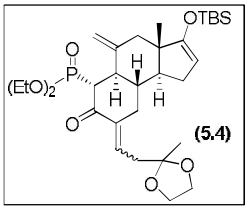
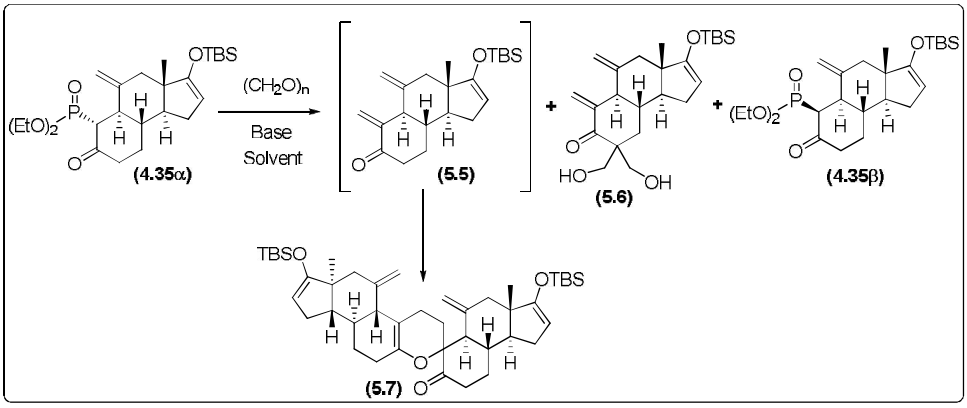


Figure 5.1

Those preliminary results were very disappointing as the phosphonate moiety didn't react with any conditions used, probably due to steric hindrance. A more reactive aldehyde had to be employed and paraformaldehyde/formaldehyde seemed the best choice. This is discussed in the section below.

5.2.2 HWE reactions with formaldehyde

The HWE reaction was investigated on the β-keto phosphonate **(4.35α)** with very different results when paraformaldehyde or formaldehyde was used, as well as the base used (Scheme 5.3).



Scheme 5.3

Table 4.2 presents a part of the results obtained during the investigation process. In each case, the reaction was carried out at room temperature on a 0.2 mmol scale.

Entry	Conditions	Yield of products (%)			
		(5.5)	(5.6)	(4.35α)	(4.35β)
1	$(CH_2O)_n$ (1.1 equiv), K_2CO_3 (1 equiv), THF, 8h	/	/	62	20
2	$(CH_2O)_n$ (3 equiv), K_2CO_3 (3 equiv), THF, 20h	traces	6	40	33
3	$(CH_2O)_n$ (1.1 equiv), K_2CO_3 8M (15 equiv), THF, 8h	8	/	43	25
4	$(CH_2O)_n$ (4 equiv), K_2CO_3 8M (15 equiv), THF, 8h	14	/	36	18
5	$(CH_2O)_n$ (4 equiv), K_2CO_3 8M (15 equiv), THF, 20h	12	15	21	25
6	CH_2O (15 equiv), K_2CO_3 8M (15 equiv), THF, 5h	**41**	5	9	29
7	CH_2O (15 equiv), KOH 1M (1 equiv), THF, 1h	/	**63**	/	/
8	CH_2O (g) (4 equiv), NaH (1 equiv), THF	/	/	/	/

Table 5.1

This HWE reaction proved to be more complicated than expected as the starting phosphonate **(4.35α)** didn't show reactivity under the usual conditions. Hence, the use of $(CH_2O)_n$ with K_2CO_3 was unsuccessful (entries 1, 2).[193] Only isomerisation of **(4.35α)** to **(4.35β)** was observed in these cases and longer reaction times led to the partial deprotection of the silyl enol ether. Under these conditions, conducting the reaction in dioxane or DMF didn't change the course of the reaction. The HWE was then attempted

using a K_2CO_3 8M solution in large excess[193] with slightly better results. Using an excess of $(CH_2O)_n$ was a little more efficient (entries 3, 4, 5) but again, lots of starting material was recovered and the reaction was too slow, meaning that longer reaction times mainly led to the formation of diol **(5.6)** resulting from a competitive aldol reaction. The fact that a mixture of isomers **(4.35α**, **4.35β)** was always obtained suggested that deprotonation of the β-keto phosphonate occurred but then only slowly reacted with the aldehyde.

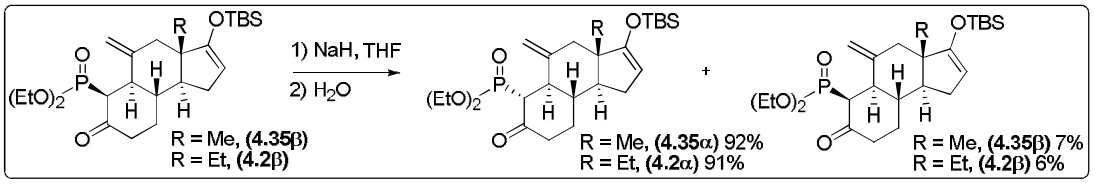
To increase the reactivity, formaldehyde as a water solution (37% w/w) was used with better results (entry 6).[193] Using a large excess (15 equiv) of formaldehyde afforded the desired enone **(5.4)** in medium yields along with still 29% of the isomer (**4.35β)**. These results actually suggested that the isomer **(4.35β)** was far less reactive and so a procedure had to be found to achieve that reaction as fast as possible in order to avoid the isomerisation as well as the competitive aldol reaction.

To do so, KOH was used as a base (entry 7). After 1 h, all the starting material was consumed but no trace of desired enone **(5.5)** was observed. Instead, only diol **(5.6)** resulting from a HWE reaction followed by an aldol reaction was obtained in 63% yield.

A final experiment was attempted by deprotonating β-keto phosphonate **(4.35α)** with NaH (1 equiv) followed by the addition of gaseous formaldehyde (entry 8). The reaction led to a very complex mixture of products.

So far, the enone **(5.5)** could only be synthesised in up to 41% which at least allowed investigating the next A-ring annelation. However, this enone couldn't be caracterized as it almost immediately dimerised, via a hetero Diels-Alder reaction, to dimer **(5.7)**. Although this fact was precedented on this type of enone,[31] attempts to purify it with a very quick column chromatography or storage were not possible neither. This meant that the crude mixture, obtained after a quick work-up, had to be used straightaway for the A-ring annelation (see part 5.3).

It seemed also very clear that minor C10-β isomer **(4.35β)**, obtained in various yields from the domino C-B reaction, would not react under those conditions. In which case it was easily converted to the C10-α isomer **(4.35α)** (Scheme 5.4).

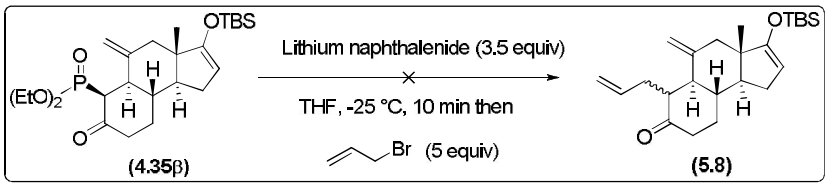


Scheme 5.4

The C10-β isomers **(4.2β**, **4.35β)** were treated with 2 equiv of NaH in THF for 1 h which almost exclusively led to the C10-α isomers after quenching **(4.2α**, **4.35α)**.

5.2.3 Attempted dephosphonylation reactions

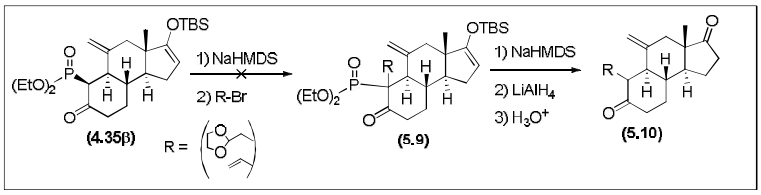
Because at that time, the 41% obtained for the HWE reaction had not been achieved, other methodologies were explored. First, Liu and co-workers[199] described that the phosphonate functionality, being α to a ketone carbonyl, could be reductively removed using lithium naphthalenide and the ensuing enolate readily trapped by an alkylating agent (Scheme 5.5).



Scheme 5.5

The reaction was attempted twice using allyl bromide as a model alkylating agent but under those conditions, only decomposition of the starting material was observed and the desired adduct **(5.8)** was not observed in any case.

Investigations also looked at the dephosphonylation of α-fully substituted β-keto phosphonates using LAH as described by Oh and co-workers.[200,201] In that case, the phosphonate is used as a temporary activating group for α-alkylation of a ketone (Scheme 5.6).

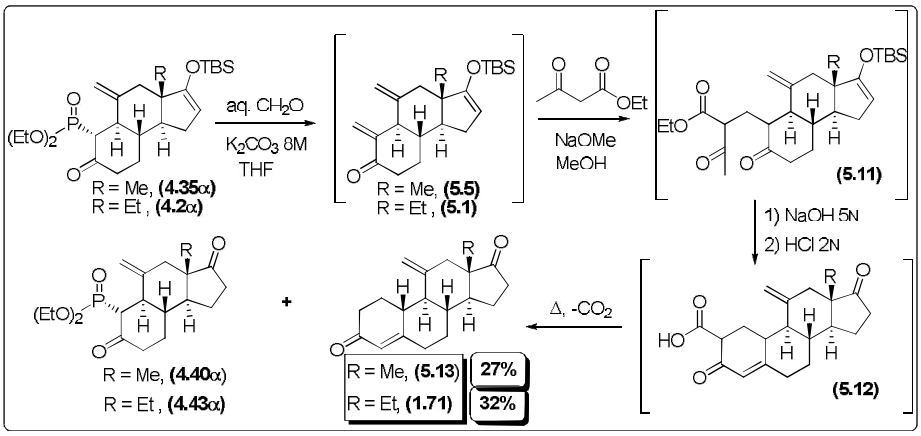


Scheme 5.6

Once again, only disappointing results were obtained as the desired alkylated products **(5.9)** couldn't be observed or isolated. However, the starting phosphonate **(4.35β)** was in each case recovered in 30-35 % along with the isomer **(4.35α)** in 60-65% meaning that the enolate intermediate was formed but the alkylation didn't take place, presumably for hindrance reasons.

5.3 A-ring formation: 7 reactions in a one-pot process

The A-ring formation, planned as the last key step of the total synthesis would be achieved via a Robinson-type annelation which has been used on separate occasions for the construction of the A, B and D rings.[51] However, in our plan, that A-ring annelation would only be achieved after a Michael condensation between the methylene ketones **(5.1**, **5.5)** and ethyl-acetoacetate (Scheme 5.7).



Scheme 5.7

The series of reactions consisting of a Michael condensation between a methylene ketone like **(5.1, 5.5)** and annulating agent, in situ alkaline cyclization-dehydration **(5.11 → 5.12)**

to form in our case the A-ring and finally decarboxylation was precedented in the literature.[31,192]

In practice, the crude methylene ketones **(5.5, 5.1)** obtained from the HWE reaction from **(4.2α**, **4.35α)** and formaldehyde were treated with 2 equiv of ethyl acetoacetate to give intermediate **(5.11)**. At this point, the reaction mixture was quenched with water in order to isolate intermediate **(5.11)**. However, upon addition of water, disappearance of **(5.11)** from the reaction mixture was observed (TLC). Unfortunately, extraction of the product proved not possible at this stage. Acidification followed by TBAF treatment did lead to the desired steroid products **(5.13)** and **(1.71)** in respectively 22% and 19%, along with the deprotected β-keto phosponates **(4.43α)** and **(4.40α)** in 31% and 26 % yields. The procedure was then improved closely following the literature, [31,192] while up-scaling, as shown in Scheme 5.7, by treating intermediate **(5.11)** with NaOH 5M for 30 min followed by the addition of HCl 2M. Decarboxylation of **(5.12)** was successfully achieved by heating the crude mixture at 70 °C under high vacuum for 1 h. The desired diketones **(5.13)** and **(1.71)** were then obtained in respectively 27% and 32% yields, on a 100 mg scale of desired products. In those experiments, β-keto phosponates **(4.43α)** and **(4.40α)** were not isolated.

X-ray crystallographic analyses (Figures 5.2 and 5.3) unambiguously proved the relative stereochemistry at the newly established C10 centres.

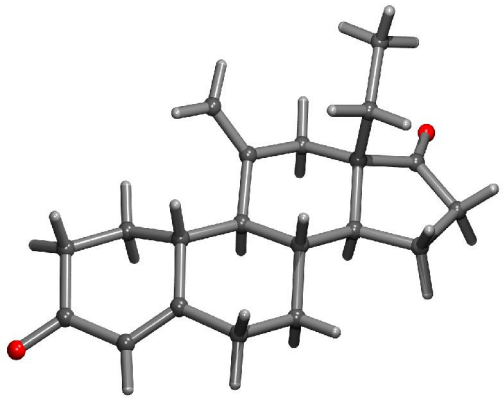


Figure 5.2: X-Ray structure of (1.71)

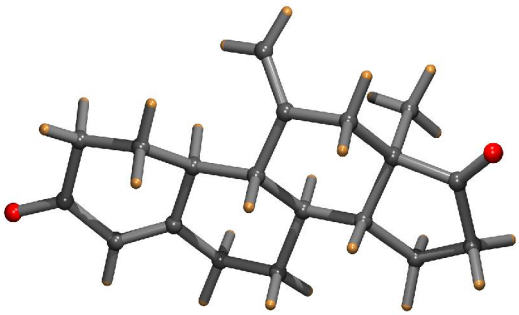


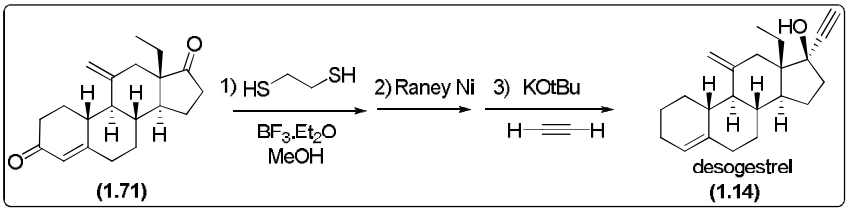
Figure 5.3: X-Ray structure of (5.13)

Even if the overall yields of **(1.71)** and **(5.13)** from **(4.2α)** and **(4.35α)** are quite low, taking in account that the HWE reaction is so far very limiting (~40% yield) and that in a single operation 7 consecutive reactions occurred, this result was obviously of great

importance as **(1.71)** and **(5.13)** are known compounds[26,27,48] and the last key intermediates in our synthesis, the latest functionalisation reactions more or less already described. This also meant that the formal syntheses of desogestrel and its C13-methyl analogue were completed.

5.4 Total synthesis of desogestrel

Although **(1.71)** is a known compound, it has only been successfully been employed in the industrial process of desogestrel.[21] However, initial experiments on very small scale were unsuccessful which compelled us to explore another route towards desogestrel (Scheme 5.8).

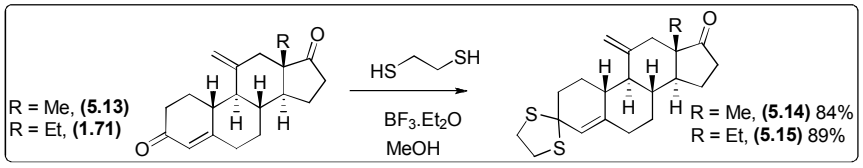


Scheme 5.8

The first step involved a C5-thioacetal protection, followed by a Raney-Ni deprotection and finally introduction of the C17-ethinyl group.

5.4.1 Dithioacetal protection

The selective protection of the C5-α,β-unsaturated ketone was easily achieved as a thioacetal (Scheme 5.9).[26]



Scheme 5.9

Steroids **(5.13)** and **(1.71)** were treated with ethane-1,2-dithiol (1.9 equiv) and boron trifluoride-etherate (0.8 equiv) in MeOH for 16 h at room temperature. The desired

thioketals **(5.14)** and **(5.15)** were obtained in excellent yields. X-ray crystallographic analyses were also obtained for both steroids (Figures 5.4, 5.5).

Figure 5.4: X-Ray structure of (5.14)

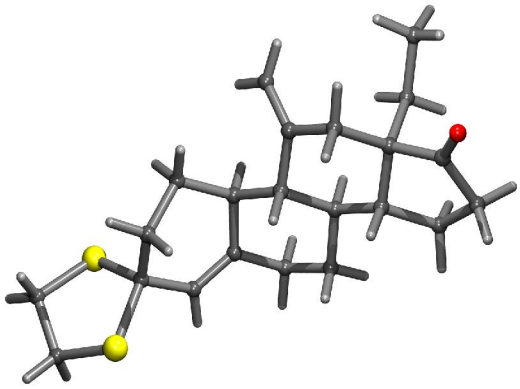
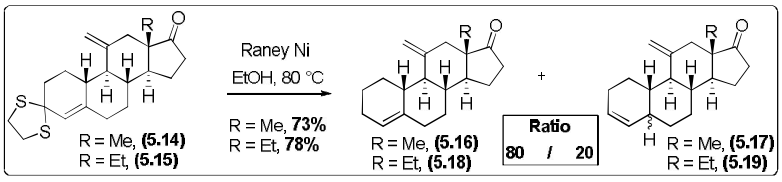


Figure 5.5: X-Ray structure of (5.15)

5.4.2 Desulfurization reactions

Although desulfurization at the C5 position has been reported on separate occasions by Corey[23] or Tietze[26] using Li/NH_3, this was not applicable with steroids **(5.14**, **5.15)** due to the C17-ketone. Instead, desulfurization was achieved with Raney nickel (Scheme 5.10).[202]



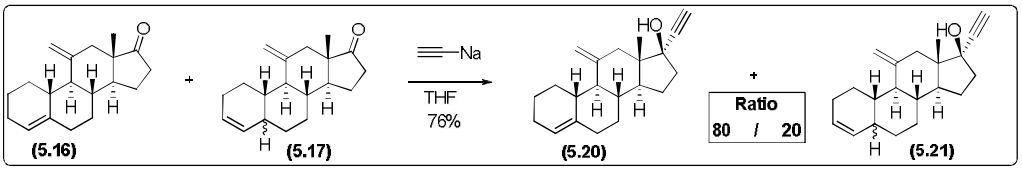
Scheme 5.10

The reaction proceeded well but in both cases, a migration of the double bond from the Δ4,5 **(5.16**, **5.18**) to the Δ3,4 **(5.17**, **5.19)** was observed and separation by chromatography or recrystallization was not successful. Thus, the synthesis had to be continued with a mixture of isomers.

5.4.3 Introduction of the C17α-ethinyl group

For the final introduction of the C17α-ethinyl group, the angular ethyl group at C13, which is responsible for a *50-fold* enhancement of biological potency relative to the C13-methyl analogue,[23] posed a great synthetic obstacle.

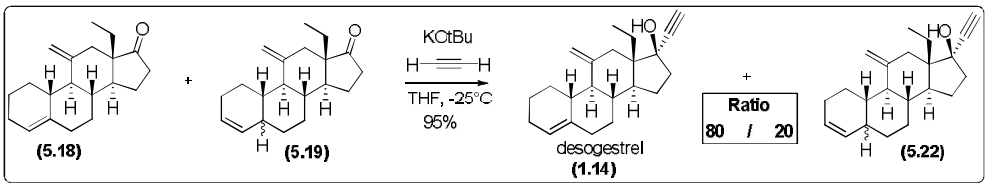
For instance, the ethinyl group was easily introduced for the C13-methyl analogue using a commercial solution of sodium acetylide (Scheme 5.11).



Scheme 5.11

The mixture of Δ4,5 **(5.16)** and Δ3,4 **(5.17)** isomers was treated with sodium acetylide (20 equiv) in THF. The reaction was repeated twice. First, by adding the acetylide at -40 °C and then slowly warming to room temperature in which case steroids **(5.20)** and **(5.21)** were obtained in 76%, as a (80/20) inseparable mixture, after 16 h of reaction. When acetylide was added at room temperature, the reaction was complete after 4 h and a yield of 74% was obtained.

Interestingly, under the same conditions, conducting the reaction with the C13-ethyl steroids **(5.18)** and **(5.19)** only led to decomposition for both attempts. However, the total synthesis of desogestrel **(1.14)** was finally completed following the procedure used by Organon for the commercial synthesis of desogestrel (Scheme 5.12).[203]



Scheme 5.12

Potassium acetylide was generated *in situ* by bubbling acetylene through a THF solution of KO*t*Bu (5 equiv) at -25 °C for 1 h. A solution of steroids **(5.18, 5.19)** (1 equiv) in THF was then added and acetylene was passed through the mixture for 1 h at -25 °C. The reaction proceeded in very high yields and desogestrel **(1.14)** was obtained along with the Δ3,4-isomer **(5.22)**. Separation of the two isomers was not achieved however.

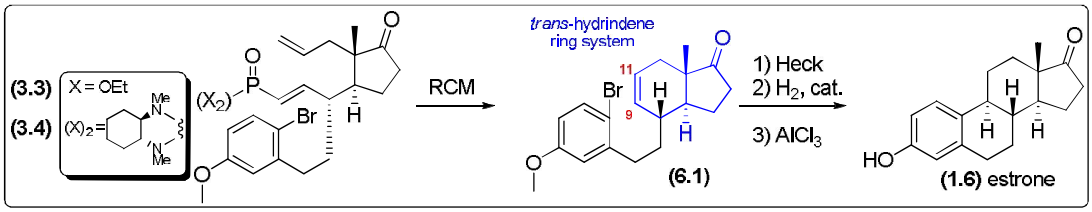
5.5 Conclusion

The total syntheses of desogestrel and its C13-methyl analogue have been successfully achieved. By employing a domino anionic cyclization, the stereoselective construction of the steroids C and B-rings was achieved, in a single operation. Construction of the A-ring was efficient, although the HWE reaction with β-keto phosphonates proceeded in quite low yields. Final conversion led to desogestrel, which unfortunately could not be obtained pure.

Chapter 6, Steroid C and B ring formation: Completion of Estrone total synthesis

6.1 Introduction

From the previously obtained phosphonate **(3.3)** and phosphonamide **(3.4)**, only a few steps were required to complete a racemic and enantioselective synthesis of estrone (Scheme 6.1).



Scheme 6.1

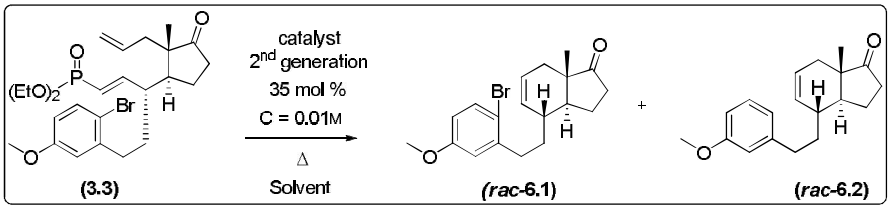
The last key step, from both **(3.3)** and **(3.4)**, was a ring closing metathesis (RCM) that would allow the formation of a *trans*-hydrindene ring system intermediate **(6.1)**. The RCM would also introduce the required C9-C11 double bond for the B-ring closure, through an intramolecular Heck reaction as described by Tietze.[34] Estrone would then be obtained in two steps via known reactions.[34,204]

6.2 The C-ring closing metathesis

Although the RCM leading to the strained *trans*-hydrindene ring system was precedented,[205,206] those examples involved two terminal double bonds. RCM reactions involving α,β-unsaturated phosphonates or phosphonamides are not well documented and have mainly been explored to enable the formation of P-heterocycles.[207-211] Achieving the RCM on phosphonate **(3.3)** and phosphonamide **(3.4)** required much optimization using different conditions,[64] and are therefore discussed separately.

6.2.1 Racemic synthesis: RCM with phosphonate (3.3)

With the phosphonate-based substrate **(3.3)**, the RCM[207,208,210-216] was achieved, taking advantage of the optimisations made by B. Guizzardi[64] whose best conditions were the use of 35 mol% 2nd generation Grubbs catalyst in DCM as a 0.01 M solution (Scheme 6.2).



Scheme 6.2

Some results obtained during the optimisation process are shown in Table 6.1.

Entry	catalyst	catalyst loading	C (mol/L)	Solvent	T (°C)	Time (h)	Yield of products (%)	
							(*rac*-6.1)	**(*rac*-6.2)**
1[a]	Grubbs II	5 mol%	0.05	DCM	40	48	24	[c]
2[a]	Grubbs II	25 mol%	0.05	DCM	40	48	42	[c]
3	Grubbs II	35 mol%	0.01	DCM	40	24	56	6-7
4	Grubbs II	35 mol%	0.01	toluene	80	48	54	2-3
5[b]	Grubbs II	35 mol%	0.01	toluene	80	48	50	3
6	Hov-Gru II	35 mol%	0.01	toluene	80	48	61	traces

[a] = previous results by B. Guizarddi, [b] = 2 x 17.5 mol %, [c] = yields not given, Grubbs II = Grubbs catalyst 2nd generation, Hov-Gru II = Hoveyda-Grubbs catalyst 2nd generation.

Table 6.1

When the reaction was carried out in DCM with 5 mol% Grubbs II catalyst and refluxing the solution for 48 h (entry 1),[215] the desired product was only isolated in 24%. Increasing the catalyst loading to 25 mol% (entry 2) led to a marked increase in yield.[213]

Since RCM reactions are also described as leading to different results depending on the concentration,[214] the reaction was repeated on a more diluted solution (entry 3). Using 35 mol % Grubbs II catalyst, the bromide **(*rac*-6.1)** was obtained in acceptable yield along with the debrominated adduct **(*rac*-6.2)**. Separation of the two products could only be achieved by HPLC. The next parameter explored was the solvent effect.[212]

The reaction in refluxing DCM seemed faster than in toluene at 80 °C, giving under the same conditions (entry 3 versus 4) better yields of cyclised adducts after 24 h of reaction.

However, the TLC profile was better with toluene and formation of debrominated adduct **(*rac*-6.2)** was almost avoided, so toluene was kept as the solvent for further experiments. Finally, replacing Grubbs catalyst for Hoveyda-Grubbs II catalyst (entry 6),[216] which was described as giving sometimes better results with toluene at 80 °C,[212] afforded **(*rac*-6.1)** in 61% yield along with only traces of debrominated-adduct **(*rac*-6.2)**.

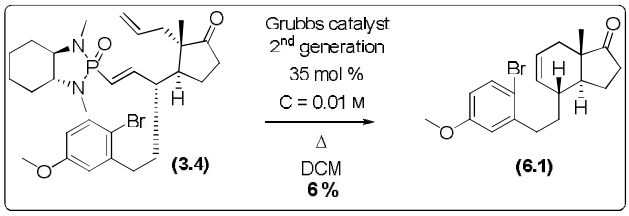
As a conclusion, the RCM C-ring closure with phophonate **(3.3)** was only achieved in moderate yields (up to 61%), requiring a pretty large 35 mol % catalyst loading, in accord with literature examples where strained ring systems are synthesised via a RCM.[213]

6.2.2 Enantioselective synthesis

For the enantioselective synthesis of estrone, from phosphonamide **(3.4)**, the RCM was only achieved at the very end of this PhD, in order to obtain clean characterization data.

6.2.2.1 Phosphonamide RCM reactions

Although RCM reactions on phosphonamides were precedented,[209] the attempts by B. Guizzardi[64] all resulted in very low yields with phosphonamide **(3.4)** (Scheme 6.3).

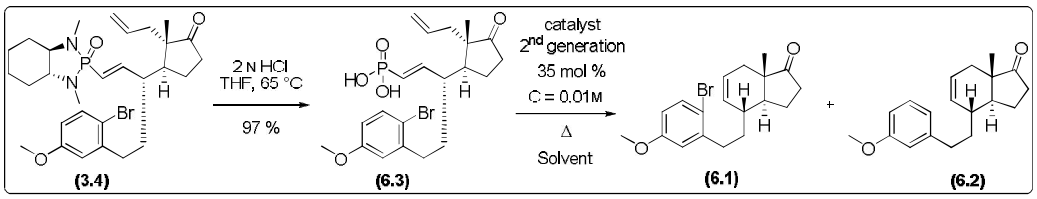


Scheme 6.3

Applying the then best conditions for the achiral phosphonate **(3.3)** (35 mol % Grubbs II catalyst in refluxing DCM as a 0.01 M solution), the desired bromide **(6.1)** was only obtained in 6% yield. The phosphonamide **(3.4)** therefore needed to be derivatised prior to undergoing the RCM reaction. Very interestingly, after extensive research, she found that phosphonamide **(3.4)** could be easily hydrolysed to the corresponding phosphonic acid **(6.3)** that did undergo C-ring cyclisation with relatively good results (Scheme 6.4).

6.2.2.2 RCM reactions with phosphonic acid **(6.3)**

The hydrolysis of phosphonamide **(3.4)** was easily achieved by treatment with 2 N HCl in refluxing THF overnight (Scheme 6.4).[112,217]



Scheme 6.4

Phosphonic acid **(6.3)** was obtained in 97% yield after simple acid work-up and was used without further purification.

The ring closing metathesis on phosphonic acid **(6.3)** was performed applying the same conditions successfully employed with the racemic phosphonate **(3.3)** (Table 6.2).

Entry	catalyst	catalyst loading	C (mol/L)	Solvent	T (°C)	Time (h)	Yield of products (%)	
							(6.1)	**(6.2)**
1	Hov-Gru II	35 mol %	0.01	toluene	80	24	41	traces
2	Grubbs II	35 mol %	0.01	DCM	40	24	44	4
3[a]	Grubbs II	35 mol %	0.01	DCM	40	24	58	n. d.

a = previous results by B. Guizarddi, Grubbs II = Grubbs catalyst 2nd generation, Hov-Gru II = Hoveyda-Grubbs catalyst 2nd generation, n.d. = not determined.

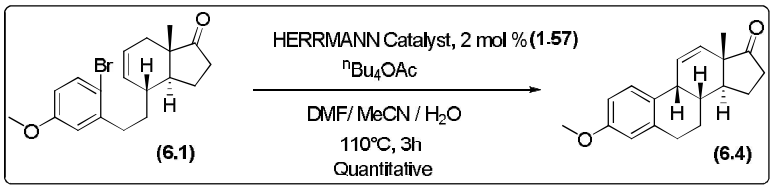
Table 6.2

Conducting the RCM with Hoveyda-Grubbs II catalyst in toluene at 80 °C (entry 1),[212] which were the best conditions found with the phosphonate **(3.3)**, the reaction was complete after 24 h but only afforded bromide **(6.1)** in 41% yield. Grubbs II catalyst in refluxing DCM gave slightly better results (entry 2).[213] The enantiopure bromide **(6.1)** was then obtained in 44% yield along with 4% of debrominated adduct **(6.2)**. Those results were quite disappointing, as previous results[64] could not be reproduced (entry 3), but at least enough material was obtained so as to complete the enantioselective synthesis of *O*-methyl-estrone **(1.113)**. However, to the best of our knowledge, this is the first example of a RCM where a phosphonic acid is present.

6.3 B-ring closure and synthesis conclusion

6.3.1 Heck reaction

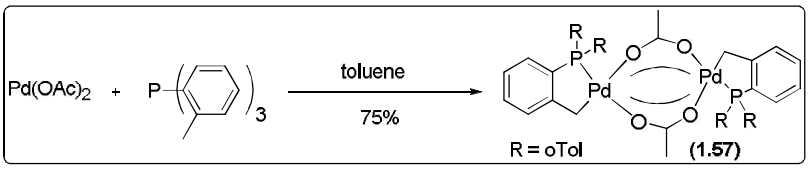
The B-ring closure was achieved through an intramolecular Heck reaction using the Herrmann catalyst **(1.57)** as described in the estrone synthesis of Tietze (Scheme 6.5).[34]



Scheme 6.5

A solution of bromide **(6.1)** and $^{n}Bu_4OAc$ in DMF/MeCN/H_2O (1/1/0.2) was stirred at 110-120 °C for 3 h in presence of 2 mol % catalyst to give steroid **(6.4)** in reproducible quantitative yields. The reaction didn't present any problem as long as the solution was carefully degassed. This condition also applied to every solvent used in the work-up, since steroid **(6.4)** proved to be air sensitive and therefore had to be used straightaway; even overnight storage in the freezer led to partial decomposition.

The Herrmann catalyst **(1.57)** was easily prepared following Herrmann and co-workers procedure as shown in Scheme 6.6.[218]

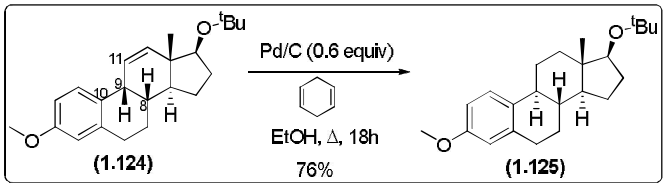


Scheme 6.6

6.3.2 Reduction of the Δ11,12-double bond: synthesis of *O*-methyl-estrone

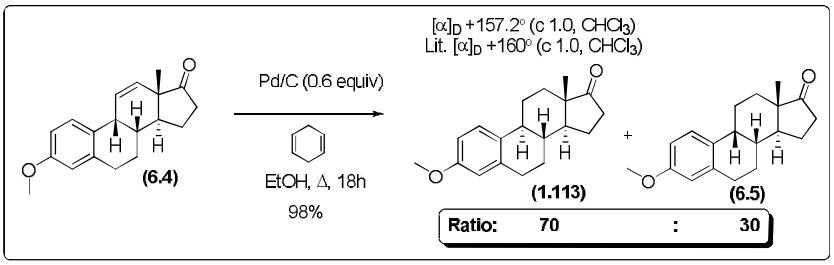
For the final conversion of the Heck-ring closure product **(6.4)** to *O*-methyl-estrone, the Δ11,12- double bond needed to be reduced but, more importantly, the C9 stereochemistry had to be inverted. To reduce the double bond, the estrone synthesis of Tietze was once again followed,[34] where the transformation was achieved through a hydrogenation

catalysed by Pd/C using 1,4-cyclohexadiene as source of hydrogen. In Tietze's estrone synthesis using intermediate **(1.124)**, the conversion was achieved by transfer hydrogenation upon isomerisation of the double bond to the Δ9-11 position, which led exclusively to the desired C9 stereochemistry **(**Scheme 6.7**)**.



Scheme 6.7

This isomerisation/hydrogenation reaction was first attempted following Tietze's procedure with however one modification: *cyclohexene* was used instead of *1,4-cyclohexadiene* as **(6.4)** couldn't be stored and *1,4-cyclohexadiene* was unavailable at this time, leading to the results shown in Scheme 6.8 and Table 6.3.



Scheme 6.8

Entry	Scale	C (mol/L)	Source of H_2	Purity of **(6.4)**	Overall yield	Ratio **(1.113)/ (6.5)**
1	0.10 mmol	0.025	cyclohexene	overnight stored	63%	70/30
2	0.15 mmol	0.05	cyclohexene	freshly prepared	82%	70/30
3	0.11 mmol	0.025	1,4-cyclohexadiene	freshly prepared	98%	70/30

Table 6.3

The reaction was attempted under different conditions, with the same ratio outcome as determined by ^{1}H NMR whatever the source of H_2 used: formation of approximately 70% of the desired C8-9 *trans*-configuration **(1.113)** along with 30% of undesired C8-9 *cis*-configuration **(6.5)**. A yield of 98% was achieved by using a freshly prepared adduct **(6.4)**

(entry 3); whereas an overnight-stored sample of **(6.4)** only led to 63% of a mixture of **(1.113)/(6.5)** with still a ratio of 70/30 (entry 1).

Despite several HPLC attempts, steroids **(1.113)** and **(6.5)** could not be separated. However, partial recrystallization in DCM/Hexane provided access to a pure sample of **(1.113)** of which analytical data corresponded well with literature data.[55,205,219]

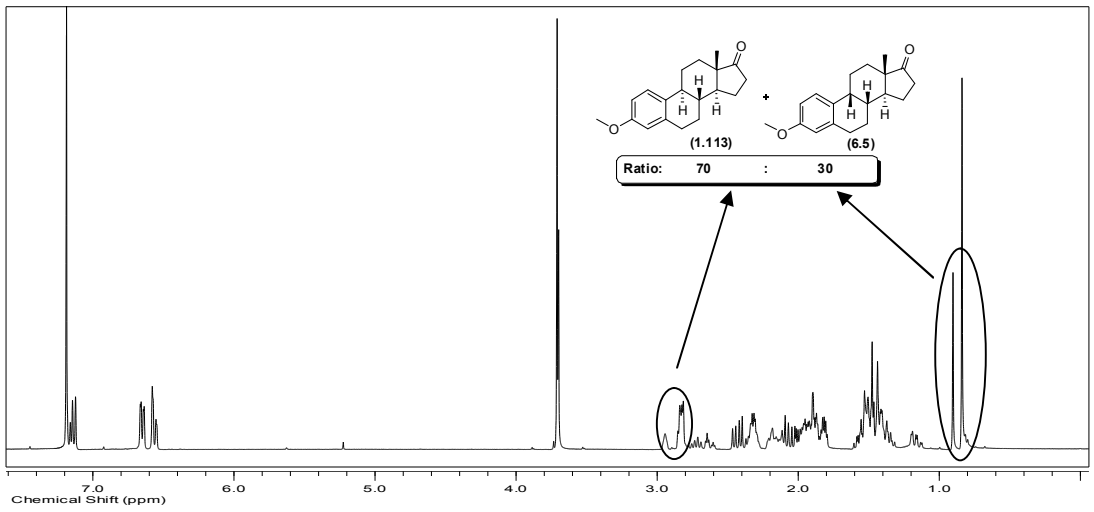
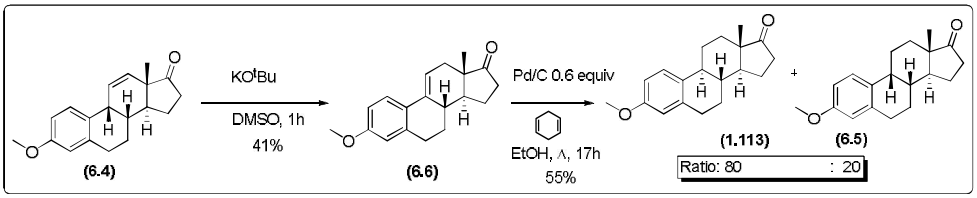


Figure 6.1

Although those results were in accord with a literature report,[220] it still remains unclear whether the lack of stereoselectivity observed was due to the presence of the C17-ketone in the substrate, due to a competitive C=C migration/hydrogenation process or due to a non-selective Δ9,11-double bond hydrogenation.

6.3.3 Isomerisation of the Δ11,12- to Δ9,11-double bond followed by hydrogenation

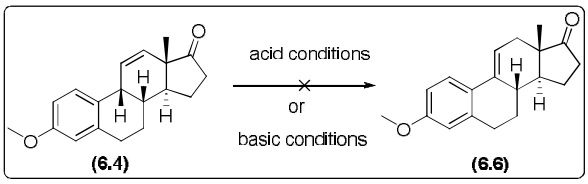
In an attempt to improve the selectivity during the hydrogenation step the Δ11,12-double bond in **(6.4)** was isomerized under basic conditions using 2.6 equiv of KO^{t}Bu in DMSO to obtain the Δ9,11-double bond steroid **(6.6)**,[205,221-223] following Tietze's desogestrel synthesis[26] which is to our knowledge the only example of a Δ11,12 to Δ9,11-double bond migration (Scheme 6.9).



Scheme 6.9

Isomerization didn't prove very efficient, presumably because of the C17-ketone, as decomposition adducts were observed by TLC, and **(6.6)** was not stable. Under hydrogenation conditions, using 1,4-cyclohexadiene, a mixture of **(1.113)** and **(6.5)** was again obtained, though in a better (85-80/15-20) ratio, meaning that with our substrate, the Δ9,11-double bond hydrogenation didn't seem to be selective. The low yield observed was explained by the use of a partially decomposed adduct **(6.6)**. Unfortunately, time constraints prevented us from investigating this control experiment with freshly-made pure **(6.6)**.

Because many examples in the literature showed stereoselective reduction of the Δ9,11-double bond using Et_3SiH,[35,55,205,224,225] we focused on isomerisation of the Δ11,12 to Δ9,11-double bond. Unfortunately, apart from Tietze's KO^{t}Bu procedure, only examples of Δ8,9 or Δ8,14 to Δ9,11-double bond migrations were found.[223]



Scheme 6.10

Unfortunately, neither acidic conditions nor basic conditions were successful (Table 6.4).

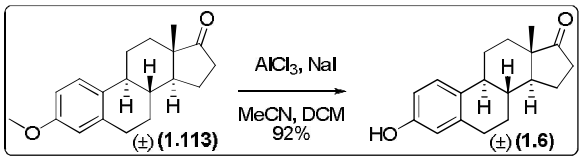
Entry	Conditions	Outcome
1	NaOMe/MeOH rt	No reaction
2	KO^{t}Bu / THF rt	decomposition
3	TFA/benzene rt then Δ	decomposition
4	HCl conc./MeOH rt and Δ	No reaction

Table 6.4

No reaction was observed when NaOMe (2 equiv)/MeOH was used even after 2 days of reaction (entry 1). Using KO^{t}Bu (2 equiv)/THF only led to decomposition after 10 min of reaction (entry 2). Under acidic conditions, with TFA (20 equiv)/benzene, no reaction was observed at room temperature and overnight reflux only led to partial decomposition (entry 3). Finally, no reaction was observed with HCl conc./MeOH even after overnight reflux (entry 4).[223]

6.3.4 Deprotection to Estrone

The final deprotection to estrone was only achieved from the racemic *O*-methyl-estrone **(1.113)** (Scheme 6.11).



Scheme 6.11

Several reagents could have been explored to achieve this final deprotection, such as pyridine hydrochloride[226] or BBr_3.[205] Instead, the $AlCl_3$/NaI couple was choosen with excellent results.[204] Estrone **(1.6)** was obtained in 92% yield after 5 h of reaction at room temperature.

6.4 Summary

The enantioselective and the racemic total syntheses of *O*-methyl-estrone **(1.113)** were successfully accomplished. The C-ring closure by RCM on an achiral phosphonate was optimised up-to 61% using Hoveyda-Grubbs II catalyst. Although the C-ring closure could not be achieved on the chiral phosphonamide, the problem was overcome by transforming the phosphonamide to a phosphonic acid on which the RCM proceeded, however, in medium yields. The Heck reaction, that constructed the steroid backbone, proceeded in quantitative yield. The reduction of the residual double bond unfortunately led to a mixture of 9α-H **(1.113)** and 9β-H **(6.5)** *O*-methyl-estrone, though in almost quantitative yield. Efforts to avoid the formation of the 9β-H isomer **(6.5)** were unsuccessful.

Chapter 7, Future directions of the research

7.1 Short term

Since the racemic and enantioselective total syntheses of estrone have been achieved, apart from improving some medium yielding reactions within the project, no further research towards this steroid seems interesting; based on the diastereoselective 1,4-addition/alkylation methodology employed during this PhD. Desogestrel however, not only because it is synthetically more demanding, has only been synthesized in racemic form. Achieving an enantioselective synthesis of desogestrel would be one of the primary objectives.

7.1.1 Enantioselective synthesis of desogestrel

7.1.1.1 Via a domino C-B reaction

Based on the same methology described in this thesis for the racemic total synthesis of desogestrel, the next aim would be to achieve an enantioselective synthesis by using one of the known chiral auxiliaries for the 1,4-addition reaction, as already achieved for estrone synthesis. Some examples are given in Figure 7.1.

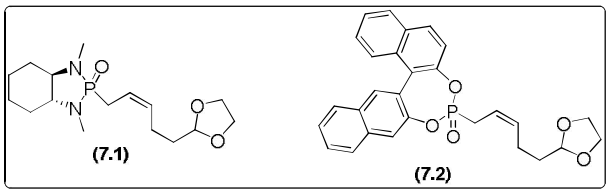
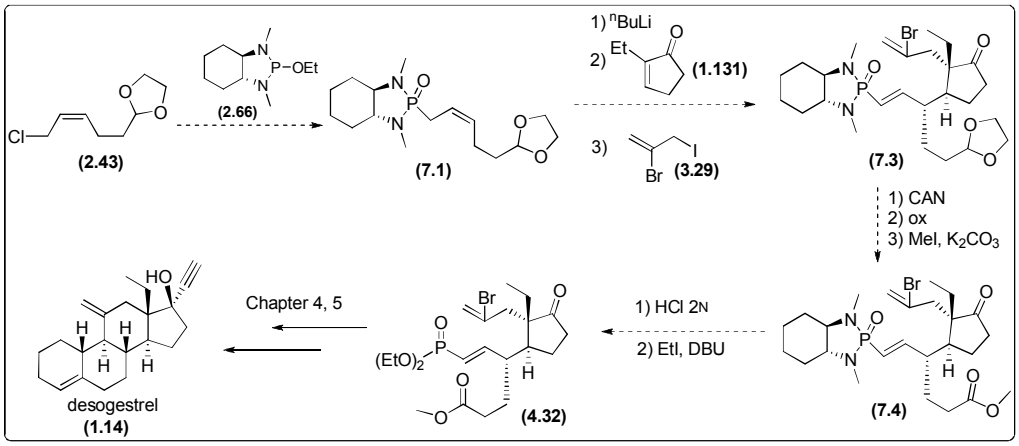


Figure 7.1

The synthesis of achiral phosphonate **(7.2)** has already been achieved by R. Clarkson. The synthesis of the homochiral version of this compound could be achieved using homochiral BINOL.[227-230]Although Fuji and co-workers[136] had reported a number of successful results using this type of compound in related diastereoselective 1,4-addition reactions, preliminary results by R. Clarkson[21] indicates that much optimisation would be required with more complex substrates like **(7.2)**.

On the other hand, the synthesis of homochiral phosphonamide **(7.1)** (Scheme 7.1) should be quite straightforward, as the synthesis of an analogue has already been achieved for estrone synthesis (part 2.3.4.2, page 51).[112,113]



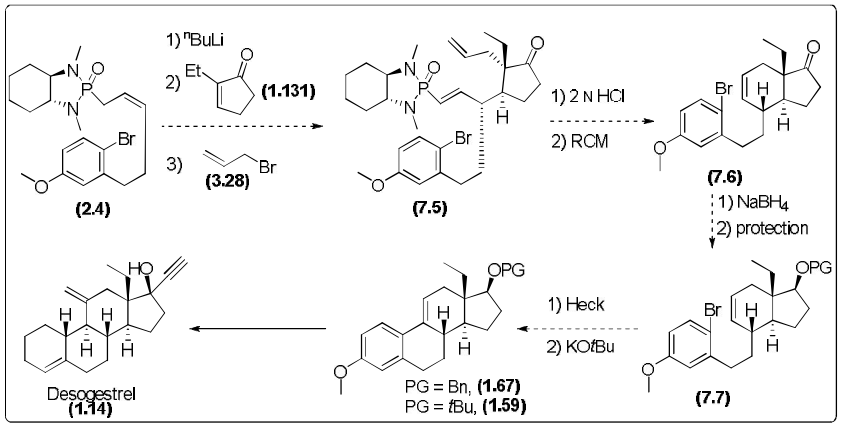
Scheme 7.1

The 1,4-γ-addition product **(7.2)** should be accessible via a diastereoselective 1,4-addition between phosphonamide **(7.1)** and ethyl-enone **(1.131)**/alkylation with iodide **(3.29)**. Taking in account the differences of reactivity observed during the 1,4-addition/alkylation step depending on the Michael acceptor and the phosphorus substrates (Chapter 3), this process would quite possibly require much optimisation: 1) Lower yields have been obtained with the ethyl-enone **(1.131)** than with the corresponding methyl-enone **(1.100)**, 2) Lower yields have been obtained with phosphonamides than with phosphonates, 3) The reaction seems to be substrate, solvent and scale dependent.

Should the synthesis of 1,4-γ-addition product **(7.3)** prove possible on large scale, the most convenient way of completing the synthesis might be through the phosphonate **(4.32)**. Conversion of the acetal to the methyl-ester has been touched upon (part 4.2.5). From a practical point of view, it seems worthwile to convert phosphonamide **(7.4)** to the corresponding phosphonate **(4.32)**, via the corresponding phosphonic acid.[231] From enantiopure phosphonate **(4.32)**, completion of the synthesis has been demonstrated in Chapters 4-5.

7.1.1.2 Via a sequential C and B-ring cyclisation

Another possible enantioselective synthesis of desogestrel would rely on the exact methodology used for the enantioselective total synthesis of estrone described in this thesis, as shown in Scheme 7.2.



Scheme 7.2

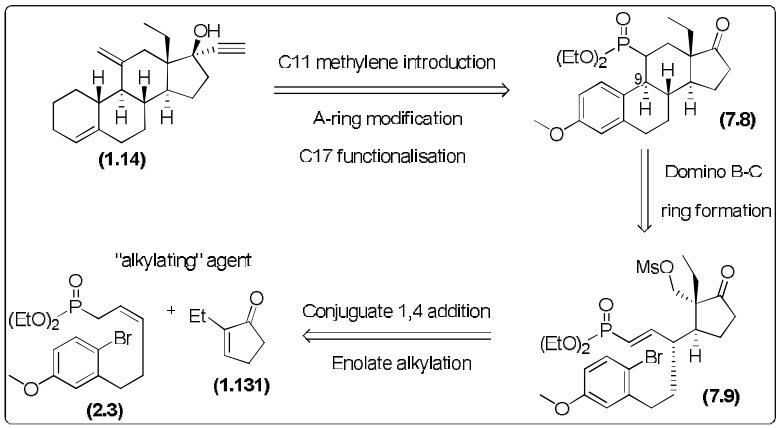
The diastereoselective 1,4-addition of phosphonamide **(2.4)** with ethyl-enone **(1.131)**/ alkylation with allyl bromide **(3.28)** would lead to the 1,4-γ-addition product **(7.5)**. The *trans*-hydrindene product **(7.6)** would be obtained by hydrolysis of the phosphonamide to the corresponding phosphonic acid, followed by RCM reaction as described in ***part 6.2.2***. Reduction of the C17-ketone with $NaBH_4$,[232] and subsequent protection of the C17-β-alcohol would give bromide **(7.7)**. Intramolecular Heck reaction, followed by Δ11-12 to Δ9-11 double bond migration with KO*t*Bu[26] (for which the C17-ketone protection seems important) would afford known steroids **(1.67)**[27] or **(1.59)**.[26] Completion of desogestrel from any of the two steroids has already been touched upon in Chapter 1.

7.2 Medium term

Although what follows could not be really classified as a primary objective, given the considerable quantities of phosphonate **(2.3)** that were still available after the completion of the racemic total synthesis of estrone, it was thought to be a better use of research-time to investigate another tandem anionic cyclisation strategy towards desogestrel.

7.2.1 Towards a new desogestrel synthesis via a domino B-C cyclisation.

So as to illustrate the versatility of our methodology towards steroid synthesis, a new strategy was considered that could eventually lead to desogestrel starting for the estrone phosphonate precursor **(2.3)** (Scheme 7.3).



Scheme 7.3

Desogestrel would be obtained from the tetracyclic phosphonate **(7.8)** which would be obtained via a domino B-C cyclisation reaction from bromide **(7.9)**. Bromine-lithium exchange of **(7.9)** with BuLi was expected to induce the intramolecular addition onto the α-β-unsaturated phosphonate, forming the B-ring (Figure 7.2). The intermediate anion would then undergo a mesylate displacement, forming the C-ring **(7.8)**. It was expected that the protons on C9 would adopt the α-position. This configuration was expected because it would be obtained through the lowest energy reactive conformation **(7.10)** (Figure 7.2).

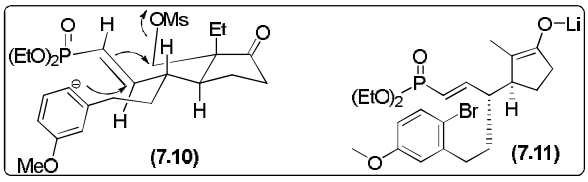


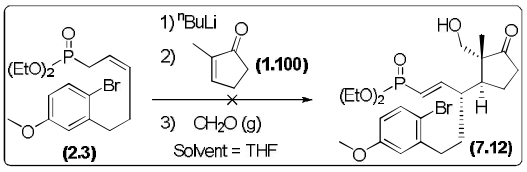
Figure 7.2

Finally, precursor **(7.9)** would be obtained via a conjuguate 1,4-addition followed by "alkylation" of the intermediate enolate starting from our estrone precursor **(2.3)**. Initial experiments were conducted using methyl-cyclopentenone **(1.100)** as it had been

demonstrated that enolate **(7.11)** (Figure 7.2) could be obtained in very high yields under our standard conditions (part 3.3.1), allowing investigations of the proper alkylating agent to use.

7.2.1.1 Investigations of direct functionalisation of enolate **(7.11)**

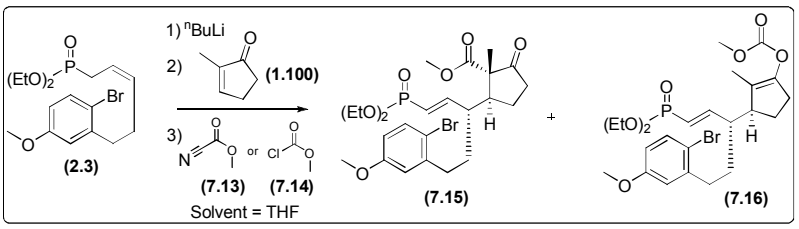
The first choice was the use of formaldehyde as alkylating agent, which would have led to the alcohol **(7.12)** via an aldol reaction (Scheme 7.4).



Scheme 7.4

The reaction was only attempted once, without the desired outcome. The use of gaseous formaldehyde[107] led to a very complex mixture of products where the desired alcohol **(7.12)** was not observed nor identified.

The use of methyl chloroformate **(7.14)** and methyl cyanoformate **(7.13)** were then considered, which would both have led to ester **(7.15)** (Scheme 7.5).



Scheme 7.5

Interestingly, reactions with **(7.13)** or **(7.14)** led to completely different results as shown in Table 7.1.

Entry	Scale of **(2.3)**	equiv of ^{n}BuLi	equiv of **(1.100)**	alkylating agent	equiv of **(7.13)** or **(7.14)**	T of alkylation	Yield of products	
							(7.15)	**(7.16)**
1	2.6 mmol	1.1	1.3	**(7.14)**	10	0 °C	0%	79%
2	2.6 mmol	1.1	1.3	**(7.14)**	5	-78 °C	0%	42%
3	2.6 mmol	1.1	1.3	**(7.13)**	2	-78 °C	Not determined	0%

Table 7.1

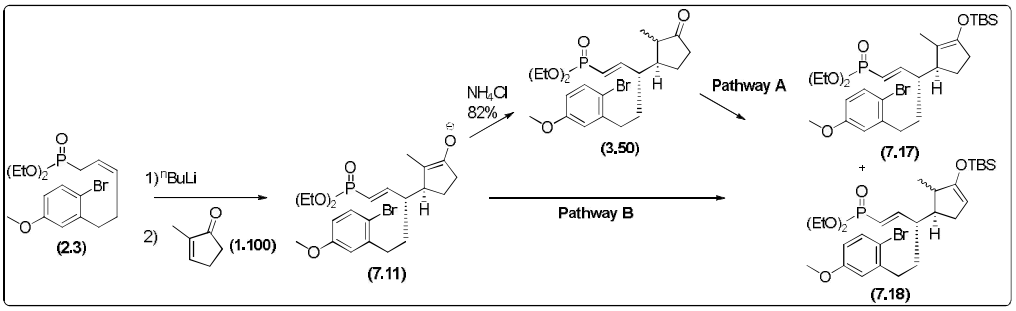
When methyl chloroformate **(7.14)** was employed (entries 1-2), no trace of desired ester **(7.15)** was observed. Instead, the undesired enolate-trapped carbonate **(7.16)** was obtained in up-to 79% when the reaction was performed at 0 °C (entry 1). The use of methyl cyanoformate **(7.13)** led to a very complex mixture of products (entry 3).

Those preliminary results suggested that many reactions would have been required in order to really investigate this reaction. Since the enolate **(7.11)** seemed relatively easily trapped, it was envisioned that the desired alcohol **(7.12)** might be accessible via a cross-aldol reaction through a silyl enol ether.

7.2.1.2 Investigations of a stepwise alkylation of enolate **(7.11)**

*7.2.1.2.1 Synthesis of the silyl enol ether **(7.17)***

As an alternative to the direct reaction of the enolate formed during the 1,4-addition reaction, attempts were made to trap the enolate **(7.11)** as a TBS enol ether **(7.17)** (Scheme 7.6, Table 7.2).



Scheme 7.6

Table 7.2

Entry	Pathway	conditions	Yield of products (%)		
			(7.17)	**(7.18)**	**(3.50)**
1	A	TBSOTf/Et_3N (3 equiv), DCM, -50 to -20 °C	0	62	ε
2	A	TBSCl/Et_3N (3 equiv), DCM, rt	0	0	98
3	A	TBSCl/Et_3N/NaI (1.5 equiv), MeCN, rt	0	0	84
4	B	TBSCl (3 equiv), 0 °C to rt	57	0	25
5	B	TBSCl/Et_3N (premixed), rt	0	0	89
6	B	TBSOTf (2 equiv), 0 °C	84	0	0

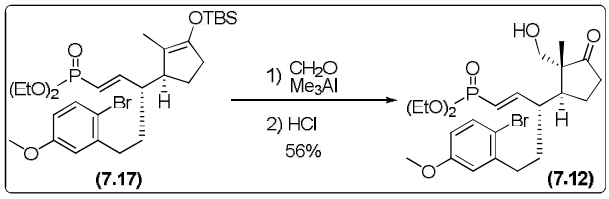
ε = not isolated

Two different pathways towards **(7.17)** were explored. Following pathway A, the 1,4-addition enolate **(7.11)** was quenched to the corresponding non-allylated product **(3.50)** in 82% yield on a 2.6 mmol scale. Protection of the C17-ketone as a silyl enol ether was expected to give the thermodynamic product **(7.17)**.[233] The use of TBSOTf/Et_3N[164] at low temperature (entry 1) exclusively led to the formation of the kinetic product **(7.18)** in 62% yield. Other attempts to favorise the thermodynamic product **(7.17)** (entries 2-3)[234] all resulted in complete recovery of the starting material **(3.50)**.

Following pathway B, the enolate was directly trapped (entries 4-6). The reaction with TBSCl was a very slow process, despite the use of 3 equiv of reagent, but at least the desired silyl enol ether was obtained in 57% yield (entry 4). Finally the use of 2 equiv TBDMSOTf (entry 6) afforded an excellent 84% yield of isolated **(7.17)**.

*7.2.1.2.2 Cross-aldol reactions: synthesis of alcohol **(7.12)***

Makaiyama and co-workers[235] have conducted significant research on cross-aldol reactions involving silyl enol ethers with carbonyl compounds activated with various metal salts. Noteworthly, they described the preparation of monomethylol compounds from silyl enol ethers and trioxane as formaldehyde source in the presence of $TiCl_4$. Despite several attempts, the desired alcohol **(7.12)** (Scheme 7.7) was not obtained under those conditions. However, **(7.12)** was synthesized following Snider and co-workers precedent as shown in Scheme 7.7.[236]

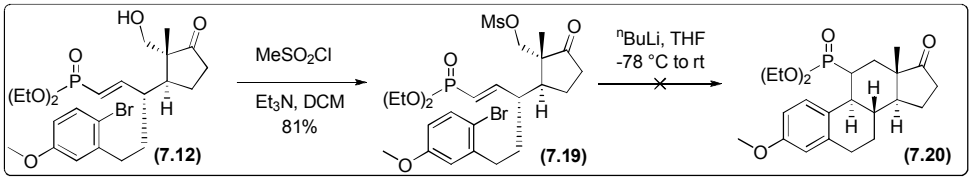


Scheme 7.7

Treatment of silyl enol ether **(7.17)** with $CH_2O.Me_3Al$ in DCM at 0 °C, followed by acid treatment of the ene-type intermediate exclusively led to alcohol **(7.12)** in medium yield. The procedure was not fully optimised, due to time-constraints and enough material was obtained towards domino B-C precursor **(7.19)**.

7.2.1.3 Attempted domino B-C reaction

With alcohol **(7.12)** in hand, the domino B-C precursor **(7.19)** was easily prepared (Scheme 7.8).

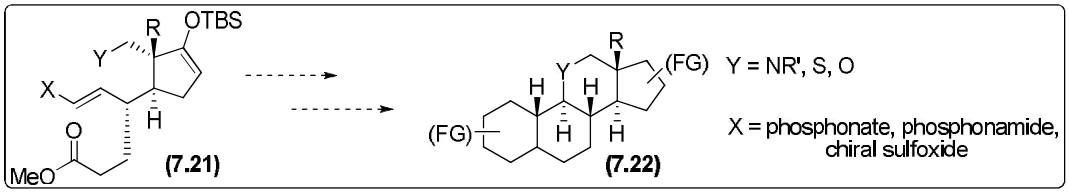


Scheme 7.8

Treatment of alcohol **(7.12)** with methanesulfonyl chloride in presence of Et_3N in DCM at 0 °C afforded the desired mesylate **(7.19)** in good yield.[237] The subsequent domino B-C reaction was however only attempted once, for project-priority reasons. Unfortunately, lithium-bromide exchange with ^{n}BuLi gave rise to a complex mixture of products. No further experiments were attempted within this strategy, as in the meantime the complete enantioselective synthesis of estrone had to be achieved.

7.3 Long term

Since this new steroid synthesis methodology, based on a D→BCD steroid skeleton construction, has been successfully employed for two structurally diverse steroids desogestrel and estrone, it could be used to make other steroids (both new and known). Simple modifications include changing the methyl/ethyl group at C13 or changing the exocyclic methylene group at C11, which are not easy transformations within existing steroid total syntheses. Also interesting, this methodology could lend itself towards the synthesis of steroids containing a heteroatom at the C11 position. To-date, all these steroids are made through hemi-syntheses via C-ring opening reactions,[238,239] but it is known that steroids with a heteroatom at C11 possess interesting biological activities. Following the proposed synthetic route (Scheme 7.9), steroids such as **(7.22)** should be accessible since for example, heteroatom conjuguate addition to α,β-unsaturated sulfoxides is known.[240,241]



Scheme 7.9

Chapter 8, Overall summary

We have demonstrated that the Hanessian 1,4-addition/alkylation can be used for the synthesis of structurally diverse steroids via a novel strategy based on prior formation of the correct C_8, C_{13} and C_{14} stereochemistry, followed by ring formation processes. The synthesis of desogestrel and estrone have been achieved using this method. Highlights of this method include:

- The development/optimization of efficient syntheses of achiral phosphonates and chiral phosphonamide 1,4-addition precursors.
- Utilization of a 1,4-addition/alkylation sequence to synthesize highly functionalized complex products with three controllable chiral centres, and identification of a few side-products.
- Optimization of the domino C-B reaction to afford cyclised products as single diastereoisomers in up to 50% yield.
- Construction of the A-ring via a seven reaction one-pot process.
- Determination of the relative stereochemistry on separate occasions by X-ray crystallographic analyses.

Areas where there is scope for improvement within this project include:

- The poor yield associated with the 1,4-addition reaction with the ethyl-cyclopentenone.
- Avoiding the formation of the side products during the domino C-B cyclisation process.
- The poor yield associated with the HWE reaction on β-keto phosphonates leading to exocyclic enones.

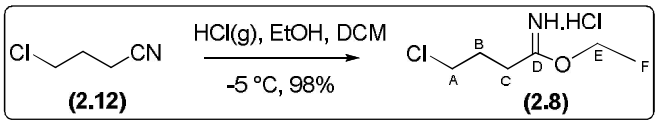
Chapter 9, Experimental

General information. 'H and ^{13}C NMR spectra were recorded on a Bruker AV300 spectrometer or Bruker AC300 or Bruker DPX400 spectrometer. 'H spectra conducted in $CDCl_3$ are referenced to $CHCl_3$ as 7.27 ppm. ^{13}C spectra conducted in $CDCl_3$ are referenced to $CHCl_3$ as 77.00 ppm. Where assignments of atoms have been made in the NMR data, this is determined by the use $^{13}C^{1}H$ correlation (HMQC) and/or $^{1}H^{1}H$ correlation (COSY) NMR experiments. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; Q, quaternary carbon centre. ^{31}P spectra were recorded on a Bruker AV300 externally referenced to 85% H_3PO_4. IR spectra were recorded on a BIORAD Golden Gate FTS 135. Optical rotations were conducted on an Optical Activity Polaar 2001. Mass spectrometry was performed using ES, EI or CI techniques. Melting points were carried out on a Gallenkamp melting point apparatus and are uncorrected. X-Ray analyses were provided at the EPSRC Crystallography Service, Southampton University. All reactions were carried out under a N_2 atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light (254 nm) as visualizing agent and $KMnO_4$, Vanillin or Anisaldehyde dyes as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. All reaction vessels were oven dried overnight or flame dried under vacuum (<1 mmHg) and cooled under N_2 prior to use. Preparative HPLC was performed using a Kontron pump KU38 with a Kontron refractive index detector 475.

Materials. THF and Et_2O were distilled from sodium/benzophenone ketyl. Toluene was distilled from sodium. MeOH and EtOH were distilled with a small amount of magnesium and I_2. DCM, MeCN, Et_3N, DIPEA and HMPA were distilled from CaH_2.

9.1 Experimental data for Chapter 2

Ethyl-4-chlorobutanimidate hydrochloride (2.8)



Into an ice cooled solution of 4-chlorobutyronitrile **(2.12)** (4.64 mL, 52 mmol, 1.0 equiv) and dry ethanol (2.70 mL, 52 mmol, 1.0 equiv) in dry DCM (50 mL) was bubbled *in situ* prepared HCl (g) until ca. 18 equiv of HCl had been absorbed. The reaction vessel was sealed and left in the fridge for 4 days. The reaction mixture was concentrated to ca. 2/3 of the original volume under vacuum and the precipitated imidate salt **(2.8)** was filtered, washed with several portions of Et_2O (5 x 20 mL) and finally dried over $CaSO_4$ in an evacuated dessicator to give the title hydrochloride as fine white crystals (8.32 g, 98%, m.p. = 99-101 °C).

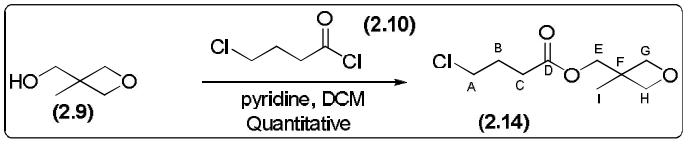
MW = 186.079 ($C_6H_{13}ONCl_2$).

^{1}H NMR (300 MHz; $CDCl_3$): δ 12.51 (1H, s, NH), 11.63 (1H, s, NH), 4.67 (2H, q, *J = 6.9 Hz,* H_E), 3.62 (2H, t, *J = 6.2 Hz*, H_A), 2.94 (2H, t, *J = 6.2 Hz*, H_C), 2.25 (2H, pentet, *J = 6.2 Hz*, H_B), 1.50 (3H, t, *J = 6.9 Hz*, H_F) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ 178.3 (Q, C_D), 71.1 (CH_2, C_E), 43.2 (CH_2, C_A), 30.8 (CH_2, C_C), 28.4 (CH_2, C_B), 13.6 (CH_3, C_F) ppm.

The NMR data correspond to the reported data.[72]

3-Methyl-3-oxetanemethyl-4-chlorobutanoate (2.14)



To an ice cooled solution of 3-hydroxymethyl-3-methyloxetane **(2.9)** (4.05 mL, 40 mmol, 1.0 equiv) and pyridine (3.88 mL, 48 mmol, 1.2 equiv) in dry DCM (20 mL) was slowly added 4-chloro-butyryl-chloride **(2.10)** (4.49 mL, 40 mmol, 1.0 equiv). After the addition, the reaction was allowed to stand at 0 °C for 1 h. The reaction mixture was droped over

crushed ice (10 g) and then extracted with DCM (3 x 20 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered and then concentrated under vacuum. This yielded **(2.14)** as a colourless oil (8.65 g, quantitative) which was found pure enough for the next step.

MW = 206.667 ($C_9H_{15}O_3Cl$).

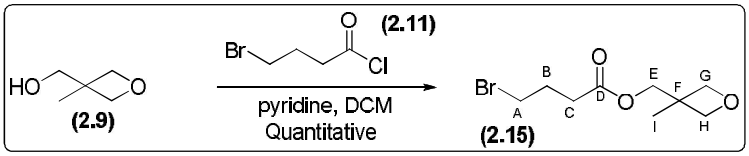
Rf = 0.53 (Petroleum ether/Acetone 60:40).

^{1}H NMR (300 MHz; $CDCl_3$): δ 4.44 (2H, d, *J = 6.2 Hz*, $H_{G/H}$), 4.31 (2H, d, *J = 6.2 Hz*, $H_{G/H}$), 4.12 (2H, s, H_E), 3.54 (2H, t, *J = 6.4 Hz*, H_A), 2.49 (2H, t, *J = 6.4 Hz*, H_C), 2.05 (2H, pentet, *J = 6.4 Hz*, H_B), 1.27 (3H, s, H_I) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ 172.4 (Q, C_D), 79(2 x CH_2, C_G+C_H), 68.5 (CH_2, C_E), 43.7 (CH_2, C_A), 38.9 (Q, C_F), 30.9 (CH_2, C_B), 27.4 (CH_2, C_C), 20.9 (CH_3, C_I) ppm.

The NMR data correspond to the literature data.[72]

3-Methyl-3-oxetanemethyl-4-bromobutanoate (2.15)



To an ice cooled solution of 3-hydroxymethyl-3-methyloxetane **(2.9)** (4.05 mL, 40 mmol, 1.0 equiv) and pyridine (3.88 mL, 48 mmol, 1.2 equiv) in dry DCM (20 mL) was slowly added 4-bromo-butyryl-chloride **(2.11)** (5.11 mL, 44 mmol, 1.1 equiv). After the addition, the reaction was allowed to stand at 0 °C for 1 h. The reaction mixture was droped over crushed ice (10 g) and then extracted with DCM (3 x 20 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered and then concentrated under vacuum. This yielded (**2.15)** as a colourless oil (10.55 g, quantitative) which was found pure enough for the next step.

MW = 251.118 ($C_9H_{15}O_3Br$).

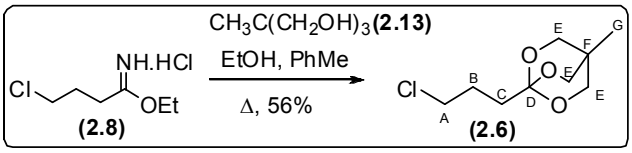
Rf = 0.55 (Petroleum ether/Acetone 60:40).

^{1}H NMR (300 MHz; $CDCl_3$): δ 4.46 (2H, d, *J = 6.0 Hz*, $H_{G/H}$), 4.34 (2H, d, *J = 6.0 Hz*, $H_{G/H}$), 4.14 (2H, s, H_E), 3.34 (2H, t, *J = 6.5 Hz*, H_A), 2.52 (2H, t, *J = 7.0 Hz*, H_C), 2.15 (2H, quintet, *J = 6.8 Hz*, H_B), 1.30 (3H, s, H_I) ppm.

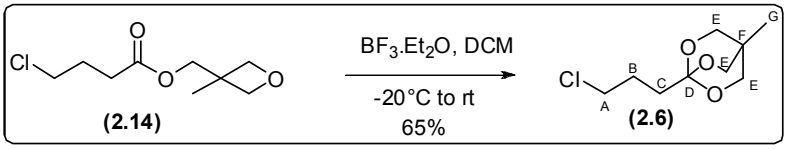
^{13}C NMR (75 MHz; $CDCl_3$): δ 172.4 (Q, C_D), 79.3 (2 x CH_2, C_G+C_H), 68.6 (CH_2, C_E), 38.9 (Q, C_F), 32.4 (CH_2, C_A), 32.2 (CH_2, C_C), 27.5 (CH_2, C_B), 21.0 (CH_3, C_I) ppm.
The NMR data correspond to the literature data.[73]

1-(3-Chloro-propyl)-4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octane (2.6)

Route 1:



Route 2:



Route 1:

To a mixture of the imidate salt **(2.8)** (5.00 g, 27 mmol, 1.0 equiv), toluene (100 mL) and 1,1,1-tris(hydroxymethyl)ethane **(2.13)** (3.23 g, 27 mmol, 1.0 equiv) was added dry ethanol (2.72 mL, 46 mmol, 1.7 equiv). The reaction mixture was refluxed for 16 h, then cooled, filtered through celite and concentrated under vacuum. Purification by column chromatography on neutralized silica (Petroleum ether/EtOAc 4:1) followed by Kugelröhr distillation yielded **(2.6)** as a colourless oil (3.10 g, 56%).

Route 2:

$BF_3.Et_2O$ (1.25 mL, 10 mmol, 0.25 equiv) was added to a cooled (-20 °C) solution of the ester **(2.14)** (8.65 g, 40 mmol, 1.0 equiv) in dry DCM (35 mL) under N_2 atmosphere. The reaction was stirred for 24 h at the same temperature and a solution of Et_3N (5.58 mL, 40 mmol, 1.0 equiv) in Et_2O (50 mL) was then added to quench the reaction. The reaction mixture was filtered and the solvent was removed under vacuum. The resulting crude was purified by column chromatography (DCM + 1% Et_3N), yielding **(2.6)** as a colourless oil which crystallised in the fridge (5.37 g, 65%).

MW = 206.666 ($C_9H_{15}O_3Cl$).

Rf = 0.48 (Petroleum ether/EtOAc 60:40).

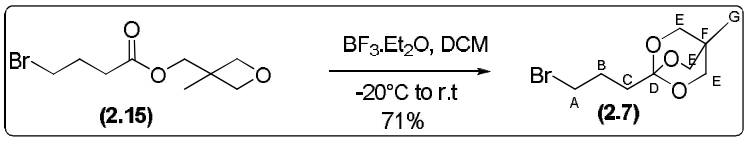
IR (neat): 2961 (w), 2932 (w), 2876 (m), 1472 (w), 1458 (w), 1446 (w), 1399 (m), 1262 (m), 1055 (s), 1101 (s), 960 (m), 948 (m), 936 (m) cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 3.87 (6H, s, H_E), 3.55 (2H, t, *J = 6.8 Hz*, H_A), 1.93-1.88 (2H, m, H_B), 1.81-1.78 (2H, m, H_C), 0.78 (3H, s, H_G) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ 108.7 (Q, C_D), 72.5 (3 x CH_2, C_E), 44.8 (CH_2, C_A), 33.8 (CH_2, $C_{B/C}$), 30.2 (Q, C_F), 26.7 (CH_2, $C_{B/C}$), 14.4 (CH_3, C_G) ppm.

The IR and NMR spectra correspond to the literature data.[72]

<u>1-(3-Bromo-propyl)-4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octane (2.7</u>)



$BF_3.Et_2O$ (1.25 mL, 10 mmol, 0.25 equiv) was added to a cooled (-20 °C) solution of the ester **(2.15)** (10.13 g, 40 mmol, 1.0 equiv) in dry DCM (35 mL) under N_2 atmosphere. The reaction was stirred for 6 h at the same temperature, then allowed to warm to room temperature for 18 h and a solution of Et_3N (5.58 mL, 40 mmol, 1.0 equiv) in Et_2O (50 mL) was then added to quench the reaction. The reaction mixture was filtered and the solvent was removed under vacuum. The resulting crude was purified by column chromatography (DCM + 1% Et_3N), yielding **(2.7)** as a colourless oil which crystallised in the fridge (7.19 g, 71%).

MW = 251.118 ($C_9H_{15}O_3Br$).

Rf = 0.46 (Petroleum ether/EtOAc 60:40).

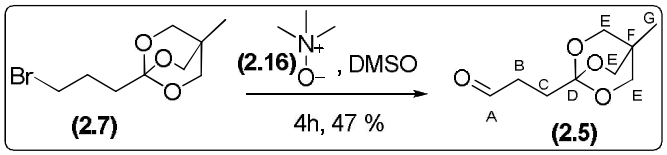
IR (neat): 2961 (w), 2932 (w), 2876 (m), 1472 (w), 1458 (w), 1446 (w), 1399 (m), 1262 (m), 1055 (s), 1101 (s), 960 (m), 948 (m), 936 (m) cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 3.87 (6H, s, H_E), 3.55 (2H, t, *J = 6.8 Hz*, H_A), 1.93-1.88 (2H, m, H_B), 1.81-1.78 (2H, m, H_C), 0.78 (3H, s, H_G) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 108.7 (Q, C_D), 72.5 (3 x CH_2, C_E), 44.8 (CH_2, C_A), 33.8 (CH_2, $C_{B/C}$), 30.2 (Q, C_F), 26.7 (CH_2, $C_{B/C}$), 14.4 (CH_3, C_G) ppm.

The IR and NMR spectra correspond to the literature data.[73]

3-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1yl)-propionaldehyde (2.5)



To a mixture of Trimethyl Amine N-Oxide (TMANO) **(2.16)** (657 mg, 8 mmol, 4.0 equiv) in dry DMSO (5 mL) was added neat bromide **(2.7)** (502 mg, 2 mmol, 1.0 equiv) at room temperature under N_2 atmosphere. The reaction mixture was stirred for 4 h and then poured into an ice cooled, half-saturated aqueous NaCl solution (10 mL) and extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude was purified by column chromatography (Petroleum ether/EtOAc 80:20 + 1% Et_3N) yielding **(2.5)** as a colourless oil crystallizing in the fridge (171 mg, 47 %).

MW = 186.205 ($C_9H_{14}O_4$).

Rf = 0.30 (Hexane/EtOAc 60:40).

IR (neat): 2959 (w), 2935 (w), 2878 (m), 1720 (s), 1473 (w), 1459 (w), 1440 (w), 1399 (m), 1354 (w), 1272 (m), 1192 (m), 1053 (s), 986 (s), 972 (s), 951 (s), 885 (m), 826 (m) cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 9.70 (1H, t, *J = 1.8 Hz*, H_A), 3.86 (6H, s, H_E), 2.51 (2H, td, J_1 *= 7.3, 1.8 Hz*, H_B), 2.02 (2H, t, *J = 7.3 Hz*, H_C), 0.78 (3H, s, H_G) ppm.

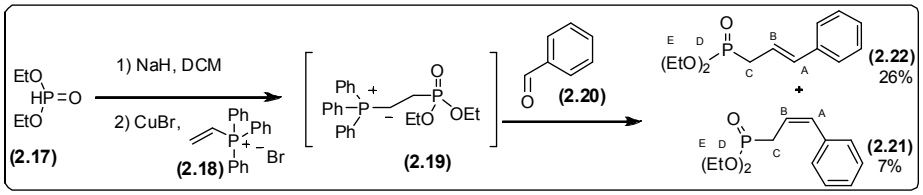
^{13}C NMR (75 MHz, $CDCl_3$): δ 202.0 (Q, C_A), 108.4 (Q, C_D), 72.5 (3 x CH_2, C_E), 38.0 (CH_2, C_B), 30.3 (Q, C_F), 29.5 (CH_2, C_C), 14.4 (CH_3, C_G) ppm.

CIMS: *m/z* (%): 187 ($(M+H)^+$, 100), 158 (24), 138 (2), 85 (42), 72 (11), 55 (12).

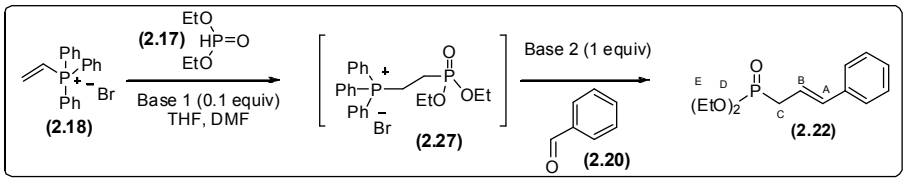
HRES$^+$MS: For $C_9H_{15}O_4$ $(M+H)^+$: calcd 187.0970, found 187.0965.

(Z)-(3-Phenyl-2-propenyl)phosphonic acid diethyl ether (2.21) and **(E)-(3-Phenyl-2-propenyl)phosphonic acid diethyl ether (2.22)**

Route 1:



Route 2:



They are known compounds,[82] but were synthesized here via two new procedures:

Route 1:

Diethyl phosphite **(2.17)** (258 µL, 2 mmol, 2.0 equiv), was added dropwise to a solution of NaH (60% dispersion in mineral oil) (56 mg, 1.4 mmol, 1.4 equiv) in dry DCM (3 mL) at 0 °C under N_2. The reaction mixture was then stirred for 1h at 0 °C and cooled to -40 °C. Then, CuBr (25 mg, 0.18 mmol, 0.18 equiv) and vinyltriphenylphosphonium bromide **(2.18)** (479 mg, 1.35 mmol, 1.35 equiv) were added and the reaction mixture was stirred for 20 min. Benzaldehyde **(2.20)** (137 µL, 1 mmol, 1.0 equiv) was added and the reaction mixture was allowed to warm to room temperature and stirred overnight. Then 5 mL of 10 % NH_4Cl solution was added followed by 5 mL of DCM. The organic layer was separated, washed with 5 mL of water and dried. Evaporation of the solvent gave a residue which was purified by column chromatography (Petroleum ether/EtOAc 70:30) to afford a colourless oil, mixture of **(2.21)** and **(2.22)**, which was further purified by preparative HPLC, yielding (*E*)-phosphonate **(2.22)** (64 mg, 26%) and (*Z*)-phosphonate **(2.21)** (17 mg, 7%) as colourless oils.

Route 2:

To a solution containing vinyltriphenylphosphonium bromide **(2.18)** (500 mg, 1.35 mmol, 1.0 equiv) and diethyl phosphite **(2.17)** (244 µL, 1.89 mmol, 1.4 equiv) in dry THF/DMF (10/1, 3 mL) was added NaH (8 mg, 0.135 mmol, 0.1 equiv) or NaHMDS (68 µL, 0.135 mmol, 0.1 equiv) and the solution was stirred at room temperature for 10 h. Then NaH (59 mg, 1.485 mmol, 1.1 equiv) or NaHMDS (743 µL, 1.485 mmol, 1.1 equiv) was added and the solution was stirred for 30 min. Then benzaldehyde **(2.20)** (137 µL, 1.35 mmol, 1.0 equiv) was added dropwise and the reaction mixture was stirred for 24 h. After evaporation of the solvent *in vacuo*, the residue was diluted with DCM (10 mL) and extracted with water (10 mL), dried over Na_2SO_4, filtered and evaporated. The resulting crude was purified by column chromatography (Petroleum ether/EtOAc 70:30) to afford **(2.22)** as the only isomer (105 mg, 31 %).

Data for (2.21):

MW = 244.267 ($C_{13}H_{19}O_3P$).

Rf = 0.39 (Petroleum ether/EtOAc 60:40).

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.40-7.20 (5H, m, phenyl), 6.56 (1H, dd, *J =13.4, 4.8 Hz*, H_A), 6.20 (1H, m, H_B), 4.28-4.02 (4H, m, H_D), 2.82 (2H, ddd, *J =22.0, 7.5, 1.3 Hz*, H_C), 1.37 (6H, t, *J = 5.7 Hz*, H_E) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ 132.7, 128.6, 128.5, 127.3, 126.2, 126.1 (5CH + 1Q, phenyl), 129.7 (CH, C_A), 104.1 (CH, C_B), 63.8 (CH_2, C_D), 28.6 (CH_2, C_C), 16.5 (CH_3, C_E) ppm.

The NMR data correspond to the literature data.[82]

Data for (2.22):

MW = 244.267 ($C_{13}H_{19}O_3P$).

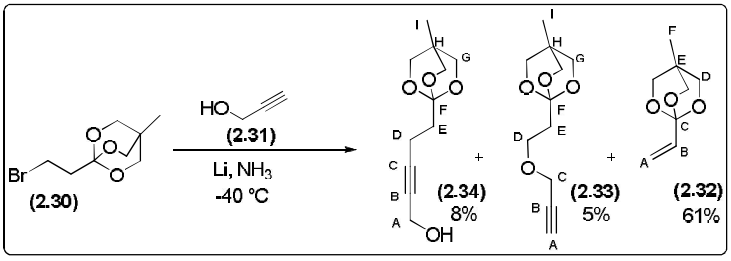
Rf = 0.38 (Petroleum ether/EtOAc 60:40).

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.40-7.20 (5H, m, phenyl), 6.55 (1H, dd, *J =16.0, 5.3 Hz*, H_A), 6.18 (1H, m, H_B), 4.30-4.05 (4H, m, H_D), 2.79 (2H, ddd, *J =22.0, 7.5, 1.3 Hz*, H_C), 1.34 (6H, t, *J = 6.3 Hz*, H_E) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ 136.7, 128.6, 128.5, 128.1, 127.5, 126.1 (5CH + 1Q, phenyl), 134.5 (CH, C_A), 118.7 (CH, C_B), 62.2 (CH_2, C_D), 31.0 (CH_2, C_C), 16.5 (CH_3, C_E) ppm.

The NMR data correspond to the literature data.[82]

5-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl)pent-2-yn-1-ol (2.34) and **4-methyl-1-(2-(prop-2-ynyloxy)ethyl)-2,6,7-trioxabicyclo[2.2.2]octane (2.33)** and **4-methyl-1-vinyl-2,6,7-trioxabicyclo[2.2.2]octane (2.32)**



Into a 500 mL, 3-neck flask equipped with a large cold finger was condensed ammonia (200 mL). An external cold bath (-78 °C) was used to aid the condensation, but throughout

the reaction temperature of this cold bath was maintained between -30 °C 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 nitrate nonahydrate (~200 mg), then lithium (394 mg, 57 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 **(2.31)** (1.57 mL, 27 mmol, 1.5 equiv) dropwise over 5 min and stirring was continued for a further 2 h. The bromide **(2.30)** (4.19 g, 17.7 mmol, 1.0 equiv) was dissolved in dry Et_2O (4 mL) and added to the reaction dropwise via cannula over 10 min. The mixture was stirred for 2 h and then dry DMSO (4 mL) was added slowly. The cold bath was removed and the ammonia was allowed to evaporate overnight (atm. pressure). Water (100 mL) was added, cautiously at first, followed by DCM (100 mL) and the biphasic mixture was vigorously stirred for 30 min. The biphasic solution was filtered through celite, washing with water and DCM (50 mL). The phases were separated and the aqueous phase was extracted with DCM (4 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (Petroleum ether/EtOAc 3:2 + 1% Et_3N) to afford **(2.34)** as a white solid (302 mg, 8%, m.p. = 87-89 °C), and **(2.34)** and **(2.32)** mixed as a yellow oil (1.96 g) which was purified by preparative HPLC to afford **(2.32)** as fine white crystals (1.69 g, 61%, m.p. = 55-57 °C) and an inseparable mixture of **(2.32)** and **(2.33)**, (265 mg, (**(2.33)**/**(2.32)** : 64/36; 5% yield of **(2.33)**).

Data for (2.32)

MW = 156.179 ($C_8H_{12}O_3$).

Rf = 0.42 (Hexane/Acetone 70:30).

IR (neat): 2966 (m), 2923 (m), 2877 (w), 1696 (s), 1632 (m), 1443 (w), 1347 (w), 1248 (m), 1001 (m), 947 (w), 940 (w), 790 (m) cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 5.82 (1H, dd, *J = 17.3, 10.5 Hz*, H_B), 5.65 (1H, dd, *J = 17.3, 1.5 Hz*, H_A), 5.31 (1H, dd, *J = 10.5, 1.5 Hz*, $H_{A'}$), 3.98 (6H, s, H_D), 0.84 (3H, s, H_F) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 133.1 (CH, C_B), 118.6 (CH_2, C_A), 105.9 (Q, C_C), 72.8 (3 x CH_2, C_D), 30.5 (Q, C_E), 14.5 (CH_3, C_F) ppm.

CIMS m/z (%): 157 ($(M+H)^+$, 100), 126 (19), 72 (3), 55 (35).

Significant data for (2.33)

MW = 212.242 ($C_{11}H_{16}O_4$).

Rf = 0.41 (Hexane/Acetone 70:30).

^{1}H NMR (300 MHz; $CDCl_3$): δ 4.13 (2H, d, *J = 2.4 Hz*, H_C), 3.88 (6H, s, H_G), 3.70-3.63 (2H, m, H_D), 2.41 (1H, t, *J = 2.4 Hz*, H_A), 2.11-1.93 (2H, m, H_E), 0.79 (3H, s, H_I) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 108.0 (Q, C_F), 79.9 (CH, C_A), 74.1 (Q, C_B), 72.5 (3 x CH_2, C_G), 65.3 (CH_2, C_C), 58.1 (CH_2, C_D), 36.5 (CH_2, C_E), 30.2 (Q, C_H), 14.4 (CH_3, C_I) ppm.

Data for (2.34)

MW = 212.242 ($C_{11}H_{16}O_4$).

Rf = 0.25 (Hexane/Acetone 70:30).

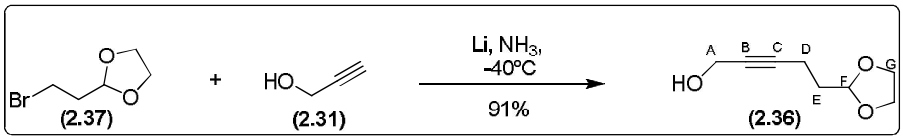
IR (neat): 3412 (br, m), 2935 (w), 2979 (m), 2360 (s), 2341 (s), 1472 (w), 1447 (w), 1399 (m), 1379 (w), 1355 (m), 1302 (m), 1251 (m), 1188 (w), 1137 (w), 1042 (s), 989 (s), 973 (s), 938 (m), 858 (s) cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 4.22-4.17 (2H, m, H_A), 3.88 (6H, s, H_G), 2.35 (2H, tt, *J = 8.4, 2.2 Hz*, H_D), 1.93-1.88 (2H, m, H_E), 1.71 (1H, br, OH), 0.79 (3H, s, H_I) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 108.05 (Q, C_F), 85.8 (Q, $C_{B/C}$), 78.1 (Q, $C_{B/C}$), 72.5 (3 x CH_2, C_G), 51.3 (CH_2, C_A), 35.8 (CH_2, C_E), 30.2 (Q, C_H), 14.4 (CH_3, C_I), 13.2 (CH_2, C_D) ppm.

CIMS m/z (%): 213 ($(M+H)^+$, 100), 212 (56), 195 (80), 183 (27), 181 (20), 164 (26), 149 (10), 144 (21), 127 (42), 125 (30), 123 (14), 122 (12).

5-(1,3-Dioxolan-2-yl)pent-2-yn-1-ol (2.36):



This is a known compound[87] but was synthesised here via a new procedure devised by R.Clarkson.[21]

Into a 2 L, 3-neck flask equipped with a large cold finger was condensed ammonia (1 L). An external cold bath (-78 °C) was used to aid the condensation, but throughout the reaction temperature of this cold bath was maintained between -30 °C 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 nitrate nonahydrate (~200 mg), then lithium (2.38 g, 342 mmol, 3.2 equiv) was added portion wise over 30 min. The grey solution was stirred for 1 h at -40 °C. To this solution was added propargyl alcohol **(2.31)** (9.48 mL, 161 mmol, 1.5 equiv) dropwise over 15 min and stirring was continued for a further 2 h. The bromide **(2.37)** (12.81 mL, 107 mmol, 1.0 equiv) was dissolved in dry Et_2O (20 mL) and added to the reaction dropwise via cannula over 10 min. The mixture was stirred for 2 h and then dry DMSO (20 mL) was added slowly. The cold bath was removed and the ammonia was allowed to evaporate overnight (atm. pressure). Water (340 mL) was added, cautiously at first, followed by DCM (200 mL) and the biphasic mixture was vigorously stirred for 30 min. The biphasic solution was filtered through celite, washing with water and DCM (200 mL). The phases were separated and the aqueous phase was extracted with DCM (4 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (Hexane/Acetone 70:30) to afford **(2.36)** as a yellow oil (15.25 g, 91%). Alternatively, the compound could also be distilled under reduced pressure (P = 1.5 mmHg, T = 106-108 °C).

MW = 156.184 ($C_8H_{12}O_3$).

Rf = 0.27 (Hexane/Acetone 70:30).

IR (neat): 3405 (br, m), 2961 (w), 2884 (m), 1433 (w), 1412 (m), 1362 (w), 1223 (w), 1133 (s), 1070 (m), 1011 (s), 943 (m), 893 (m) cm^{-1}.

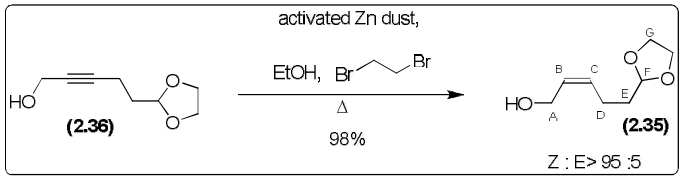
^{1}H NMR (300 MHz; $CDCl_3$): δ 4.90 (1H, t, *J = 4.7 Hz*, H_F), 4.15 (2H, t, *J = 2.2 Hz*, H_A), 3.95-3.75 (4H, m, H_G), 2.73 (1H, br s, OH), 2.29 (2H, tt, *J = 7.5, 2.1 Hz*, H_D), 1.81 (2H, td, *J = 7.5, 4.7 Hz*, H_E) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 103.1 (CH, C_F), 85.1 (Q, $C_{B/C}$), 78.7 (Q, $C_{B/C}$), 64.9 (2 x CH_2, C_G), 51.1 (CH_2, C_A), 32.7 (CH_2, C_E), 13.5 (CH_2, C_D) ppm.

CIMS: *m/z* (%): 174 ($(M+NH_4)^+$, 10), 157 ($(M+H)^+$, 11), 139 (41), 112 (5), 95 (3), 86 (4), 73 (100), 45 (5).

The IR and NMR spectra correspond to the reported data.[87]

5-(1,3)-Dioxolan-2-yl-2-(Z)-penten-1-ol (2.35)



Pre-Activation of Zinc dust: The Zn dust (20 g) was activated by stirring it in a 0.1 M HCl solution (300 mL) for ca. 15 min, until the gas evolution stopped. The grey solid was filtered off, washed with plenty of water then plenty of EtOH and dried under high vacuum for at least 4 hours.

Procedure: Into a 50 mL 2-neck flask equipped with a condenser was added activated zinc (8.37 g, 128 mmol, 4.0 equiv) followed by dry EtOH (30 mL) and 1,2-dibromoethane (970 μL, 11.2 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 that 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 **(2.36)** (5.00 g, 32 mmol, 1.0 equiv) was added neat, washing through with EtOH (5 mL). The reaction was stirred overnight (~14 h), cooled and filtered through celite, washing with DCM. The solvents were evaporated *in vacuo* and then DCM was added (100 mL). This solution was poured onto a room temperature, stirred solution of 7.5% (w/w) aqueous KOH and stirred for 5 min. The mixture was filtered through celite, washing with 50 mL DCM. The phases were separated and the aqueous phase extracted with DCM (4 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated. This yielded **(2.35)** as a light yellow oil (4.92 g, 98%). (E/Z ratio = 4/96 based on ^{1}H NMR).

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

Rf = 0.30 (Hexane/EtOAc 50:50).

IR (neat): 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 (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 x 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 and NMR data correspond to the reported data.[88]

5-(1,3)-Dioxolan-2-yl)-2-(E)-penten-1-ol (2.42)

This is a known compound[98] but no experimental procedure or analytical data has been reported apart from R.Clarkson.[21]

A solution of the alkyne **(2.36)** (5.02 g, 32 mmol, 1.0 equiv) in THF (20 mL) was added dropwise to a pre-cooled suspension of LAH (7.31 g, 192 mmol, 6.0 equiv) in THF (100 mL). The dark grey suspension was refluxed for 100 min, and then cooled to 0 °C. The reaction was quenched by dropwise addition of 0.5 M H_2SO_4 (10 mL). Dry THF (100 mL) was added to prevent the mixture from solidifying. Water (50 mL) was added slowly until a white suspension was obtained. This was filtered, the solids were washed with EtOAc (100 mL), and the filtrate was evaporated *in vacuo*. The residue was partitionned between EtOAc/water (100 mL/50 mL), separated, and the aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (Hexane/EtOAc 40:60). This yielded **(2.42)** as a pale yellow oil (3.76 g, 75%).

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

Rf = 0.30 (Hexane/EtOAc 50:50).

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

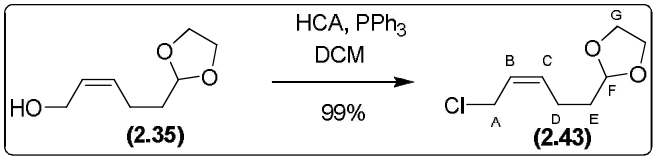
^{1}H NMR (300 MHz; $CDCl_3$): δ 5.76-5.62 (2H, m, H_B + H_C), 4.88 (1H, t, *J = 4.9 Hz*, H_F), 4.09 (2H, d, *J = 6.8 Hz*, H_A), 4.00-3.83 (4H, m, H_G), 2.19 (2H, q, *J = 7.6 Hz*, H_D), 1.75 (2H, td, *J = 7.6, 4.9 Hz*, H_E), 1.60 (1H, s, OH) ppm.

^{13}C NMR (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 x 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.

2-(5-Chloropent-3-(Z)-enyl)-[1,3]-dioxolane (2.43)



The allylic alcohol **(2.35)** (9.27 g, 58.6 mmol, 1.0 equiv) was dissolved in DCM (50 mL) and added via cannula to a solution of triphenyphosphine (16.91 g, 64.5 mmol, 1.1 equiv) in DCM (50 mL). Upon complete dissolution, the mixture was cooled to 0 °C with stirring. To this mixture was added via cannula a solution of hexachloroacetone (HCA) (9.76 mL, 64.5 mmol, 1.1 equiv) in DCM (30 mL) over 2 min. The cold bath was then removed and the reaction was stirred for 10 min. The solvent was evaporated and the resulting crude (solid + oil) was taken in 150 mL of hot hexane and stirred for 5 min. After filtration, the resulting triphenylphosphine oxide was washed with 200 mL of hot hexane. The filtrate was concentrated and the resulting crude oil was distilled under reduced pressure (P = 0.96 mmHg, T= 72-76 °C) to afford **(2.43)** as a colourless oil (10.22 g, 99%).

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

Rf = 0.30 (Hexane/EtOAc 90:10).

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

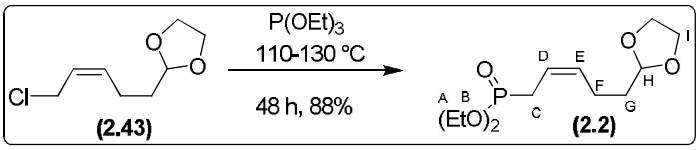
^{1}H NMR (300 MHz; $CDCl_3$): δ 5.68-5.63 (2H, m, H_B + H_C), 4.88 (1H, t, *J = 4.9 Hz*, H_F), 4.12 (2H, d, *J = 6.8 Hz*, H_A), 4.00-3.83 (4H, m, H_G), 2.28 (2H, m, H_D), 1.76 (2H, dt, *J = 7.6, 4.9 Hz*, H_E) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ 134.1 (CH, $C_{B/C}$), 126.0 (CH, $C_{B/C}$), 103.6 (CH, C_F), 64.9 (2 x CH_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).

HREIMS For $C_8H_{13}O_2{}^{35}Cl$ $(M-H)^+$: calcd 175.0526, found 175.0520.

Diethyl-[5-(1,3-dioxolan-2-yl)-2-(Z)-pentenyl]phosphonate (2.2)



The allylic chloride **(2.43)** (10.22 g, 57.9 mmol, 1.0 equiv) and triethyl phosphite (19.84 mL, 116 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 (0.55 mmHg). Excess triethyl phosphite was collected at 46 to 50 °C (colourless oil) and the phosphonate **(2.2)** was collected at 140 to 146 °C as a colourless oil (14.17 g, 88%).

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

Rf = 0.17 (Hexane/Acetone 80:20).

IR (neat): 2974 (m), 2884 (w), 1394 (w), 1393 (w), 1252 (m), 1139 (m), 1053 (s), 1025 (s), 927 (s) cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 5.58 (1H, m, H_E), 5.39 (1H, m, H_D), 4.80 (1H, t, *J = 4.6 Hz*, H_H), 4.09-3.99 (4H, m, H_B), 3.92-3.76 (4H, m, H_I), 2.56 (2H, dd, *J = 22.2, 7.7 Hz*, H_C), 2.20 (2H, m, H_F), 1.71-1.66 (2H, m, H_G), 1.26 (6H, t, *J = 7.1 Hz*, H_A) ppm.

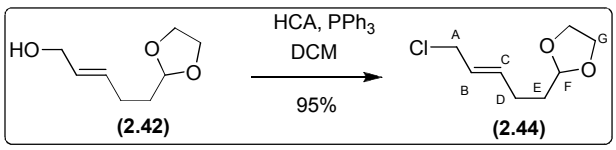
^{13}C NMR (75 MHz; $CDCl_3$): δ 133.2 (d, *J = 14.3 Hz*, CH, C_E), 118.4 (d, *J = 11.0 Hz,* CH, C_D), 103.7 (CH, C_H), 64.7 (2 x CH_2, C_I), 61.6 (d, *J = 6.6 Hz*, 2 x CH_2, 2 x C_B), 33.2 (d, *J = 2.6 Hz*, CH_2, C_G), 25.6 (d, *J = 140.0 Hz*, CH_2, C_C), 21.7 (d, *J = 2.1 Hz*, CH_2, C_F), 16.3 (d, *J = 6.0 Hz*, 2 x CH_3, 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 $C_{12}H_{23}O_5PNa$ $(M+Na)^+$: calcd 301.1175, found 301.1171.

2-(5-Chloropent-3-(E)-enyl)-[1,3]-dioxolane (2.44)



The allylic alcohol **(2.42)** (3.76 g, 23.8 mmol, 1.0 equiv) was dissolved in DCM (20 mL) and added via cannula to a solution of triphenyphosphine (6.87 g, 26.2 mmol, 1.1 equiv) in DCM (50 mL). Upon complete dissolution, the mixture was cooled to 0 °C with stirring. To this mixture was added via cannula a solution of hexachloroacetone (3.97 mL, 26.2 mmol, 1.1 equiv) in DCM (30 mL) over 2 min. The cold bath was then removed and the reaction was stirred for 10 min. The solvent was evaporated and the resulting crude (solid + oil) was taken in 150 mL of hot hexane and stirred for 5 min. After filtration, the resulting triphenylphosphine oxide was washed with 100 mL of hot hexane. The filtrate was concentrated and the resulting crude oil was distilled under reduced pressure (P= 0.53 mmHg, T= 68-70 °C) to afford **(2.44)** as a colourless oil (3.99 g, 95%).

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

Rf = 0.30 (Hexane/EtOAc 90:10).

IR (neat): 2957 (s), 2889 (s), 1668 (w), 1441 (m), 1408 (m), 1252 (m), 1134 (s), 1039 (s), 963 (s), 902 (m) cm^{-1}.

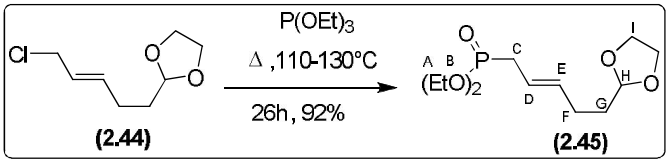
^{1}H NMR (300 MHz; $CDCl_3$): δ 5.81 (1H, dt, *J = 15.1, 6.7 Hz*, H_C), 5.65 (1H, dtt, *J = 15.1, 7.0, 1.4 Hz,* H_B), 4.88 (1H, t, *J = 4.6 Hz*, H_F), 4.03 (2H, dd, *J = 7.0, 0.8 Hz*, H_A), 3.99-3.81 (4H, m, H_G), 2.32-2.24 (2H, m, H_D), 1.80-1.72 (2H, m, H_E) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ 135.0 (CH, C_C), 126.3 (CH, C_B), 103.8 (CH, C_F), 64.9 (CH_2, 2 x 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 $C_8H_{13}O_2{}^{35}Cl$ $(M-H)^+$: calcd 175.0526, found 175.0524.

Diethyl-[5-(1,3-dioxolan-2-yl)-2-(E)-pentenyl]phosphonate (2.45)



The allylic chloride **(2.44)** (3.95 g, 22.4 mmol, 1.0 equiv) and triethyl phosphite (7.68 mL, 44.8 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 (0.76 mmHg). Excess triethyl phosphite was collected at 46 to 50 °C (colourless oil) and the phosphonate **(2.45)** was collected at 136 to 142 °C as a colourless oil (5.64 g, 92%).

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

Rf = 0.44 (Hexane/Acetone 60:40).

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

^{1}H NMR (300 MHz; $CDCl_3$): δ 5.64 (1H, m, H_E), 5.45 (1H, m, H_D), 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.

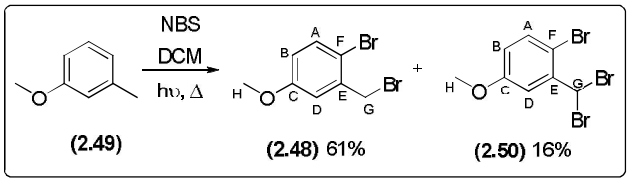
^{13}C NMR (75 MHz; $CDCl_3$): δ 134.9 (d, *J = 14.6 Hz*, CH, C_E), 119.1 (d, *J = 11.2 Hz,* CH, C_D), 103.9 (CH, C_H), 64.8 (CH_2, 2 x C_I), 61.8 (d, *J = 6.8 Hz*, CH_2, 2 x C_B), 33.3 (d, *J = 3.3 Hz*, CH_2, C_G), 30.4 (d, *J = 139.7 Hz*, CH_2, C_C), 27.0 (d, *J = 2.2 Hz*, CH_2, C_F), 16.4 (d, *J = 6.0 Hz*, 2 x CH_3, C_A) ppm.

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

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

HRES$^+$MS: For $C_{12}H_{23}O_5P$ $(M+Na)^+$: calcd 301.1175, found 301.1176.

<u>1-bromo-2-(bromomethyl)-4-methoxybenzene (2.48)</u> and **<u>1-bromo-2-(dibromomethyl)-4-methoxybenzene (2.50)</u>**



A solution of 3-methylanisole **(2.49)** (12.4 mL, 98 mmol, 1.0 equiv) and N-bromosuccinimide (37.2 g, 209 mmol, 2.0 equiv) in DCM (500 mL) was refluxed for 4 h while exposed to light from 2 x 100 W incandescent bulbs placed within 2 cm of the reaction vessel. The mixture was then cooled to room temperature, diluted with DCM (400 mL) and washed with water (2 x 400 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was recrystallized with Hexanes (250 mL) to give dibromide **(2.48)** as a light yellow solid (16.8 g, 61%). Tribromide **(2.50)** was isolated by column chromatography of the residue, eluting (Hexane/Acetone) = (99:1) as a colourless liquid (5.61 g, 16%).

Data for (2.48)

Mw = 279.957 ($C_8H_8OBr_2$).

m.p. = 85-89 °C.

Rf = 0.18 (neat Hexane).

IR (film): 3080, 3012, 2941, 1571, 1476, 1283, 1250, 1145, 1051, 1013, 925, 876 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.45 (1H, d, *J = 9.0 Hz*, H_A), 6.99 (1H, d, *J = 3.0 Hz*, H_D), 6.74 (1H, dd, *J = 9.0, 3.0 Hz*, H_B), 4.56 (2H, s, H_G), 3.80 (3H, s, H_H) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 159.6 (Q, C_C), 138.2 (Q, C_F), 134.3 (CH, C_A), 116.9 (CH, C_D), 116.5 (CH, C_B), 115.1 (Q, C_E), 56.0 (CH_3, C_H), 33.9 (CH_2, C_G) ppm.

CIMS: m/z (%): 281/279 ($M+H^+$, 10), 202/200 (100), 186/184 (14), 159/157 (20), 122 (72).

The experimental data correspond well with the literature data.[104]

Data for (2.50)

Mw = 358.853 ($C_8H_7OBr_3$).

Rf = 0.18 (neat Hexane).

IR (film): 3023 (w), 2935 (w), 2835 (w), 1592 (m), 1468 (s), 1279 (s), 1241 (m), 1015 (s), 806 (m), 714 (m) cm^{-1}.

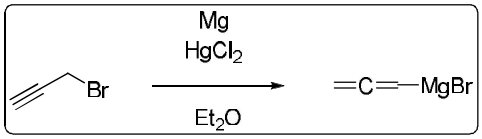
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.54 (1H, d, *J = 8.8 Hz*, H_A), 7.39 (1H, d, *J = 2.9 Hz*, H_D), 7.03 (1H, s, H_G), 6.76 (1H, dd, *J = 8.8, 2.9 Hz*, H_B), 3.86 (3H, s, H_H) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 159.7 (Q, C_C), 141.3 (Q, C_F), 133.4 (CH, C_A), 118.0 (CH, C_D), 116.1 (CH, C_B), 110.1 (Q, C_E), 55.8 (CH_3, C_H), 40.1 (CH_2, C_G) ppm.

CIMS: m/z (%): 364/362/360/358 ($M+H^+$, 6), 282/280/278 (54), 215/213 (26), 202/200 (70), 122 (100).

HRMS (CI) for $C_8H_7O^{79}Br_3$: calcd 355.80470, found 355.80477.

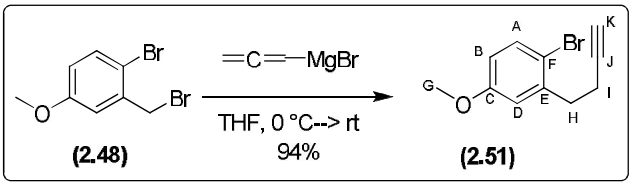
Preparation of allenyl magnesium bromide.[105,106]



A 500 mL three-necked flask was charged with magnesium turnings (5.30 g, 218.1 mmol) and $HgCl_2$ (88 mg, 0.32 mmol), dried by heating under high vacuum and flushed with

nitrogen. A solution of 0.99 mL (10.1 mmol) of propargylbromide (80% wt in toluene) in 20 mL of Et_2O was added. When Et_2O began to reflux, the mixture was cooled to 5 °C under stirring and a solution of propargylbromide (15.6 mL, 173 mmol) in Et_2O (90 mL) was added at such a rate to keep the temperature under 10 °C. The mixture was stirred at room temperature for 1 h until it became dark green.

1-bromo-2-(but-3-ynyl)-4-methoxybenzene (2.51)



(2.48) **(2.51)**

To a stirred solution of dibromide **(2.48**) (17.0 g, 63 mmol, 1.0 equiv) in dry THF (50 mL) cooled to 0 °C, allenylmagnesium bromide (132 mmol in 80 mL of Et_2O, 2.1 equiv) was slowly added at such a rate to keep the temperature under 10 °C. The mixture was allowed to warm to room temperature and stirred for 4 h. After cooling to 0 °C, the mixture was quenched with water (150 mL), 1 M HCl (150 mL) and extracted with Et_2O (2 x 200 mL). After evaporation of the solvent, the crude product was purified by distillation (b.p. = 96-98 °C/ 0.3 mmHg) to afford alkyne **(2.51)** (13.6 g, 94%) as a yellow liquid.

Mw = 239.108 ($C_{11}H_{11}OBr$).

Rf = 0.53 (Hexane/Acetone 90:10).

IR (film): 3295 (m), 2936 (w), 2835 (w), 2117 (w), 1595 (m), 1573 (m), 1472 (s), 1241 (s) cm^{-1}.

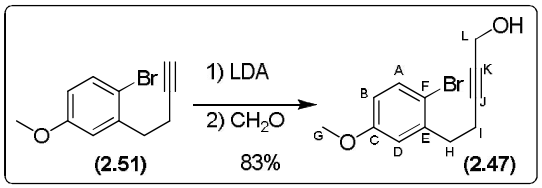
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.43 (1H, d, *J = 8.8 Hz*, H_A), 6.86 (1H, d, *J = 3.1 Hz*, H_D), 6.67 (1H, dd, *J = 8.8, 3.1 Hz*, H_B), 3.80 (3H, s, H_G), 2.93 (2H, t, *J = 7.5 Hz*, H_H), 2.52 (2H, td, *J = 7.5, 2.6 Hz*, H_I), 2.01 (1H, t, *J = 2.6 Hz*, H_K) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 159.0 (Q, C_C), 140.5 (Q, C_F), 133.4 (CH, C_A), 116.6 (CH, C_D), 114.8 (Q, C_E), 113.8 (CH, C_B), 83.5 (Q, C_J), 69.3 (CH, C_K), 55.6 (CH_3, C_G), 35.5 (CH_2, C_H), 18.9 (CH_2, C_I) ppm.

EIMS m/z (%): 240/238 (M^+, 11), 201/199 (27), 159 (100), 144 (21), 128 (11).

Elemental analysis calcd for $C_{11}H_{11}OBr$: C, 55.26; H, 4.64. Found: C, 54.90; H, 4.69.

5-(2-bromo-5-methoxyphenyl)pent-2-yn-1-ol (2.47)



To a solution of alkyne **(2.51)** (13.62 g, 56.9 mmol, 1.0 equiv) in THF (50 mL), cooled to 0 °C, was slowly added a solution of LDA (34.15 mL, 68.3 mmol, 2 M solution in THF, 1.2 equiv). The resulting black solution was stirred at 0 °C for 1 h. Gaseous formaldehyde, obtained from 12 g of paraformaldehyde by heating to approximately 400 °C with a heatgun, was added by mean of a nitrogen stream, and the orange mixture obtained was stirred at room temperature for 30 min. After cooling to 0 °C, the reaction was quenched with NH_4Cl/H_2O 1:1 (100 mL) and extracted with DCM (3 x 100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (Hexane/Acetone 70:30) gave alcohol **(2.47)** (12.71 g, 83%) as a yellow oil which solidified upon storage in the fridge.

Mw = 269.134 ($C_{12}H_{13}O_2Br$).

m.p. = 50-52 °C.

Rf = 0.36 (Hexane/Acetone 70:30).

IR (film): 3302 (m), 3219 (m), 2910 (w), 2832 (w), 1596 (m), 1571 (m), 1468 (s), 1248 (s) cm^{-1}.

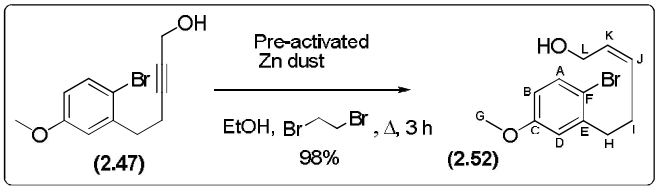
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41 (1H, d, *J = 8.6 Hz*, H_A), 6.82 (1H, d, *J = 3.1 Hz*, H_D), 6.66 (1H, dd, *J = 8.6, 3.1 Hz*, H_B), 4.25 (2H, dt, *J = 5.5, 2.2 Hz*, H_L), 3.80 (3H, s, H_G), 2.91 (2H, t, *J = 7.5 Hz*, H_H), 2.52 (2H, tt, *J = 7.5, 2.2 Hz*, H_I), 1.58 (br s, OH) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 159.0 (Q, C_C), 140.7 (Q, C_F), 133.4 (CH, C_A), 116.6 (CH, C_D), 114.8 (Q, C_E), 113.8 (CH, C_B), 85.4 (Q, C_J), 79.5 (Q, C_K), 55.6 (CH_3, C_G), 51.5 (CH_2, C_L), 35.6 (CH_2, C_H), 19.3 (CH_2, C_I) ppm.

CIMS m/z (%): 288/286 ($M+NH_4^+$, 26), 270/268 ($M+H^+$, 20), 240/238 (8), 201/200 (40), 189 (100).

Elemental analysis calcd for $C_{12}H_{13}O_2Br$: C, 53.55; H, 4.87. Found: C, 53.51; H, 4.90.

(Z)-5-(2-bromo-5-methoxyphenyl)pent-2-en-1-ol (2.52)



Pre-Activation of Zinc dust: The Zn dust (20 g) was activated by stirring it in a 0.1 M HCl solution (300 mL) for ca. 15 min, until the gas evolution stopped. The grey solid was filtered off, washed with plenty of water then plenty of EtOH and dried under high vacuum for at least 4 hours.

Procedure: Into a 250 mL 3-neck flask equipped with a condenser was added activated zinc (14.14 g, 216 mmol, 4.0 equiv) followed by dry EtOH (50 mL) and 1,2-dibromoethane (1.63 mL, 18.9 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), a solution of the alkyne **(2.47)** (14.54 g, 54 mmol, 1.0 equiv) in 60 mL dry EtOH was added. The reaction was refluxed for 3 h, cooled and filtered through celite, washing with DCM. The solvents were evaporated *in vacuo* and then DCM was added (100 mL) followed by water (100 mL). The phases were separated and the aqueous phase extracted with DCM (4 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated. This yielded **(2.52)** as a light yellow oil (14.35 g, 98%).

Mw = 271.150 ($C_{12}H_{15}O_2Br$).

Rf = 0.34 (Hexane/Acetone 70:30).

IR (film): 3314 (m, br), 2935 (m), 1594 (m), 1572 (m), 1469 (s), 1240 (s), 1016 (s) cm^{-1}.

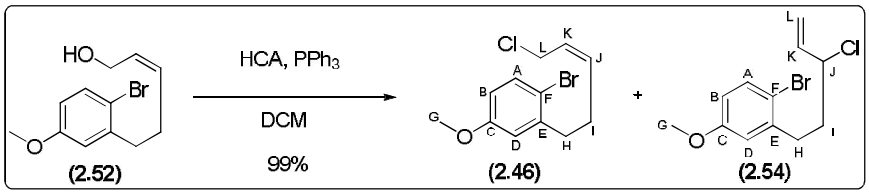
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.40 (1H, d, *J = 8.7 Hz*, H_A), 6.74 (1H, d, *J = 3.0 Hz*, H_D), 6.62 (1H, dd, *J = 8.7, 3.0 Hz*, H_B), 5.74-5.48 (2H, m, H_K + H_J), 4.09 (2H, d, *J = 5.4 Hz*, H_L), 3.76 (3H, s, H_G), 2.74 (2H, t, *J = 7.6 Hz*, H_H), 2.39 (2H, dd, *J = 14.9, 6.5 Hz*, H_I), 1.88 (1H, br s, OH) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 158.9 (Q, C_C), 141.8 (Q, C_F), 133.5 (CH, C_A), 131.2 (CH, C_K), 129.8 (CH, C_J), 116.6 (CH, C_D), 115.0 (Q, C_E), 113.3 (CH, C_B), 58.6 (CH_2, C_L), 55.6 (CH_3, C_G), 36.4 (CH_2, C_H), 27.7 (CH_2, C_I) ppm.

CIMS m/z (%): 290/288 (M+ NH_4^+, 2), 272/270 ($M+H^+$, 13), 201/200 (50), 191 (21), 147 (100).

Elemental analysis calcd for $C_{12}H_{15}O_2Br$: C, 53.16; H, 5.58. Found: C, 53.24; H, 5.68.

(Z)-1-bromo-2-(5-chloropent-3-enyl)-4-methoxybenzene (2.46) and **1-bromo-2-(4-chlorohex-5-enyl)-4-methoxybenzene (2.54)**



The allylic alcohol **(2.52)** (14.35 g, 53 mmol, 1.0 equiv) was dissolved in DCM (100 mL) and added via cannula to a solution of triphenyphosphine (15.71 g, 60 mmol, 1.1 equiv) in DCM (50 mL). Upon complete dissolution, the mixture was cooled to 0 °C with stirring. To this mixture was added via cannula a solution of hexachloroacetone (9.00 mL, 60 mmol, 1.1 equiv) in DCM (100 mL) over 15 min. The cold bath was then removed and the reaction was stirred for 10 min. The solvent was evaporated and the resulting crude (solid + oil) was taken in 150 mL of hot hexane and stirred for 5 min. After filtration, the resulting triphenylphosphine oxide was washed with 200 mL of hot hexane. The filtrate was concentrated and the resulting crude oil was purified by column chromatography (Hexane/Acetone 90:10) to afford **(2.46)** as a colourless oil (15.09 g, 99%).

When purification by distillation was attempted instead of column chromatography, an inseparable mixture of **(2.46/2.54)** (70/30) was obtained in 94% yield (b.p. = 126-130 °C/ 0.2 mmHg).

Data for (2.46)

Mw = 289.596 ($C_{12}H_{14}OBrCl$).

Rf = 0.47 (Hexane/Acetone 90:10).

IR (film): 2935 (m), 2836 (w), 1594 (m), 1572 (m), 1470 (s), 1240 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41 (1H, d, *J = 8.6 Hz*, H_A), 6.77 (1H, d, *J = 3.1 Hz*, H_D), 6.64 (1H, dd, *J = 8.6, 3.1 Hz*, H_B), 5.75-5.62 (2H, m, H_K + H_J), 4.14 (2H, d, *J = 6.8 Hz*, H_L), 3.80 (3H, s, H_G), 2.78 (2H, t, *J = 7.8 Hz*, H_H), 2.48-2.43 (2H, m, H_I) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 159.0 (Q, C_C), 141.5 (Q, C_F), 133.6 (CH, C_A), 133.5 (CH, C_K), 126.5 (CH, C_J), 116.5 (CH, C_D), 114.1 (Q, C_E), 113.4 (CH, C_B), 55.6 (CH_3, C_G), 39.5 (CH_2, C_L), 36.2 (CH_2, C_H), 27.5 (CH_2, C_I) ppm.

CIMS m/z (%): 290/288 ($M+H^+$, 6), 254 (13), 201/200 (55), 175 (100).

Elemental analysis calcd for $C_{12}H_{14}OBrCl$: C, 49.77; H, 4.87. Found: C, 49.72; H, 4.88.

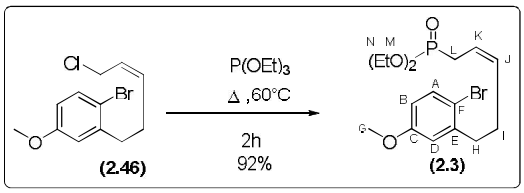
Significant data for (2.54)

Mw = 289.596 ($C_{12}H_{14}OBrCl$).

Rf = 0.47 (Hexane/Acetone 90:10).

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.41 (1H, d, *J = 8.6 Hz*, H_A), 6.81 (1H, d, *J = 3.0 Hz*, H_D), 6.64 (1H, dd, *J = 8.6, 3.1 Hz*, H_B), 5.96 (1H, ddd, *J = 17.0, 10.1, 8.0 Hz*, H_K), 5.32 (1H, td, *J = 17.0, 0.8 Hz*, H_L), 5.20 (1H, d, *J = 10.1 Hz*, $H_{L'}$), 4.37 (1H, m, H_J), 3.80 (3H, s, H_G), 2.95-2.83 (2H, m, H_H), 2.12 (1H, m, H_I) ppm.

(Z)-diethyl 5-(2-bromo-5-methoxyphenyl)pent-2-enylphosphonate (2.3)



The allylic chloride **(2.46)** (14.22 g, 49.1 mmol, 1.0 equiv) and triethylphosphite (16.85 mL, 98.2 mmol, 2.0 equiv) were combined followed by the addition of NaI (7.36 g, 49.1 mmol, 1.0 equiv). The mixture was heated at 60 °C for 2 h. The mixture was cooled, diluted with DCM (100 mL), filtered through celite and concentrated *in vacuo*. The resulting crude was subjected to distillation to remove the excess of triethylphosphite (P = 0.7 mmHg, b.p. = 46-50°C). The resulting residue was purified by column chromatography (Hexane/Acetone 60:40) yielding phosphonate **(2.3)** as a light yellow oil (17.62 g, 92%).

Mw = 391.237 ($C_{16}H_{24}O_4BrP$).

Rf = 0.38 (Hexane/Acetone 65:35).

IR (film): 2980 (s), 2934 (s), 2906 (s), 1594 (s), 1571 (s), 1472 (m), 1240 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41 (1H, d, *J = 8.8 Hz*, H_A), 6.77 (1H, d, *J = 2.9 Hz*, H_D), 6.64 (1H, dd, *J = 8.8, 2.9 Hz*, H_B), 5.68 (1H, m, H_K), 5.49 (1H, m, H_J), 4.22-3.98 (4H, m, H_M), 3.80 (3H, s, H_G), 2.76 (2H, t, *J = 8.1 Hz*, H_H), 2.58 (2H, dd, *J = 21.3, 7.3 Hz*, H_L), 2.43-2.35 (2H, m, H_I), 1.31 (6H, t, *J = 7.0 Hz*, H_N) ppm.

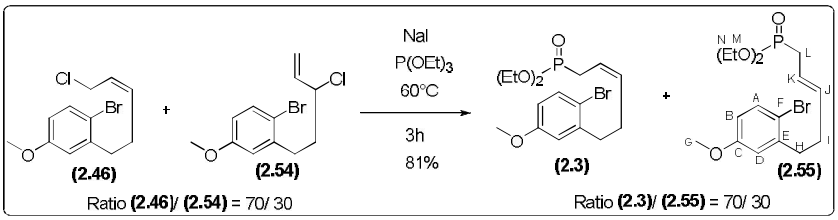
^{13}C NMR (100 MHz; $CDCl_3$): δ 159.0 (Q, C_C), 141.9 (Q, C_F), 133.4 (CH, C_A), 133.0 (CH, d, *J = 13.1 Hz*, C_K), 119.1 (CH, d, *J = 11.3 Hz*, C_J), 116.4 (CH, C_D), 114.9 (Q, C_E), 113.3 (CH, C_B), 62.0 (2 x CH_2, d, *J = 6.8 Hz*, C_M), 55.6 (CH_3, C_G), 36.1 (CH_2, C_I), 27.6 (CH_2, C_H), 25.9 (CH_2, d, *J = 140.2 Hz*, C_L), 16.6 (2 x CH_3, d, *J = 5.6 Hz*, C_N) ppm.

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

CIMS m/z (%): 393/391 ($M+H^+$, 16), 313/311 (3), 202/200 (13), 175 (18), 161 (57).

Elemental analysis calcd for $C_{16}H_{24}O_4BrP$: C, 49.12; H, 6.18; P, 7.92. Found: C, 48.80; H, 6.35; P, 7.87.

(E)-diethyl 5-(2-bromo-5-methoxyphenyl)pent-2-enylphosphonate (2.55)



Following the same procedure described for the synthesis of *Z*-allylic phosphonate **(2.3)** above, a mixture of allylic chlorides (**2.46/2.54** = 70/30) (11.17 g, 38.6 mmol) afforded an inseparable mixture of allylic phosphonates (**2.3/2.55** = 70/30) (11.99 g , 81%).

Significant data for (2.55)

Mw = 391.237 ($C_{16}H_{24}O_4BrP$).

Rf = 0.38 (Hexane/Acetone 65:35).

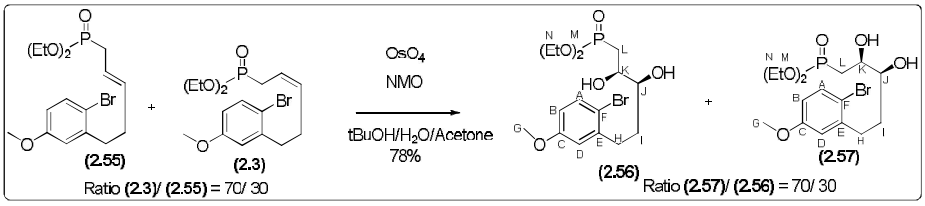
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.40 (1H, d, *J = 8.7 Hz*, H_A), 6.76 (1H, d, *J = 4.4 Hz*, H_D), 6.64 (1H, m, H_B), 5.68 (1H, m, H_K), 5.49 (1H, m, H_J), 4.22-3.98 (4H, m, H_M), 3.80 (3H, s, H_G), 2.76 (2H, t, *J = 8.1 Hz*, H_H), 2.63-2.53 (2H, m, H_L), 2.43-2.35 (2H, m, H_I), 1.31 (6H, t, *J = 7.0 Hz*, H_N) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 159.0 (Q, C_C), 141.8 (Q, C_F), 134.6 (CH, d, *J = 14.4 Hz*, C_K), 133.2 (CH, C_A), 119.6 (CH, d, *J = 11.0 Hz*, C_J), 116.4 (CH, C_D), 114.9 (Q, C_E), 113.3

(CH, C_B), 62.0 (2 x CH_2, d, *J = 6.8 Hz*, C_M), 55.6 (CH_3, C_G), 36.2 (CH_2, C_I), 32.7 (CH_2, C_H), 30.5 (CH_2, d, *J = 140.0 Hz*, C_L), 16.6 (2 x CH_3, d, *J = 5.6 Hz*, C_N) ppm.

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

Diethyl-(2R,3S)-5-(2-bromo-5-methoxyphenyl)-2,3-dihydroxypentylphosphonate (2.56) and **Diethyl-(2S,3S)-5-(2-bromo-5-methoxyphenyl)-2,3-dihydroxypentylphosphonate (2.57)**



To a mixture of NMO.$2H_2O$ (0.329 g, 2.82 mmol, 1.1 equiv), 10 mL of water, 5 mL of acetone and osmium tetroxide (7.5 mg, 0.026 mmol, 0.01 equiv) in 2 mL *t*BuOH was added the mixture of phosphonates **(2.55**, **2.3)** (1.02 g, 2.56 mmol, 1.0 equiv). The reaction was complete after stirring overnight at room temperature under nitrogen. Water was added (10 mL), then DCM (20 mL). After separation of the two phases, the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (DCM/MeOH 95:5) to afford inseparable diols **(2.56)** and **(2.57)** (0.847 g, 78%). Ratio **(2.57)**/**(2.56)** = 70/30, determined by ^{31}P NMR.

Mw = 424.065 ($C_{16}H_{26}BrO_6P$).

Rf = 0.32 (DCM/MeOH 95:5).

IR (neat): 3378 (br, w), 2983 (w), 2906 (w), 1462 (w), 1238 (m), 1086 (m), 1026 (s), 1011 (s), 969 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): ***Characteristic peaks*** δ 7.34 (1H, d, *J = 8.7 Hz*, H_A), 6.79 (1H, d, *J = 3.0 Hz*, H_D), 6.57 (1H, dd, *J = 8.7, 3.0 Hz*, H_B), 3.72 (3H, s, H_G), 1.28 (3H, t, *J = 7.1 Hz*, H_N), 1.28 (3H, t, *J = 7.1 Hz*, $H_{N'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): **For (2.57)** δ 158.8 (Q, C_C), 142.1 (Q, C_F), 133.0 (CH, C_A), 116.0 (CH, C_D), 114.6 (Q, C_E), 113.1 (CH, C_B), 73.5 (d, *J = 15.5 Hz*, CH, C_K), 69.5 (d, *J = 5.6 Hz*, CH, C_J), 61.9 (d, *J = 6.4 Hz*, CH_2, C_M), 61.8 (d, *J = 6.7 Hz*, CH_2, $C_{M'}$), 55.2

(CH_3, C_G), 32.7 (CH_2), 32.1 (CH_2), 27.5 (d, *J = 140.8 Hz*, CH_2, C_L), 16.2 (d, *J = 5.8 Hz*, CH_3, C_N), 16.2 (d, *J = 6.0 Hz*, CH_3, $C_{N'}$) ppm.

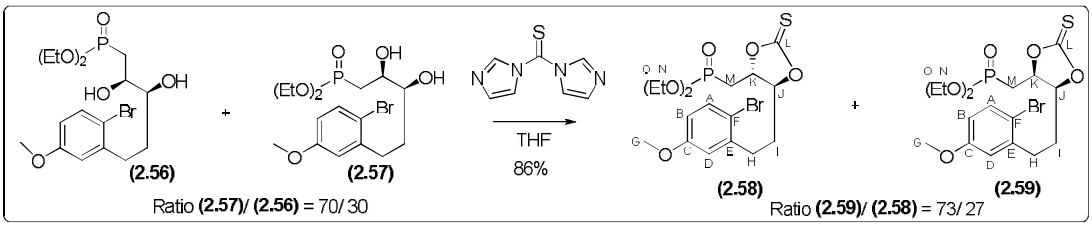
For (2.56) δ 158.8 (Q, C_C), 142.2 (Q, C_F), 133.0 (CH, C_A), 116.0 (CH, C_D), 114.6 (Q, C_E), 113.1 (CH, C_B), 73.6 (d, *J = 15.4 Hz*, CH, C_K), 68.9 (d, *J = 5.0 Hz*, CH, C_J), 61.9 (d, *J = 6.4 Hz*, CH_2, C_M), 61.8 (d, *J = 6.7 Hz*, CH_2, $C_{M'}$), 55.2 (CH_3, C_G), 33.2 (CH_2), 32.5 (CH_2), 30.1 (d, *J = 139.7 Hz*, CH_2, C_L), 16.2 (d, *J = 5.8 Hz*, CH_3, C_N), 16.2 (d, *J = 6.0 Hz*, CH_3, $C_{N'}$) ppm

^{31}P NMR (121 MHz; $CDCl_3$): **For (2.57)** δ 32.56 ppm, **For (2.56)** δ 31.46 ppm.

ES$^+$MS m/z (%): 875/873/871 (1:2:1, $(2M+Na)^+$, 100), 449/447 (1:1, $(M+Na)^+$, 58), 427/425 (1:1, $(M+H)^+$, 38).

HRES$^+$MS For $C_{16}H_{26}O_6P^{79}BrNa$ $(M+Na)^+$: calcd 447.0543, found 447.0552.

Diethyl-((4R,5S)-5-(2-bromo-5-methoxyphenethyl)-2-thioxo-1,3-dioxolan-4-yl)methylphosphonate (2.58) and **Diethyl-((4S,5S)-5-(2-bromo-5-methoxyphenethyl)-2-thioxo-1,3-dioxolan-4-yl)methylphosphonate (2.59).**



A THF (5 mL) solution of diols **(2.56)** and **(2.57)** (0.417 g, 0.98 mmol, 1.0 equiv) was added at room temperature to a THF (5 mL) solution of 1,1-thiocarbonyldiimidazole (0.175 g, 0.98 mmol, 1.0 equiv). The reaction mixture was stirred for 4 days at room temperature until completion. DCM (10 mL) was added, followed by HCl 1M (10 mL). After separation of the two phases, the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 70:30) to afford *trans*-isothiocarbonate **(2.58)** (0.110 g, 24%) and *cis*-isothiocarbonate **(2.59)** (0.285 g, 62%) as light yellow oils.

Data for (2.58)

Mw = 467.312 ($C_{17}H_{24}O_6PSBr$).

Rf = 0.43 (Hexane/Acetone 60:40).

IR (neat): 2980 (w), 1572 (w), 1474 (m), 1277 (s), 1240 (s), 1160 (m), 1015 (s), 950 (br s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41 (1H, d, *J = 8.8 Hz*, H_A), 6.89 (1H, d, *J = 3.0 Hz*, H_D), 6.66 (1H, dd, *J = 8.8, 3.0 Hz*, H_B), 4.90-4.72 (2H, m, H_J + H_K), 4.23-4.00 (4H, m, H_N), 3.77 (3H, s, H_G), 2.95 (1H, ddd, *J = 14.5, 10.0, 5.0 Hz*, H_H), 2.81 (1H, ddd, *J = 13.7, 9.7, 6.8 Hz*, $H_{H'}$), 2.39 (1H, ddd, *J = 19.9, 15.1, 4.5 Hz*, H_M), 2.28-1.97 (3H, m, $H_{M'}$ + H_I), 1.32 (3H, t, *J = 7.1 Hz*, H_O), 1.31 (3H, t, *J = 7.1 Hz*, $H_{O'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 190.3 (CH, C_L), 159.1 (Q, C_C), 139.9 (Q, C_F), 133.5 (CH, C_A), 116.2 (CH, C_D), 114.4 (Q, C_E), 114.0 (CH, C_B), 86.0 (CH, d, *J = 4.8 Hz*, C_K), 81.2 (CH, C_J), 62.6 (CH_2, d, *J = 6.5 Hz*, C_N), 62.4 (CH_2, d, *J = 6.5 Hz*, $C_{N'}$), 55.5 (CH_3, C_G), 33.2 (CH_2, C_H), 31.4 (CH_2, C_I), 30.6 (CH_2, d, *J = 139.6 Hz*, C_M), 16.4 (CH_3, d, *J = 5.2 Hz*, C_O), 16.3 (CH_3, d, *J = 5.3 Hz*, $C_{O'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 22.82 ppm.

ES$^+$MS m/z (%): 491/489 (1:1, $(M+Na)^+$, 53), 469/467 (1:1, $(M+H)^+$, 23).

HRES$^+$MS For $C_{17}H_{24}O_6PS^{79}BrNa$ $(M+Na)^+$: calcd 489.0112, found 489.0108.

<u>Data for (2.59)</u>

Mw = 467.312 ($C_{17}H_{24}O_6PSBr$).

Rf = 0.37 (Hexane/Acetone 60:40).

IR (neat): 2980 (w), 1803 (w), 1572 (w), 1473 (m), 1278 (s), 1239 (s), 1160 (m), 1017 (s), 963 (br s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.39 (1H, d, *J = 8.8 Hz*, H_A), 6.79 (1H, d, *J = 3.0 Hz*, H_D), 6.65 (1H, dd, *J = 8.8, 3.0 Hz*, H_B), 5.18 (1H, p, *J = 7.3 Hz*, H_J), 4.89 (1H, ddd, *J = 10.5, 7.2, 3.0 Hz*, H_K), 4.20-4.01 (4H, m, H_N), 3.76 (3H, s, H_G), 3.00 (1H, ddd, *J = 13.9, 9.3, 4.8 Hz*, H_H), 2.80 (1H, ddd, *J = 13.7, 8.7, 7.6 Hz*, $H_{H'}$), 2.30 (1H, ddd, *J = 19.5, 15.3, 7.3 Hz*, H_M), 2.21-1.88 (3H, m, $H_{M'}$ + H_I), 1.30 (3H, t, *J = 7.1 Hz*, H_O), 1.29 (3H, t, *J = 7.1 Hz*, $H_{O'}$) ppm.

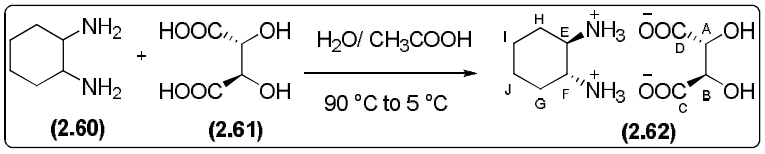
^{13}C NMR (100 MHz; $CDCl_3$): δ 190.1 (CH, C_L), 159.0 (Q, C_C), 139.8 (Q, C_F), 133.5 (CH, C_A), 116.3 (CH, C_D), 114.4 (Q, C_E), 114.0 (CH, C_B), 83.1 (CH, d, *J = 8.5 Hz*, C_K), 79.0 (CH, C_J), 62.6 (CH_2, d, *J = 6.5 Hz*, C_N), 62.3 (CH_2, d, *J = 6.4 Hz*, $C_{N'}$), 55.4 (CH_3, C_G), 31.9 (CH_2, C_H), 28.6 (CH_2, C_I), 25.9 (CH_2, d, *J = 142.7 Hz*, C_M), 16.3 (CH_3, d, *J = 4.4 Hz*, C_O), 16.2 (CH_3, d, *J = 4.3 Hz*, $C_{O'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 23.18 ppm.

ES$^+$MS m/z (%): 491/489 (1:1, $(M+Na)^+$, 56), 469/467 (1:1, $(M+H)^+$, 16).

HRES$^+$MS For $C_{17}H_{24}O_6PS^{79}BrNa$ $(M+Na)^+$: calcd 489.0112, found 489.0114.

Resolution of *cis/trans*-1,2-diaminocyclohexane (2.60)[114]



(2.60) (2.61) (2.62)

A 250 mL three-necked flask equipped with an overhead stirrer and a thermometer, was charged with L-(+)-tartaric acid **(2.61)** (30.0 g, 198 mmol, 1.0 equiv) and distilled water (80 mL). The mixture was stirred at room temperature until complete dissolution occurred. A mixture of commercially available *cis/trans*-1,2-diaminocyclohexane **(2.60)** (48.1 mL, 388 mmol, 2.0 equiv) was added at such a rate that the temperature reached 70 °C. Glacial acetic acid (20.0 mL, 35 mmol, 0.18 equiv) was added at such a rate the temperature reached 90 °C. The slurry was stirred for 2 h, then cooled to 0 °C for 2 h. The precipitate was filtered, washed with cooled (5 °C) water (20 mL) and rinsed with cooled (5 °C) MeOH (5 x 20 mL). The solid was dried under reduced pressure overnight to afford enantiopure **(2.62)** (34.3 g, 129 mmol) as a white solid.

Mw = 264.276 ($C_{10}H_{20}O_6N_2$).

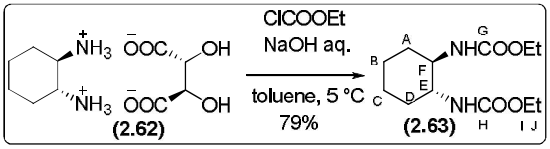
IR (film): 2913 (w), 2857 (w), 1581 (m), 1562 (m), 1397 (s), 1379 (s), 1308 (s), 1136 (m), 1054 (s) cm^{-1}.

^{1}H NMR (400 MHz; D_2O): δ 4.38 (2H, s, H_A+H_B), 3.41 (2H, m, H_E+H_F), 2.24-2.15 (2H, m, $H_{G/H}$), 1.90-1.82 (2H, m, $H_{G/H}$), 1.65-1.45 (2H, m, $H_{I/J}$), 1.45-1.32 (2H, m, $H_{I/J}$) ppm.

^{13}C NMR (100 MHz; D_2O): δ 178.5 (2 x Q, C_{D+C}), 73.9 (2 x CH, C_{A+B}), 52.2 (2 x CH, C_{E+F}), 29.4 (2 x CH_2, C_{H+G}), 22.8 (2 x CH_2, C_{I+J}) ppm.

The NMR data correspond well with literature data.[114]

Diethyl (1R,2R)-cyclohexane-1,2-diyldicarbamate (2.63)



(2.62) (2.63)

A 500 mL three-necked flask equipped with an overhead stirrer and a thermometer was charged with the diammonium salt **(2.62)** (32.0 g, 120 mmol, 1.0 equiv), toluene (320 mL) and cooled to 0 °C. Ethyl chloroformate (25.2 mL, 260 mmol, 2.2 equiv) and aqueous sodium hydroxide (20.2 g, 500 mmol in 26 mL of water, 4.2 equiv) were simultaneously added at such a rate to keep the temperature below 10 °C. The mixture was stirred for 3 h at room temperature and the precipitated salt was filtered-off, dissolved in DCM (250 mL) and washed with water (100 mL). The toluene phase was concentrated *in vacuo*, and the residue added to the DCM solution. The crude product was recrystallized from DCM/Hexane (5/1) to afford carbamate **(2.63)** as a white solid (24.4 g, 79%).

Mw = 258.314 ($C_{12}H_{22}O_4N_2$).

m.p. = 165-169 °C.

IR (film): 3320 (w), 2933 (w), 1680 (m), 1540 (m), 1240 (s), 1068 (s), 1046 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 4.99 (2H, 2 x NH), 4.09 (4H, q, *J = 7.2 Hz*, H_I), 3.39-3.36 (2H, m, H_{E+F}), 2.05 (2H, d, *J = 12.1 Hz*, $H_{A/D}$), 1.80-1.70 (2H, m, $H_{A/D}$), 1.20 (6H, t, *J = 7.2 Hz*, H_J), 1.33-1.10 (4H, m, H_{B+C}) ppm.

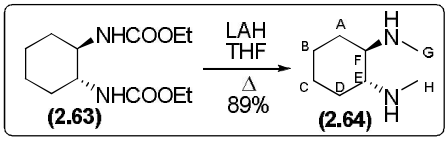
^{13}C NMR (100 MHz; $CDCl_3$): δ 157.2 (2 x Q, C_{G+H}), 60.9 (2 x CH_2, C_I), 55.5 (2 x CH, C_{E+F}), 33.0 (2 x CH_2, C_{A+D}), 24.9 (2 x CH_2, C_{B+C}), 14.7 (2 x CH_3, C_J) ppm.

ES$^+$MS m/z (%): 259 ($M+H^+$, 15).

$[\alpha]_D$ = +44.8 ° (c 1.06, $CHCl_3$).

The experimental data correspond well to the reported data.[112]

(1R,2R)-N,N-dimethylcyclohexane-1,2-diamine (2.64)



(2.63) (2.64)

To a freshly prepared 1 M solution of LAH in THF (100 mL, 100 mmol, 4.0 equiv), cooled to 0 °C, was added dicarbamate **(2.63)** (6.21 g, 25.0 mmol, 1.0 equiv). The mixture was stirred 1 h at 0 °C, 1 h at room temperature and finally refluxed for 2 h. After cooling to 0 °C, water (2.5 mL), NaOH 4 M (2.5 mL) and water (10 mL) were sequentially added to the reaction mixture and stirring was continued for 1 h at room temperature. The thus formed white precipitate was filtered and rinsed with hot THF (2 x 50 mL). After evaporation of

the THF, the residue was diluted with NaOH 4 M (50 mL) and extraction achieved with DCM (3 x 40 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford pure diamine **(2.64)** (2.94 g, 89%).

Mw = 142.242 ($C_8H_{18}N_2$).

IR (film): 3300 (w), 2850 (w), 1500 (m), 1440 (s), 1140 (s), 1100 (s), 830 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 2.36 (6H, s, H_{G+H}), 2.12-2.03 (2H, m, H_{F+E}), 2.02-1.96 (2H, m, H_{A+D}), 1.74-1.67 (2H, m, H_{A+D}), 1.64 (2H, br s, NH), 1.25-1.115 (2H, m, $H_{B/C}$), 1.02-0.81 (2H, m, $H_{B/C}$) ppm.

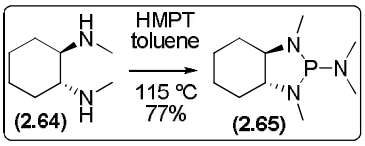
^{13}C NMR (100 MHz; $CDCl_3$): δ 63.1 (2 x CH, C_{F+E}), 33.6 (2 x CH_3, C_{G+H}), 30.7 (2 x CH_2, C_{A+D}), 25.1 (2 x CH_2, C_{B+C}) ppm.

ES$^+$MS m/z (%): 143 ($M+H^+$, 34).

$[\alpha]_D$ = -148.0° (c 0.77, $CHCl_3$).

The experimental data correspond well to the reported data.[112]

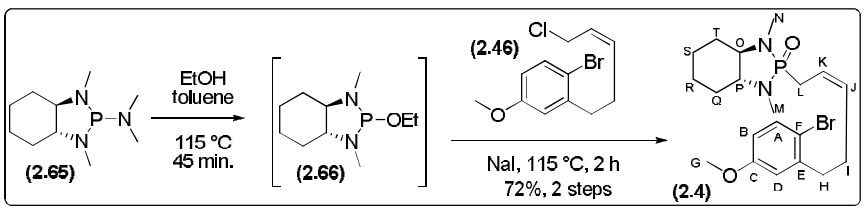
The phospholidine (2.65)[112,115]



A solution of diaminocyclohexane **(2.64)** (2.94 g, 20.7 mmol, 1.0 equiv) and HMPT (4.36 mL, 24.0 mmol, 1.2 equiv) in toluene (20 mL) was heated to 115 °C for 16 h under nitrogen. After cooling to room temperature, the solvent was evaporated and the residue distilled with Kugelröhr (135-139 °C, 0.35 mmHg) to afford phospholidine **(2.65)** as a colourless oil (3.43 g, 77%). The phospholidine **(2.65)** was dissolved in 80 mL of toluene and stored as a 0.2 M solution at room temperature under nitrogen.

Data for **(2.65)** are unavailable due to the unstability of the compound.

The Z-allylic phosphonamide (2.4)



A 0.2 M solution of phospholidine **(2.65)** (48.4 mL, 9.69 mmol, 1.0 equiv) in toluene was refluxed for 45 min at 115 °C, with dry EtOH (0.66 mL, 11.14 mmol, 1.15 equiv) under nitrogen. After cooling to room temperature, the supposed 0.2 M solution of phospholane **(2.66)** (49.6 mL, 9.69 mmol, 1.0 equiv) in toluene was added to a mixture of allylic chloride **(2.46)** (1.81 g, 6.25 mmol, 0.75 equiv) and NaI (0.94 g, 6.25 mmol, 0.75 equiv) at room temperature. The mixture was stirred for 2 h at 110 °C. Once cooled, the solvent was evaporated and the residue was purified by column chromatography (EtOAc, then EtOAc/MeOH 95:5) to afford phosphonamide **(2.4)** as a yellow sticky oil (2.32 g, 72% over 2 steps).

Mw = 441.342 ($C_{20}H_{30}O_2BrPN_2$).

Rf = 0.40 (EtOAc/MeOH 94:6).

IR (film): 2938 (m), 2869 (w), 1584 (w), 1481 (m), 1250 (s), 1218 (s), 1170 (s), 1019 (s), 814 (m), 755 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.40 (1H, d, *J = 8.7 Hz*, H_A), 6.75 (1H, d, *J = 3.0 Hz*, H_D), 6.63 (1H, dd, *J = 8.7, 3.1 Hz*, H_B), 5.60 (1H, m, H_K), 5.45 (1H, m, H_J), 3.78 (3H, s, H_G), 2.77-2.35 (8H, m), 2.56 (3H, d, *J = 0.9 Hz*, $H_{M/N}$), 2.52 (3H, d, *J = 2.1 Hz*, $H_{M/N}$), 2.04-1.93 (2H, m), 1.81 (2H, d, *J = 8.9 Hz*), 1.39-0.99 (4H, m, H_{S+R}) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 158.9 (Q, C_C), 141.8 (Q, C_F), 133.2 (CH, C_A), 131.5 (CH, d, *J = 13.0 Hz*, C_K), 120.7 (CH, d, *J = 9.7 Hz*, C_J), 116.3 (CH, C_D), 114.8 (Q, C_E), 113.1 (CH, C_B), 64.4 (CH, d, *J = 4.5 Hz*, $C_{O/P}$), 64.4 (CH, d, *J = 6.6 Hz*, $C_{O/P}$), 55.4 (CH_3, C_G), 36.1 (CH_2, d, *J = 2.3 Hz*), 29.8 (CH_3, $C_{M/N}$), 28.6 (CH_2, d, *J = 9.9 Hz*), 28.2 (CH_3, d, *J = 4.7 Hz*, $C_{M/N}$), 28.1 (CH_2, d, *J = 7.5 Hz*), 27.6 (CH_2, d, *J = 1.8 Hz*), 26.7 (CH_2, d, *J = 110.1 Hz*, C_L), 24.3 (CH_2, $C_{S/R}$), 24.2 (CH_2, $C_{S/R}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 42.13 ppm

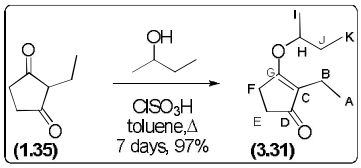
ES$^+$MS m/z (%): 481/479 (1:1, ($M+K^+$, 20)).

HRES$^+$MS For $C_{20}H_{31}N_2O_2P^{79}Br$ $(M+H)^+$: calcd 441.1301, found 441.1313.

$[\alpha]_D$ = -17.7 ° (c 0.96, acetone).

9.2 Experimental data for Chapter 3

3-sec-Butoxy-2-ethylcyclopent-2-enone (3.31)



This compound has been previously synthesized by Organon N.V, but no procedure or analytical data has been published:

2-Ethyl-1,3-cyclopentanedione **(1.35)** (20.06 g, 159 mmol, 1.0 equiv), *sec*-butyl alcohol (102 mL, 1113 mmol, 7.0 equiv), $ClSO_3H$ (0.63 mL, 9.5 mmol, 0.06 equiv) and toluene (272 mL) were refluxed for 7 days, separating water from the reaction mixture in a Dean-Stark trap. The reaction was then cooled and the excess solvent was evaporated under reduced pressure. The crude product was purified by vacuum distillation (94-96 °C/0.4 mmHg). This yielded **(3.31)** as a light yellow oil (27.42 g, 97%).

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

Rf = 0.50 (Petroleum ether/Acetone 60:40).

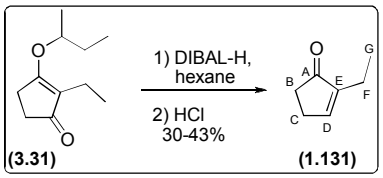
IR (neat): 2968 (s), 2933 (m), 2877 (w), 1684 (s), 1616 (s), 1462 (m), 1376 (s), 1343 (s), 1312 (s), 1266 (s), 1233 (m), 1120 (s), 990 (m), 877(m) cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 4.37 (1H, sextet, *J = 6.2 Hz*, H_H), 2.59-2.57 (2H, m, $H_{E/F}$), 2.40-2.36 (2H, m, $H_{E/F}$), 2.10 (2H, q, *J = 7.7 Hz*, H_B), 1.75-1.53 (2H, m, H_J), 1.27 (3H, d, *J = 6.2 Hz*, H_I), 0.94 (3H, t, *J = 7.7 Hz*, H_A), 0.93 (3H, t, *J = 7.3 Hz*, H_K) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ 205.7 (Q, C_D), 185.5 (Q, C_G), 122.4 (Q, C_C), 77.1 (CH, C_H), 33.5 (CH_2, $C_{E/F}$), 29.8 (CH_2, C_J), 24.9 (CH_2, $C_{E/F}$), 20.6 (CH_3, C_I), 14.5 (CH_2, C_B), 12.5 (CH_3, C_A), 9.5 (CH_3, C_K) ppm.

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

2-Ethylcyclopent-2-en-1-one (1.131)



This a known compound[56,137] but was synthesized here via an adaptation of an unpublished procedure devised by Organon N. V.; (Oss):

To a stirred solution of the enol ether **(3.31)** (27.42 g, 150 mmol, 1.0 equiv) in dry hexane (207 mL) at 0 °C was added DIBAL-H (1 M in hexanes, 240 mL, 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 1 M HCl (322 mL) (precooled to 0 °C) was slowly poured in, followed by the addition of conc. HCl (30 mL). The biphasic mixture was vigorously stirred for 2 h and then separated, washing the organic phase with water (2 x 50 mL). The combined aqueous phases were extracted with Et_2O (3 x 50 mL), the combined organic layer was then washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (Petroleum ether/Acetone 80:20) followed by vacuum distillation (47-49 °C/5 mmHg), yielding **(1.131)** as a light yellow oil (4.95 g, 30%).

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

Rf = 0.41 (Petroleum ether/Acetone 80:20).

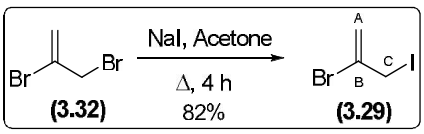
IR (neat): 2966 (m), 2923 (m), 2877 (w), 1696 (s), 1632 (m), 1443 (w), 1347 (w), 1248 (m), 1001 (m), 947 (w), 940 (w), 790 (m) cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.29-7.25 (1H, m, H_D), 2.55-2.50 (2H, m, $H_{B/C}$), 2.37-2.34 (2H, m, $H_{B/C}$), 2.19-2.11 (2H, m, H_F), 1.06 (3H, t, *J = 7.5 Hz*, H_G) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ 209.7 (Q, C_A), 156.4 (CH, C_D), 147.7 (Q, C_E), 34.6 (CH_2, $C_{B/C}$), 26.2 (CH_2, $C_{B/C}$), 17.9 (CH_2, C_F), 11.9 (CH_3, C_G) ppm.

The IR and NMR spectra correspond to the reported data.[56,137]

2-Bromo-3-iodo-1-propene (3.29):



This is a known compound[138] but was prepared via the following procedure:

In a 50 mL 2-neck flask equipped with a condenser was added dropwise 2,3-dibromo-1-propene **(3.32)** (2.44 mL, 25 mmol, 1.0 equiv) to a solution of NaI (6.75 g, 45 mmol, 1.8 equiv) in 20 mL of dry acetone. After refluxing for 4 h, the reaction mixture was cooled and 20 mL of water was added followed by 40 mL of Et_2O. The two phases were separated and the dark purple organic layer was washed with 20 mL of diluted $NaHCO_3$, 20 mL of brine, dried over Na_2SO_4, filtered through celite and concentrated under vacuum. The resulting crude was purified by vacuum distillation (68-72 °C/ 5 mmHg), yielding **(3.29)** as a dark-purple oil (5.10 g, 82%).

MW = 246.872 (C_3H_4BrI).

Rf = 0.55 (Hexane/Acetone 1:1).

IR (neat): 2359 (w), 1614 (m), 1421 (w), 1367 (w), 1190 (m), 1153 (s), 1088 (w), 1072 (w), 892 (s), 828 (m), 694 (w), 670 (w), 581 (s), 558 (m), 541 (s) cm^{-1}.

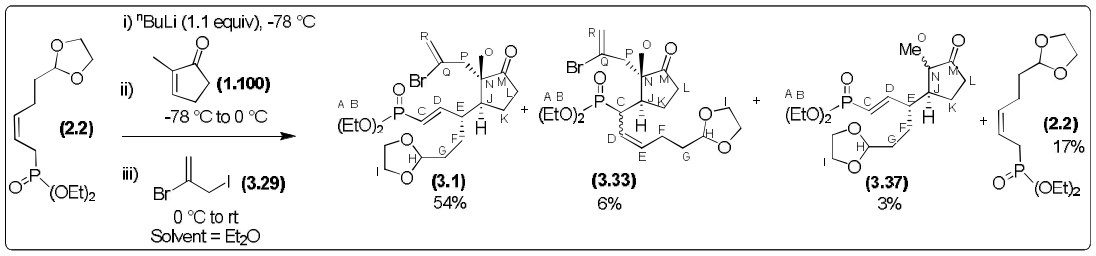
^{1}H NMR (300 MHz; $CDCl_3$): δ 6.02 (1H, m, H_A), 5.54 (1H, d, *J = 2.2 Hz*, $H_{A'}$), 4.22 (2H, d, *J = 0.7 Hz*, H_C) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ 129.5 (Q, C_B), 120.1 (CH_2, C_A), 20.0 (CH_2, C_C) ppm.

CIMS m/z (%): 248/246 ($(M+H)^+$, 20), 167 (6), 138/136 (63), 95/93 (3), 79 (4), 78 (2), 58 (7), 57 (100), 56 (24), 54 (9).

The IR and NMR spectra correspond to the reported data.[138]

<u>The γ-1,4-addition compound (3.1)</u> and **<u>the α-1,4-addition compound (3.33)</u>** and **<u>the non-alkylated compound (3.37).</u>**



To a cooled (-78 °C) solution of the phosphonate **(2.2)** (8.41 g, 30.24 mmol, 1.2 equiv) in Et_2O (80 mL) was added ^{n}BuLi (2.5 M in hexanes) (13.30 mL, 33.27 mmol, 1.32 equiv). The red solution was stirred for 30 min at -78 °C, and then a Et_2O (20 mL) solution of the

enone **(1.100)** (2.42 g, 25.20 mmol, 1.0 equiv) was added via cannula over 2 min. After the addition, the flask was placed in a 0 °C cold bath. After 1 h, 2-bromo-3-iodopropene **(3.29)** (11.19 g, 43.36 mmol, 1.8 equiv) was added neat over 30 seconds, followed by HMPA (20 mL) and the reaction mixture was warmed to room temperature over 1 h. Water (40 mL) was added and the reaction was extracted with EtOAc (4 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 60:40) followed by preparative HPLC (Hexane/Acetone 65:35). This yielded **(3.1)** (6.71 g, 54%), **(3.33)** (746 mg, 6%), **(3.37)** (283 mg, 3%) and **(2.2)** (1.19 g, 17%) as light yellow oils.

Data for (3.1):

Mw = 493.381 ($C_{21}H_{34}O_6PBr$).

Rf = 0.39 (Hexane/Acetone 60:40).

IR (neat): 2960 (br m), 1739 (m), 1621 (w), 1451 (w), 1403 (w), 1361 (w), 1238 (m), 1134 (m), 1049 (s), 1025 (s), 963 (m), 841 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.61 (1H, ddd, *J = 21.8, 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 = 4.5 Hz*, H_H), 4.17-4.07 (4H, m, H_B), 3.99-3.81 (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 (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.

ES$^+$MS m/z (%): 493/495 (1:1, $(M+H)^+$, 100), 515/517 (1:1, $(M+Na)^+$, 24), 987 ($(2M+H)^+$, 9).

Elemental analysis calcd for $C_{21}H_{34}O_6PBr$: C, 51.12; H, 6.95. Found: C, 50.83; H, 7.11.

Data for (3.33):

Mw = 493.381 ($C_{21}H_{34}O_6PBr$).

Rf = 0.39 (Hexane/Acetone 60:40).

IR (neat): 2978 (br m), 1737 (m), 1624 (w), 1444 (w), 1392 (w), 1361 (w), 1240 (m), 1138 (m), 1049 (s), 1020 (s), 958 (m), 899 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.88-5.33 (4H, m, H_R + H_D + H_E), 4.87 (1H, t, *J = 4.7 Hz*, H_H), 4.21-4.00 (4H, m, H_B), 4.00-3.76 (4H, m, H_I), 3.04 (1H, d, *J = 14.9 Hz*, H_P), 2.90 (1H, m, H_C), 2.78 (1H, m, H_J), 2.67-2.48 (2H, m, H_K+$H_{P'}$), 2.42-2.31 (2H, m, H_L), 2.28-2.08 (2H, m, H_F), 1.85-1.54 (3H, m, H_G+$H_{K'}$), 1.34-1.27 (6H, m, H_A), 0.82 (3H, s, H_O) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 221.2 (Q, C_M), 132.6 (d, *J = 12.9 Hz*, CH, C_D), 130.0 (Q, C_Q), 124.6 (d, *J = 11.8 Hz*, CH, C_E), 121.7 (CH_2, C_R), 103.8 (CH, C_H), 64.9 (2 x CH_2, C_I), 62.7 (d, *J = 7.3 Hz*, CH_2, C_B), 61.4 (d, *J = 7.3 Hz*, CH_2, $C_{B'}$), 52.4 (d, *J = 17.1 Hz*, Q, C_N), 47.4 (CH_2, C_P), 40.4 (d, *J = 136.5 Hz*, CH, C_C), 40.2 (d, *J = 2.4 Hz*, CH, C_J), 37.7 (CH_2, C_L), 33.0 (d, *J = 2.7 Hz*, CH_2, C_G), 25.4 (CH_2, C_K), 22.5 (d, *J = 2.5 Hz*, CH_2, C_F), 18.4 (CH_3, C_O), 16.5 (d, *J = 5.8 Hz*, CH_3, C_A), 16.4 (d, *J = 6.2 Hz*, $C_{A'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 28.02 ppm.

ES$^+$MS m/z (%): 493/495 (1:1, $(M+H)^+$, 100), 515/517 (1:1, $(M+Na)^+$, 36), 987 ($(2M+H)^+$, 15).

HRES$^+$MS For $C_{21}H_{34}O_6P^{79}BrNa$ $(M+Na)^+$: calcd 515.1169, found 515.1171.

Data for (3.37):

This compound was isolated as a mixture of diastereoisomers (ratio 75:25) that could be separated by repeated preparative HPLC (Hexane/Acetone 2:1).[21]

For Major Diastereoisomer:

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

Rf = 0.22 (Hexane/Acetone 60:40).

IR (neat): 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 (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 x 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 x C_A), 14.5 (CH_3, C_O) ppm.

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

CIMS m/z (%): 375 ((M+H)+, 100).

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

For Minor Diastereoisomer:

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

Rf = 0.22 (Hexane/Acetone 60:40).

IR (neat): 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 Hz*, H_A), 0.97 (3H, d, *J = 6.8 Hz*, H_O) ppm.

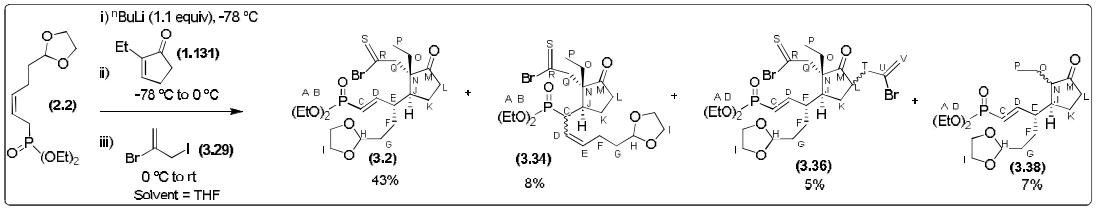
^{13}C NMR (100 MHz; $CDCl_3$): δ 221.1 (Q, C_M), 154.7 (d, *J = 3.9 Hz*, CH, C_D), 118.7 (d, *J = 186.6 Hz*, CH, C_C), 104.1 (CH, C_H), 65.0 (CH_2, C_I), 64.9 (CH_2, $C_{I'}$), 61.7 (d, *J = 4.9 Hz*, CH_2, 2 x C_B), 45.2 (CH), 44.8 (CH), 43.9 (CH), 37.1 (CH_2), 31.0 (CH_2), 25.4 (CH_2), 24.0 (CH_2), 16.4 (d, *J = 6.3 Hz*, CH_3, 2 x C_A), 8.4 (CH_3, C_O) ppm.

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

<u>The γ-1,4-addition compound (3.2)</u> and **<u>the α-1,4-addition compound (3.34)</u>** and **<u>the dialkylated compound (3.36)</u>** and **<u>the non-alkylated compound (3.38).</u>**



To a cooled (-78 °C) solution of the phosphonate **(2.2)** (4.94 g, 17.76 mmol, 1.2 equiv) in THF (50 mL) was added ^{n}BuLi (1.6 M in Hexanes) (8.62 mL, 19.54 mmol, 1.32 equiv). The red solution was stirred for 15 min at -78 °C, and then a THF (15 mL) solution of 2-ethyl-cyclopentenone **(1.131)** (1.63 g, 14.80 mmol, 1.0 equiv) was added via cannula over 2 min. After the addition, the flask was placed in a 0 °C cold bath. After 1 h, 2-bromo-3-iodopropene **(3.29)** (6.57 g, 26.64 mmol, 1.8 equiv) was added neat over 30 seconds and the reaction mixture was warmed to room temperature over 1 h. Water (50 mL) was added and the reaction mixture was extracted with Et_2O (4 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 65:35) followed by preparative HPLC (Hexane/Acetone 65:35). This yielded **(3.2)** (3.22 g, 43%), **(3.34)** (601 mg, 8%), **(3.36)** (464 mg, 5%) and **(3.38)** (402 mg, 7%) as light yellow oils.

Data for (3.2):

Mw = 507.408 ($C_{22}H_{36}O_6PBr$).

Rf = 0.41 (Hexane/Acetone 60:40).

IR (neat): 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 = 1.5 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), 1.88 (1H, m), 1.68 (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 (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 $C_{22}H_{36}O_6P^{79}BrNa$ $(M+Na)^{+}$: calcd 529.1325, found 529.1329.

Data for (3.34):

Mw = 507.408 ($C_{22}H_{36}O_6PBr$).

Rf = 0.41 (Hexane/Acetone 60:40).

IR (neat): 2975 (m), 2878 (m), 1730 (s), 1630 (m), 1455 (w), 1403 (w), 1397 (w), 1249 (s), 1053 (s), 1025 (s), 963 (m), 840 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.69-5.37 (4H, m, H_S + H_D + H_E), 4.82 (1H, t, *J = 4.7 Hz*, H_H), 4.13-3.95 (4H, m, H_B), 3.93-3.78 (4H, m, H_I), 3.08 (1H, d, *J = 14.9 Hz*, H_Q), 2.99 (1H, ddd, *J = 21.6, 10.7, 10.7 Hz*, H_C), 2.80 (1H, m, H_J), 2.51 (1H, ddt, *J = 10.3, 6.9, 3.8 Hz*, H_K), 2.40 (1H, d, *J = 14.9 Hz*, $H_{Q'}$), 2.35-2.27 (2H, m, H_L), 2.22-2.09 (2H, m, H_F), 1.82-1.57 (3H, m, H_G + $H_{K'}$), 1.44-1.28 (2H, m, H_O), 1.26 (3H, t, *J = 7.0 Hz*, H_A), 1.25 (3H, t, *J = 7.0 Hz*, $H_{A'}$), 0.76 (3H, t, *J = 7.5 Hz*, H_P) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 220.0 (Q, C_M), 132.6 (d, *J = 13.0 Hz*, CH, C_D), 130.6 (Q, C_R), 124.8 (d, *J = 12.0 Hz*, CH, C_E), 121.6 (CH_2, C_S), 103.8 (CH, C_H), 64.9 (2 x CH_2, C_I), 62.7 (d, *J = 7.3 Hz*, CH_2, C_B), 61.4 (d, *J = 7.3 Hz*, CH_2, $C_{B'}$), 54.8 (d, *J* = 16.8 Hz, Q, C_N), 45.9 (Q, C_Q), 40.5 (d, *J = 1.6 Hz*, CH, C_J), 39.8 (d, *J = 131.6 Hz*, CH, C_C), 37.6 (CH_2, C_L), 33.1 (d, *J = 2.6 Hz*, C_G), 25.5 (CH_2, $C_{K/O}$), 25.2 (CH_2, $C_{K/O}$), 22.5 (d, *J = 2.4 Hz*, C_F), 16.5 (d, *J = 5.8 Hz*, CH_3, C_A), 16.4 (d, *J = 6.2 Hz*, CH_3, $C_{A'}$), 8.5 (CH_3, C_P) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 27.06 ppm.

ES$^+$MS m/z (%): 1039/1037/1035 (1:2:1, $(2M+Na)^+$, 100), 531/529 (1:1, $(M+Na)^+$, 50), 509/507 (1:1, $(M+H)^+$, 48).

HRES$^+$MS For $C_{22}H_{37}O_6P^{79}Br$ $(M+H)^+$: calcd 507.1506, found 507.1514.

Data for (3.36):

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

Mw = 626.355 ($C_{25}H_{39}O_6PBr_2$).

Rf = 0.44 (Hexane/Acetone 60:40).

IR (neat): 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, $H_{V'}$), 4.56-5.42 (1H, m, $H_{V'(minor\ only)}$), 4.85-4.80 (1H, m, H_H), 4.14-4.03 (4H, m, 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 (100 MHz; $CDCl_3$): ***Major diastereoisomer***: δ 218.4 (Q, C_M), 155.2 (d, *J = 4.2 Hz*, 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, $C_{I'}$), 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. ***Minor diastereoisomer***: δ 219.4 (Q, C_M), 155.5 (d, *J = 4.2 Hz*, 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 (%): 651/649/647 (1:2:1, $(M+Na)^+$, 34), 625/627/629 (1:2:1, $(M+H)^+$, 100).

HRES$^+$MS For $C_{25}H_{39}O_6P^{79}Br_2$ $(M+H)^+$: calcd 625.0924, found 625.0933.

<u>Data for (3.38):</u>

Mw = 388.447 ($C_{19}H_{33}O_6PBr$).

Rf = 0.22 (Hexane/Acetone 60:40).

IR (neat): 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, 9.4 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.

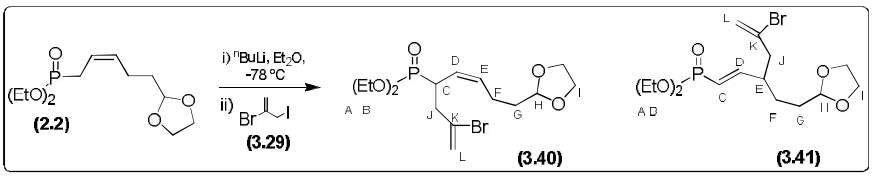
^{13}C NMR (100 MHz; $CDCl_3$): δ 220.1 (Q, C_M), 154.6 (d, *J = 4.1 Hz*, CH, C_D), 119.0 (d, *J = 186.4 Hz*, CH, C_C), 104.0 (CH, C_H), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.7 (d, *J = 5.6 Hz*, CH, C_B), 61.6 (d, *J = 5.6 Hz*, CH_2, $C_{B'}$), 53.0 (CH, $C_{J/N}$), 48.5 (d, *J = 20.6 Hz*, CH,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

(Z)-diethyl-2-bromo-8-(1,3-dioxolan-2-yl)octa-1,5-dien-4-ylphosphonate (3.40) and **(E)-diethyl-3-(2-(1,3-dioxolan-2-yl)ethyl)-5-bromohexa-1,5-dienylphosphonate (3.41).**



To a cooled solution (-78 °C) of the phosphonate **(2.2)** (200 mg, 0.72 mmol, 1.0 equiv) in Et_2O (5mL) was added ^{n}BuLi (2.5 M in Hexanes) (154 µL, 0.79 mmol, 1.1 equiv) dropwise over 2 min. The red solution was stirred at -78 °C for 15 min and then for 5 min at 0 °C before the iodide **(3.29)** (267 mg, 1.08 mmol, 1.5 equiv) was added neat over 30 seconds. The reaction mixture was warmed to room temperature over 1 h. Water (5 mL) was added and the reaction was extracted with Et_2O (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 70:30) followed by preparative HPLC (Hexane/Acetone 70:30). This yielded **(3.40)** (230 mg, 81%) and **(3.41)** (27 mg, 9%) as colourless oils.

Data for (3.40):

Mw = 397.251 ($C_{15}H_{26}O_5PBr$).

Rf = 0.33 (Hexane/Acetone 70:30).

IR (neat): 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 (m, 4H, 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 (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 x 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_2, 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 $C_{15}H_{26}O_5P^{79}Br$ $(M+H)^+$: calcd 397.0774, found 397.0771.

<u>Data for (3.41):</u>

Mw = 397.251 ($C_{15}H_{26}O_5PBr$).

Rf = 0.26 (Hexane/Acetone 70:30).

IR (neat): 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), 5.47 (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 + $H_{F'}$), 1.48 (1H, m, H_F), 1.32 (6H, d, *J = 7.0 Hz*, H_A) ppm.

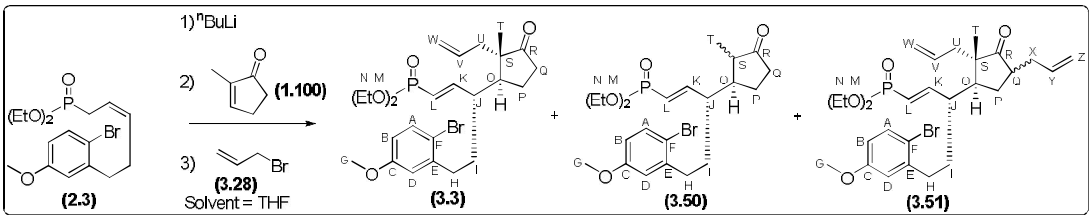
^{13}C NMR (100 MHz; $CDCl_3$): δ 154.5 (d, *J = 4.4 Hz*, CH, C_D), 131.6 (Q, C_K), 118.8 (CH_2, C_L), 118.6 (d, *J = 184.7 Hz,* CH, C_C), 104.0 (CH, C_H), 64.9 (CH_2, 2 x C_I), 61.7 (d, *J = 5.3 Hz*, CH_2, C_B), 61.6 (d, *J = 5.3 Hz*, CH_2, $C_{B'}$), 45.9 (d, *J = 1.5 Hz*, CH_2, C_J), 42.3 (d, *J = 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 x 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 $C_{15}H_{26}O_5P^{79}Br$ $(M+H)^+$: calcd 397.0774, found 397.0771.

The γ-1,4-addition compound (3.3) and **the non-allylated compound (3.50)** and **the *bis*-allylated compound (3.51).**



To a solution of the *Z*-allylic phosphonate **(2.3)** (0.990 g, 2.53 mmol, 1.0 equiv) in THF (20 mL), cooled to -78 °C, ^{n}BuLi (2.5 M in Hexane, 1.11 mL, 2.78 mmol, 1.1 equiv) was added slowly and the mixture was stirred for 15 min at -78 °C. After warming to 0 °C, a solution of 2-methyl-2-cyclopentenone **(1.100)** (0.322 mL, 3.29 mmol, 1.3 equiv) in THF (10 mL) was immediately added over 2 min. via cannula. The solution was stirred for 1 h at 0 °C and then quenched with freshly distilled allyl bromide **(3.28)** (2.19 mL, 25.3 mmol, 10 equiv). The solution was warmed to room temperature and stirred for 1 h. Water (50 mL) was added and the reaction was extracted with DCM (3 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 65:35) to afford **(3.3)** as a light yellow oil (921 mg, 69%), **(3.50)** as a light yellow oil (141 mg, 11%), and **(3.51)** as a colourless oil (72 mg, 5%). Recrystallization of **(3.3)** in DCM/Hexane gave colourless crystals.

Data for 3.3:

Mw = 527.428 ($C_{25}H_{36}O_5BrP$).

Rf = 0.42 (Hexane/Acetone 65:35).

IR (film): 2975 (m), 1740 (s), 1629 (w), 1472 (m), 1575 (m), 1239 (s), 1022 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.39 (1H, d, *J = 8.7 Hz*, H_A), 6.71 (1H, d, *J = 2.9 Hz*, H_D), 6.64 (1H, ddd, *J = 17.1, 11.0, 7.3 Hz*, H_K), 6.63 (1H, dd, *J = 8.8, 3.0 Hz*, H_B), 5.77 (1H, dd, *J = 20.6, 17.2 Hz*, H_L), 5.45 (1H, dtd, *J = 17.1, 9.6, 5.3 Hz*, H_V), 5.18 (1H, d, *J = 17.0 Hz*, H_W), 5.08 (1H, d, *J = 10.2 Hz*, $H_{W'}$), 4.16-4.09 (4H, m, H_M), 3.77 (3H, s, H_G), 2.68 (1H, ddd, *J = 13.3, 11.8, 5.0 Hz*, H_H), 2.53-2.45 (2H, m, $H_{H'}$ + H_Q), 2.41-2.31 (2H, m, H_U + H_J), 2.22-2.09 (3H, m, H_O + H_I + $H_{Q'}$), 2.04-1.89 (2H, m, $H_{U'}$ + H_P), 1.58-1.46 (2H, m, $H_{I'}$ + $H_{P'}$), 1.35 (6H, td, *J = 7.0, 2.0 Hz*, H_N), 0.91 (3H, s, H_T) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 222.1 (Q, C_R), 159.0 (Q, C_C), 155.3 (CH, d, *J = 3.6 Hz*, C_K), 142.0 (Q, C_E), 134.1 (CH, C_V), 133.3 (CH, C_A), 118.9 (CH_2, C_W), 118.7 (CH, d, *J* =

186.0 Hz, C_L), 116.0 (CH, C_D), 114.6 (Q, C_F), 113.2 (CH, C_B), 61.7 (CH_2, d, *J = 5.5 Hz,* C_M), 61.6 (CH_2, d, *J = 5.6 Hz*, $C_{M'}$), 55.4 (CH_3, C_G), 52.1 (Q, C_S), 46.8 (CH, d, *J = 20.9 Hz*, C_J), 44.4 (CH, C_O), 40.8 (CH_2, C_U), 37.1 (CH_2, C_I), 34.0 (CH_2, C_Q), 31.8 (CH_2, C_H), 23.6 (CH_2, C_P), 18.2 (CH_3, C_T), 16.5 (CH_3, C_N), 16.4 (CH_3, $C_{N'}$) ppm.

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

ES$^+$MS m/z (%): 552/551/550/549 (1:5:1:5, ($M+Na^+$, 90)), 530/529/528/527 (1:6:1:6, ($M+H^+$, 100)).

HRES$^+$MS For $C_{25}H_{37}O_5P^{79}Br$ $(M+H)^+$: calcd 527.1557, found 527.1551.

X-Ray: X-Ray data available in Appendix II.

Data for (3.50)

This compound was isolated as an inseparable mixture of diastereoisomers in approximately in a 75:25 ratio.

Mw = 487.117 ($C_{22}H_{32}O_5BrP$).

Rf = 0.35 (Hexane/Acetone 65:35).

IR (film): 2977 (w), 1737 (s), 1472 (m), 1240 (s), 1022 (s), 959 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): **Major diastereoisomer** δ 7.40 (1H, d, *J = 8.7 Hz*, H_A), 6.75 (1H, m, H_K), 6.72 (1H, d, *J = 3.0 Hz*, H_D), 6.63 (1H, dd, *J = 8.8, 3.1 Hz*, H_B), 5.79 (1H, dd, *J = 20.4, 17.1 Hz*, H_L), 4.16-4.06 (4H, m, H_M), 3.78 (3H, s, H_G), 2.77-2.48 (2H, m), 2.39-2.26 (2H, m), 2.18-2.04 (2H, m), 1.96-1.45 (5H, m), 1.34 (6H, t, *J = 7.2 Hz*, H_N), 1.08 (3H, d, *J = 6.4 Hz*, H_T) ppm. **Minor diastereoisomer observed** δ 7.39 (1H, d, *J = 8.7 Hz*, H_A), 3.77 (3H, s, H_G), 1.06 (3H, d, *J = 7.5 Hz*, H_T) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): **Major diastereoisomer** δ 219.9 (Q, C_R), 159.0 (Q, C_C), 154.7 (CH, d, *J = 4.0 Hz*, C_K), 141.8 (Q, C_F), 133.4 (CH, C_A), 119.2 (CH, d, *J = 186.3 Hz*, C_L), 116.0 (CH, C_D), 114.6 (Q, C_F), 113.3 (CH, C_B), 61.7 (2 x CH_2, d, *J = 5.5 Hz*, C_M), 55.4 (CH_3, C_G), 48.5 (CH, d, *J = 20.9 Hz*, C_J), 48.3 (CH, $C_{S/O}$), 47.5 (CH, $C_{S/O}$), 36.9 (CH_2, C_I), 34.5 (CH_2, C_Q), 30.5 (CH_2, C_H), 24.6 (CH_2, C_P), 16.4 (2 x CH_3, d, *J = 6.0 Hz*, C_N), 14.4 (CH_3, C_T) ppm. **Minor diastereoisomer observed** δ 218.7 (Q, C_R), 142.1 (Q, C_F), 133.2 (CH, C_A), 115.8 (CH, C_D), 113.2 (CH, C_B), 48.8 (CH, d, *J = 11.8 Hz*, C_J), 44.7 (CH), 40.4 (CH), 38.3 (CH, d, *J = 4.5 Hz*), 35.2 (CH_2), 32.9 (CH_2), 32.0 (CH_2), 31.5 (CH_2), 30.9 (CH_2), 14.1 (CH_3, C_T) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): **Major diastereoisomer** δ 17.53 ppm. **Minor diastereoisomer** δ 28.81 ppm.

ES$^+$MS m/z (%): 511/509 (1:1, (M+Na$^+$, 100)), 489/487 (1:1 (M+H$^+$, 60)).

HRES$^+$MS For $C_{22}H_{32}O_5P^{79}BrNa$ $(M+Na)^+$: calcd 509.1068, found 509.1063.

Data for (3.51):

This compound was isolated as an inseparable mixture of diastereoisomers in approximately a 80:20 ratio.

Mw = 567.492 ($C_{28}H_{40}O_5BrP$).

Rf = 0.44 (Hexane/Acetone 65:35).

IR (film): 2977 (w), 2934 (w), 1733 (m), 1472 (m), 1240 (s), 1051 (s), 1022 (s), 859 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): **Major diastereoisomer** δ 7.41 (1H, d, *J = 8.7 Hz*, H_A), 6.72 (1H, d, *J = 3.0 Hz*, H_D), 6.68 (1H, m, H_K), 6.64 (1H, dd, *J = 8.7, 3.0 Hz*, H_B), 5.78 (1H, dd, *J = 20.7, 17.2 Hz*, H_L), 5.72 (1H, m, H_Y), 5.46 (1H, dtd, *J = 16.9, 9.7, 5.3 Hz*, H_V), 5.24-4.99 (4H, m, H_W+H_Z), 4.19-4.09 (4H, m, H_M), 3.78 (3H, s, H_G), 2.69 (1H, m), 2.56-2.45 (2H, m), 2.43-2.25 (3H, m), 2.24-2.07 (2H, m), 2.02-1.86 (3H, m), 1.70 (1H, m), 1.55 (1H, m), 1.37 (3H, t, *J = 7.1 Hz*, H_N), 1.36 (3H, t, *J = 7.1 Hz*, $H_{N'}$), 0.94 (3H, s, H_T) ppm. **Minor diastereoisomer observed** δ 0.88 (3H, s, H_T) ppm.

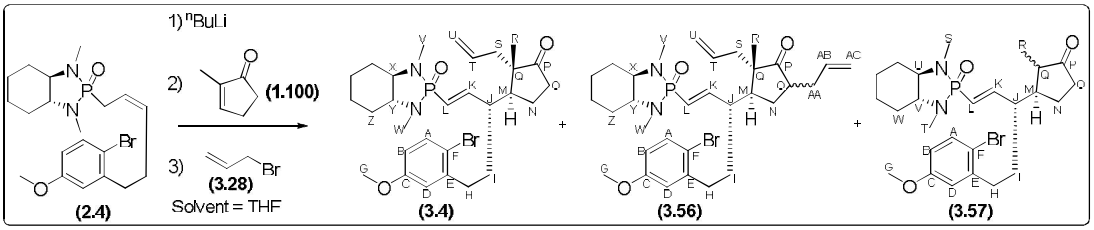
^{13}C NMR (100 MHz; $CDCl_3$): **Major diastereoisomer** δ 223.2 (Q, C_R), 159.0 (Q, C_C), 155.3 (CH, d, *J = 3.7 Hz*, C_K), 142.1 (Q, C_E), 135.6 (CH, C_Y), 134.2 (CH, C_V), 133.4 (CH, C_A), 119.0 (CH_2, C_W), 118.9 (CH, d, *J = 187.1 Hz*, C_L), 117.0 (CH_2, C_Z), 116.1 (CH, C_D), 114.6 (Q, C_F), 113.3 (CH, C_B), 61.8 (CH_2, d, *J = 10.6 Hz*, C_M), 61.7 (CH_2, d, *J = 10.6 Hz*, $C_{M'}$), 55.4 (CH_3, C_G), 53.0 (Q, C_S), 47.0 (CH, d, *J = 20.9 Hz*, C_J), 44.6 (CH, $C_{O/Q}$), 41.9 (CH, $C_{O/Q}$), 40.4 (CH_2, C_U), 34.8 (CH_2), 34.0 (CH_2), 31.9 (CH_2), 28.5 (CH_2), 18.6 (CH_3, C_T), 16.5 (2 x CH_3, d, *J = 6.3 Hz*, C_N) ppm.

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

ES$^+$MS m/z (%): 589/591 (1:1, (M+Na$^+$, 100)), 567/569 (1:1, (M+H$^+$, 47)).

HRES$^+$MS For $C_{28}H_{40}O_5P^{79}BrNa$ $(M+Na)^+$: calcd 589.1694, found 589.1650.

The γ-1,4-addition compound (3.4) and **the *bis*-allylated compound (3.56)** and **the non-allylated compound (3.57).**



To a solution of the *Z*-allylic phosphonamide **(2.4)** (0.393 g, 0.89 mmol, 1.0 equiv) in THF (4 mL), cooled to -78 °C, ^{n}BuLi (2.5 M in hexane, 0.392 mL, 0.98 mmol, 1.1 equiv) was added slowly and the mixture was stirred for 45 min at -78 °C. After warming to 0 °C, 2-methyl-2-cyclopentenone (0.096 mL, 1.16 mmol, 1.3 equiv) was immediately added. The solution was stirred for 1 h at 0 °C and then quenched with freshly distilled allyl bromide (0.336 mL, 4.45 mmol, 5.0 equiv). HMPA (2 mL) was added and the solution was warmed to room temperature and stirred for 1 h. Water (5 mL) was added and the reaction was extracted with DCM (3 x 25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc, then EtOAc/MeOH 99/1) to afford **(3.4)** as a light yellow oil (267 mg, 52%), **(3.57)** as a colourless oil (43 mg, 9%), and **(3.56)** as a colourless oil (38 mg, 7%).

Data for (3.4):

Mw = 577.553 ($C_{29}H_{42}BrN_2O_3P$).

Rf = 0.40 (EtOAc/MeOH 99/1).

IR (film): 2936 (m), 2864 (w), 1735 (m), 1470 (m), 1243 (s), 1210 (s), 1169 (s), 1008 (s), 830 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.40 (1H, d, *J = 8.7 Hz*, H_A), 6.72 (1H, d, *J = 3.1 Hz*, H_D), 6.64 (1H, dd, *J = 8.7, 3.1 Hz*, H_B), 6.64 (1H, m, H_K), 5.61 (1H, dd, *J = 21.3, 16.7 Hz*, H_L), 5.51 (1H, m, H_T), 5.23 (1H, d, *J = 17.0 Hz*, H_U), 5.11 (1H, d, *J = 10.2 Hz*, $H_{U'}$), 3.79 (3H, s, H_G), 2.86-2.63 (2H, m), 2.60-2.32 (4H, m), 2.59 (3H, d, *J = 3.2 Hz*, $H_{V/W}$), 2.55 (3H, d, *J = 2.6 Hz*, $H_{V/W}$), 2.26-2.13 (3H, m), 2.08-1.80 (6H, m), 1.60-1.43 (2H, m), 1.40-1.06 (5H, m), 0.95 (3H, s, H_R) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 222.4 (Q, C_P), 159.0 (Q, C_C), 155.3 (CH, d, *J = 1.8 Hz*, C_K), 142.2 (Q, C_E), 133.8 (CH, C_T), 133.3 (CH, C_A), 121.8 (CH, d, *J = 150.4 Hz*, C_L),

119.3 (CH_2, C_U), 115.8 (CH, C_D), 114.7 (Q, C_F), 113.3 (CH, C_B), 64.7 (CH, d, *J = 7.2 Hz*, $C_{X/Y}$), 63.9 (CH, d, *J = 5.2 Hz*, $C_{X/Y}$), 55.5 (CH_3, C_G), 52.2 (Q, C_Q), 47.2 (CH, d, *J = 18.2 Hz*, C_J), 44.5 (CH, C_M), 41.1 (CH_2), 37.3 (CH_2), 34.3 (CH_2), 31.8 (CH_2), 29.0 (CH_3, d, *J = 1.1 Hz*, $C_{V/W}$), 28.9 (CH_3, d, *J = 5.2 Hz*, $C_{V/W}$), 28.8 (CH_2, d, *J = 10.3 Hz*, C_Z), 28.2 (CH_2, d, *J = 7.6 Hz*, $C_{Z'}$), 24.3 (CH_2), 24.2 (CH_2), 23.8 (CH_2), 18.3 (CH_3, C_R) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 32.14 ppm.

ES$^+$MS m/z (%): 617/615 (1:1, ($M+K^+$, 100)).

HRES$^+$MS For $C_{29}H_{43}N_2O_3P^{79}Br$ $(M+H)^+$: calcd 577.2189, found 577.2198.

$[\alpha]_D$ = +114.6° (c 0.65, DCM).

<u>Data for (3.56):</u>

This compound was isolated as an inseparable mixture of diastereoisomers in approximately a 75:25 ratio.

Mw = 617.597 ($C_{32}H_{46}BrN_2O_3P$).

Rf = 0.47 (EtOAc/MeOH 99:1).

IR (film): 2936 (w), 1733 (m), 1471 (m), 1210 (m), 1169 (m), 908 (s), 725 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): **Major diastereoisomer** δ 7.40 (1H, d, *J = 8.7 Hz*, H_A), 6.76-6.58 (3H, m, H_B+H_D+H_K), 5.62 (1H, dd, *J = 21.3, 16.7 Hz*, H_L), 5.79-5.42 (2H, m, H_T+H_{AB}), 5.32-4.96 (4H, m, H_U+H_{AC}), 3.79 (3H, s, H_G), 2.84-1.07 (29H, m), 0.97 (3H, s, H_R) ppm, **Minor diastereoisomer observed** δ 0.91 (3H, s, H_R) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): **Major diastereoisomer** δ 223.4 (Q, C_P), 159.1 (Q, C_C), 155.2 (CH, d, *J = 2.0 Hz*, C_K), 142.3 (Q, C_E), 135.6 (CH, $C_{T/AB}$), 133.9 (CH, $C_{T/AB}$), 133.3 (CH, C_A), 121.7 (CH, d, *J = 150.3 Hz*, C_L), 119.3 (CH_2, $C_{U/AC}$), 117.0 (CH_2, $C_{U/AC}$), 115.9 (CH, C_D), 114.7 (Q, C_F), 113.3 (CH, C_B), 64.7 (CH, d, *J = 7.2 Hz*, $C_{X/Y}$), 63.9 (CH, d, *J = 5.2 Hz*, $C_{X/Y}$), 55.5 (CH_3, C_G), 53.1 (Q, C_Q), 47.3 (CH, d, *J = 18.3 Hz*, C_J), 44.7 (CH, C_M), 41.9 (CH, C_O), 40.7 (CH_2), 34.8 (CH_2), 34.3 (CH_2), 31.9 (CH_2), 29.1 (CH_3, $C_{V/W}$), 28.9 (CH_3, $C_{V/W}$), 28.8 (CH_2), 28.7 (CH_2), 28.2 (CH_2, d, *J = 7.6 Hz*, C_Z), 24.3 (CH_2), 24.2 (CH_2), 18.6 (CH_3, C_R) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): **Major diastereoisomer** δ 32.23 ppm, **Minor diastereoisomer** δ 32.16 ppm.

ES$^+$MS m/z (%): 639/641 (1:1, ($M+Na^+$, 100)), 617/619 (1:1, ($M+H^+$, 78)).

HRES$^+$MS For $C_{32}H_{46}O_3P^{79}BrN_2Na$ calcd 639.2327, found 639.2322.

Data for (3.57):

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

Mw = 537.469 ($C_{26}H_{38}BrN_2O_3P$).

Rf = 0.27 (EtOAc/MeOH 99:1).

IR (film): 2934 (m), 1737 (s), 1445 (m), 1242 (m), 1170 (s), 1008 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41 (1H, d, *J = 8.7 Hz*, H_A), 6.74 (1H, d, *J = 3.0 Hz*, H_D), 6.73 (1H, ddd, *J = 20.1, 16.8, 9.5 Hz*, H_K), 6.64 (1H, dd, *J = 8.7, 3.0 Hz*, H_B), 5.59 (1H, dd, *J = 20.5, 16.6 Hz*, H_L), 3.79 (3H, s, H_G), 2.83-2.71 (2H, m), 2.58-2.46 (2H, m), 2.56 (3H, s, $H_{T/S}$), 2.53 (3H, d, *J = 0.5 Hz*, $H_{T/S}$), 2.40-2.32 (2H, m), 2.19-1.80 (9H, m), 1.70-1.51 (3H, m), 1.39-1.27 (3H, m), 1.12 (3H, d, *J = 6.6 Hz*, H_R) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 220.3 (Q, C_P), 159.0 (Q, C_C), 155.0 (CH, C_K), 142.1 (Q, C_E), 133.4 (CH, C_A), 121.8 (CH, d, *J = 150.0 Hz*, C_L), 116.0 (CH, C_D), 114.7 (Q, C_F), 113.2 (CH, C_B), 64.8 (CH, d, *J = 7.4 Hz*, $C_{U/V}$), 63.8 (CH, d, *J = 5.3 Hz*, $C_{U/V}$), 55.5 (CH_3, C_G), 49.2 (CH, d, *J = 18.0 Hz*, C_J), 48.4 (CH, $C_{M/Q}$), 47.8 (CH, $C_{M/Q}$), 37.0 (CH_2), 34.7 (CH_2), 33.0 (CH_2), 30.8 (CH_2), 29.0 (CH_3, d, *J = 1.4 Hz*, $C_{S/T}$), 28.7 (CH_3, d, *J = 5.1 Hz*, $C_{S/T}$), 28.2 (CH_2, d, *J = 7.3 Hz*, C_W), 24.9 (CH_2), 24.3 (CH_2), 24.2 (CH_2), 14.8 (CH_3, C_R) ppm.

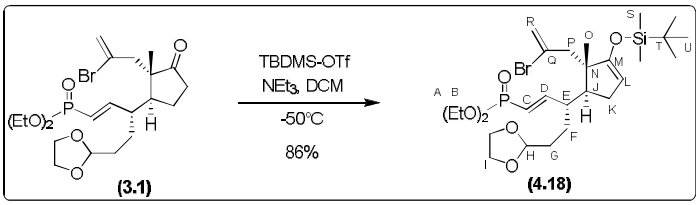
^{31}P NMR (121 MHz; $CDCl_3$): δ 32.22 ppm.

ES$^+$MS m/z (%): 539/537 (1:1, $(M+H)^+$, 100).

HRES$^+$MS For $C_{26}H_{39}O_3PN_2{}^{79}Br$ ($M+H^+$): calcd 537.1876, found 537.1880.

9.3 Experimental data for Chapter 4

The silyl enol ether (4.18)



To a cooled solution (-50 °C) of the ketone **(3.1)** (292 mg, 0.59 mmol, 1.0 equiv) in DCM (5 mL) was added Et_3N (247 μL, 1.8 mmol, 3.0 equiv) then TBDMS-OTf (407 μL, 1.8 mmol, 3.0 equiv) dropwise. The reaction was stirred for 3 h at -50 °C and then sat. aq. $NaHCO_3$ (5 mL) was added and the reaction was warmed to room temperature. The phases were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 80:20) whereby the silica was pre-neutralized by making the slurry in the said solvent system, containing ~1% of Et_3N. This yielded **(4.18)** as a colourless oil (309 mg, 86%).

Mw = 607.630 ($C_{27}H_{48}O_6PBrSi$).

Rf = 0.42 (Hexane/Acetone 75:25).

IR (neat): 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) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.63 (1H, ddd, *J = 21.8, 17.2, 9.5 Hz*, H_D), 5.81 (s, 1H, H_R), 5.64 (1H, dd, *J = 21.8, 17.2 Hz*, H_C), 5.53 (1H, br s, $H_{R'}$), 4.78 (1H, t, *J = 4.5 Hz*, H_H), 4.40 (1H, br s, H_L), 4.09-4.01 (4H, m , H_B), 3.92-3.76 (4H, m, H_I), 2.76 (1H, d, J = *15.2 Hz*, H_P), 2.38-2.23 (5H, m), 1.91-1.84 (1H, m), 1.74-1.58 (2H, m), 1.49-1.41 (1H, m), 1.30 (6H, t, *J = 7.1 Hz*, H_A), 0.90 (9H, s, H_U), 0.87 (3H, H_O), 0.14 (3H, s, H_S), 0.10 (3H, s, $H_{S'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 157.9 (Q, C_M), 156.5 (d, *J = 3.6 Hz*, CH, C_D), 130.5 (Q, C_Q), 120.7 (CH_2, C_R), 118.4 (d, *J = 186.6 Hz*, CH, C_C), 104.3 (CH, C_H), 96.9 (CH, C_L), 64.8 (CH_2, C_I), 64.7 (CH_2, $C_{I'}$), 61.6 (d, *J = 5.6 Hz*, CH_2, C_B), 61.5 (d, *J = 5.6 Hz*, CH_2, $C_{B'}$), 49.7 (Q, C_N), 46.9 (d, *J = 20.7 Hz*, CH, C_E), 45.8 (CH_2, C_P), 43.2 (CH, C_J), 31.2

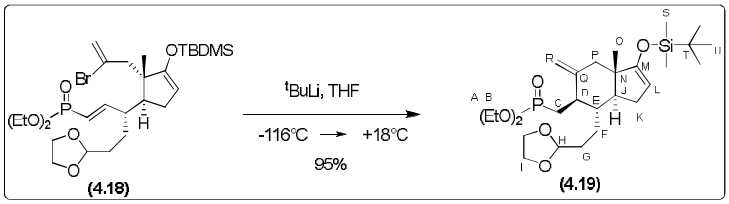
(CH_2, $C_{G/K}$), 31.0 (CH_2, $C_{K/G}$), 26.1 (d, *J = 2.1 Hz*, CH_2, C_F), 25.6 (CH_3, 3 x C_U), 20.0 (CH_3, C_O), 18.0 (Q, C_T), 16.4 (d, *J = 6.3 Hz*, 2 x CH_3, C_A), -4.8 (CH_3, C_S), -5.5 (CH_3, $C_{S'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.30 ppm.

ES$^+$MS m/z (%): 1249/1251/1253 (1:2:1, $(2M+Na)^+$, 29), 670/672 (1:1, $(M+Na+MeCN)^+$, 100), 629/631 (1:1, $(M+Na)^+$, 81).

HRES$^+$MS: We have not obtained HRMS or elemental analysis of this compound, but copies of the ^{1}H and ^{13}C NMR spectra are included in Appendix I.

<u>The C-ring cyclised silyl enol ether (4.19)</u>



A solution of the vinyl bromide **(4.18)** (301 mg, 0.50 mmol, 1.0 equiv) in THF (10 mL) was cooled to -116 °C in an EtOH/liquid N_2 cold bath and treated with ^{t}BuLi (1.5 M in pentanes) (727 μL, 1.1 mmol, 2.2 equiv). After the dropwise addition, the reaction was stirred for 15 min, then the cold bath was removed and the reaction was allowed to warm to room temperature over 1 h. Saturated aq. $NaHCO_3$ (10 mL) was added and the reaction was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/EtOAc 1:1). This yielded **(4.19)** as a colourless oil (242 mg, 95%), as a single diastereoisomer.

Mw = 528.734 ($C_{27}H_{49}O_6PSi$).

Rf = 0.22 (Hexane/EtOAc 1:1).

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}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.00 (1H, s, H_R), 4.93 (1H, s, $H_{R'}$), 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_P), 2.23-1.90 (6H, m), 1.87-1.69 (2H, m), 1.65-1.49 (4H, m), 1.28

(6H, t, *J = 7.0 Hz*, H_A), 0.90 (9H, s, H_U), 0.72 (3H, H_O), 0.16 (3H, s, H_S), 0.14 (3H, s, $H_{S'}$) ppm.

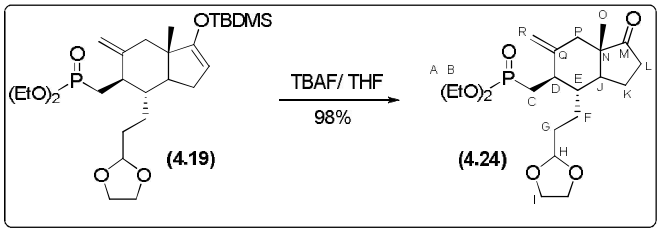
^{13}C NMR (100 MHz; $CDCl_3$): δ 163.4 (Q, C_M), 147.3 (d, *J = 1.3 Hz*, Q, C_Q), 111.7 (CH_2, C_R), 104.8 (CH, C_H), 99.2 (CH, C_L), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.5 (d, *J = 6.6 Hz*, CH_2, C_B), 61.4 (d, *J = 5.6 Hz*, CH_2, $C_{B'}$), 54.1 (d, *J = 1.7 Hz*, CH, C_D), 47.8 (Q, C_N), 46.9 (d, *J = 20.7 Hz*, CH, C_E), 42.1 (CH_2, C_P), 42.1 (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), 25.5 (CH_3, 3 x C_U), 24.2(CH_2, C_F), 22.4 (CH_3, C_O), 17.9 (Q, C_T), 16.4 (d, *J = 6.2 Hz*, CH_3, 2 x C_A), -4.6 (CH_3, C_S), -5.1 (CH_3, $C_{S'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 32.50 ppm.

ES$^+$MS m/z (%): 551 ($(M+Na)^+$, 100), 529 ($(M+H)^+$, 46).

HRES$^+$MS For $C_{27}H_{50}O_6PSi$ $(M+H)^+$: calcd 529.3109, found 529.3118.

The C-ring cyclised ketone (4.24)



A solution of the silyl enol ether **(4.19)** (259 mg, 0.49 mmol, 1.0 equiv) in THF (5 mL) was treated with TBAF (1 M in THF, 489 µL, 1.3 equiv) and the mixture was stirred at room temperature for 30 min. Saturated aq. $NaHCO_3$ (5 mL) was added and the reaction was extracted with DCM (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 60:40). This yielded **(4.24)** as a colourless oil (198 mg, 98%), as a single diastereoisomer.

Mw = 414.473 ($C_{21}H_{35}O_6P$).

Rf = 0.42 (Hexane/Acetone 60:40).

IR (film): 2959 (w), 2887 (w), 1737 (s), 1643 (w), 1453 (w), 1406 (w), 1239 (m), 1138 (m), 1058 (s), 1023 (s), 947 (s), 902 (m), 729 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.01 (1H, s, H_R), 4.91 (s, 1H, $H_{R'}$), 4.81 (1H, t, *J = 4.3 Hz*, H_H),, 4.05-3.98 (4H, m, H_B), 3.93-3.78 (4H, m, H_I), 2.44-2.37 (1H, m, H_L), 2.35 (1H, d, *J = 13.0 Hz*, H_P), 2.18-1.96 (6H, m), 1.74-1.44 (7H, m), 1.25 (3H, t, *J = 7.1 Hz*, H_A), 1.24 (3H, t, *J = 7.1 Hz*, $H_{A'}$), 0.74 (3H, H_O) ppm.

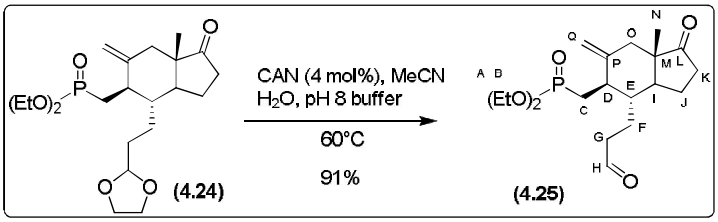
^{13}C NMR (100 MHz; $CDCl_3$): δ 219.8 (Q, C_M), 145.2 (d, *J = 1.3 Hz*, Q, C_Q), 112.6 (CH_2, C_R), 104.3 (CH, C_H), 64.9 (CH_2, C_I), 64.8 (CH_2, $C_{I'}$), 61.4 (d, *J = 6.6 Hz*, CH_2, C_B), 61.3 (d, *J = 5.6 Hz*, CH_2, $C_{B'}$), 48.6 (d, *J = 1.7 Hz*, CH, C_D), 48.5 (Q, C_N), 42.9 (CH_2, C_P), 40.7 (d, *J = 4.6 Hz*, CH, C_J), 40.6 (d, *J = 13.6 Hz*, CH, C_E), 35.8 (CH_2, C_L), 28.2 (CH_2, $C_{G/K}$), 24.8 (d, *J = 142.0 Hz*, CH_2, C_C), 22.9 (CH_2, C_F), 22.3 (CH_2, $C_{G/K}$), 16.3 (d, *J = 6.2 Hz*, CH_3, 2 x C_A), 14.0 (CH_3, C_O) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 31.72 ppm.

ES^{+}MS m/z (%): 851 ($(2M+Na)^+$, 26), 437 ($(M+Na)^+$, 100), 415 ($(M+H)^+$, 28).

HRES^{+}MS For $C_{21}H_{36}O_6P$ $(M+H)^+$: calcd 415.224, found 415.2243.

The C-ring cyclised aldehyde (4.25)



To a solution of the acetal **(4.24)** (180 mg, 0.43 mmol, 1.0 equiv) in MeCN (5 mL) and a borate-HCl buffer (pH 8) (5 mL) was added CAN (16 mg, 0.03 mmol, 0.06 equiv) in one portion and the mixture was heated at 60 °C for 18 h. The reaction was cooled to room temperature, water (5 mL) and DCM (10 mL) were added and the phases were separated. The aqueous phase was extracted with DCM (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The orange crude oil was purified by column chromatography eluting (Hexane/Acetone 7:3) to afford **(4.25)** as a light yellow oil (145 mg, 91%).

Mw = 370.420 ($C_{19}H_{31}O_5P$).

Rf = 0.45 (Hexane/Acetone 60:40).

IR (film): 2978 (w), 2936 (w), 2907 (w), 1736 (s), 1723 (s), 1642 (w), 1453 (w), 1391 (w), 1237 (m), 1162 (m), 1054 (s), 1023 (s), 956 (s), 897 (m), 795 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 9.79 (1H, H_H), 5.03 (1H, s, H_Q), 4.96 (s, 1H, $H_{Q'}$), 4.08-3.99 (4H, m, H_B), 2.67-2.58 (1H, m), 2.48-2.37 (3H, m), 2.19-1.92 (6H, m), 1.89-1.84 (2H, m), 1.27 (3H, t, *J = 7.1 Hz*, H_A), 1.26 (3H, t, *J = 7.1 Hz*, $H_{A'}$), 0.76 (3H, H_O) ppm.

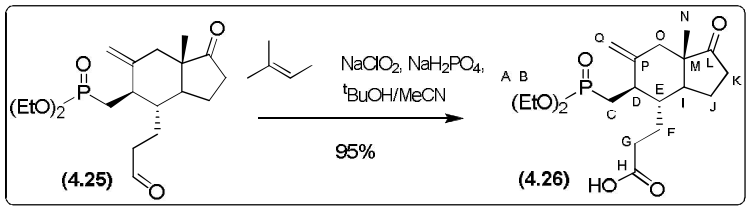
^{13}C NMR (100 MHz; $CDCl_3$): δ 219.3 (Q, C_L), 201.5 (CH, C_H), 144.8 (d, *J = 1.4 Hz*, Q, C_P), 112.9 (CH_2, C_Q), 61.6 (d, *J = 6.6 Hz*, CH_2, C_B), 61.5 (d, *J = 5.6 Hz*, CH_2, $C_{B'}$), 48.6 (d, *J = 1.7 Hz*, CH, C_D), 48.5 (Q, C_M), 42.8 (CH_2, C_O), 40.4 (d, *J = 9.7 Hz*, CH, C_E), 40.3 (CH, C_I), 38.7 (CH_2, C_K), 35.8 (CH_2, C_G), 24.9 (d, *J = 142.3 Hz*, CH_2, C_C), 22.5 (CH_2, $C_{F/J}$), 21.1 (CH_2, $C_{F/J}$), 16.4 (d, *J = 6.1 Hz*, CH_3, C_A), 16.3 (d, *J = 6.1 Hz*, CH_3, $C_{A'}$), 14.0 (CH_3, C_N) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 31.69 ppm.

ES^{+}MS m/z (%): 763 ($(2M+Na)^+$, 21), 393 ($(M+Na)^+$, 100), 371 ($(M+H)^+$, 70).

HRES^{+}MS For $C_{19}H_{31}O_5PNa$ $(M+Na)^+$: calcd 393.1801, found 393.1800.

<u>The C-ring cyclised carboxylic acid (4.26)</u>



To a stirred and cooled (0 °C) solution of the aldehyde **(4.25)** (93 mg, 0.25 mmol, 1.0 equiv) in 2-methyl-2-propanol (^{t}BuOH) (2 mL) and acetonitrile (1.50 mL) was added 2-methyl-2-butene (309 µL, 3.0 mmol, 12.0 equiv). Sodium chlorite (165 mg, 1.5 mmol, 6.0 equiv) and sodium dihydrogen phosphate (175 mg, 1.5 mmol, 6.0 equiv) were combined and dissolved in H_2O (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 (2.5 mL). The pH was adjusted (pH 6) before extraction of the crude mixture with DCM (3 x 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (DCM/MeOH 95:5) to afford **(4.26)** (92 mg, 95%) as a colourless oil. Recrystallization in Et_2O afforded **(4.26)** as fine white crystals (m.p. = 143-145 °C).

Mw = 386.419 ($C_{19}H_{31}O_6P$).

Rf = 0.38 (DCM/MeOH 95:5).

IR (film): 3446 (br w), 2978 (w), 2936 (w), 2907 (w), 1736 (s), 1642 (w), 1453 (w), 1391 (w), 1237 (m), 1162 (m), 1054 (s), 1023 (s), 956 (s), 897 (m), 795 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.40 (1H, br hump, OH), 5.00 (1H, s, H_Q), 4.98 (s, 1H, $H_{Q'}$), 4.15-4.03 (4H, m, H_B), 2.66 (1H, d, *J = 13.5 Hz*, H_O), 2.53-2.38 (2H, m), 2.32-1.83 (9H, m), 1.73-1.57 (3H, m), 1.31 (3H, t, *J = 7.1 Hz*, H_A), 1.29 (3H, t, *J = 7.1 Hz*, $H_{A'}$), 0.74 (3H, H_N) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 218.2 (Q, C_L), 176.2 (Q, C_H), 145.0 (d, *J = 2.9 Hz*, Q, C_P), 112.2 (CH_2, C_Q), 62.2 (d, *J = 6.9 Hz*, CH_2, C_B), 62.1 (d, *J = 6.9 Hz*, CH_2, $C_{B'}$), 48.7 (d, *J = 1.8 Hz*, CH, C_E), 48.4 (Q, C_M), 42.9 (CH_2, C_O), 41.6 (d, *J = 9.8 Hz*, CH, C_D), 40.3 (CH, C_I), 38.7 (CH_2, C_K), 36.4 (CH_2, C_G), 24.9 (d, *J = 142.6 Hz*, CH_2, C_C), 22.8 (CH_2, $C_{F/J}$), 21.6 (CH_2, $C_{F/J}$), 16.3 (d, *J = 6.1 Hz*, CH_3, C_A), 16.2 (d, *J = 6.1 Hz*, CH_3, $C_{A'}$), 14.0 (CH_3, C_N) ppm.

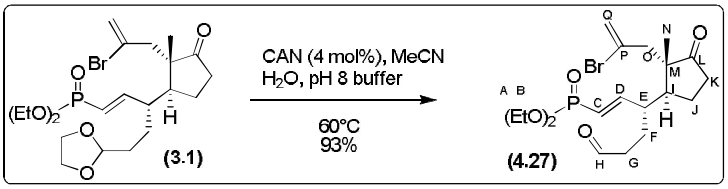
^{31}P NMR (121 MHz; $CDCl_3$): δ 32.29 ppm.

ES$^+$MS m/z (%): 795 ($(2M+Na)^+$, 36), 409 ($(M+Na)^+$, 70), 387 ($(M+H)^+$, 100).

HRES$^+$MS For $C_{19}H_{32}O_6P$ $(M+H)^+$: calcd 387.1931, found 387.1934.

X-ray: X-ray data available in Appendix II.

<u>The aldehyde (4.27)</u>



To a solution of the acetal **(3.1)** (1.03 g, 2.03 mmol, 1.0 equiv) in MeCN (10 mL) and a borate-HCl buffer (pH 8) (10 mL) was added CAN (44 mg, 0.08 mmol, 0.04 equiv) in one portion and the mixture was heated at 60 °C for 18 h. The reaction was cooled to room temperature, water (20 mL) and DCM (20 mL) were added and the phases were separated. The aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The orange crude oil was purified by column chromatography eluting (Hexane/EtOAc 1:9) to afford **(4.27)** as a light yellow oil (875 mg, 93%).

Mw = 449.327 ($C_{19}H_{30}O_5PBr$).

Rf = 0.24 (Hexane/EtOAc 1:4).

IR (neat): 2988 (m), 2935 (m), 2902 (m), 1730 (s), 1621 (m), 1446 (w), 1389 (m), 1243 (s), 1162 (m), 1049 (s), 1020 (s), 964 (s), 845 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 9.75 (1H, s, H_H), 6.56 (1H, ddd, *J = 21.7, 17.2, 10.0 Hz*, H_D), 5.97 (1H, t, *J = 1.7 Hz*, H_Q), 5.66 (1H, dd, *J = 20.5, 17.3 Hz*, H_C), 5.55 (1H, br s, $H_{Q'}$), 4.16-4.04 (4H, m, H_B), 3.06 (1H, d, *J = 14.8 Hz*, H_O), 2.48 (1H, d, *J = 14.8 Hz*, $H_{O'}$), 2.53-2.20 (7H, m, H_G+H_I+H_J+H_K), 2.19-2.07 (1H, m, H_E), 1.56-1.43 (2H, m, H_F), 1.33 (6H, t, *J = 7.1 Hz*, H_A), 0.86 (3H, s, H_N) ppm.

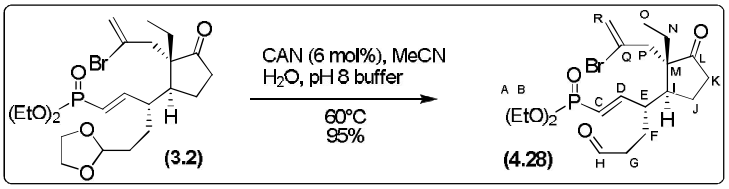
^{13}C NMR (100 MHz; $CDCl_3$): δ 221.1 (Q, C_L), 201.1 (CH, C_H), 154.3 (d, *J = 3.9 Hz*, CH, C_D), 129.8 (Q, C_P), 122.5 (CH_2, C_Q), 119.9 (d, *J = 187.5 Hz*, CH, C_C), 61.8 (d, *J = 8.6 Hz*, CH_2, C_B), 61.7 (d, *J = 8.6 Hz*, CH_2, $C_{B'}$), 51.7 (Q, C_M), 47.0 (CH_2, C_O), 46.7 (d, *J = 21.0 Hz*, CH, C_E), 43.8 (CH, C_I), 40.9 (CH_2, C_K), 36.8 (CH_2, C_G), 23.9 (CH_2, C_J), 23.8 (d, *J = 2.1 Hz*, CH_2, C_F), 18.7 (CH_3, C_N), 16.4 (d, *J = 6.0 Hz*, CH_3, 2 x C_A) ppm.

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

ES^{+}MS m/z (%): 901/899/897 (1:2:1, $(2M+H)^+$, 18), 449/451 (1:1, $(M+H)^+$, 100).

HRES^{+}MS For $C_{19}H_{30}O_5PBr$ $(M+H)^+$: calcd 449,1087, found 449.1094.

The aldehyde (4.28)



To a solution of the acetal **(3.2)** (760 mg, 1.50 mmol, 1.0 equiv) in MeCN (15 mL) and a borate-HCl buffer (pH 8) (10 mL) was added CAN (50 mg, 0.09 mmol, 0.06 equiv) in one portion and the mixture was heated at 60 °C for 18 h. The reaction was cooled to room temperature, water (20 mL) and DCM (20 mL) were added and the phases were separated. The aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The orange crude oil was purified by column chromatography eluting (Hexane/Acetone 60:40) to afford **(4.28)** as a light yellow oil (669 mg, 95%).

Mw = 463.354 ($C_{20}H_{32}O_5PBr$).

Rf = 0.38 (Hexane/Acetone 60:40).

IR (neat): 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), 2.48 (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, s, H_O) ppm.

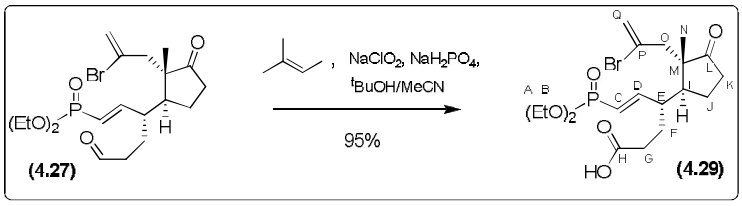
^{13}C NMR (100 MHz; $CDCl_3$): δ 220.0 (Q, C_L), 201.3 (CH, C_H), 154.6 (d, *J = 3.9 Hz*, CH, C_D), 130.4 (Q, C_Q), 122.7 (CH_2, C_R), 119.8 (d, *J = 187.4 Hz*, CH, C_C), 61.9 (d, *J = 5.9 Hz*, CH_2, C_B), 61.8 (d, *J = 5.9 Hz*, CH_2, $C_{B'}$), 54.1 (Q, C_M), 46.1 (d, *J = 21.0 Hz*, CH, C_E), 45.3 (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, C_F), 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, $(2M+H)^+$, 14), 485/487 (1:1 $(M+Na)^+$, 25), 463/465 (1:1, $(M+H)^+$, 100).

HRES$^+$MS For $C_{20}H_{32}O_5PBr$ $(M+Na)^+$: calcd 485.1063, found 485.1073.

<u>The carboxylic acid (4.29)</u>



To a stirred and cooled (0 °C) solution of the aldehyde **(4.27)** (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 chlorite (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 DCM (3 x 15 mL). The combined organic phases were dried over

$MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (DCM/MeOH 95:5) to afford **(4.29)** (348 mg, 95%) as a colourless oil. Recrystallization in Et_2O afforded **(4.29)** as fine white crystals (m.p. = 165-167 °C).

Mw = 465.327 ($C_{19}H_{30}O_6PBr$).

Rf = 0.24 (DCM/MeOH 97:3).

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}.

^{1}H 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 = 14.8 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 (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 = 8.6 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, C_F), 23.9 (CH_2), 19.0 (CH_3, C_N), 16.3 (d, *J = 6.2 Hz*, CH_3, 2 x C_A) ppm.

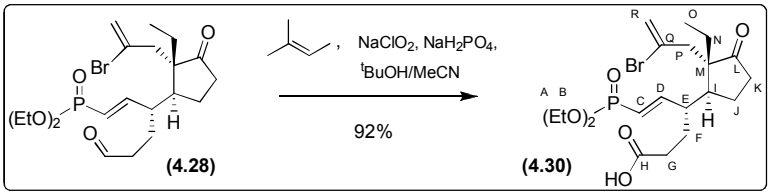
^{31}P NMR (121 MHz; $CDCl_3$): δ 17.88 ppm.

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

HRES$^+$MS: For $C_{19}H_{30}O_6P^{79}Br$ $(M+Na)^+$: calcd 487.0861, found 487.0875.

X-ray: X-ray data available in Appendix II.

The carboxylic acid (4.30)



To a stirred and cooled (0 °C) solution of the aldehyde **(4.28)** (344 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 chlorite (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 DCM (3 x 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (DCM/MeOH 95:5) to afford **(4.30)** (362 mg, 95%) as a colourless oil.

Mw = 479.354 ($C_{20}H_{32}O_6PBr$).

Rf = 0.28 (DCM/MeOH 95:5).

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 8.50 (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.

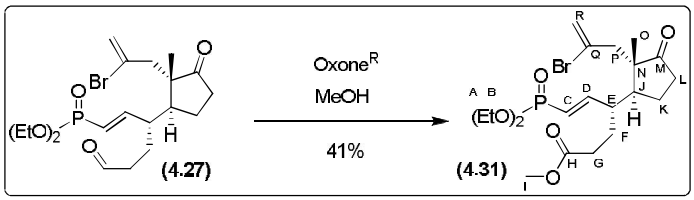
^{13}C NMR (100 MHz; $CDCl_3$): δ 220.2 (Q, C_L), 176.3 (Q, C_H), 155.1 (d, *J = 4.0 Hz*, CH, C_D), 130.4 (Q, C_Q), 122.5 (CH_2, C_R), 119.2 (d, *J = 188.0 Hz*, CH, C_C), 62.1 (d, *J = 5.9 Hz*, CH_2, C_B), 62.0 (d, *J = 5.9 Hz*, CH_2, $C_{B'}$), 54.1 (Q, C_M), 46.3 (d, *J = 21.1 Hz*, CH, C_E), 45.3 (CH_2, C_P), 44.0 (CH, C_I), 36.9 (CH_2), 31.0 (CH_2), 26.6 (d, *J = 1.9 Hz*, CH_2, C_F), 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.

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.02 ppm.

ES$^+$MS m/z (%): 481/479 (1:1, $(M+H)^+$, 100).

HRES$^+$MS For $C_{20}H_{32}O_6P^{79}Br$ $(M+H)^+$: calcd 479.1193, found 479.1197.

<u>The methyl ester (4.31)</u>



To a solution of the aldehyde **(4.27)** (200 mg, 0.45 mmol, 1.0 equiv) in dry MeOH (2 mL) was added Oxone^R (274 mg, 0.47 mmol, 1.05 equiv) in one portion. The mixture was

stirred at room temperature for 18 h, then DCM (5 ml) was added. The reaction was filtered through celite and the solvent was evaporated *in vacuo*. The resulting crude oil was purified by column chromatography eluting (Hexane/EtOAc 30:70) to afford **(4.31)** as a light yellow oil (88 mg, 41%) along with 21% of recovered **(4.27)**.

Mw = 479.342 ($C_{20}H_{32}O_6PBr$).

Rf = 0.61 (Hexane/EtOAc 20:80).

IR (neat): 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 6.56 (1H, ddd, *J = 21.7, 17.2, 10.0 Hz*, H_D), 5.98 (1H, t, *J = 1.5 Hz*, H_R), 5.66 (1H, dd, *J = 20.6, 17.2 Hz*, H_C), 5.54 (1H, br s, $H_{R'}$), 4.13-4.04 (4H, m, H_B), 3.66 (3H, s, H_I), 3.06 (1H, d, *J = 14.8 Hz*, H_P), 2.48 (1H, d, *J = 14.8 Hz*, $H_{P'}$), 2.42-2.06 (8H, m), 1.56-1.44 (2H, m), 1.32 (6H, t, *J = 7.1 Hz*, H_A), 0.85 (3H, s, H_O) ppm.

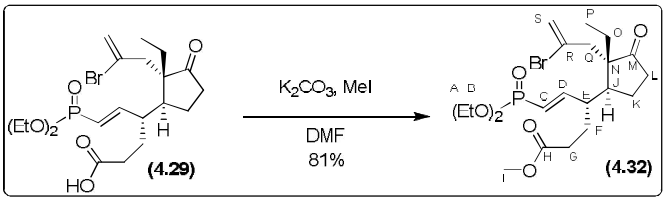
^{13}C NMR (100 MHz; $CDCl_3$): δ 221.1 (Q, C_M), 173.3 (Q, C_H), 154.4 (d, *J = 3.9 Hz*, CH, C_D), 129.8 (Q, C_Q), 122.5 (CH_2, C_R), 118.8 (d, *J = 187.5 Hz*, CH, C_C), 61.8 (d, *J = 8.6 Hz*, CH_2, C_B), 61.7 (d, *J = 8.6 Hz*, CH_2, $C_{B'}$), 51.7 (Q, C_N), 51.6 (CH_3, C_I), 47.1 (CH_2, C_P), 46.8 (d, *J = 21.0 Hz*, CH, C_E), 43.7 (CH, C_J), 36.8 (CH_2), 31.0 (CH_2), 26.6 (d, *J = 1.2 Hz*, CH_2, C_F), 23.9 (CH_2), 18.7 (CH_3, C_O), 16.4 (d, *J = 6.0 Hz*, 2 x CH_3, C_A) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.32 ppm.

ES$^+$MS m/z (%) : 961/959/957 (1:2:1, $(2M+H)^+$, 18), 479/481 (1:1, $(M+H)^+$, 100).

HRES$^+$MS For $C_{20}H_{32}O_6P^{79}BrNa$ $(M+Na)^+$: calcd 501.1012, found 501.1011.

The methyl ester (4.32)



To a solution of the acid **(4.29)** (471 mg, 0.98 mmol, 1.0 equiv) in DMF (5 mL) was added K_2CO_3 (677 mg, 4.95 mmol, 5.0 equiv). The mixture was stirred 15 min at room temperature before the dropwise addition of MeI (175 µL, 2.94 mmol, 3.0 equiv). The reaction mixture was stirred for a further 2 h at room temperature, filtered through celite, washed with DCM (50 mL) and concentrated *in vacuo*. The crude oil was partitioned

between water/DCM (30 mL) and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 70:30) to afford **(4.32)** (393 mg, 81%) as a light yellow oil.

Mw = 493.369 ($C_{21}H_{34}O_6PBr$).

Rf = 0.28 (Hexane/Acetone 60:40).

IR (neat): 2979 (br w), 2906 (w), 1733 (s), 1624 (m), 1437 (w), 1388 (m), 1242 (s), 1163 (m), 1051 (s), 1023 (s), 960 (s), 845 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.52 (1H, ddd, *J = 21.7, 17.2, 10.0 Hz*, H_D), 5.95 (1H, t, *J = 1.5 Hz*, H_S), 5.63 (1H, dd, *J = 20.6, 17.3 Hz*, H_C), 5.54 (1H, br s, $H_{S'}$), 4.07-3.99 (4H, m, H_B), 3.61 (3H, s, H_I), 3.08 (1H, d, *J = 14.8 Hz*, H_Q), 2.37-2.04 (9H, m), 1.55-1.42 (2H, m), 1.39 (2H, q, *J = 7.5 Hz*, H_O), 1.27 (6H, t, *J = 7.1 Hz*, H_A), 0.74 (3H, s, H_P) ppm.

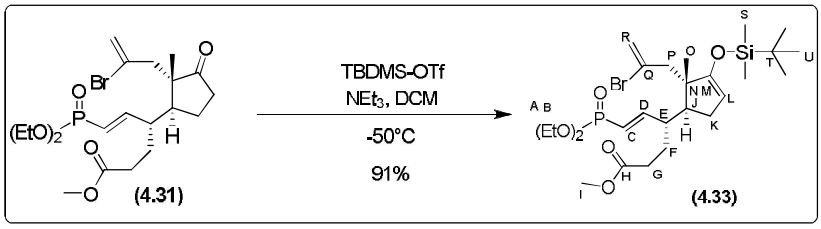
^{13}C NMR (100 MHz; $CDCl_3$): δ 219.9 (Q, C_M), 173.3 (Q, C_H), 154.6 (d, *J = 4.0 Hz*, CH, C_D), 130.4 (Q, C_R), 122.6 (CH_2, C_S), 120.6 (d, *J = 186.7 Hz*, CH, C_C), 61.8 (d, *J = 8.6 Hz*, CH_2, C_B), 61.7 (d, *J = 8.6 Hz*, CH_2, $C_{B'}$), 54.1 (Q, C_N), 51.6 (CH_3, C_I), 46.2 (d, *J = 21.0 Hz*, CH, C_E), 45.3 (CH_2, C_Q), 44.1 (CH, C_J), 36.9 (CH_2), 31.0 (CH_2), 26.7 (d, *J = 1.2 Hz*, CH_2, C_F), 25.4 (CH_2, C_O), 24.1 (CH_2), 16.4 (d, *J = 6.0 Hz*, CH_3, 2 x C_A), 8.30 (CH_3, C_P) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.50 ppm.

ES$^+$MS m/z (%): 1009/1011 (2:1, $(2M+Na)^+$, 20), 515/517 (1:1, $(M+Na)^+$, 24), 493/495 (1:1, $(M+H)^+$, 100).

HRES$^+$MS For $C_{21}H_{34}O_6P^{79}BrNa$ $(M+Na)^+$: calcd 515.1169, found 515.1163.

<u>The silyl enol ether (4.33</u>)



To a cooled solution (-50 °C) of the ketone **(4.31)** (1.18 mg, 2.5 mmol, 1.0 equiv) in DCM (10 mL) was added Et_3N (1.02 mL, 7.5 mmol, 3.0 equiv) and TBDMS-OTf (1.69

mL, 7.5 mmol, 3.0 equiv). The reaction was stirred for 2 h at -50 °C and then sat.aq. $NaHCO_3$ (10 mL) was added and the reaction was warmed to room temperature. The phases were separated and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 80:20) whereby the silica was pre-neutralized by making the slurry in the said solvent system, containing ~1% of Et_3N. This yielded **(4.33)** as a colourless oil (1.18 mg, 91%).

Mw = 593.603 ($C_{26}H_{46}O_6PSiBr$).

Rf = 0.41 (Hexane/Acetone 70:30).

IR (film): 2961 (m), 2926 (m), 2855 (m), 1734 (s), 1621 (m), 1460 (m), 1393 (w), 1346 (m), 1255 (s), 1229 (s), 1138 (m) 1056 (s), 1025 (s), 954 (s), 902 (m), 851 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.62 (1H, ddd, *J = 21.7, 17.2, 10.0 Hz*, H_D), 5.81 (1H, br s, H_R), 5.65 (1H, dd, *J = 20.6, 17.2 Hz*, H_C), 5.55 (1H, br s, $H_{Q'}$), 4.42 (1H, br s, H_L), 4.11-4.04 (4H, m, H_B), 3.64 (3H, s, H_I), 2.79 (1H, d, *J = 14.8 Hz*, H_P), 2.27 (1H, d, *J = 14.8 Hz*, $H_{P'}$), 2.40-2.21 (4H, m), 2.19-2.11 (1H, m), 2.02-1.87 (2H, m), 1.49-1.38 (1H, m), 1.32 (6H, t, *J = 7.1 Hz*, H_A), 0.91 (9H, s, H_U), 0.87 (3H, s, H_N), 0.15 (3H, s, H_S), 0.12 (3H, s, $H_{S'}$) ppm.

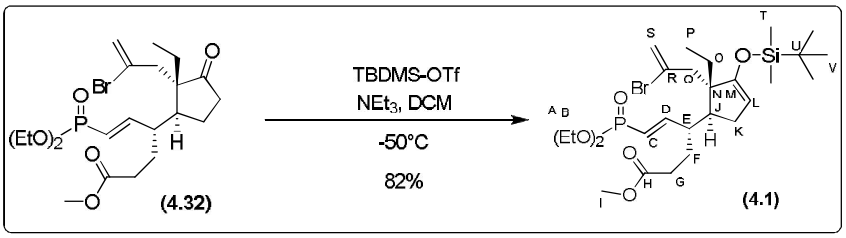
^{13}C NMR (100 MHz; $CDCl_3$): δ 173.6 (Q, C_H), 157.8 (Q, C_M), 155.5 (d, *J = 3.3 Hz*, CH, C_D), 130.5 (Q, C_Q), 122.7 (CH_2, C_R), 119.1 (d, *J = 186.8 Hz*, CH, C_C), 97.0 (CH, C_L), 61.7 (d, *J = 5.7 Hz*, CH_2, C_B), 61.6 (d, *J = 5.7 Hz*, CH_2, $C_{B'}$), 51.6 (CH_3, C_I), 49.8 (Q, C_N), 46.6 (d, *J = 20.7 Hz*, CH, C_E), 45.9 (CH_2, C_P), 43.2 (CH, C_J), 31.2 (2 x CH_2, C_G + C_K), 27.0 (CH_2, C_F), 25.6 (CH_3, 3 x C_U), 20.0 (CH_3, C_O), 18.0 (Q, C_T), 16.4 (d, *J = 2.5 Hz*, CH_3, 2 x C_A), -4.7 (CH_3, C_S), -5.5 (CH_3, $C_{S'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.32 ppm.

ES$^+$MS m/z (%): 593/595 (1:1, $(M+H)^+$, 100), 616/618 (1:1, $(M+Na)^+$, 24), 1188/1190 (1:1, $(2M+H)^+$, 8).

HRES$^+$MS For $C_{26}H_{46}O_6PSi^{79}BrNa$ $(M+Na)^+$: calcd 615.1877, found 615.1885.

The silyl enol ether (4.1)



To a cooled solution (-50 °C) of the ketone **(4.32)** (1.58 g, 3.21 mmol, 1.0 equiv) in DCM (5 mL) was added Et_3N (1.34 mL, 9.63 mmol, 3.0 equiv) then, dropwisely over 2 min, TBDMS-OTf (2.21 mL, 9.63 mmol, 3.0 equiv) was added. The reaction was stirred for 2 h at -50/-40 °C and then sat. aq. $NaHCO_3$ (10 mL) was added and the reaction was warmed to room temperature. The phases were separated and the aqueous phase was extracted with DCM (5 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 80:20) whereby the silica was pre-neutralized by making the slurry in the said solvent system, containing ~1% of Et_3N. This yielded **(4.1)** as a colourless oil (1.59 g, 82%).

Mw = 607.630 ($C_{27}H_{48}O_6PSiBr$).

Rf = 0.42 (Hexane/Acetone 70:30).

IR (film): 2956 (m), 2922 (m), 2855 (m), 1733 (s), 1621 (m), 1460 (m), 1393 (w), 1346 (m), 1252 (s), 1228 (s), 1138 (m) 1058 (s), 1025 (s), 954 (s), 850 (s), 779 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.62 (1H, ddd, *J = 21.7, 17.2, 9.4 Hz*, H_D), 5.83 (1H, br s, H_S), 5.65 (1H, dd, *J = 21.2, 17.2 Hz*, H_C), 5.56 (1H, br s, $H_{S'}$), 4.56 (1H, br s, H_L), 4.11-4.04 (4H, m, H_B), 3.64 (3H, s, H_I), 2.82 (1H, d, *J = 15.2 Hz*, H_Q), 2.20 (1H, d, *J = 15.2 Hz*, $H_{Q'}$), 2.40-2.12 (6H, m), 2.01-1.85 (2H, m), 1.53-1.16 (2H, m, H_O), 1.32 (6H, t, *J = 7.0 Hz*, H_A), 0.91 (9H, s, H_V), 0.81 (3H, t, *J = 7.5 Hz*, H_P), 0.18 (3H, s, H_T), 0.17 (3H, s, $H_{T'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 173.6 (Q, C_H), 156.0 (d, *J = 3.5 Hz*, CH, C_D), 155.2 (Q, C_M), 131.0 (Q, C_R), 120.9 (CH_2, C_S), 119.1 (d, *J = 186.7 Hz*, CH, C_C), 98.4 (CH, C_L), 61.7 (d, *J = 5.7 Hz*, CH_2, C_B), 61.6 (d, *J = 5.7 Hz*, CH_2, $C_{B'}$), 53.0 (Q, C_N), 51.5 (CH_3, C_I), 46.2 (d, *J = 20.7 Hz*, CH, C_E), 45.7 (CH_2, C_Q), 43.1 (CH, C_J), 32.5 (CH_2), 31.2 (CH_2), 28.0

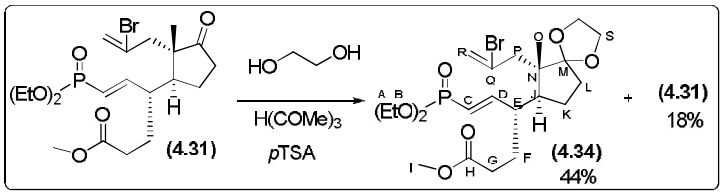
(CH_2, C_O), 27.2 (CH_2, C_F), 25.6 (CH_3, 3 x C_V), 17.9 (Q, C_U), 16.4 (d, *J = 2.7 Hz*, CH_3, 2 x C_A), 9.4 (CH_3, C_P), -4.7 (CH_3, C_T), -5.5 (CH_3, $C_{T'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.90 ppm.

ES$^+$MS m/z (%): 607/609 (1:1, $(M+H)^+$, 100), 629/631 (1:1, $(M+Na)^+$, 34).

HRES$^+$MS For $C_{27}H_{49}O_6PSi^{79}Br$ $(M+H)^+$: calcd 607.2214, found 607.2226.

The acetal (4.34)



In a dry 5 mL pear shape flask were combined the ketone **(4.31)** (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, 0.007 mmol, 0.03 equiv). The reagents were stirred for 28 h, then EtOAc (10 mL) was added and the solution was washed with sat. aq. $NaHCO_3$ (5 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 60:40) to afford **(4.34)** (54 mg, 44%) as a light yellow oil and **(4.31)** (23 mg, 18%).

Mw = 523.395 ($C_{22}H_{36}O_7PBr$).

Rf = 0.36 (Hexane/Acetone 70:30).

IR (film): 3248 (br, m), 2969 (w), 1734 (s), 1621 (w), 1432 (w), 1366 (w), 1233 (m), 1162 (m), 1053 (s), 1020 (s) 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 (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, 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),

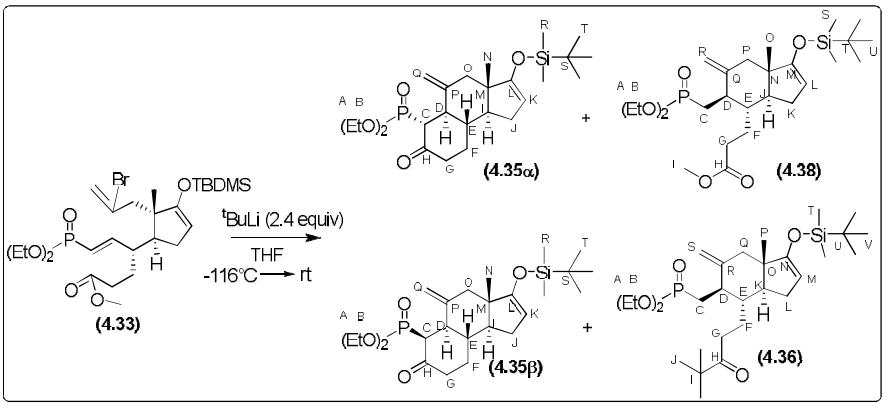
31.0 (CH_2), 26.6 (d, *J = 2.1 Hz*, CH_2, C_F), 24.0 (CH_2), 16.4 (CH_3, C_O), 16.4 (d, *J = 6.0 Hz*, 2 x CH_3, C_A) ppm.

^{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).

HRES$^+$MS For $C_{22}H_{36}O_7P^{79}BrNa$ $(M+Na)^+$: calcd 545.1274, found 545.1280.

<u>The β-keto phosphonate (4.35α)</u> and **<u>the β-keto phosphonate (4.35β)</u>** and **<u>the monocyclised ketone (4.36)</u>** and **<u>the monocyclised ester (4.38)</u>**



A solution of the vinyl bromide **(4.33)** (1.14 g, 1.92 mmol, 1.0 equiv) in THF (10 mL) was cooled to -116 °C in an EtOH/liquid N_2 cold bath and treated with ^{t}BuLi (1.5 M in pentanes) (3.07 mL, 5.89 mmol, 2.4 equiv). After the quick addition (over 20 seconds), the reaction was stirred for 15 min, then the cold bath was removed and the reaction was allowed to warm to room temperature over 1 h. Saturated aq. $NaHCO_3$ (10 mL) was added and H_2O (20 mL) and the reaction was extracted with DCM (3 x 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/EtOAc 70:30) using pre-neutralised silica gel. This yielded **(4.35α)** (424 mg, 46%), **(4.35β)** (45 mg, 5%), **(4.36)** (140 mg, 13%) and **(4.38)** (109 mg, 11%) as light yellow oils.

<u>Data for (4.35α)</u>

Mw = 482.665 ($C_{25}H_{43}O_5PSi$).

Rf = 0.36 (Hexane/EtOAc 60:40).

IR (film): 2958 (m), 2854 (m), 1721 (m), 1625 (m), 1472 (w), 1334 (w), 1251 (s), 1236 (s), 1161 (w), 1054 (s), 1025 (s), 963 (m), 840 (s), 784 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 4.93 (1H, s, H_Q), 4.85 (1H, s, $H_{Q'}$), 4.46 (1H, dd, *J = 3.0, 1.4 Hz*, H_K), 4.13-4.02 (4H, m, H_B), 3.43 (1H, ddd, *J = 26.1, 8.6, 1.9 Hz*, H_C), 2.86 (1H, ddd, *J = 17.3, 9.7, 2.6 Hz*, H_G), 2.75-2.65 (1H, m, H_D), 2.41-2.25 (2H, m, $H_{G'}$+H_O), 2.17-1.69 (6H, m, $H_{O'}$+2H_F+H_J+ $H_{J'}$+H_I), 1.39-1.30 (1H, m, H_E), 1.31 (3H, t, *J = 6.6 Hz*, H_A), 1.29 (3H, t, *J = 6.6 Hz*, $H_{A'}$), 0.93 (9H, s, H_T), 0.73 (3H, s, H_N), 0.17 (3H, s, H_R), 0.15 (3H, s, $H_{R'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 207.2 (d, *J = 4.7 Hz*, Q, C_H), 163.5 (Q, C_L), 145.4 (Q, C_P), 110.8 (CH_2, C_Q), 98.4 (CH, C_K), 62.8 (d, *J = 7.3 Hz*, CH_2, C_B), 62.7 (d, *J = 7.3 Hz*, CH_2, $C_{B'}$), 54.0 (CH, C_I), 51.8 (d, *J = 123.1 Hz*, CH, C_C), 47.2 (d, *J = 4.0 Hz*, CH, C_E), 45.5 (Q, C_M), 45.2 (CH_2, C_O), 37.9 (d, *J = 9.2 Hz*, CH, C_D), 37.5 (CH_2, C_G), 28.1 (2 x CH_2, C_J), 25.8 (CH_2, C_F), 25.7 (3 x CH_3, C_T), 18.1 (Q, C_S), 16.3 (d, *J = 6.1 Hz*, CH_2, C_A), 16.3 (d, *J = 6.2 Hz*, CH_2, $C_{A'}$), 15.6 (CH_3, C_N), -4.7 (CH_3, C_T), -5.00 (CH_3, $C_{T'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 23.14 ppm.

ES$^+$MS m/z (%): 988 ($(2M+Na)^+$, 22), 483 ($(M+H)^+$, 100).

HRES$^+$MS For $C_{25}H_{44}O_5PSi$ $(M+H)^+$: calcd 483.2690, found 483.2684.

<u>Data for (4.35β)</u>

Mw = 482.665 ($C_{25}H_{43}O_5PSi$).

Rf = 0.48 (Hexane/EtOAc 60:40).

IR (film): 2956 (m), 2931 (m), 2857 (m), 1717 (m), 1621 (m), 1472 (w), 1334 (w), 1252 (s), 1232 (s), 1161 (w), 1051 (s), 1025 (s), 963 (m), 840 (s), 784 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.03 (1H, t, *J = 1.6 Hz*, H_Q), 4.93 (1H, *J = 1.6 Hz*, $H_{Q'}$), 4.44 (1H, dd, *J = 3.0, 1.4 Hz*, H_K), 4.18-4.01 (4H, m, H_B), 3.56 (1H, ddd, *J = 20.0, 4.0, 1.8 Hz*, H_C), 2.85 (1H, dt, *J = 14.0, 6.9 Hz*, H_G), 2.61 (1H, dq, *J = 11.4, 3.5 Hz*, H_I), 2.33 (1H, m, $H_{G'}$), 2.26 (1H, m, H_O), 2.24-1.91 (4H, m), 1.85 (1H, m, H_F), 1.39 (1H, m, H_E), 1.28 (6H, t, *J = 6.6 Hz*, H_A), 1.27 (1H, m, H_J), 0.95 (9H, s, H_T), 0.93 (3H, s, H_N), 0.17 (3H, s, H_R), 0.15 (3H, s, $H_{R'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 205.6 (Q, C_H), 163.3 (Q, C_L), 144.9 (d, *J = 2.2 Hz*, Q, C_P), 111.7 (CH_2, C_Q), 98.3 (CH, C_K), 62.6 (d, *J = 7.0 Hz*, CH_2, C_B), 61.9 (d, *J = 7.0 Hz*, CH_2, $C_{B'}$), 54.3 (d, *J = 127.2 Hz*, CH, C_C), 53.8 (CH, C_I), 50.8 (d, *J = 4.5 Hz*, CH, C_D), 45.2 (Q, C_M), 44.7 (CH_2, C_O), 40.2 (CH_2, C_G), 34.2 (d, *J = 1.2 Hz*, CH, C_E), 31.2 (CH_2,

C_J), 28.3 (CH_2, C_F), 25.6 (3 x CH_3, C_T), 18.0 (Q, C_S), 16.3 (d, *J = 5.7 Hz*, CH_3, C_A), 16.2 (d, *J = 5.7 Hz*, CH_3, $C_{A'}$), 15.9 (CH_3, C_N), -4.7 (CH_3, C_R), -5.00 (CH_3, $C_{R'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 23.05 ppm.

ES$^+$MS m/z (%): 988 ($(2M+Na)^+$, 33), 483 ($(M+H)^+$, 100).

HRES$^+$MS For $C_{25}H_{44}O_5PSi$ $(M+H)^+$: calcd 483.2690, found 483.2699.

Data for (4.36)

Mw = 540.787 ($C_{29}H_{53}O_5PSi$).

Rf = 0.40 (Hexane/EtOAc 60:40).

IR (film): 2956 (w), 2931 (w), 1704 (m), 1621 (m), 1249 (s), 1229 (s), 1054 (s), 1026 (s), 951 (s), 836 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.04 (1H, s, H_S), 4.93 (1H, s, $H_{S'}$), 4.45 (1H, m, H_M), 4.17-4.00 (4H, m, H_B), 2.67-2.43 (2H, m), 2.28 (1H, d, *J = 12.8 Hz*, H_Q), 2.25-2.01 (5H, m), 1.96-1.60 (4H, m), 1.43 (1H, m), 1.31 (3H, t, *J = 7.1 Hz*, H_A), 1.30 (3H, t, *J = 7.1 Hz*, $H_{A'}$), 1.16 (9H, s, H_J), 0.94 (9H, s, H_V), 0.74 (3H, s, H_P), 0.17 (3H, s, H_T), 0.15 (3H, s, $H_{T'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 215.9 (Q, C_H), 163.6 (Q, C_N), 147.1 (Q, C_R), 112.1 (CH_2, C_S), 98.2 (CH, C_M), 61.4 (d, *J = 6.4 Hz*, 2 x CH_2, C_B), 52.7 (CH, C_K), 45.33 (Q, C_O), 45.30 (CH, C_K), 44.2 (Q, C_I), 41.4 (d, *J = 4.5 Hz*, CH, C_E), 40.0 (d, *J = 13.2 Hz*, CH, C_D), 31.5 (CH_2), 29.3 (CH_2), 26.4 (3 x CH_3, C_J), 25.6 (3 x CH_3, C_V), 24.5 (CH_2), 25.1 (d, *J = 141.0 Hz*, CH_2, C_C), 18.0 (Q, C_T), 16.4 (d, *J = 6.0 Hz*, 2 x CH_3, C_A), 15.3 (CH_3, C_P), -4.7 (CH_3, C_T), -5.1 (CH_3, $C_{T'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 32.79 ppm.

ES$^+$MS m/z (%): 563 ($(M+Na)^+$, 100), 540 ($(M+H)^+$, 64).

HRES$^+$MS For $C_{29}H_{53}O_5PSiNa$ $(M+Na)^+$: calcd 563.3298, found 563.3300.

Data for (4.38)

Mw = 514.707 ($C_{26}H_{47}O_6PSi$).

Rf = 0.18 (Hexane/EtOAc 1:1).

IR (film): 2978 (w), 2936 (w), 2907 (w), 1736 (s), 1642 (w), 1453 (w), 1391 (w), 1237 (m), 1162 (m), 1054 (s), 1023 (s), 956 (s), 897 (m), 795 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.03 (1H, s, H_R), 4.94 (1H, s, $H_{R'}$), 4.45 (1H, dd, *J = 2.9, 1.3 Hz*, H_L), 4.12-4.05 (4H, m, H_B), 3.68 (3H, s, H_I), 2.51-2.43 (1H, m), 2.34-2.07 (7H,

m), 1.94-1.67 (4H, m), 1.43-1.42 (1H, m), 1.30 (6H, t, *J = 7.0 Hz*, H_A), 0.94 (9H, H_U), 0.74 (3H, H_O), 0.17 (3H, H_S), 0.15 (3H, $H_{S'}$) ppm.

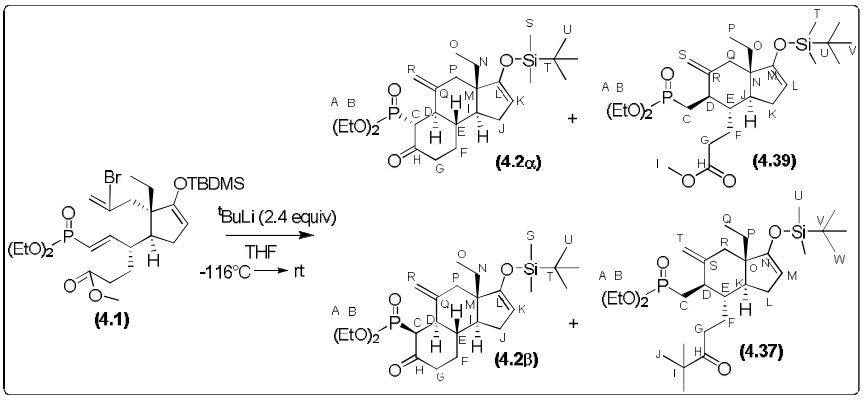
^{13}C NMR (100 MHz; $CDCl_3$): δ 174.6 (Q, C_H), 164.0 (Q, C_M), 147.5 (d, *J = 1.3 Hz*, Q, C_Q), 112.7 (CH_2, C_R), 99.2 (CH, C_L), 62.0 (d, *J = 6.6 Hz*, CH_2, C_B), 61.9 (d, *J = 6.6 Hz*, CH_2, $C_{B'}$), 52.9 (d, *J = 1.7 Hz*, CH, C_D), 51.9 (CH_3, C_I), 45.8 (CH_2), 45.7 (Q, C_N), 41.6 (d, *J = 4.7 Hz*, CH, C_J), 40.5 (CH, d, *J = 12.6 Hz*, C_E), 30.1 (CH_2, $C_{G/K}$), 29.6 (CH_2, $C_{G/K}$), 25.9 (d, *J = 141.8 Hz*, CH_2, C_C), 26.1 (CH_3, 3 x C_U), 25.9 (CH_2, C_F), 18.5 (CH_3, C_O), 16.8 (d, *J = 6.2 Hz*, CH_3, 2 x C_A), 17.9 (Q, C_T), -4.6 (CH_3, C_S), -5.1 (CH_3, $C_{S'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 31.64 ppm.

ES$^+$MS m/z (%): 515 ($(M+H)^+$, 100).

HRES$^+$MS For $C_{26}H_{48}O_6PSi$ $(M+H)^+$: calcd 515.2952, found 515.2945.

<u>The β-keto phosphonate (4.2α)</u> and **<u>the β-keto phosphonate (4.2β)</u>** and **<u>the monocyclised ketone (4.37)</u>** and **<u>the monocyclised ester (4.39)</u>**



A solution of the vinyl bromide **(4.1)** (994 mg, 1.64 mmol, 1.0 equiv) in THF (8 mL) was cooled to -116 °C in an EtOH/liquid N_2 cold bath and treated with ^{t}BuLi (1.5 M in pentanes) (2.31 mL, 3.94 mmol, 2.4 equiv). After the quick addition (over 10 seconds), the reaction was stirred for 15 min, then the cold bath was removed and the reaction was allowed to warm to room temperature over 1 h. Saturated aq. $NaHCO_3$ (10 mL) was added and H_2O (20 mL) and the reaction was extracted with DCM (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/EtOAc 70:30) using pre-neutralized silica gel. This afforded **(4.2α)** as a colourless oil (306 mg, 39%), **(4.2β)** as a

colourless oil (54 mg, 11%), **(4.37)** as a colourless oil (177 mg, 15%) and **(4.39)** as a colourless oil (90 mg, 10%).

Data for (4.2α)

Mw = 496.692 ($C_{26}H_{45}O_5PSi$).

Rf = 0.36 (Hexane/EtOAc 1:1).

IR (neat): 2956 (m), 2931 (m), 2854 (m), 1706 (m), 1617 (m), 1462 (w), 1352 (w), 1243 (s), 1229 (s), 1053 (s), 1024 (s), 960 (s), 841 (s), 783 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 4.94 (1H, s, H_R), 4.82 (1H, s, $H_{R'}$), 4.52 (1H, d, *J = 1.8 Hz*, H_K), 4.25-3.98 (4H, m, H_B), 3.41 (1H, ddd, *J = 25.9, 8.7, 1.7 Hz*, H_C), 2.85 (1H, ddd, *J = 17.2, 9.8, 2.5 Hz*, H_G), 2.69 (1H, m, H_D), 2.59 (1H, d, *J = 13.0 Hz*, H_P), 2.12-1.66 (6H, m), 1.47-1.35 (1H, m, H_E), 1.30 (3H, t, *J = 7.0 Hz*, H_A), 1.29 (3H, t, *J = 7.0 Hz*, $H_{A'}$), 1.26-1.14 (2H, m, H_N), 0.92 (9H, s, H_U), 0.83 (3H, t, *J = 7.4 Hz*, H_O), 0.16 (3H, s, H_S), 0.15 (3H, s, $H_{S'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 207.3 (d, *J = 5.1 Hz*, Q, C_H), 163.3 (Q, C_L), 145.2 (Q, C_Q), 110.5 (CH_2, C_R), 99.0 (CH, C_K), 62.8 (d, *J = 6.1 Hz*, CH_2, C_B), 62.7 (d, *J = 6.1 Hz*, CH_2, $C_{B'}$), 55.5 (CH, C_I), 51.8 (d, *J = 123.0 Hz*, CH, C_C), 48.1 (Q, C_M), 47.0 (d, *J = 4.1 Hz*, CH, C_D), 41.8 (CH_2, C_P), 37.6 (d, *J = 9.4 Hz*, CH, C_E), 37.4 (CH_2, C_G), 27.9 (CH_2, C_J), 25.8 (CH_2, C_F), 25.6 (3 x CH_3, C_U), 22.6 (CH_2, C_N), 17.9 (Q, C_T), 16.3 (d, *J = 6.1 Hz*, CH_3, C_A), 16.2 (d, *J = 6.1 Hz*, CH_3, $C_{A'}$), 8.3 (CH_3, C_O), -4.6 (CH_3, C_S), -5.1 (CH_3, $C_{S'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 22.66 ppm.

ES$^+$MS m/z (%): 1016 ($(2M+Na)^+$, 100), 497 ($(M+H)^+$, 44).

HRES$^+$MS For $C_{26}H_{46}O_5PSi$ $(M+H)^+$: calcd 497.2847, found 497.2833.

Data for (4.2β)

Mw = 496.692 ($C_{26}H_{45}O_5PSi$).

Rf = 0.48 (Hexane/EtOAc 1:1).

IR (neat): 2956 (m), 2931 (m), 2857 (m), 1717 (m), 1619 (m), 1472 (w), 1334 (w), 1252 (s), 1232 (s), 1161 (w), 1051 (s), 1025 (s), 963 (m), 840 (s), 784 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.03 (1H, s, H_R), 4.93 (1H, s, $H_{R'}$), 4.52 (1H, t, *J = 2.1 Hz*, H_K), 4.16-4.01 (4H, m, H_B), 3.56 (1H, ddd, *J = 20.0, 4.0, 1.8 Hz*, H_C), 2.87 (1H, td, *J = 14.0, 6.9 Hz*), 2.66 (1H, qd, *J = 11.4, 3.5 Hz*), 2.61 (1H, d, *J = 13.8 Hz*, H_P), 2.46 (1H, m),

2.26-1.98 (3H, m), 1.93 (1H, d, *J = 13.6 Hz*, $H_{P'}$), 1.67-1.52 (2H, m), 1.44-1.05 (3H, m), 1.31 (3H, t, *J = 7.1 Hz*, H_A), 1.31 (3H, t, *J = 7.1 Hz*, $H_{A'}$), 0.93 (9H, s, H_U), 0.90 (3H, t, *J = 7.5 Hz*, H_O), 0.18 (3H, s, H_S), 0.15 (3H, s, $H_{S'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 205.8 (Q, C_H), 163.0 (Q, C_L), 144.7 (d, *J = 2.1 Hz*, Q, C_Q), 111.6 (CH_2, C_R), 98.9 (CH, C_K), 62.6 (d, *J = 7.1 Hz*, CH_2, C_B), 62.0 (d, *J = 7.1 Hz*, CH_2, $C_{B'}$), 55.4 (CH, C_I), 54.3 (d, *J = 127.1 Hz*, CH, C_C), 50.8 (d, *J = 4.1 Hz*, CH, C_D), 47.8 (Q, C_M), 41.7 (CH_2, C_P), 40.2 (CH, C_E), 34.1 (CH_2, C_G), 31.4 (CH_2, C_J), 28.2 (CH_2, C_F), 25.6 (3 x CH_3, C_U), 22.9 (CH_2, C_N), 17.9 (Q, C_T), 16.2 (d, *J = 6.2 Hz*, CH_3, C_A), 16.2 (d, *J = 6.1 Hz*, CH_3, $C_{A'}$), 8.5 (CH_3, C_O), -4.6 (CH_3, C_S), -5.1 (CH_3, $C_{S'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 22.56 ppm.

ES$^+$MS: m/z (%): 1016 ($(2M+Na)^+$, 32), 519 ($(M+Na)^+$, 100), 497 ($(M+H)^+$, 12).

HRES$^+$MS For $C_{26}H_{46}O_5PSi$ $(M+H)^+$: calcd 497.2847, found 497.2844.

<u>Data for (4.37)</u>

Mw = 554.814 ($C_{30}H_{55}O_6PSi$).

Rf = 0.40 (Hexane/EtOAc 1:1).

IR (neat): 2957 (m), 2931 (m), 2858 (w), 1704 (m), 1620 (m), 1462 (w), 1391 (w), 1352 (m), 1230 (s), 1161 (w), 1055 (s), 1026 (s), 960 (s), 841 (s), 763 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.00 (1H, s, H_T), 4.91 (1H, s, $H_{T'}$), 4.50 (1H, t, *J = 2.2 Hz*, H_M), 4.12-4.00 (4H, m, H_B), 2.67-2.39 (3H, m), 2.23-2.08 (3H, m), 2.01-1.89 (3H, m), 1.86-1.73 (2H, m), 1.60 (1H, ddd, *J = 14.9, 10.7, 5.4 Hz*), 1.45 (1H, m), 1.28 (3H, t, *J = 7.1 Hz*, H_A), 1.27 (3H, t, *J = 7.1 Hz*, $H_{A'}$), 1.34-1.15 (2H, m, H_P), 1.12 (9H, s, H_J), 0.91 (9H, s, H_W), 0.82 (3H, t, *J = 7.4 Hz*, H_Q), 0.15 (3H, s, H_U), 0.14 (3H, s, $H_{U'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 215.9 (Q, C_H), 163.4 (Q, C_N), 147.0 (Q, C_S), 111.9 (CH_2, C_T), 98.9 (CH, C_M), 61.42 (d, *J = 6.5 Hz*, CH_2, C_B), 61.41 (d, *J = 6.4 Hz*, CH_2, C_B), 54.4 (CH, C_K), 47.9 (Q, C_I), 44.2 (CH_2, C_R), 42.1 (Q, C_O), 41.3 (d, *J = 4.5 Hz*, CH, C_E), 39.9 (d, *J = 13.2 Hz*, CH, C_D), 31.9 (CH_2, C_G), 29.2 (CH_2, C_L), 26.4 (CH_2, C_F), 25.6 (3 x CH_3, C_J), 24.8 (3 x CH_3, C_W), 25.3 (d, *J = 140.9 Hz*, CH_2, C_C), 22.4 (CH_2, C_P), 17.9 (Q, C_V), 16.4 (d, *J = 6.1 Hz*, 2 x CH_2, C_A), 8.3 (CH_3, C_Q), -4.6 (CH_3,C_U), -5.1 (CH_3, $C_{U'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 32.92 ppm.

ES$^+$MS m/z (%): 1132 ($(2M+Na)^+$, 15), 577 ($(M+Na)^+$, 100), 555 ($(M+H)^+$, 82).

HRES$^+$MS For $C_{30}H_{55}O_6PSi$ $(M+H)^+$: calcd 555.3629, found 555.3628.

Data for (4.39)

Mw = 528.734 ($C_{27}H_{49}O_6PSi$).

Rf = 0.18 (Hexane/EtOAc 1:1).

IR (neat): 2978 (w), 2931 (w), 2907 (w), 1737 (s), 1619 (w), 1462 (w), 1437 (w), 1390 (w), 1229 (s), 1164 (m), 1054 (s), 1026 (s), 959 (s), 839 (s), 782 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.00 (1H, s, H_S), 4.93 (1H, s, $H_{S'}$), 4.50 (1H, s, H_L), 4.18-3.99 (4H, m, H_B), 3.65 (3H, s, H_I), 2.53 (1H, d, *J = 13.1 Hz*, H_Q), 2.44 (1H, ddd, *J = 15.8, 10.6, 5.2 Hz*), 2.26 (1H, ddd, *J = 15.9, 11.2, 6.0 Hz*), 2.21-1.67 (9H, m, $H_{Q'}$ + 8H), 1.48 (1H, td, *J = 16.1, 8.3 Hz*), 1.29 (6H, t, *J = 7.0 Hz*, H_A), 1.36-1.14 (2H, m, H_O), 0.91 (9H, s, H_V), 0.83 (3H, t, *J = 7.4 Hz*, H_P), 0.15 (3H, s, H_T), 0.13 (3H, s, $H_{T'}$) ppm.

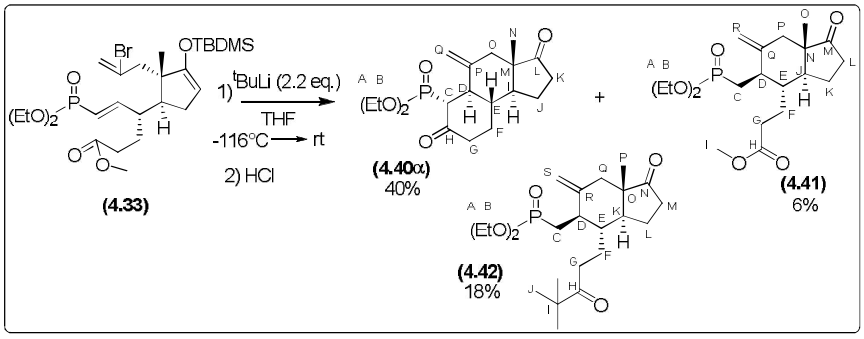
^{13}C NMR (100 MHz; $CDCl_3$): δ 174.2 (Q, C_H), 163.3 (Q, C_M), 146.9 (Q, C_R), 112.0 (CH_2, C_S), 99.0 (CH, C_L), 61.5 (d, *J = 6.6 Hz*, CH_2, C_B), 61.5 (d, *J = 6.5 Hz*, CH_2, $C_{B'}$), 54.2 (CH, C_D), 51.5 (CH_3, C_I), 47.8 (Q, C_N), 42.0 (CH_2, C_Q), 40.9 (d, *J = 4.7 Hz*, CH, C_J), 39.9 (d, *J = 12.7 Hz*, CH, C_E), 29.8 (CH_2, $C_{G/K}$), 29.0 (CH_2, $C_{G/K}$), 25.6 (CH_2, C_F), 25.6 (3 x CH_3, C_V), 25.5 (d, *J = 141.4 Hz*, CH_2, C_C), 22.5 (CH_2, C_O), 17.9 (Q, C_U), 16.4 (d, *J = 6.1 Hz*, 2 x CH_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 32.46 ppm.

ES$^+$MS m/z (%): 1080 ($(2M+Na)^+$, 12), 551 ($(M+Na)^+$, 100), 529 ($(M+H)^+$, 50).

HRES$^+$MS For $C_{27}H_{50}O_6PSi$ $(M+H)^+$: calcd 529.3114, found 529.3111.

The β-keto phosphonate (4.40α) and **the monocyclised ketone (4.42)** and **the monocyclised ester (4.41)**



A solution of the vinyl bromide **(4.33)** (350 mg, 0.59 mmol, 1.0 equiv) in THF (10 mL) was cooled to -116 °C in an EtOH/liquid N_2 cold bath and treated with ^{t}Butyllithium (1.5 M in pentanes) (965 μL, 1.1 mmol, 2.2 equiv). After the dropwise addition, the reaction

was stirred for 15 min, then the cold bath was removed and the reaction was allowed to warm to room temperature over 1 h. Saturated aq. $NaHCO_3$ (10 mL) was added and the reaction was extracted with DCM (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was dissolved in THF (5 mL) and treated with HCl 2M (5 mL) and the mixture was stirred for 30 min at room temperature. Water was added (10 mL) and the mixture was extracted with DCM (3 x 20 mL), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 60:40). This yielded **(4.40α)** as a colourless oil (89 mg, 41%) as a single diastereoisomer , **(4.42)** as a colourless oil (40 mg, 18%) and **(4.41)** as a colourless oil (14 mg, 6%). Recrystallization of **(4.40α)** in (DCM/Hexane 1:3) afforded fine colourless needles.

Data for (4.40α)

Mw = 368.404 ($C_{19}H_{29}O_5P$).

Rf = 0.38 (Hexane/Acetone 60:40).

IR (film): 2978 (w), 2936 (w), 2907 (w), 1736 (s), 1707 (s), 1644 (w), 1453 (w), 1391 (w), 1242 (m), 1163 (w), 1049 (s), 1018 (s), 959 (s), 852 (m), 784 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 4.96 (1H, t, *J = 1.7 Hz*, H_Q), 4.87 (1H, s, $H_{Q'}$), 4.13-4.02 (4H, m, H_B), 3.38 (1H, ddd, *J = 26.4, 8.4, 1.9 Hz*, H_C), 2.85 (1H, ddd, *J = 17.4, 9.5, 2.8 Hz*, H_G), 2.75-2.60 (1H, m, H_D), 2.51-2.29 (3H, m, $H_{G'}$+H_K+H_O), 2.20-1.74 (5H, m, $H_{K'}$+$H_{O'}$+2H_F+H_J), 1.68-1.47 (2H, m, $H_{J'}$+H_I), 1.39-1.29 (1H, m, H_E), 1.28 (3H, t, *J = 6.6 Hz*, H_A), 1.24 (3H, t, *J = 6.6 Hz*, $H_{A'}$), 0.78 (3H, H_N) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 218.9 (Q, C_L), 206.4 (d, *J = 5.2 Hz*, Q, C_H), 143.5 (d, *J = 1.8 Hz*, Q, C_P), 111.3 (CH_2, C_Q), 62.9 (d, *J = 7.0 Hz*, CH_2, C_B), 62.7 (d, *J = 7.0 Hz*, CH_2, $C_{B'}$), 50.3 (d, *J = 123.9 Hz*, CH, C_C), 50.5 (CH, C_I), 48.8 (Q, C_M), 46.4 (d, *J = 4.0 Hz*, CH, C_D), 42.8 (CH_2, C_O), 38.8 (d, *J = 9.2 Hz*, CH, C_E), 37.4 (CH_2, C_G), 35.8 (CH_2, C_K), 25.3 (CH_2, C_F), 21.6 (CH_2, C_J), 16.2 (d, *J = 6.1 Hz*, 2 x CH_3, C_A), 14.2 (CH_3, C_N) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 22.67 ppm.

ES$^+$MS m/z (%): 759 ($(2M+Na)^+$, 42), 369 ($(M+H)^+$, 100).

HRES$^+$MS: not necessary, X-ray obtained instead.

X-ray: X-ray data available in Appendix II.

Data for (4.41)

Mw = 400.446 ($C_{20}H_{33}O_6P$).

Rf = 0.22 (Hexane/Acetone 60:40).

IR (film): 2978 (w), 2936 (w), 2907 (w), 1736 (s), 1723 (s), 1642 (w), 1453 (w), 1391 (w), 1237 (m), 1162 (m), 1054 (s), 1023 (s), 956 (s), 897 (m), 795 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.05 (1H, s, H_R), 4.97 (1H, s, $H_{R'}$), 4.10-4.03 (4H, m, H_B), 3.67 (3H, s, H_I), 2.50-2.39 (3H, m), 2.32-2.24 (1H, m), 2.18-1.99 (6H, m), 1.92-1.87 (2H, m), 1.68-1.46 (3H, m), 1.29 (6H, t, *J = 7.0 Hz*, H_A), 0.78 (3H, H_O), ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 219.5 (Q, C_M), 173.8 (Q, C_H), 144.9 (d, *J = 1.4 Hz*, Q, C_Q), 112.9 (CH_2, C_R), 61.6 (d, *J = 6.5 Hz*, CH_2, C_B), 61.5 (d, *J = 6.5 Hz*, CH_2, $C_{B'}$), 51.6 (CH_3, C_I), 48.9 (d, *J = 1.7 Hz*, CH, C_J), 48.6 (Q, C_N), 42.9 (CH_2, C_P), 40.7 (d, *J = 8.7 Hz*, CH, C_D), 40.6 (CH, C_E), 35.9 (CH_2, $C_{K/L}$), 29.2 (CH_2, $C_{F/G}$), 24.9 (d, *J = 142.3 Hz*, CH_2, C_C), 24.6 (CH_2, $C_{F/G}$), 22.6 (CH_2, $C_{K/L}$), 16.4 (d, *J = 6.1 Hz*, 2 x CH_3, C_A), 14.1 (CH_3, C_O) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 31.64 ppm.

ES$^+$MS m/z (%): 823 ($(2M+Na)^+$, 33), 423 ($(M+Na)^+$, 75), 401 ($(M+H)^+$, 70).

HRES$^+$MS For $C_{20}H_{34}O_6P$ $(M+H)^+$: calcd 401.2093, found 401.2100.

Data for (4.42)

Mw = 426.527 ($C_{23}H_{39}O_5P$).

Rf = 0.41 (Hexane/Acetone 60:40).

IR (film): 2965 (m), 2905 (w), 1737 (s), 1703 (m), 1239 (m), 1052 (s), 1024 (s), 956 (s), 730 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.04 (1H, s, H_S), 4.95 (1H, s, $H_{S'}$), 4.09-3.99 (4H, m, H_B), 2.68-2.58 (1H, m, H_G), 2.50-2.34 (3H, m, H_M+H_Q+$H_{G'}$), 2.26-2.01 (5H, m, H_C+$H_{C'}$+$H_{M'}$+H_D+$H_{Q'}$), 1.96 (1H, m), 1.89-1.70 (2H, m), 1.69-1.53 (2H, m, contains H_K), 1.52-1.41 (1H, m, H_E), 1.27 (3H, t, *J* = 7.1 Hz, H_A), 1.26 (3H, t, *J* = 7.1 Hz, $H_{A'}$), 1.13 (9H, s, H_J), 0.76 (3H, s, H_P) ppm.

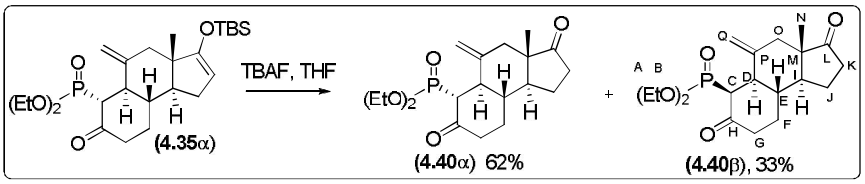
^{13}C NMR (100 MHz; $CDCl_3$): δ 219.9 (Q, C_N), 215.8 (Q, C_H), 145.3 (Q, C_R), 112.9 (CH_2, C_S), 61.8 (d, *J = 6.5 Hz*, CH_2, $C_{B'}$), 61.8 (d, *J = 6.4 Hz*, CH_2, C_B), 49.1 (Q, C_O), 48.8 (CH, C_K), 44.5 (Q, C_I), 43.2 (CH_2, C_Q), 41.1 (d, *J = 4.2 Hz*, CH, C_E), 40.9 (d, *J = 13.8 Hz*, CH, C_D), 36.1 (CH_2, C_M), 31.2 (CH_2, C_G), 26.6 (3 x CH_3, C_J), 24.9 (d, *J = 142.0 Hz*, CH_2, C_C), 23.9 (CH_2, $C_{F/L}$), 22.9 (CH_2, $C_{F/L}$), 16.6 (d, *J = 6.0 Hz*, 2 x CH_2, C_A), 14.3 (CH_3, C_P) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 32.05 ppm.

ES$^+$MS m/z (%): 875 ($(2M+Na)^+$, 32), 427 ($(M+H)^+$, 100).

HRES$^+$MS For $C_{23}H_{39}O_5PNa$ $(M+Na)^+$: calcd 449.2427, found 449.2418.

The β-keto phosphonate (4.40β)



The silyl enol **(4.35α)** (119 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (5 mL) and treated with TBAF (1 M in THF, 0.50 mL, 0.50 mmol, 2.0 equiv) and the mixture was stirred for 1 h at room temperature. Water was added (5 mL) and the reaction was extracted with DCM (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 60:40). This yielded **(4.40α)** as a colourless oil (57 mg, 62%) and **(4.40β)** as a colourless oil (30 mg, 33%).

Data for (4.40α)

Mw = 368.404 ($C_{19}H_{29}O_5P$).

Rf = 0.56 (Hexane/Acetone 60:40).

IR (film): 2970 (w), 2936 (w), 1733 (s), 1706 (s), 1644 (w), 1445 (w), 1391 (w), 1242 (m), 1049 (s), 1019 (s), 955 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.11 (1H, t, *J = 2.2 Hz*, H_Q), 5.02 (1H, t, *J = 2.2 Hz*, $H_{Q'}$), 4.24-4.02 (4H, m, H_B), 3.58 (1H, ddd, *J = 19.9, 4.1, 2.0 Hz*, H_C), 2.88 (1H, dt, *J = 14.0, 6.9 Hz*, H_G), 2.73 (1H, dq, *J = 11.2, 3.6 Hz*, H_E), 2.56-2.47 (3H, m, $H_{G'}$+H_O+H_K), 2.33-2.02 (5H, m, $H_{O'}$+$H_{K'}$+H_D+H_F+H_J), 1.69 (1H, tt, *J = 12.4, 9.1 Hz*, $H_{J'}$), 1.41 (1H, m, H_I), 1.33 (3H, t, *J = 7.0 Hz*, H_A), 1.32 (3H, t, *J = 7.0 Hz*, $H_{A'}$), 1.31 (1H, m, $H_{F'}$) 0.99 (3H, s, H_N) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 219.9 (Q, C_L), 204.8 (Q, C_H), 143.2 (d, *J = 2.3 Hz*, Q, C_P), 112.8 (CH_2, C_Q), 62.8 (d, *J = 7.1 Hz*, CH_2, C_B), 62.2 (d, *J = 7.3 Hz*, CH_2, $C_{B'}$), 54.1 (d, *J = 127.1 Hz*, CH, C_C), 50.5 (CH, C_I), 49.9 (d, *J = 4.7 Hz*, CH, C_D), 48.3 (Q, C_M), 42.3

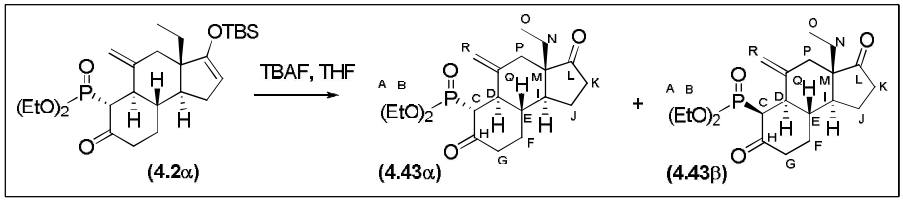
(CH_2, C_O), 40.0 (CH_2, C_G), 36.0 (CH_2, C_K), 35.3 (CH, C_E), 30.8 (CH_2, C_F), 22.0 (CH_2, C_J), 16.2 (d, *J = 6.6 Hz*, CH_3, C_A), 16.2 (d, *J = 7.4 Hz*, CH_3, C_A), 14.5 (CH_3, C_N) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 22.66 ppm.

ES$^+$MS m/z (%): 759 ($(2M+Na)^+$, 100), 391 ($(M+Na)^+$, 17), 369 ($(M+H)^+$, 14).

HRES$^+$MS For $C_{19}H_{30}O_5P$ $(M+H)^+$: calcd 369.1825, found 369.1828.

<u>The β-keto phosphonate (4.43α)</u> and **<u>the β-keto phosphonate (4.43β)</u>**



The silyl enol **(4.2α)** (123 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (5 mL) and treated with TBAF (1 M in THF, 0.50 mL, 0.50 mmol, 2.0 equiv) and the mixture was stirred for 1 h at room temperature. Water was added (5 mL) and the reaction was extracted with DCM (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 60:40). This yielded **(4.43α)** as a colourless oil (58 mg, 66%) and **(4.43β)** as a colourless oil (25 mg, 30%) which was recrystallized in (DCM/Hexane 1:3) to afford fine colourless needles.

<u>Data for (4.43α)</u>

Mw = 382.431 ($C_{20}H_{31}O_5P$).

Rf = 0.46 (Hexane/Acetone 60:40).

IR (neat): 2970 (w), 2936 (w), 1733 (s), 1706 (s), 1644 (w), 1445 (w), 1391 (w), 1242 (m), 1049 (s), 1019 (s), 955 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 4.99 (1H, s, H_R), 4.87 (1H, s, $H_{R'}$), 4.15-4.02 (4H, m, H_B), 3.39 (1H, ddd, *J = 26.2, 8.5, 1.8 Hz*, H_C), 2.87 (1H, ddd, *J = 17.3, 9.8, 2.8 Hz*, H_G), 2.70 (1H, d, *J = 13.5 Hz*, H_P), 2.76-2.60 (1H, m, H_D), 2.49-2.31 (2H, m), 2.14 (1H, ddd, *J = 10.1, 8.7, 5.6 Hz*), 1.98 (2H, ddd, *J = 9.5, 6.4, 3.5 Hz*), 1.92 (1H, d, *J = 13.9 Hz*, $H_{P'}$), 1.87-1.73 (1H, m), 1.73-1.57 (2H, m), 1.28 (6H, dd, *J = 14.8, 7.2 Hz*, H_A), 1.48-1.21 (3H, m, H_E + H_N), 0.73 (3H, t, *J = 7.4 Hz,* H_O) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 217.6 (Q, C_L), 206.6 (d, *J = 5.2 Hz*, Q, C_H), 143.5 (d, *J = 1.4 Hz*, Q, C_Q), 111.0 (CH_2, C_R), 62.9 (d, *J = 7.0 Hz*, CH_2, C_B), 62.8 (d, *J = 6.9 Hz*, CH_2, C_B), 52.0 (Q, C_M), 51.3 (CH, C_I), 51.4 (d, *J = 124.0 Hz*, CH, C_C), 46.2 (d, *J = 3.9 Hz*, CH,

C_D), 38.8 (CH_2, C_P), 38.6 (d, *J = 9.4 Hz*, CH, C_E), 37.4 (CH_2, C_G), 35.8 (CH_2, C_K), 25.4 (CH_2, C_F), 20.9 (CH_2, C_J), 18.3 (CH_2, C_N), 16.3 (d, *J = 6.0 Hz*, CH_3, C_A), 16.2 (d, *J = 6.2 Hz*, CH_3, $C_{A'}$), 6.9 (CH_3, C_O) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 22.67 ppm.

ES$^+$MS m/z (%): 787 ($(2M+Na)^+$, 40), 405 ($(M+Na)^+$, 100), 383 ($(M+H)^+$, 13).

HRES$^+$MS For $C_{20}H_{31}O_5PNa$ $(M+Na)^+$: calcd 405.1801, found 405.1808.

Data for (4.43β)

Mw = 382.431 ($C_{20}H_{31}O_5P$).

Rf = 0.58 (Hexane/Acetone 60:40).

IR (neat): 2964 (w), 2937 (w), 1732 (s), 1716 (s), 1644 (w), 1444 (w), 1391 (w), 1244 (m), 1044 (s), 1019 (s), 952 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.08 (1H, s, H_R), 5.00 (1H, s, $H_{R'}$), 4.20-4.00 (4H, m, H_B), 3.56 (1H, ddd, *J = 19.9, 3.9, 1.9 Hz*, H_C), 2.87 (1H, dt, *J = 14.1, 7.0 Hz*), 2.78 (1H, dd, *J = 11.2, 3.4 Hz*), 2.72 (1H, d, *J = 14.3 Hz*, H_P), 2.51 (1H, m), 2.47 (1H, dd, *J = 19.2, 9.1 Hz*), 2.33-2.08 (3H, m), 2.07-1.96 (1H, m), 1.87 (1H, d, *J = 14.2 Hz*, $H_{P'}$), 1.83-1.70 (2H, m), 1.50-1.42 (1H, m), 1.31 (3H, t, *J = 7.1 Hz*, H_A), 1.31 (3H, t, *J = 7.1 Hz*, $H_{A'}$), 1.40-1.24 (2H, m), 0.78 (3H, t, *J = 7.4 Hz*, H_O) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 218.4 (Q, C_L), 204.9 (Q, C_H), 143.0 (d, *J = 2.2* Hz, Q, C_Q), 112.4 (CH_2, C_R), 62.8 (d, *J* = 7.0 Hz, CH_2, C_B), 62.2 (d, *J* = 7.1 Hz, CH_2, C_B), 54.1 (d, *J* = 127.0 Hz, CH, C_C), 51.5 (Q, C_M), 51.3 (CH, C_I), 49.8 (d, *J* = 4.8 Hz, CH, C_E), 40.0 (CH_2, C_P), 38.6 (CH_2, C_G), 35.9 (CH_2, C_K), 35.1 (d, *J* = 1.3 Hz, CH, C_D), 31.0 (CH_2, C_F), 21.3 (CH_2, C_J), 18.5 (CH_2, C_N), 16.2 (d, *J* = 5.8 Hz, CH_3, C_A), 16.2 (d, *J* = 5.8 Hz, CH_3, $C_{A'}$), 7.0 (CH_3, C_O) ppm.

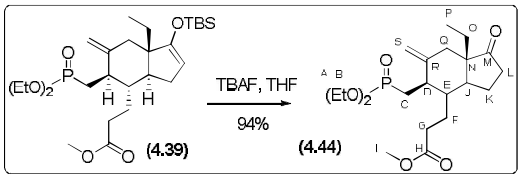
^{31}P NMR (121 MHz; $CDCl_3$): δ 22.68 ppm.

ES$^+$MS: m/z (%): 787 ($(2M+Na)^+$, 24), 405 ($(M+Na)^+$, 81), 383 ($(M+H)^+$, 100).

HRMS: not necessary, X-ray obtained instead.

X-ray: X-ray data available in Appendix II.

The C-ring cyclised ester (4.44)



The ester **(4.39)** (90 mg, 0.17 mmol, 1.0 equiv) was dissolved in THF (5 mL) and treated with TBAF (1 M in THF, 0.34 mL, 0.34 mmol, 2.0 equiv) and the mixture was stirred for 30 min at room temperature. H_2O was added (5 mL) and the reaction was extracted with DCM (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 60:40). This yielded **(4.44)** as a colourless oil (65 mg, 94%).

Mw = 414.473 ($C_{21}H_{35}O_6P$).

Rf = 0.39 (Hexane/Acetone 60:40).

IR (film): 2971 (w), 2955 (w), 2905 (w), 1731 (s), 1641 (w), 1438 (m), 1390 (w), 1233 (m), 1172 (m), 1050 (s), 1023 (s), 958 (s), 891 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.03 (1H, s, H_S), 4.97 (1H, s, $H_{S'}$), 4.17-3.95 (4H, m, H_B), 3.66 (3H, s, H_I), 2.63 (1H, d, *J = 13.5 Hz*, H_Q), 2.48-2.37 (2H, m), 2.26 (1H, td, *J = 9.8, 8.0 Hz*), 2.21-2.03 (4H, m), 2.00-1.92 (1H, m), 1.86 (1H, d, *J = 13.6 Hz*, $H_{Q'}$), 1.87 (2H, m), 1.76-1.52 (3H, m), 1.46-1.34 (1H, m, H_O), 1.28 (6H, t, *J = 7.1 Hz*, H_A), 1.27-1.17 (1H, m, $H_{O'}$), 0.72 (3H, t, *J = 7.4 Hz*, H_P) ppm.

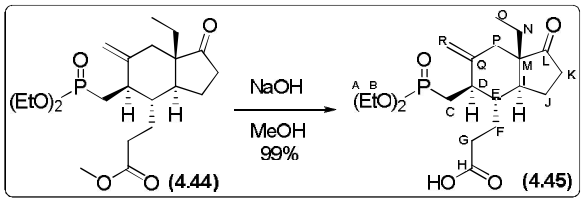
^{13}C NMR (100 MHz; $CDCl_3$): δ 218.1 (Q, C_M), 173.8 (Q, C_H), 144.9 (Q, C_R), 112.5 (CH_2, C_S), 61.6 (d, *J = 2.7 Hz*, CH_2, C_B), 61.5 (d, *J = 2.6 Hz*, CH_2, $C_{B'}$), 51.7 (Q, C_N), 51.6 (CH_3, C_I), 49.6 (CH, C_J), 40.4 (CH, C_E), 40.4 (d, *J* = 17.6 Hz, CH, C_D), 38.8 (CH_2, C_Q), 35.8 (CH_2, C_L), 29.1 (CH_2, C_G), 24.7 (CH_2, C_F), 25.0 (d, *J = 142.2 Hz*, CH_2, C_C), 21.9 (CH_2, C_K), 18.1 (CH_2, C_O), 16.3 (d, *J = 6.2 Hz*, 2 x CH_3, C_A), 6.8 (CH_3, C_P) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 31.69 ppm.

ES$^+$MS m/z (%): 852 ($(2M+Na)^+$, 7), 437 ($(M+Na)^+$, 100), 415 ($(M+H)^+$, 8).

HRES$^+$MS For $C_{21}H_{35}O_6PNa$ $(M+Na)^+$: calcd 437.2063, found 437.2063.

The C-ring cyclised carboxylic acid (4.45)



To a solution of the ester **(4.44)** (60 mg, 0.14 mmol, 1.0 equiv) in MeOH (5 mL) was added NaOH 4 M (3 mL). The mixture was stirred at room temperature for 90 min until completion. The pH was adjusted (pH 6) before extraction of the crude mixture with DCM (3 x 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (DCM/MeOH 95:5) to afford **(4.45)** (55 mg, 99 %) as a colourless oil. Recrystallization in (DCM/Hexane) afforded **(4.45)** as fine white crystals (m.p. = 108-112 °C).

Mw = 400.446 ($C_{20}H_{33}O_6P$).

Rf = 0.38 (DCM/MeOH 95:5).

IR (film): 3446 (br w), 2978 (w), 2936 (w), 2907 (w), 1736 (s), 1642 (w), 1453 (w), 1391 (w), 1237 (m), 1162 (m), 1054 (s), 1023 (s), 956 (s), 897 (m), 795 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.40 (1H, br hump, OH), 5.00 (1H, s, H_R), 4.98 (s, 1H, $H_{R'}$), 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), 1.41-1.22 (2H, m, H_N), 1.31 (3H, t, *J = 7.1 Hz*, H_A), 1.29 (3H, t, *J = 7.1 Hz*, $H_{A'}$), 0.74 (3H, t, *J = 7.4 Hz*, H_O) ppm.

^{13}C NMR (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_I), 40.8 (d, *J = 12.1 Hz*, CH, C_D), 39.5 (d, *J = 4.4 Hz*, CH, C_E), 38.8 (CH_2, C_P), 35.8 (CH_2), 29.2 (CH_2), 25.0 (d, *J = 142.4 Hz*, C_C), 24.6 (CH_2), 21.7 (CH_2), 18.1 (CH_2, C_N), 16.3 (d, *J = 6.1 Hz*, 2 x CH_3, C_A), 6.8 (CH_3, C_O) ppm.

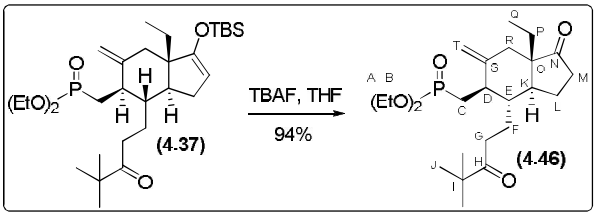
^{31}P NMR (121 MHz; $CDCl_3$): δ 32.38 ppm.

ES$^+$MS m/z (%): 824 ($(2M+Na)^+$, 36), 423 ($(M+Na)^+$, 70), 401 ($(M+H)^+$, 100).

HRES$^+$MS For $C_{20}H_{33}O_6P$ $(M+H)^+$: calcd 401.2088, found 401.2088.

X-ray: X-ray data available in Appendix II.

The C-ring cyclised ketone (4.46)



The ketone **(4.37)** (0.150 g, 0.27 mmol, 1.0 equiv) was dissolved in THF (5 mL) and treated with TBAF (1 M in THF, 0.54 mL, 0.54 mmol, 2.0 equiv) and the mixture was stirred for 30 min at room temperature. Water was added (5 mL) and the reaction was extracted with DCM (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 70:30). This yielded **(4.46)** as a colourless oil (0.107 g, 94%).

Mw = 440.269 ($C_{24}H_{41}O_5P$).

Rf = 0.35 (Hexane/Acetone 70:30).

IR (film): 2968 (w), 2906 (w), 1734 (s), 1702 (s), 1461 (w), 1233 (m), 1051 (s), 1024 (s), 957 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.04 (1H, s, H_T), 4.97 (1H, s, $H_{T'}$), 4.11-3.96 (4H, m, H_B), 2.68-2.56 (2H, m, H_G+H_R), 2.48-2.36 (2H, m, $H_{G'}$+H_M), 2.27-2.03 (4H, m, H_D+$H_{M'}$+H_C+$H_{C'}$), 2.00-1.51 (7H, m, H_K+H_E+H_F+$H_{F'}$+H_L+$H_{L'}$+$H_{R'}$), 1.41 (1H, m, H_P), 1.28 (3H, t, *J = 7.0 Hz*, H_A), 1.28 (3H, t, *J = 7.1 Hz*, $H_{A'}$), 1.22 (1H, m, $H_{P'}$), 1.14 (9H, s, H_J), 0.72 (3H, t, *J = 7.4 Hz*, H_Q) ppm.

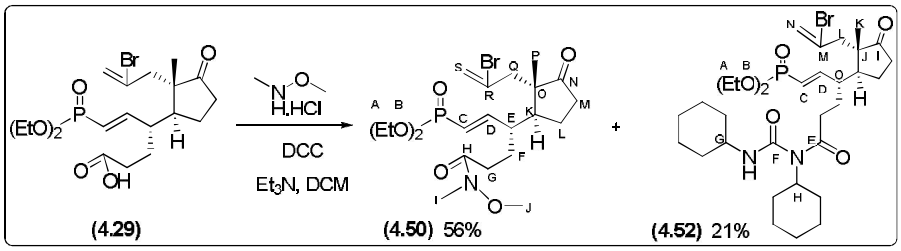
^{13}C NMR (100 MHz; $CDCl_3$): δ 218.2 (Q, C_N), 215.5 (Q, C_H), 145.0 (Q, C_S), 112.3 (CH_2, C_T), 61.5 (d, *J = 6.5 Hz*, CH_2, C_B), 61.5 (d, *J = 6.5 Hz*, CH_2, $C_{B'}$), 51.8 (Q, C_O), 49.7 (CH, C_K), 44.3 (Q, C_I), 40.6 (d, *J = 4.3 Hz*, CH, C_E), 40.4 (d, *J = 13.7 Hz*, CH, C_D), 38.9 (CH_2, C_R), 35.8 (CH_2, C_M), 30.9 (CH_2, C_G), 26.3 (3 x CH_3, C_J), 24.7 (d, *J = 141.9 Hz*, CH_2, C_C), 23.8 (CH_2, C_F), 22.0 (CH_2, C_L), 18.1 (CH_2, C_P), 16.4 (d, *J = 6.1 Hz*, 2 x CH_2, C_A), 6.9 (CH_3, C_Q) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 32.14 ppm.

ES$^+$MS m/z (%): 464/463 (1:3, $(M+Na)^+$, 100), 442/441 (1:3, $(M+H)^+$, 12).

HRES$^+$MS For $C_{24}H_{41}O_5PNa$ $(M+Na)^+$: calcd 463.2584, found 463.2587.

The Weinreb amide (4.50) and **the urea (4.52)**



(4.29) (4.50) 56% (4.52) 21%

To a DCM (7 mL) solution of acid **(4.29)** (246 mg, 0.53 mmol, 1.0 equiv) were successively added at room temperature *N,O*-dimethylhydroxylamine hydrochloride (52 mg, 0.53 mmol, 1.0 equiv), Et_3N (0.074 mL, 0.53 mmol, 1.0 equiv) and finally DCC (110 mg, 0.53 mmol, 1.0 equiv). After an overnight stirring at room temperature under N_2, 0.5 equiv of all the reagents were added in the same order and stirring continued for 4 h. Et_2O (10 mL) was added and the precipitated solid filtered and rinsed with Et_2O. The combined etherate phases were concentrated and the resulting crude purified by column chromatography (Hexane/Acetone 60:40) to afford Weinreb amide **(4.50)** (150 mg, 56%) as a colourless oil, and urea **(4.52)** (75 mg, 21%) as a white solid.

Data for (4.50)

Mw = 508.383 ($C_{21}H_{35}BrNO_6P$).

Rf = 0.42 (Hexane/Acetone 60:40).

IR (neat): 2972 (w), 2937 (w), 1737 (s), 1656 (s), 1388 (w), 1240 (s), 1020 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.60 (1H, ddd, *J = 21.7, 17.2, 9.7 Hz*, H_D), 5.97 (1H, s, H_S), 5.68 (1H, dd, *J = 20.9, 17.2 Hz*, H_C), 5.54 (1H, s, $H_{S'}$), 4.18-3.97 (4H, m, H_B), 3.64 (3H, s, H_J), 3.15 (3H, s, H_I), 3.05 (1H, d, *J = 14.9 Hz*, H_Q), 2.49 (1H, d, *J = 14.9 Hz*, $H_{Q'}$), 2.44-2.23 (7H, m, contains H_E+H_K+H_M), 2.13 (1H, m), 1.64-1.40 (2H, m), 1.32 (3H, t, *J = 7.0 Hz*, H_A), 1.31 (3H, t, *J = 7.0 Hz*, $H_{A'}$), 0.86 (3H, s, H_P) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 221.4 (Q, C_N), 173.6 (Q, C_H), 155.0 (d, *J = 3.8 Hz*, CH, C_D), 129.9 (Q, C_R), 122.4 (CH_2, C_S), 119.3 (d, *J = 187.1 Hz*, CH, C_C), 61.7 (d, *J = 5.8 Hz*, CH_2, C_B), 61.6 (d, *J = 5.7 Hz*, CH_2, $C_{B'}$), 61.2 (CH_3, C_J), 51.7 (Q, C_O), 47.0 (CH_2, C_Q), 46.8 (d, *J = 20.9 Hz*, CH, C_E), 43.8 (CH, C_K), 36.9 (CH_2, C_M), 32.2 (CH_3, C_I), 28.6 (CH_2), 26.1 (CH_2), 23.8 (CH_2), 18.7 (CH_3, C_P), 16.4 (d, *J = 5.8 Hz*, CH_3, C_A), 16.4 (d, *J = 6.0 Hz*, CH_3, $C_{A'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.73 ppm.

ES$^+$MS m/z (%): 510/508 (1:1, $(M+H)^+$, 100).

HRES$^+$MS For $C_{21}H_{35}{}^{79}BrNO_6PNa$ $(M+Na)^+$: calcd 530.1278, found 530.1275.

Data for (4.52)

Mw = 671.643 ($C_{32}H_{52}BrN_2O_6P$).

Rf = 0.66 (Hexane/Acetone 60:40).

IR (film): 3249 (br w), 2933 (m), 2855 (w), 1742 (m), 1687 (s), 1651 (s), 1537 (m), 1226 (s), 1022 (s), 969 (s) cm^{-1}

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.34 (1H, br s, NH), 6.50 (1H, ddd, *J = 21.3, 17.1, 9.9 Hz*, H_D), 5.84 (1H, s, H_N), 5.62 (1H, dd, *J = 21.8, 17.1 Hz*, H_C), 5.53 (1H, s, $H_{N'}$), 4.18-4.03 (4H, m, H_B), 4.02-3.90 (1H, m, H_H), 3.73-3.54 (1H, m, H_G), 3.06 (1H, d, *J = 14.9 Hz*, H_L), 2.46-2.24 (7H, m, contains $H_{L'}$), 2.08 (1H, m), 2.02-1.44 (14H, m), 1.39-1.07 (15H, m), 0.85 (3H, s, H_K) ppm.

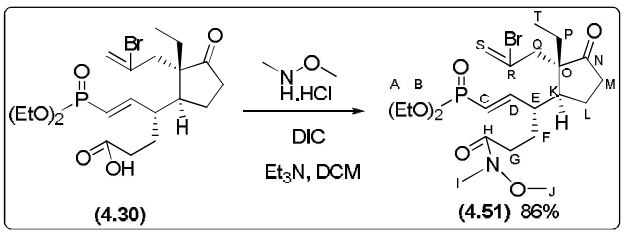
^{13}C NMR (100 MHz; $CDCl_3$): δ 221.3 (Q, C_I), 171.0 (Q, C_E), 153.8 (d, *J = 18.6 Hz*, CH, C_D), 153.7 (Q, C_F), 130.0 (Q, C_M), 122.0 (CH_2, C_N), 118.9 (d, *J = 188.1 Hz*, CH, C_C), 62.0 (d, *J = 6.1 Hz*, CH_2, C_B), 61.9 (d, *J = 6.1 Hz*, CH_2, $C_{B'}$), 54.8 (CH, C_H), 52.3 (Q, C_J) 50.1 (CH, C_G), 47.0 (CH_2, C_L), 47.0 (d, *J = 20.9 Hz*, CH, C_O), 44.1 (CH), 37.4 (CH_2), 33.03 (CH_2), 33.00 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 31.2 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 24.3 (CH_2), 19.3 (CH_3, C_K), 16.91 (d, *J = 6.1 Hz*, CH_3, C_A), 16.90 (d, *J = 6.1 Hz*, CH_3, $C_{A'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.43 ppm.

ES$^-$MS m/z (%): 671/669 (1:1, $(M-H)^+$, 62).

HRES$^+$MS For $C_{32}H_{52}{}^{79}BrN_2O_6PNa$ $(M+Na)^+$: calcd 693.2639, found 693.2632.

The Weinreb amide (4.51)



(4.30) (4.51) 86%

To a DCM (10 mL) solution of acid **(4.30)** (540 mg, 1.17 mmol, 1.0 equiv) were successively added at room temperature *N,O*-dimethylhydroxylamine hydrochloride (227 mg, 2.34 mmol, 2.0 equiv), Et_3N (0.326 mL, 2.34 mmol, 2.0 equiv) and finally DIC (0.362 mL, 2.34 mmol, 2.0 equiv). After an overnight stirring at room temperature (16 h) under N_2, Et_2O (20 mL) was added and the precipitated solid filtered and rinsed with Et_2O. The combined etherate phases were concentrated and the resulting crude purified by column chromatography (Hexane/Acetone 60:40) to afford Weinreb amide **(4.51)** (525 mg, 86%) as a light yellow oil.

Mw = 522.410 ($C_{22}H_{37}BrNO_6P$).

Rf = 0.22 (Hexane/Acetone 70:30).

IR (neat): 2974 (w), 2939 (w), 1735 (s), 1658 (s), 1390 (w), 1238 (s), 1020 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.60 (1H, ddd, *J = 21.8, 17.2, 9.9 Hz*, H_D), 5.98 (1H, s, H_S), 5.69 (1H, dd, *J = 20.9, 17.2 Hz*, H_C), 5.54 (1H, s, $H_{S'}$), 4.12-3.99 (4H, m, H_B), 3.64 (3H, s, H_J), 3.15 (3H, s, H_I), 3.13 (1H, d, *J = 15.4 Hz*, H_Q), 2.50-2.23 (7H, m), 2.37 (1H, d, *J = 14.9 Hz*, $H_{Q'}$), 2.15 (1H, m), 1.62 (1H, m), 1.46 (1H, m), 1.44 (2H, q, *J = 7.4 Hz*, H_P), 1.32 (3H, t, *J = 7.0 Hz*, H_A), 1.30 (3H, t, *J = 7.0 Hz*, $H_{A'}$), 0.78 (3H, t, *J = 7.5 Hz*, H_T) ppm.

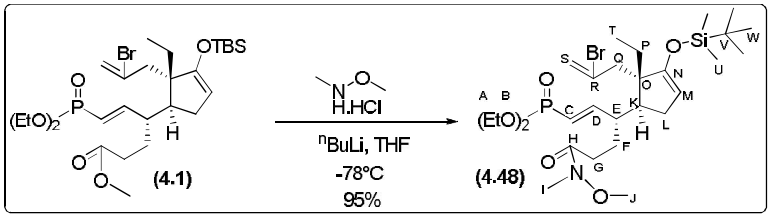
^{13}C NMR (100 MHz; $CDCl_3$): δ 220.2 (Q, C_N), 173.7 (Q, C_H) 155.4 (d, *J* = 3.9 Hz, CH, C_D), 130.5 (Q, C_R), 122.5 (CH_2, C_S), 119.3 (d, *J* = 187.1 Hz, CH, C_C), 61.7 (d, *J* = 5.7 Hz, CH_2, C_B), 61.6 (d, *J* = 5.8 Hz, CH_2, $C_{B'}$), 61.2 (CH_3, C_J), 54.1 (Q, C_O), 46.3 (d, *J = 20.8 Hz*, CH, C_E), 45.3 (CH_2, C_Q), 44.3 (CH, C_K), 37.0 (CH_2, C_M), 30.7 (CH_3, C_I) 28.7 (CH_2), 26.3 (CH_2), 25.4 (CH_2, C_P), 24.0 (CH_2), 16.4 (d, *J* = 5.9 Hz, CH_3, C_A), 16.4 (d, *J* = 6.1 Hz, CH_3, $C_{A'}$), 8.3 (CH_3, C_T) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.82 ppm.

ES$^+$MS: m/z (%): 546/544 (1:1, $(M+Na)^+$, 100), 524/522 (1:1, $(M+H)^+$, 63).

HRES$^+$MS For $C_{22}H_{37}{}^{79}BrNO_6PNa$ $(M+Na)^+$: calcd 544.1434, found 544.1434.

<u>The Weinreb amide (4.48)</u>



To a stirred solution of $Me(OMe)NH_2Cl$ (192 mg, 1.97 mmol, 6.0 equiv) in THF (3 mL) was added *n*-BuLi (2.5 M hexane solution) (1.18 mL, 2.96 mmol, 9.0 equiv) at -78 °C under N_2, and the resulting solution was allowed to warm to room temperature and stirred for further 15 min at the same temperature. The solution was cooled to -78 °C again, and a solution of methyl ester **(4.1)** (199 mg, 0.33 mmol, 1.0 equiv) in THF (3 mL) was added to the solution, and the resulting solution was stirred for further 45 min at the same temperature. The solution was treated with saturated aqueous ammonium chloride solution and extracted with Et_2O. The extract was washed with brine, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography using pre-neutralized silica gel (Hexane/Acetone 70:30) to afford **(4.48)** (189 mg, 95%) as a colourless oil.

Mw = 636.670 ($C_{28}H_{51}BrNO_6PSi$).

Rf = 0.34 (Hexane/Acetone 70:30).

IR (neat): 2930 (w), 2856 (w), 1650 (m), 1231 (s), 1024 (s), 961 (s), 839 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.64 (1H, ddd, *J = 21.8, 17.2, 9.4 Hz*, H_D), 5.80 (1H, s, H_S), 5.67 (1H, dd, *J = 21.5, 17.2 Hz*, H_C), 5.55 (1H, s, $H_{S'}$), 4.54 (1H, s, H_M), 4.18-3.93 (4H, m, H_B), 3.62 (3H, s, H_J), 3.12 (3H, s, H_I), 2.81 (1H, d, *J = 15.2 Hz*, H_Q), 2.44-2.23 (5H, m), 2.20 (1H, d, *J = 15.2 Hz*, $H_{Q'}$), 2.03-1.90 (2H, m), 1.54-1.35 (2H, m, H_P + 1H), 1.30 (3H, t, *J = 7.1 Hz*, H_A), 1.29 (3H, t, *J = 7.0 Hz*, $H_{A'}$), 1.25-1.13 (1H, m, $H_{P'}$), 0.89 (9H, s, H_W), 0.81 (3H, t, *J = 7.4 Hz*, H_T), 0.16 (3H, s, H_U), 0.15 (3H, s, $H_{U'}$) ppm.

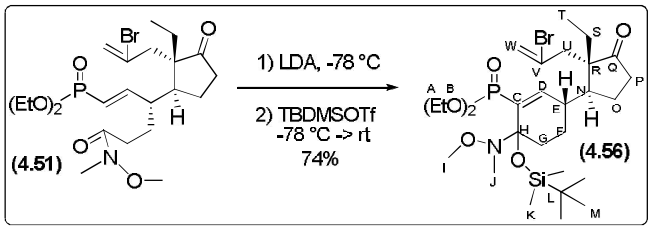
^{13}C NMR (100 MHz; $CDCl_3$): δ 157.3 (d, *J = 3.4 Hz*, CH, C_D), 155.2 (Q, C_N), 131.1 (Q, C_R), 120.9 (CH_2, C_S), 118.7 (d, *J = 186.8 Hz*, CH, C_C), 98.6 (CH, C_M), 61.7 (d, *J = 5.5 Hz*, CH_2, C_B), 61.5 (d, *J = 5.7 Hz*, CH_2, $C_{B'}$), 61.3 (CH_3, C_J), 53.1 (Q, C_O), 46.3 (d, *J = 20.9 Hz*, CH, C_E), 45.7 (CH_2, C_Q), 43.3 (CH, C_K), 30.6 (CH_3, C_I), 32.5 (CH_2), 29.0 (CH_2), 28.1 (CH_2), 26.8 (d, *J = 1.4 Hz*, CH_2, C_F), 25.7 (3 x CH_3, C_W), 18.0 (Q, C_V), 16.5 (d, *J = 6.1 Hz*, CH_3, C_A), 16.4 (d, *J = 6.1 Hz*, CH_3, $C_{A'}$), 9.5 (CH_3, C_T), -4.9 (CH_3, C_U), -5.2 (CH_3, $C_{U'}$) ppm. (C_H not observed).

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.15 ppm.

ES$^+$MS m/z (%): 660/658 (1:1, $(M+Na)^+$, 100), 638/636 (1:1, $(M+H)^+$, 65).

HRES$^+$MS For $C_{28}H_{51}{}^{79}BrNO_6PSiNa$ $(M+Na)^+$: calcd 658.2299, found 658.2292.

The B-ring cyclised phosphonate (4.56)



To a cooled (-78 °C) solution of Weinreb amide **(4.51)** (0.115 g, 0.22 mmol, 1.0 equiv) in THF (10 mL) was slowly added LDA (2 M in THF, 0.275 mL, 0.55 mmol, 2.5 equiv). The reaction mixture was stirred at -78 °C for 2 h, then TBDMSOTf (0.126 mL, 0.55 mmol, 2.5 equiv) was added and stirring continued for 15 min at -78°C. The mixture was warmed to room temperature and then sat.aq. $NaHCO_3$ (5 mL) was added followed by DCM (10 mL). The phases were separated and the aqueous phase was extracted with DCM (5 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 70:30) whereby the silica was pre-neutralized by making the slurry in the said solvent system, containing ~1% of Et_3N. This yielded **(4.56)** as a colourless oil (0.104 g, 74%), as an inseparable mixture of diastereoisomers in approximately a 4:1 ratio.

Mw = 636.671 ($C_{28}H_{51}BrNO_6PSi$).

Rf = 0.55 (Hexane/Acetone 70:30).

IR (neat): 2930 (w), 2854 (w), 1736 (m), 1245 (s), 1096 (s), 1024 (s), 834 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): ***Major diastereoisomer*** δ 6.99 (1H, dd, *J = 22.2, 2.5 Hz*, H_D), 5.97 (1H, s, H_W), 5.50 (1H, s, $H_{W'}$), 4.20-3.95 (4H, m, H_B), 3.50 (3H, s, H_I), 3.29 (1H, d, *J = 15.0 Hz*, H_U), 2.72-2.52 (5H, m, H_E+H_J+$H_{U'}$), 2.50-2.28 (4H, m), 2.25-1.99 (2H, m), 1.60-1.42 (5H, m), 1.31 (6H, dt, *J = 7.1, 4.0 Hz*, H_A), 0.94 (9H, s, H_M), 0.86 (3H, t, *J = 7.5 Hz*, H_T), 0.17 (3H, s, H_K), 0.14 (3H, s, $H_{K'}$) ppm; ***Minor diastereoisomer observed*** δ 6.92-6.82 (1H, m, H_D), 5.45 (1H, s, $H_{W'}$), 3.25 (1H, d, *J = 17.2 Hz*, H_U), 0.17 (3H, s, H_K), 0.11 (3H, s, $H_{K'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): ***Major Diastereoisomer*** δ 220.3 (Q, C_Q), 150.6 (d, *J = 7.1 Hz*, CH, C_D), 135.5 (d, *J = 184.5 Hz*, Q, C_C), 130.2 (Q, C_V), 122.1 (CH_2, C_W), 91.6 (d, *J = 4.9 Hz*, Q, C_H), 61.5 (d, *J = 6.7 Hz*, CH_2, C_B), 61.3 (d, *J = 5.6 Hz*, CH_2, $C_{B'}$), 59.0 (CH_3, C_I), 54.1 (Q, C_R), 46.4 (CH_2, C_U), 45.3 (CH, C_N), 37.4 (CH_3, C_J), 37.4 (CH_2, C_P), 35.3 (d,

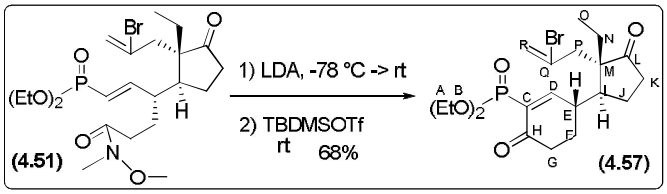
J = 15.4 Hz, CH, C_E), 31.9 (d, *J = 3.9 Hz*, CH_2, C_G), 26.2 (3 x CH_3, C_M), 25.9 (CH_2), 24.1 (CH_2), 23.5 (CH_2), 18.9 (Q, C_L), 16.4 (d, *J = 6.3 Hz*, CH_3, C_A), 16.3 (d, *J = 7.3 Hz*, CH_3, $C_{A'}$), 8.5 (CH_3, C_T), -1.8 (CH_3, C_K), -1.9 (CH_3, $C_{K'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): ***Major diastereoisomer*** δ 18.33 ppm, ***Minor diastereoisomer*** δ 19.48 ppm.

ES$^+$MS m/z (%): 659/657 (1:1, $(M+Na)^+$, 100).

HRES$^+$MS For $C_{28}H_{51}{}^{79}BrNO_6PSiNa$ $(M+Na)^+$: calcd 658.2299, found 658.2305.

<u>The B-ring cyclised β-keto phosphonate (4.57)</u>



To a cooled (-78 °C) solution of Weinreb amide **(4.51)** (0.054 g, 0.10 mmol, 1.0 equiv) in THF (2 mL) was slowly added LDA (2 M in THF, 0.129 mL, 0.26 mmol, 2.5 equiv). The reaction mixture was stirred at -78 °C for 15 min, then warmed to room temperature and stirring continued for 30 min. and TBDMSOTf (0.059 mL, 0.26 mmol, 2.5 equiv) was added. The mixture was stirred at room temperature for 15 min and then sat.aq. $NaHCO_3$ (2 mL) was added followed by DCM (5 mL). The phases were separated and the aqueous phase was extracted with DCM (5 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 60:40) to afford **(4.57)** as a light yellow oil (0.032 g, 68%).

Mw = 461.327 ($C_{20}H_{30}BrO_5$).

Rf = 0.33 (Hexane/Acetone 60:40).

IR (neat): 2978 (w), 1732 (m), 1190 (s), 1086 (m), 1016 (s) 971 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.92 (1H, d, *J = 21.4 Hz*, H_D), 5.96 (1H, s, H_R), 5.46 (1H, s, $H_{R'}$), 4.36-4.04 (4H, m, H_B), 3.37 (1H, d, *J = 15.0 Hz*, H_P), 2.80-2.57 (3H, m, H_E+H_G+$H_{P'}$), 2.53-2.38 (4H, H_K+$H_{K'}$+H_I+$H_{G'}$), 2.33-2.15 (2H, m, H_J+H_F), 1.88 (1H, ddt, *J = 13.3, 9.3, 4.2 Hz*, $H_{F'}$), 1.75-1.64 (1H, m, $H_{J'}$), 1.58 (2H, q, *J = 7.6 Hz*, H_N), 1.33 (6H, t, *J = 7.1 Hz*, H_A), 0.91 (3H, t, *J = 7.4 Hz*, H_O) ppm.

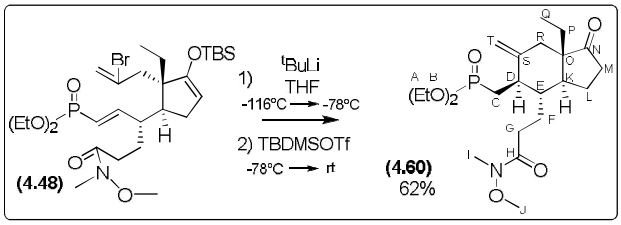
^{13}C NMR (100 MHz; $CDCl_3$): δ 219.1 (Q, C_L), 195.5 (d, *J = 5.2 Hz*, Q, C_H), 164.7 (d, *J = 5.8 Hz*, CH, C_D), 131.2 (d, *J = 180.8 Hz*, Q, C_C), 129.6 (Q, C_Q), 122.4 (CH_2, C_R), 62.6 (d, *J = 6.3 Hz*, CH_2, C_B), 62.5 (d, *J = 6.3 Hz*, CH_2, $C_{B'}$), 53.7 (Q, C_M), 46.6 (CH_2, C_P), 44.1 (CH, C_I), 38.6 (d, *J = 14.2 Hz*, CH, C_E), 37.5 (d, *J = 7.8 Hz*, CH_2, C_G), 37.1 (CH_2, C_K), 27.1 (CH_2), 26.1 (CH_2), 24.5 (CH_2), 16.4 (d, *J = 6.3 Hz*, 2 x CH_3, C_A), 8.5 (CH_3, C_O) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 13.96 ppm.

ES$^+$MS m/z (%): 485/483 (1:1, $(M+Na)^+$, 100), 463/461 (1:1, $(M+H)^+$, 45).

HRES$^-$MS For $C_{20}H_{29}{}^{79}BrO_5P$ $(M-H)^+$: calcd 459.0930, found 459.0931.

The C-ring cyclised Weinreb amide (4.60)



A solution of the vinyl bromide **(4.48)** (0.190 g, 0.298 mmol, 1.0 equiv) in THF (2 mL) was cooled to -116 °C in an EtOH/liquid N_2 cold bath and treated with ^{t}BuLi (1.6 M in pentanes) (0.447 mL, 0.715 mmol, 2.4 equiv). After the quick addition (over 20 seconds), the reaction was stirred for 15 min, then the reaction was allowed to warm to -78 °C and stirring continued for 30 min. TBDMSOTf (0.204 mL, 0.894 mmol, 3.0 equiv) was added at -78 °C and the reaction mixture was warmed to room temperature over 1 h. Saturated aq. $NaHCO_3$ (3 mL) was added and H_2O (10 mL) and the reaction was extracted with DCM (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 70:30) to afford **(4.60)** as a colourless oil (0.082 g, 62%).

Mw = 443.243 ($C_{22}H_{38}NO_6P$).

Rf = 0.22 (Hexane/Acetone 70:30).

IR (neat): 2966 (w), 1732 (s), 1655 (m), 1387 (m), 1231 (m), 1023 (s), 957 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.06 (1H, s, H_T), 4.99 (1H, s, $H_{T'}$), 4.19-3.97 (4H, m, H_B), 3.71 (3H, s, H_J), 3.18 (3H, s, H_I), 2.65 (1H, d, *J = 13.5 Hz*, H_R), 2.54 (1H, m), 2.48-2.33 (2H, m), 2.28-2.08 (4H, m), 2.01 (1H, m), 1.93-1.84 (3H, m), 1.82-1.58 (4H, m), 1.44 (1H,

m), 1.30 (3H, t, *J = 6.9 Hz*, H_A), 1.29 (3H, t, *J = 7.1 Hz*, $H_{A'}$), 0.74 (3H, t, *J = 7.4 Hz*, H_Q) ppm.

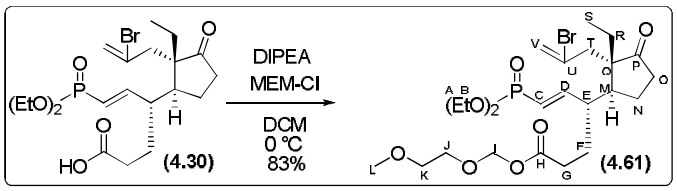
^{13}C NMR (100 MHz; $CDCl_3$): δ 218.3 (Q, C_N), 174.1 (Q, C_H), 145.1 (Q, C_S), 112.4 (CH_2, C_T), 61.6 (d, *J = 6.9 Hz*, CH_2, C_B), 61.5 (d, *J = 6.8 Hz*, CH_2, $C_{B'}$), 61.3 (CH_3, C_J), 51.8 (Q, C_O), 49.6 (CH, C_K), 40.6 (d, *J = 2.0 Hz*, CH, C_E), 40.5 (d, *J = 20.4 Hz*, CH, C_D), 38.9 (CH_2, C_R), 35.9 (CH_2), 32.2 (CH_3, C_I), 26.9 (CH_2), 24.3 (CH_2), 24.9 (d, *J = 141.9 Hz*, CH_2, C_C), 21.9 (CH_2), 18.1 (CH_2), 16.4 (d, *J = 6.1 Hz*, 2 x CH_3, C_A), 6.9 (CH_3, C_Q) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 32.04 ppm.

ES$^+$MS m/z (%): 466 ($(M+Na)^+$, 100), 444 ($(M+H)^+$, 63).

HRES$^+$MS For $C_{22}H_{38}NO_6PNa$ $(M+Na)^+$: calcd 466.2329, found 466.2331.

The MEM-ester (4.61)



To a stirred, precooled (0 °C) solution of **(4.30)** (0.232 g, 0.501 mmol, 1.0 equiv) in DCM (5 mL) under N_2 were added DIPEA (0.137 mL, 0.551 mmol, 1.1 equiv) and MEMCl (0.098 mL, 0.601 mmol, 1.2 equiv), and the resulting solution was stirred at 0 °C for 2 h under N_2. The reaction was quenched by adding 0.1 N HCl (3 mL). The product was extracted into DCM (3 x 10 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 60:40), affording **(4.61)** (0.235 g, 83%) as a light yellow oil.

Mw = 567.447 ($C_{24}H_{40}BrO_8P$).

Rf = 0.37 (Hexane/Acetone 60:40).

IR (neat): 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 6.58 (1H, ddd, *J = 21.7, 17.2, 9.9 Hz*, H_D), 6.01 (1H, s, H_V), 5.70 (1H, dd, *J = 20.5, 17.3 Hz*, H_C), 5.55 (1H, s, $H_{V'}$), 5.34-5.29 (2H, m, H_I), 4.17-4.02 (4H, m, H_B), 3.79-3.75 (2H, m, $H_{J/K}$), 3.58-3.51 (2H, m, $H_{J/K}$), 3.37 (3H, s, H_L), 3.14

(1H, d, *J = 14.8 Hz*, H_T), 2.47-2.10 (9H, m), 1.64-1.48 (2H, m), 1.44 (2H, q, *J = 7.4 Hz*, H_R), 1.33 (6H, t, *J = 7.1 Hz*, H_A), 0.79 (3H, t, *J = 7.5 Hz*, H_S) ppm.

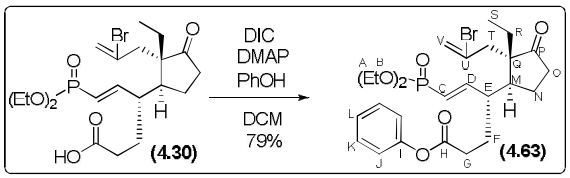
^{13}C NMR (100 MHz; $CDCl_3$): δ 219.9 (Q, C_P), 172.4 (Q, C_H), 154.5 (d, *J = 4.0 Hz*, CH, C_D), 130.4 (Q, C_U), 122.6 (CH_2, C_V), 119.8 (d, *J = 186.8 Hz*, CH, C_C), 89.4 (CH_2, C_I), 71.5 (CH_2, $C_{J/K}$), 69.6 (CH_2, $C_{J/K}$), 61.7 (d, *J = 5.2 Hz*, CH_2, C_B), 61.7 (d, *J = 5.1 Hz*, CH_2, $C_{B'}$), 59.0 (CH_3, C_L), 54.1 (Q, C_Q), 46.1 (d, *J = 21.1 Hz*, CH, C_E), 45.3 (CH_2, C_T), 44.1 (CH, C_M), 36.9 (CH_2, C_O), 31.2 (CH_2, C_G), 26.6 (d, *J = 1.5 Hz*, CH_2, C_F), 25.3 (CH_2, C_R), 24.1 (CH_2, C_N), 16.4 (d, *J = 6.2 Hz*, CH_3, C_A), 16.4 (d, *J = 6.1 Hz*, CH_3, $C_{A'}$), 8.3 (CH_3, C_S) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.56 ppm.

ES$^+$MS m/z (%): 591/589 (1:1, $(M+Na)^+$, 60), 569/567 (1:1, $(M+H)^+$, 40).

HRES$^+$MS: We have not obtained HRMS or elemental analysis of this compound, but copies of the ^{1}H and ^{13}C NMR spectra are included in Appendix I.

<u>The phenyl ester (4.63)</u>



To a solution of carboxylic acid **(4.30)** (0.558 g, 1.21 mmol, 1.0 equiv) in DCM (10 mL) were successively added PhOH (0.170 g, 1.81 mmol, 1.5 equiv), DIC (0.284 mL, 1.21 mmol, 1.5 equiv) and finally DMAP (0.032 g, 0.24 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature for 5 days, then water (10 mL) was added. The phases were separated and the aqueous phase extracted with DCM (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The resulting crude was purified by column chromatography (Hexane/Acetone 70:30) to afford **(4.63)** as a light yellow oil (0.530 g, 79%).

Mw = 555.438 ($C_{26}H_{36}BrO_6P$).

Rf = 0.34 (Hexane/Acetone 60:40).

IR (neat): 2978 (w), 1755 (m), 1734 (m), 1241 (m), 1129 (m), 1021 (s), 957 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.44-7.36 (2H, m, H_J), 7.25 (1H, m, H_L), 7.10-7.06 (2H, m, H_K), 6.66 (1H, ddd, *J = 21.7, 17.2, 10.1 Hz*, H_D), 6.08-5.99 (1H, s, H_V), 5.78 (1H, dd, *J = 20.5, 17.3 Hz*, H_C), 5.59 (1H, s, $H_{V'}$), 4.22-4.05 (4H, m, H_B), 3.17 (1H, d, *J = 14.8 Hz*, H_T), 2.62 (1H, ddd, *J = 16.5, 8.0, 5.0 Hz*, H_G), 2.53-2.24 (7H, m, contains $H_{T'}$+$H_{G'}$), 1.72-1.58 (3H, m), 1.51-1.45 (2H, m, H_R), 1.35 (3H, t, *J = 7.0 Hz*, H_A), 0.82 (3H, t, *J = 7.5 Hz*, H_S) ppm.

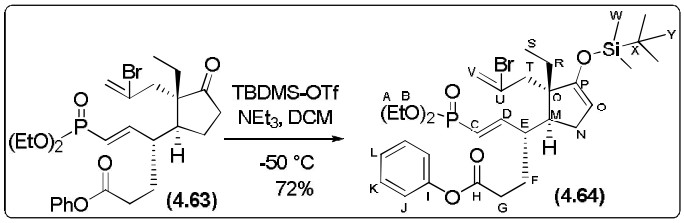
^{13}C NMR (100 MHz; $CDCl_3$): δ 219.9 (Q, C_P), 171.5 (Q, C_H), 154.8 (d, *J = 3.9 Hz*, CH, C_D), 150.5 (Q, C_I), 130.4 (Q, C_U), 129.5 (2 x CH, C_J), 125.9 (CH, C_L), 122.7 (CH_2, C_V), 121.4 (2 x CH, C_K), 119.6 (d, *J = 186.5 Hz*, CH, C_C), 61.8 (d, *J = 4.0 Hz*, CH_2, C_B), 61.8 (d, *J = 3.9 Hz*, CH_2, $C_{B'}$), 54.1 (Q, C_Q), 46.1 (d, *J = 21.0 Hz*, CH, C_E), 45.4 (CH_2, C_T), 44.2 (CH, C_M), 36.9 (CH_2, C_O), 31.3 (CH_2, C_G), 26.7 (CH_2), 25.4 (CH_2), 24.1 (CH_2), 16.5 (d, *J = 3.2 Hz*, CH_3, $C_{A'}$), 16.4 (d, *J = 3.1 Hz*, CH_3, C_A), 8.4 (CH_3, C_S) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.52 ppm.

ES^{+}MS m/z (%): 579/577 (1:1, $(M+Na)^+$, 100), 557/555 (1:1, $(M+H)^+$, 28).

HRES^{+}MS For $C_{26}H_{36}{}^{79}BrO_6PNa$ $(M+Na)^+$: calcd 577.1325, found 577.1322.

The silyl enol ether (4.64)



To a cooled solution (-50 °C) of the ketone **(4.63)** (0.497 g, 0.895 mmol, 1.0 equiv) in DCM (1.5 mL) was added Et_3N (0.374 mL, 2.69 mmol, 3.0 equiv) then, dropwisely over 2 min, TBDMS-OTf (0.616 mL, 2.69 mmol, 3.0 equiv) was added. The reaction mixture was stirred for 2 h at -50/-40 °C and then sat.aq. $NaHCO_3$ (5 mL) was added and the reaction was warmed to room temperature. The phases were separated and the aqueous phase was extracted with DCM (5 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 70:30) whereby the silica was pre-neutralized by making the slurry in the said solvent system, containing ~1% of Et_3N. This yielded **(4.64)** as a colourless oil (0.358 g, 72%).

Mw = 669.699 ($C_{32}H_{50}BrO_6PSi$).

Rf = 0.42 (Hexane/Acetone 65:35).

IR (neat): 2929 (w), 2855 (w), 1756 (m), 1232 (m), 1134 (m), 1022 (s), 836 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.39-7.35 (2H, m, H_J), 7.22 (1H, m, H_L), 7.08-7.06 (2H, m, H_K), 6.71 (1H, ddd, *J = 21.7, 17.2, 9.6 Hz*, H_D), 5.87 (1H, br s, H_V), 5.77 (1H, dd, *J = 21.1, 17.2 Hz*, H_C), 5.60 (1H, br s, $H_{V'}$), 4.59 (1H, s, H_O), 4.16-4.08 (4H, m, H_B), 2.87 (1H, d, *J = 15.2 Hz*, H_T), 2.58 (1H, ddd, *J = 16.2, 8.5, 5.0 Hz*, H_G), 2.53-2.33 (4H, m, $H_{G'}$+H_M+H_E+$H_{G'}$), 2.25 (1H, d, *J = 15.2 Hz*, $H_{T'}$), 2.14 (1H, m, H_F), 2.98 (1H, m, $H_{N'}$), 1.71-1.44 (2H, m, $H_{F'}$+H_R), 1.35 (6H, t, *J = 7.1 Hz*, H_A), 1.25 (1H, m, $H_{R'}$) 0.93 (9H, s, H_Y), 0.85 (3H, t, *J = 7.4 Hz*, H_S), 0.20 (3H, s, H_W), 0.19 (3H, s, $H_{W'}$)ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 171.6 (Q, C_H), 155.9 (d, *J = 3.5 Hz*, CH, C_D), 155.2 (Q, C_P), 150.6 (Q, C_I), 131.0 (Q, C_U), 129.4 (2 x CH, C_J), 125.8 (CH, C_L), 121.4 (2 x CH, C_K), 121.0 (CH_2, C_V), 119.4 (d, *J = 186.7 Hz*, CH, C_C), 98.4 (CH, C_O), 61.7 (d, *J = 5.8 Hz*, CH_2, C_B), 61.6 (d, *J = 5.9 Hz*, CH_2, $C_{B'}$), 53.0 (Q, C_Q), 45.9 (d, *J = 20.8 Hz*, CH, C_E), 45.7 (CH_2, C_T), 43.2 (CH, C_M), 32.5 (CH_2, C_N), 31.4 (CH_2, C_G), 28.0 (CH_2, C_R), 27.1 (CH_2, C_F), 25.6 (3 x CH_3, C_Y), 17.9 (Q, C_X), 16.5 (d, *J = 2.7 Hz*, CH_3, C_A), 16.4 (d, *J = 2.7 Hz*, CH_3, $C_{A'}$), 9.5 (CH_3, C_S), -5.0 (CH_3, C_W), -5.3 (CH_3, $C_{W'}$) ppm.

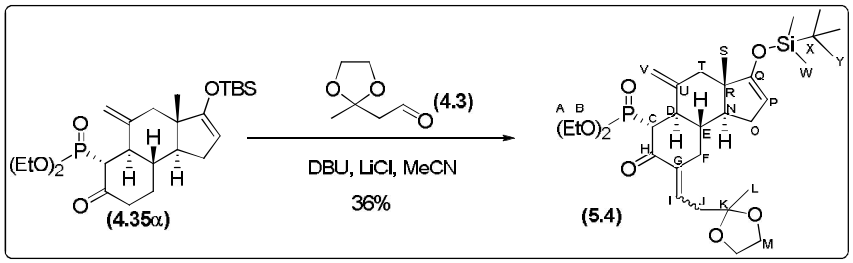
^{31}P NMR (121 MHz; $CDCl_3$): δ 17.86 ppm.

ES$^+$MS m/z (%): 693/691 ($(M+Na)^+$, 100), 671/669 ($(M+H)^+$, 10).

HRES$^+$MS For $C_{32}H_{51}{}^{79}BrO_6PSi$ ($M+H^+$): calcd 669.2370, found 669.2365.

9.4 Experimental data for Chapter 5

The aldol compound (5.4)



To a stirred suspension of LiCl (5 mg, 0.115 mmol, 1.5 equiv) in dry MeCN (5 mL) under nitrogen at room temperature, was added a MeCN (2 mL) solution of β-ketophosphonate **(4.35α)** (37 mg, 0.077 mmol, 1.0 equiv), DBU (14 mL, 0.092 mmol, 1.2 equiv) and finally aldehyde **(4.3)** (20 mg, 0.154 mmol, 2.0 equiv). Almost all of the salt soon dissolved and the reaction mixture was stirred overnight at room temperature (16 h). Saturated aq. $NaHCO_3$ was added (5 mL) and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/EtOAc 45:55) using pre-neutralized silica gel to afford **(5.4)** as a colourless oil (17 mg, 36%).

Mw = 594.792 ($C_{31}H_{51}O_7PSi$).

Rf = 0.34 (Hexane/EtOAc 45:55).

^{1}H NMR (300 MHz; $CDCl_3$): δ 6.69 (1H, m, H_I), 4.96 (1H, br s, H_V), 4.87 (1H, br s, $H_{V'}$), 4.45 (1H, m, H_P), 4.17-4.02 (4H, m, H_B), 4.03-3.91 (4H, m, H_M), 3.57 (1H, dd, *J = 27.3, 8.6 Hz*, H_C), 2.75-1.73 (11H, m), 1.36 (3H, s, H_L), 1.28 (6H, q, *J = 6.7 Hz*, H_A), 0.95 (9H, s, H_Y), 0.75 (3H, s, H_S), 0.18 (3H, s, H_W), 0.16 (3H, s, $H_{W'}$) ppm.

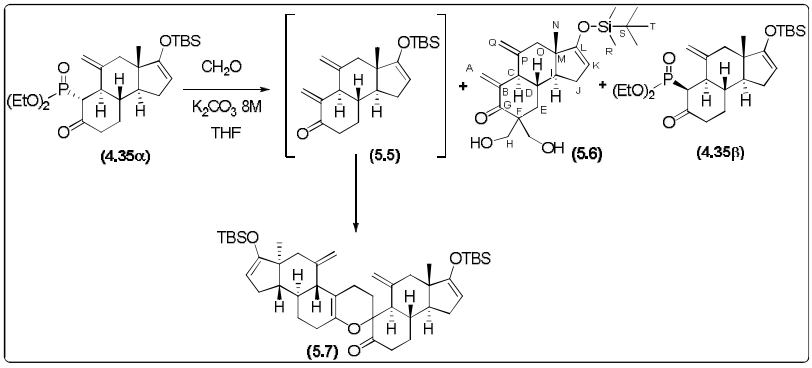
^{13}C NMR (75 MHz; $CDCl_3$): δ 190.6 (Q, C_H), 163.6 (Q, C_Q), 145.3 (d, *J = 1.5 Hz*, Q, C_U), 137.8 (Q, C_G), 134.0 (CH, C_I), 110.7 (CH_2, C_V), 109.5 (Q, C_K), 98.3 (CH, C_P), 64.9 (2 x CH_2, C_M), 62.9 (d, *J = 7.1 Hz*, CH_2, C_B), 62.6 (d, *J = 6.9 Hz*, CH_2, $C_{B'}$), 53.6 (CH, C_N), 49.8 (d, *J = 123.3 Hz*, CH, C_C), 46.9 (Q, C_R), 45.6 (CH, C_E), 45.2 (CH_2, C_T), 38.0 (CH_2), 37.3 (d, *J = 8.5 Hz*, CH, C_D), 30.0 (CH_2), 28.1 (CH_2), 25.6 (3 x CH_3, C_Y), 24.5 (CH_3, C_L), 18.1 (Q, C_X), 16.3 (d, *J = 6.4 Hz*, 2 x CH_3, C_A), 15.6 (CH_3, C_S), -4.7 (CH_3, C_W), -5.0 (CH_3, $C_{W'}$) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 23.84 ppm.

ES$^+$MS m/z (%): 618/617 (1:3, $(M+Na)^+$, 100), 596/595 (1:3, $(M+H)^+$, 80).

HRES$^+$MS For $C_{31}H_{51}O_7PSiNa$ $(M+Na)^+$: calcd 617.3039, found 617.3044.

<u>The HWE product (5.5)</u> and **<u>the diol (5.6)</u>** and **<u>the dimer (5.7)</u>**



To a solution of the phosphonate **(4.35α)** (125 mg, 0.26 mmol, 1.0 equiv) and formaldehyde (37% w/w in H_2O, 400 µL, ca. 15.0 equiv) in THF (1.5 mL) was added a solution of K_2CO_3 (8 M, 500 µL, 15.0 equiv) dropwise. The mixture was stirred for 5 h at room temperature then H_2O (5 mL) was added and the reaction was extracted with DCM (4 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 90:10 to 70:30) to afford **(5.5)** (38 mg, 41%) as a colourless oil that dimerized to **(5.7)**, **(5.6)** as a white solid (7 mg, 6%), **(4.35β)** (36 mg, 29%) as a colourless oil and **(4.35α)** (14 mg, 11%) as a colourless oil.

<u>Data for (5.5)</u>

Mw = 358.590 ($C_{22}H_{34}O_2Si$).

Rf = 0.79 (Hexane/Acetone 95:5).

No other data available, compound too unstable.

<u>Data for (5.6)</u>

Mw = 418.642 ($C_{24}H_{38}O_4Si$).

Rf = 0.36 (Hexane/Acetone 70:30).

IR (film): 3422 (br w), 2958 (m), 2930 (m), 2857 (m), 1681 (w), 1644 (w), 1619 (m), 1472 (w), 1369 (m), 1253 (m), 1228 (m), 1044 (w), 839 (s), 782 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 6.08 (1H, t, *J = 2.5 Hz*, H_A), 5.81 (1H, t, *J = 2.5 Hz*, $H_{A'}$), 4.82 (1H, s, H_Q), 4.72 (1H, s, $H_{Q'}$), 4.35 (1H, s, H_K), 3.90 (1H, d, *J = 9.5 Hz*, H_H), 3.51

(3H, m, $H_{H'}$), 2.76 (1H, d, *J = 8.4 Hz*, H_C), 2.68 (1H, br s, OH), 2.50 (1H, br s, OH), 2.22-1.16 (8H, m), 0.83 (9H, s, H_T), 0.61 (3H, s, H_N), 0.18 (3H, s, H_R), 0.16 (3H, s, $H_{R'}$) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 209.6 (Q, C_G), 163.6 (Q, C_L), 145.1 (Q, C_B), 144.1 (Q, C_P), 126.5 (CH_2, C_A), 111.4 (CH_2, C_Q), 98.4 (CH, C_K), 67.4 (CH_2, C_H), 65.8 (CH_2, $C_{H'}$), 54.2 (CH), 52.3 (Q, C_F), 52.1 (CH), 46.2 (Q, C_M), 45.2 (CH_2), 35.7 (CH), 31.7 (CH_2), 27.8 (CH_2), 25.6 (3 x CH_3, C_T), 18.1 (Q, C_S), 15.8 (CH_3, C_N), -4.6 (CH_3, C_R), -4.8 (CH_3, $C_{R'}$) ppm.

ES$^+$MS m/z (%): 419 ($(M+H)^+$, 100).

HRES$^+$MS For $C_{24}H_{39}O_4Si$ $(M+H)^+$: calcd 419.2612, found 419.2620.

<u>Data for (5.7)</u>

Mw = 717.179 ($C_{44}H_{68}O_4Si_2$).

Rf = 0.82 (Hexane/Acetone 95:5).

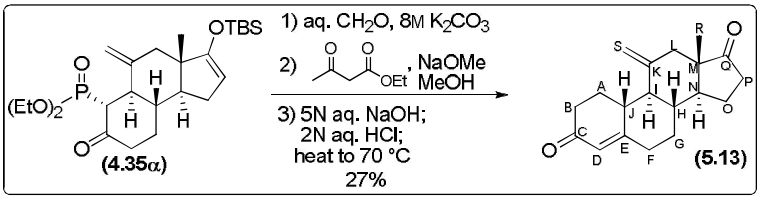
IR (film): 2955 (m), 2930 (m), 2855 (m), 1727 (m), 1678 (w), 1618 (s), 1471 (w), 1463 (w), 1450 (w), 1332 (w), 1250 (m), 1227 (m), 1156 (m), 1104 (m), 835 (s), 781 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.11 (1H, s), 4.95 (1H, s), 4.68 (1H, s), 4.39 (3H, br s), 2.65-2.48 (2H, m), 2.16-2.05 (3H, m), 2.14-1.62 (12H, m), 1.54-1.06 (9H, m), 0.80 (9H, s), 0.78 (9H, s), 0.68 (3H, s), 0.67 (3H, s), 0.17 (6H, s), 0.15 (6H, s) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 208.9 (Q), 165.3 (Q), 164.5 (Q), 149.6 (Q), 149.5 (Q), 142.7 (Q), 116.0 (CH_2), 110.6 (CH_2), 103.3 (Q), 99.9 (CH), 99.4 (CH), 85.7 (Q), 56.7 (CH), 55.7(CH), 54.5 (CH), 54.0 (CH), 47.8 (CH_2), 47.6 (Q), 46.4 (Q), 45.9 (CH_2), 41.7 (CH), 37.2 (CH_2), 36.7 (CH), 31.8 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 26.8 (CH_2), 26.6 (6 x CH_3), 23.2 (CH_2), 19.1 (2 x Q), 19.0 (CH_2), 16.8 (CH), 16.6 (CH), -3.7 (2 x CH_3), -4.1 (2 x CH_3) ppm.

MS: We have not been able to obtain MS data, but copies of ^{1}H and ^{13}C are included in Appendix I.

The A-ring annelated steroid (5.13)



This is known compound but no NMR data have been reported.[48]

To a solution of the phosphonate **(4.35α)** (0.633 g, 1.28 mmol, 1.0 equiv) and formaldehyde (37% w/w in H_2O, 1.43 mL, 19.13 mmol, 15.0 equiv) in THF (10 mL) was added an aqueous solution of K_2CO_3 (8M, 2.39 mL, 19.13 mmol, 15.0 equiv) dropwise. The mixture was stirred for 5 h at room temperature then H_2O (10 mL) was added and the reaction was extracted with DCM (5 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Ethylacetoacetate (322 μL, 2.55 mmol, 2.0 equiv) was slowly added to a 0.3 M solution of NaOMe in MeOH (8.49 mL, 2.55 mmol, 2.0 equiv). The mixture was stirred for 15 min before being added by cannula to a solution of the previously obtained crude enone in dry MeOH (5 mL). The resulting mixture was stirred for 1 h at room temperature then NaOH 5 N (4 mL) was added and stirring continued for 30 min. The biphasic mixture was acidified with HCl 2 N until two clean phases were obtained and efficient stirring was continued for 30 min. The reaction mixture was extracted with DCM (5 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* for 1 h so as to achieve complete decarboxylation (P = 5 torr, water bath = 70 °C). The final crude product was purified by column chromatography (Hexane/Acetone 70:30) followed by preparative HPLC (Hexane/Acetone 80:20). This yielded **(5.13)** (98 mg, 27%) as colourless crystals.

Mw = 284.393 ($C_{19}H_{24}O_2$).

m.p. = 188-192 °C.

Rf = 0.47 (Hexane/Acetone 60:40).

IR (film): 2930 (w), 2875 (w), 1737 (s), 1670 (s), 1616 (w), 1454 (w), 1353 (w), 1258 (w), 1039 (w), 902 (w) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.90 (1H, br s, H_D), 4.95 (1H, s, H_S), 4.86 (1H, s, $H_{S'}$), 2.59-1.14 (18H, m), 0.89 (3H, s, H_R) ppm.

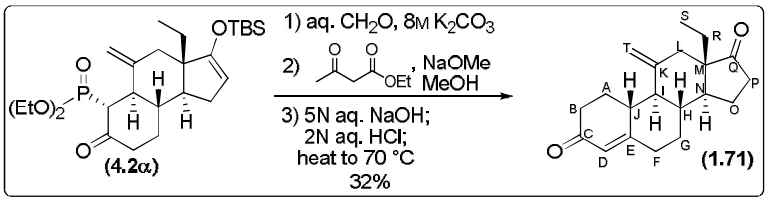
^{13}C NMR (100 MHz; $CDCl_3$): δ 219.4 (Q, C_Q), 199.8 (Q, C_C), 165.6 (Q, C_E), 144 9 (Q, C_K), 125.9 (CH, C_D), 110.9 (CH_2, C_S), 54.2 (CH), 51.2 (CH), 49.4 (Q, C_M), 43.8 (CH_2, C_L), 41.1 (CH), 37.5 (CH), 36.9 (CH_2), 36.0 (CH_2), 35.1 (CH_2), 29.4 (CH_2), 28.2 (CH_2), 21.5 (CH_2), 14.3 (CH_3, C_R) ppm.

CIMS m/z (%): 285 ($(M+H)^+$, 100).

HRMS: not necessary, X-ray obtained instead.

X-ray: X-ray data available in Appendix II.

The A-ring annelated steroid (1.71)



This is a known compound but only partial analytical data are described in the literature.[27,43]

To a solution of the phosphonate **(4.2α)** (0.482 g, 0.97 mmol, 1.0 equiv) and formaldehyde (37% w/w in H_2O, 1.09 mL, 14.55 mmol, 15.0 equiv) in THF (10 mL) was added an aqueous solution of K_2CO_3 (8 M, 1.82 mL, 14.55 mmol, 15.0 equiv) dropwise. The mixture was stirred for 5 h at room temperature then H_2O (10 mL) was added and the reaction was extracted with DCM (5 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Ethylacetoacetate (245 μL, 1.94 mmol, 2.0 equiv) was slowly added to a 0.3 M solution of NaOMe in MeOH (6.46 mL, 1.94 mmol, 2.0 equiv). The mixture was stirred for 15 min before being added by cannula to a solution of the previously obtained crude enone in dry MeOH (5 mL). The resulting mixture was stirred for 1 h at room temperature then NaOH 5 N (4 mL) was added and stirring continued for 30 min. The biphasic mixture was acidified with HCl 2 N until two clean phases were obtained and efficient stirring was continued for 30 min. The reaction mixture was extracted with DCM (5 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* for 1 h so as to achieve complete decarboxylation (P = 5 torr, water bath = 70 °C). The final crude product was purified by column chromatography (Hexane/Acetone 70:30) followed by preparative HPLC (Hexane/Acetone 80:20). This yielded **(1.71)** (93 mg, 32%) as colourless crystals.

MW = 298.419 ($C_{20}H_{26}O_2$).

m.p. = 148-152 °C.

Rf = 0.47 (Hexane/Acetone 60:40).

IR (film): 2961 (w), 2876 (w), 1727 (m), 1662 (m), 1460 (w), 1352 (w), 1258 (s), 1220 (w), 1074 (s), 1018 (s), 901 (m), 796 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.91 (1H, br s, H_D), 5.02 (1H, s, H_T), 4.91 (1H, s, $H_{T'}$), 2.68-2.60 (2H, m), 2.56-2.11 (7H, m), 1.99-1.92 (2H, m), 1.87 (1H, d, *J* = 12.9 Hz), 1.76-1.49 (6H, m, contains $H_{R'}$), 1.32 (1H, m, H_R), 1.17 (1H, m), 0.79 (3H, t, *J* = 7.4 Hz, H_S) ppm.

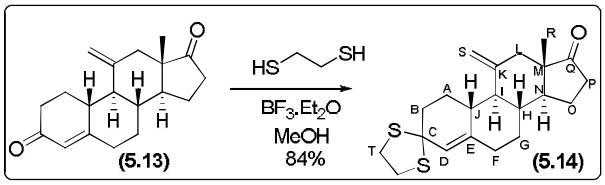
^{13}C NMR (100 MHz; $CDCl_3$): δ 217.9 (Q, C_Q), 199.7 (Q, C_C), 165.6 (Q, C_E), 144.9 (Q, C_K), 125.9 (CH, C_D), 110.4 (CH_2, C_T), 54.1 (CH), 52.7 (Q, C_M), 52.0 (CH), 40.9 (CH), 39.5 (CH_2), 37.6 (CH), 36.9 (CH_2), 36.0 (CH_2), 35.1 (CH_2), 29.5 (CH_2), 28.3 (CH_2), 20.8 (CH_2), 18.2 (CH_2), 7.1 (CH_3, C_S) ppm.

CIMS m/z (%): 299 ($(M+H)^+$, 100).

HRMS: not necessary, X-ray obtained instead.

X-ray: X-ray data available in Appendix II.

<u>The thioketal steroid (5.14)</u>



To **(5.13)** (0.097 g, 0.311 mmol, 1.0 equiv) was slowly added, over 15 min at room temperature, MeOH (6 mL) so as to achieve complete dissolution. Ethane-1,2-dithiol (54 μL, 0.616 mmol, 1.8 equiv) was added followed by dropwise addition of $BF_3.Et_2O$ (34 μL, 0.259 mmol, 0.9 equiv) and the mixture was stirred for 16 hours. After usual work-up, the crude product was purified by column chromatography (Hexane/Acetone 80:20) to afford **(5.15)** as a white solid (98 mg, 84%).

MW = 360.576 ($C_{21}H_{28}OS_2$).

Rf = 0.46 (Hexane/Acetone 80:20).

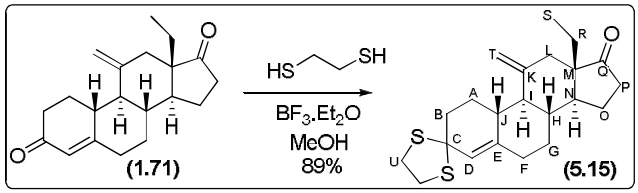
IR (film): 2958 (m), 2917 (s), 2848 (w), 1729 (s), 1448 (m), 1258 (m), 1037 (m), 1004 (w), 889 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.69 (1H, s, H_D), 4.93 (1H, s, H_S), 4.84 (1H, s, $H_{S'}$), 3.41-3.22 (4H, m, H_T), 2.48 (1H, m), 2.34-1.91 (10H, m), 1.83 (1H, m), 1.60-1.27 (5H, m), 1.07 (1H, m), 0.85 (3H, s, H_R) ppm**.**

^{13}C NMR (100 MHz; $CDCl_3$): δ 219.8 (Q, C_Q), 145.6 (Q, C_K), 141.0 (Q, C_E), 126.6 (CH, CD), 110.6 (CH_2, C_S), 65.7 (Q, C_C), 54.7 (CH), 51.5 (CH), 49.6 (Q, C_M), 44.0 (CH_2, C_L), 41.6 (CH), 40.4 (CH_2), 40.0 (CH_2), 39.7 (CH_2), 36.1 (CH_2), 35.9 (CH), 34.7 (CH_2), 30.4 (CH_2), 28.6 (CH_2), 21.5 (CH_2), 14.3 (CH_3, C_R) ppm.

X-ray: X-ray data available in Appendix II.

The thioketal steroid (5.15)



To steroid **(1.71)** (0.093 g, 0.311 mmol, 1.0 equiv) was slowly added, over 15 min at room temperature, MeOH (6 mL) so as to achieve complete dissolution. Ethane-1,2-dithiol (52 μL, 0.591 mmol, 1.8 equiv) was added followed by dropwise addition of $BF_3.Et_2O$ (33 μL, 0.249 mmol, 0.9 equiv) and the mixture was stirred for 16 hours. After usual work-up, the crude product was purified by column chromatography (Hexane/Acetone 80:20) to afford **(5.15)** as a white solid (103 mg, 89%).

MW = 374.603 ($C_{22}H_{30}OS_2$).

Rf = 0.49 (Hexane/Acetone 80:20).

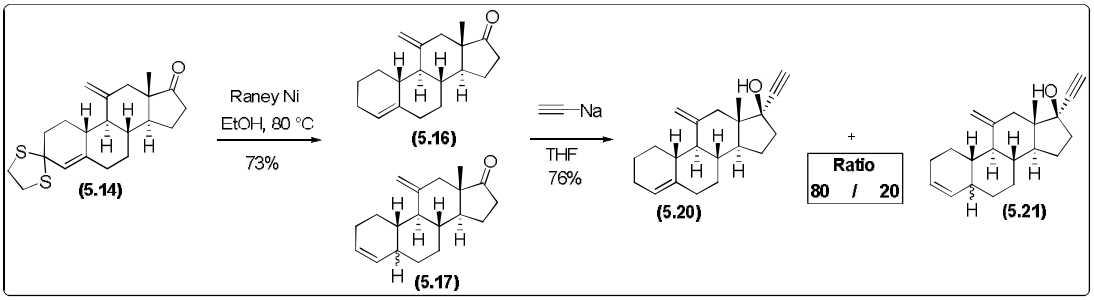
IR (film): 2960 (m), 2918 (m), 2850 (w), 1733 (m), 1456 (w), 1258 (m), 1011 (s), 789 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.68 (1H, br s, H_D), 4.95 (1H, s, H_T), 4.84 (1H, s, $H_{T'}$), 3.41-3.34 (3H, m, H_U), 3.25 (1H, m, H_U), 2.59 (1H, d, *J = 12.7 Hz*, H_L), 2.42 (1H, dd, *J = 19.3, 8.8 Hz*), 2.36-1.78 (10H, m), 1.71-1.37 (5H, m, contains H_R), 1.33-1.24 (2H, m, contains $H_{R'}$), 1.04 (1H, m), 0.77 (3H, t, *J = 7.4 Hz*, H_S) ppm**.**

^{13}C NMR (100 MHz; $CDCl_3$): δ 218.5 (Q, C_O), 145.7 (Q, C_K), 141.0 (Q, C_E), 125.6 (CH, C_D), 110.2 (CH_2, C_T), 65.7 (Q, C_C), 54.6 (CH), 52.9 (Q, C_M), 52.2 (CH), 41.3 (CH), 40.4 (CH_2), 40.0 (CH_2), 39.6 (CH_2), 39.6 (CH_2), 36.1 (CH_2), 35.9 (CH), 34.7 (CH_2), 30.5 (CH_2), 28.6 (CH_2), 20.8 (CH_2, C_R), 18.1 (CH_2), 7.2 (CH_3, C_S) ppm.

X-ray: X-ray data available in Appendix II.

<u>The C17α-ethinyl steroid (5.20)</u> and **<u>the Δ3,4-steroid (5.21)</u>**



Thioketal **(5.14)** (0.019 g, 0.053 mmol) was dissolved in ethanol (3 mL), and Raney nickel was added. The mixture was refluxed (80 °C) with sequential addition of Raney nickel every 2 h until completion (4 h overall). The reaction mixture was cooled to room temperature, water (5 mL) and DCM (5 mL) were added and the phases were separated. The aqueous phase was extracted with DCM (3 x 10 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (Hexane/Acetone 90:10) to afford **(5.16)** and **(5.17)** as an unseparable mixture (0.010 g, 73%) (ratio **(5.16)**/**(5.17)** = 80:20).

To a cooled (-40 °C) solution of steroids **(5.16)**/**(5.17)** (0.010 g, 0.037 mmol, 1.0 equiv) in dry THF (2 mL) was added sodium acetylide (18% wt in Xylene, 0.224 mL, 0.740 mmol, 20 equiv). The reaction mixture was stirred at -40 °C for 30 min, then 30 min at 0 °C. The mixture was allowed to warm up to room temperature and stirring continued for 14 h. The mixture was diluted with DCM (5 mL) and slowly poured onto water (5 mL). After extraction with DCM (3 x 5 mL), the combined organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 85:15) to afford steroid **(5.20)** and its Δ3,4-isomer **(5.21)** as an unseparable mixture (0.008 g, 76%) (ratio **(5.20)**/**(5.21)** = 80:20).

Significant data for (5.20)

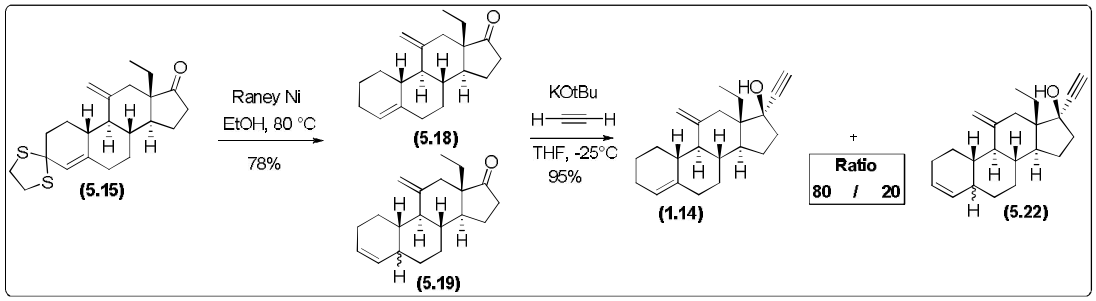
MW = 296.446 ($C_{21}H_{28}O$).

Rf = 0.34 (Hexane/Acetone 85:15).

^{1}H NMR (400 MHz; $CDCl_3$): ***Characteristic peaks*** δ 5.48 (1H, br s), 4.86 (1H, m), 4.79 (1H, br s), 2.59 (1H, s), 2.44 (1H, d, *J = 11.9 Hz*), 0.83 (3H, s) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 147.6 (Q), 139.9 (Q), 121.3 (CH), 109.1 (CH_2), 87.3 (Q), 79.0 (Q), 74.0 (CH), 54.8 (CH), 50.8 (CH), 48.9 (Q), 45.5 (CH_2), 42.8 (CH), 39.3 (CH_2), 36.6 (CH), 35.5 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 25.7 (CH_2), 22.6 (CH_2), 21.9 (CH_2), 13.0 (CH_3) ppm.

Desogestrel (1.14) and **the Δ3,4-steroid (5.22)**



Thioketal **(5.15)** (0.065 g, 0.174 mmol) was dissolved in ethanol (10 mL), and Raney nickel was added. The mixture was refluxed (80 °C) with sequential addition of Raney nickel every 2 h until completion (6 h overall). The reaction mixture was cooled to room temperature, water (15 mL) and DCM (15 mL) were added and the phases were separated. The aqueous phase was extracted with DCM (3 x 10 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (Hexane/Acetone 90:10) to afford **(5.18)** and **(5.19)** as an unseparable mixture (0.039 g, 78%) (ratio **(5.18)**/**(5.19)** = 80:20).

Acetylene was passed through a suspension of KO^{t}Bu (0.056 g, 0.499 mmol, 5.0 equiv) in dry THF (0.6 mL) at -25 °C for 1 hour. A solution of steroids **(5.18)**/**(5.19)** (0.028 g, 0.098 mmol, 1.0 equiv) in dry THF (300 µL) was added and acetylene was passed through the mixture for 1 h at -25 °C. The resulting mixture was allowed to warm up to room temperature, diluted with DCM (5 mL) and slowly poured onto water (5 mL). After extraction with DCM (3 x 5 mL), the combined organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by column

chromatography (Hexane/Acetone 85:15) to afford desogestrel **(1.14)** and its $\Delta_{3,4}$-isomer **(5.22)** as an unseparable mixture (0.029 g, 95%) (ratio **(1.14)**/**(5.22)** = 80:20).

Significant data for desogestrel (1.14)

MW = 310.473 ($C_{22}H_{30}O$).

Rf = 0.36 (Hexane/Acetone 85:15).

^{1}H NMR (400 MHz; $CDCl_3$): ***Characteristic peaks*** δ 5.48 (1H, s), 4.99 (1H, s), 4.79 (1H, s), 2.62 (1H, d, *J = 9.0 Hz*), 2.61 (1H, s), 1.05 (3H, t, *J = 7.4 Hz*) ppm.

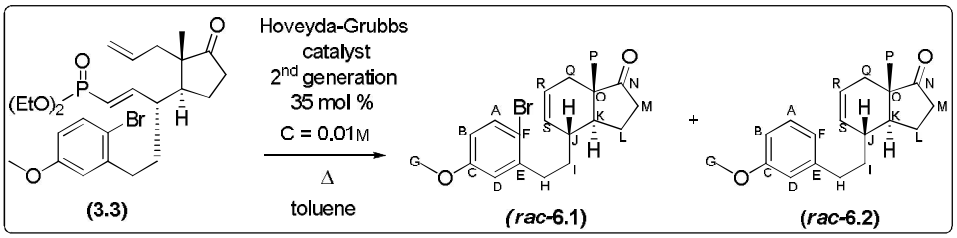
^{13}C NMR (100 MHz; $CDCl_3$): δ 147.5 (Q), 139.9 (Q), 121.3 (CH), 108.5 (CH_2), 87.9 (Q), 81.1 (Q), 74.0 (CH), 54.7 (CH), 52.4 (CH), 50.4 (Q), 42.6 (CH), 40.6 (CH_2), 39.8 (CH_2), 36.6 (CH), 35.5 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 25.7 (CH_2), 22.0 (CH_2), 21.9 (CH_2), 19.8 (CH_2), 9.1 (CH_3) ppm.

These data correspond to literature data.[26]

9.5 Experimental data for Chapter 6

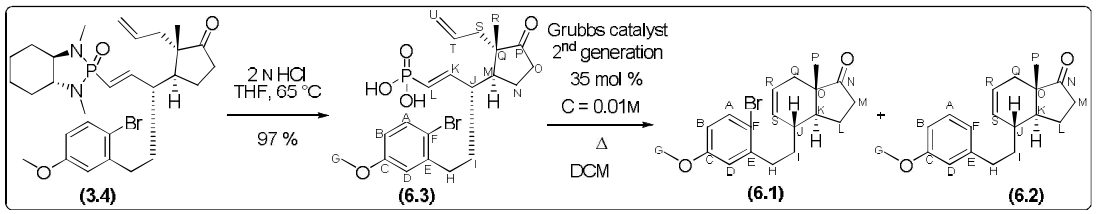
The C-ring cyclised bromide (*rac*-6.1, 6.1) and **the C-ring cyclised debrominated adduct (*rac*-6.2, 6.2)** and **the phosphonic acid (6.3).**

Route 1:



A 0.01 M solution of phosphonate **(3.3)** (246 mg, 0.47 mmol, 1.0 equiv) in toluene (47 mL) was degassed by bubbling nitrogen through it for 10 minutes. The 2nd generation Hoveyda-Grubbs catalyst (102 mg, 0.165 mmol, 0.35 equiv) was added and the solution was heated to 80 °C for 2 days. After cooling to room temperature, the solvent was removed and the crude product was purified by column chromatography (Hexane/Acetone 80:20) followed by HPLC (Hexane/Acetone 95:5) to afford (***rac*-6.1)** as a brown oil (103 mg, 61%) and **(*rac*-6.2)** as a colourless oil (1-2 mg, traces).

Route 2:



To a solution of phosphonamide **(3.4)** (0.189 g, 0.327 mmol, 1.0 equiv) in THF (3 mL) was added 2 N HCl (0.335 mL, 0.670 mmol). The mixture was stirred at 65 °C for 16 hours, then diluted with EtOAc and washed with 1 N HCl. The organic layer was dried over $MgSO_4$ and evaporated to give phosphonic acid **(6.3)** (0.144 g, 97 %), which was used in the next step without further purification. A 0.01 M solution of phosphonic acid **(6.3)** in DCM (32 mL) was degassed by bubbling nitrogen through it for a few minutes.

The 2nd generation Grubbs catalyst (0.095 g, 0.115 mmol, 0.35 equiv) was added and the mixture was refluxed for 24 hours. After cooling to room temperature, the solvent was evaporated and the crude mixture was purified by column chromatography (Hexane/Acetone 80:20) followed by HPLC (Hexane/Acetone 95:5) to afford **(6.1)** as a brown oil (0.053 g, 44%) and **(6.2)** (3 mg, 4%) as a colourless oil.

Data for (*rac*-6.1, 6.1):

Mw = 363.289 ($C_{19}H_{23}BrO_2$).

Rf = 0.44 (Hexane/Acetone 80:20).

IR (neat): 2962 (m), 2911 (m), 2835 (m), 1727 (s), 1570 (m), 1463 (m), 1239 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.42 (1H, d, *J = 8.7 Hz*, H_A), 6.79 (1H, d, *J = 3.0 Hz*, H_D), 6.64 (1H, dd, *J = 8.7, 3.0 Hz,* H_B), 5.82-5.61 (2H, m, $H_R + H_S$), 3.79 (3H, s, H_G), 2.85 (1H, ddd, *J = 12.9, 12.0, 5.1 Hz*, H_H), 2.68 (1H, ddd, *J = 13.3, 11.7, 5.3 Hz*, $H_{H'}$), 2.45 (1H, m, H_M), 2.25-2.03 (5H, m, $H_J + H_L + H_{M'} + 2H_Q$), 1.85 (1H, m, H_I), 1.67-1.58 (3H, m, $H_{I'} + H_{L'} + H_K$), 0.92 (3H, s, H_P) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 221.6 (Q, C_N), 159.0 (Q, C_C), 142.8 (Q, C_E), 133.3 (CH, C_A), 130.3 (CH, C_S), 125.8 (CH, C_R), 116.0 (CH, C_D), 114.8 (Q, C_F), 113.0 (CH, C_B), 55.4 (CH_3, C_G), 46.8 (Q, C_O), 46.0 (CH, C_K), 38.1 (CH, C_J), 35.8 (CH_2, C_I), 33.5 (CH_2, C_M), 33.4 (CH_2, C_H), 32.7 (CH_2, C_Q), 22.8 (CH_2, C_L), 14.3 (CH_3, C_P) ppm.

CIMS m/z (%): 382/380 ($M+NH_4^+$, 8), 365/363 ($M+H^+$, 2), 347/345 (12), 302 (47), 285/283 (30), 267 (84), 122 (100).

HRES$^+$MS For $C_{19}H_{24}O_2{}^{79}Br$ $(M+H)^+$: calcd 363.0954, found 363.0951.

$[\alpha]_D$ = +31.3 ° (c 0.82, $CHCl_3$).

Data for (*rac*-6.2, 6.2):

Mw = 284.178 ($C_{19}H_{24}O_2$).

Rf = 0.44 (Hexane/Acetone 80:20).

IR (neat): 2918 (w), 2857 (w), 1736 (s), 1584 (m), 1453 (m), 1259 (s), 1152 (m), 1046 (m), 780 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.22 (1H, dd, *J = 8.8, 7.3 Hz*, H_A), 6.83-6.72 (3H, m, $H_B + H_F + H_D$), 5.74-5.66 (2H, m, $H_R + H_S$), 3.80 (3H, s, H_G), 2.78 (1H, ddd, *J = 13.5, 11.0, 5.5 Hz*, H_H), 2.61 (1H, ddd, *J = 13.5, 10.6, 5.8 Hz*, $H_{H'}$), 2.47 (1H, m, H_M), 2.22-2.04 (5H, m,

H_J + H_L + $H_{M'}$ + 2H_Q), 1.90 (1H, dddd, *J = 17.2, 11.1, 6.4, 4.2 Hz*, H_I), 1.71-1.51 (3H, m, $H_{I'}$ + $H_{L'}$ + H_K), 0.88 (3H, s, H_P) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 221.6 (Q, C_N), 159.7 (Q, C_C), 144.1 (Q, C_E), 130.3 (CH, C_S), 129.3 (CH, C_A), 125.6 (CH, C_R), 120.7 (CH, C_F), 114.2 (CH, C_D), 111.0 (CH, C_B), 55.1 (CH_3, C_G), 46.8 (Q, C_O), 46.3 (CH, C_K), 37.9 (CH, C_J), 35.8 (CH_2, C_M), 34.3 (CH_2, C_I), 33.5 (CH_2, C_H), 32.8 (CH_2, C_Q), 22.8 (CH_2, C_L), 14.3 (CH_3, C_P) ppm.

CIMS m/z (%): 302 ($(M+NH_4)^+$, 6), 285 ($(M+H)^+$, 8), 267 (30), 122 (100).

HRMS (CI) For $C_{19}H_{24}O_2$: calcd 284.17763, found 284.17803.

<u>Data for (6.3):</u>

Mw = 471.322 ($C_{21}H_{28}BrO_5P$).

IR (neat): 2936, 2870, 1734, 1471, 1240, 1161, 992, 929, 808 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.46 (1H, d, *J = 8.5 Hz*, H_A), 6.89 (1H, d, *J = 3.0 Hz*, H_D), 6.76 (1H, dd, *J = 8.5, 3.0 Hz*, H_B), 6.33 (1H, ddd, *J = 21.1, 17.1, 10.0 Hz*, H_K), 5.85 (1H, dd, *J = 19.6, 17.1 Hz*, H_L), 5.45 (1H, m, H_T), 5.18 (1H, d, *J = 17.1 Hz*, H_U), 5.06 (1H, d, *J = 10.0 Hz*, $H_{U'}$), 3.76 (3H, s, H_G), 2.65 (1H, td, *J = 13.0, 4.5 Hz*, H_H), 2.48 (1H, td, *J = 13.0, 5.0 Hz*, $H_{H'}$), 2.37-2.25 (2H, m), 2.18 (1H, dd, *J = 14.0, 9.0 Hz*, H_S), 2.20-1.93 (4H, m), 1.85 (1H, m), 1.55-1.40 (2H, m), 0.94 (3H, s, H_R) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 222.0 (Q, C_P), 158.7 (Q, C_C), 149.2 (CH, C_K), 142.3 (Q, C_E), 134.7 (CH, C_T), 133.1 (CH, C_A), 123.7 (CH, d, *J = 179.3 Hz*, C_L), 118.4 (CH_2, C_U), 116.0 (CH, C_D), 113.7 (CH + Q, C_B+C_F), 55.3 (CH_3, C_G), 51.6 (Q), 45.7 (CH, d, *J = 20.4 Hz*, C_J), 43.9 (CH, C_M), 40.2 (CH_2, C_S), 36.6 (CH_2, C_I), 33.2 (CH_2, C_O), 31.7 (CH_2, C_H), 23.0 (CH_2, C_N), 17.7 (CH_3, C_R) ppm.

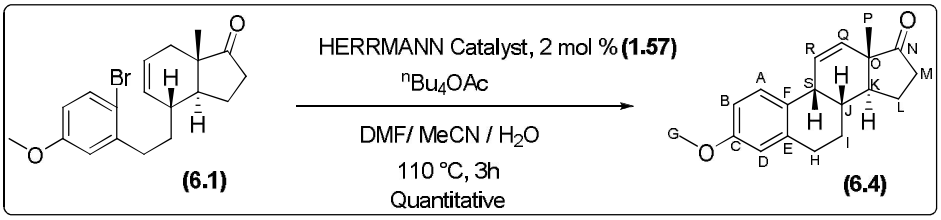
^{31}P NMR (121 MHz; $CDCl_3$): δ 12.41 ppm.

ES$^+$MS m/z (%): 472/470 (1:1, $(M+H)^+$, 100).

HRES$^+$MS For $C_{21}H_{29}{}^{79}BrO_5P$ $(M+H)^+$: calcd 471.0930, found 471.0929.

$[\alpha]_D$ = +34.0 ° (c 0.60, $CHCl_3$).

The Δ11,12-steroid (6.4).



To a carefully degassed solution of bromide **(6.1)** (35 mg, 0.096 mmol, 1.0 equiv) and $^{n}Bu_4OAc$ (100 mg, 0.333 mmol, 3.5 equiv) in DMF/MeCN/H_2O (1:1:0.2, 1.2 mL) was added the Herrmann catalyst (2.5 mg, 1.92 μmol, 0.02 equiv) at 50 °C. The mixture was stirred at 115 °C for 3 h. After cooling to room temperature, the mixture was diluted with Et_2O, washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo* yielding **(6.4)** as a colourless oil (27 mg, quantitative).

Mw = 282.377 ($C_{19}H_{22}O_2$).

Rf = 0.46 (Hexane/Acetone 80:20).

IR (film): 2921 (m), 2852 (w), 1738 (s), 1609 (w), 1499 (m), 1465 (m), 1247 (s), 1037 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.20 (1H, d, *J = 8.6 Hz*, H_A), 6.75 (1H, dd, *J = 8.6, 2.7 Hz*, H_B), 6.65 (1H, d, *J = 2.7 Hz*, H_D), 6.18 (1H, dd, *J = 9.9, 1.6 Hz*, H_Q), 6.06 (1H, dd, *J = 9.9, 4.1 Hz*, H_R), 3.78 (3H, s, H_G), 3.54 (1H, m, H_S), 2.79 (1H, ddd, *J = 15.4, 10.8, 4.3 Hz*, H_H), 2.61 (1H, td, *J = 15.9, 4.9 Hz*, $H_{H'}$), 2.55-2.47 (2H, m, H_M + H_J), 2.19 (1H, m, $H_{M'}$), 2.03-1.92 (2H, m, H_L + H_I), 1.85 (1H, dt, *J = 12.4, 5.4 Hz*, H_K), 1.76 (1H, ddd, *J = 17.1, 8.9, 4.0 Hz*, $H_{I'}$), 1.66 (1H, ddd, *J = 17.8, 10.8, 6.1 Hz*, $H_{L'}$), 1.03 (3H, s, H_P) ppm.

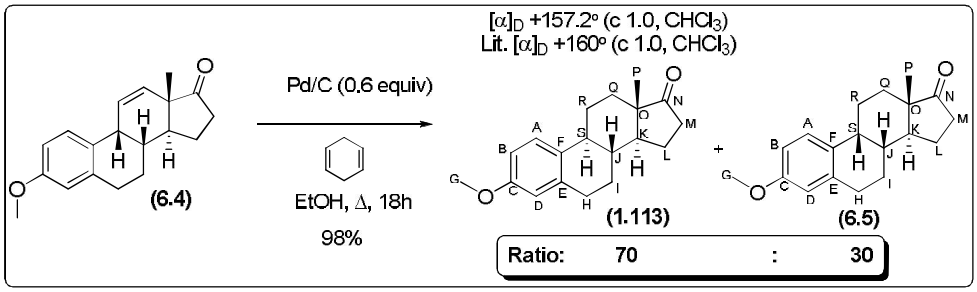
^{13}C NMR (100 MHz; $CDCl_3$): δ 216.5 (Q, C_N), 157.3 (Q, C_C), 138.6 (Q, C_E), 130.5 (CH, C_R), 130.4 (CH, C_Q), 130.4 (Q, C_F), 128.8 (CH, C_A), 113.4 (CH, C_B), 112.2 (CH, C_D), 55.2 (CH_3, C_G), 49.6 (Q, C_O), 43.3 (CH, C_K), 38.7 (CH, C_S), 36.6 (CH_2, C_M), 31.4 (CH, C_J), 26.4 (CH_2, C_H), 25.0 (CH_2, C_I), 20.9 (CH_2, C_L), 17.6 (CH_3, C_P) ppm.

CIMS m/z (%): 300 ($M+NH_4^+$, 18), 283 ($M+H^+$, 100).

HRMS we were not able to obtain HRMS data, product too unstable.

$[\alpha]_D$ = -119.2 ° (c 0.25, $CHCl_3$).

3-*O*-Methyl-Estrone (1.113) and **the *cis*-C8,9-steroid (6.5)**



A solution of alkene **(6.4)** (43 mg, 0.15 mmol, 1.0 equiv), cyclohexadiene (1.54 mL, 15 mmol, 100 equiv) and Pd/C (10% wt, 97 mg, 0.6 equiv) in dry EtOH (4 mL) was stirred for 20 h at 110 °C. Once cooled, the reaction mixture was diluted with DCM, filtered on celite and evaporated. The crude product was purified by column chromatography (Hexane/Acetone 80:20) to give a mixture of **(1.113)/(6.5)** in a 70/30 ratio (42 mg, 98%). Recrystallization in DCM/Hexane afforded pure **(1.113)** as fine white crystals.

Mw = 284.393 ($C_{19}H_{24}O_2$).

m.p. = 144-147 °C.

Rf = 0.45 (Hexane/Acetone 80:20).

IR (film): 2914 (m), 2848 (w), 1736 (s), 1608 (m), 1504 (m), 1245 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.22 (1H, d, *J = 8.6 Hz*, H_A), 6.73 (1H, dd, *J = 8.6, 2.6 Hz*, H_B), 6.66 (1H, d, *J = 2.6 Hz*, H_D), 3.79 (3H, s, H_G), 2.94-2.90 (2H, m, H_H), 2.51 (1H, dd, *J = 18.8, 8.3 Hz*, H_K), 2.41 (1H, m, H_I), 2.27 (1H, m), 2.20-1.95 (4H, m), 1.69-1.40 (6H, m), 0.92 (3H, s, H_P) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 220.9 (Q, C_N), 157.6 (Q, C_C), 137.7 (Q, C_E), 132.0 (Q, C_F), 126.3 (CH, C_A), 113.9 (CH, C_D), 111.6 (CH, C_B), 55.2 (CH_3, C_G), 50.4 (CH, C_J), 48.0 (Q, C_O), 44.0 (CH, C_S), 38.4 (CH, C_K), 35.9 (CH_2, C_M), 31.7 (CH_2, C_Q), 29.7 (CH_2, C_H), 26.6 (CH_2, C_I), 25.9 (CH_2, C_R), 21.6 (CH_2, C_L), 13.9 (CH_3, C_P) ppm.

CIMS m/z (%): 285 ($M+H^+$, 100).

$[\alpha]_D$ = +157.2 ° (c 1.0, $CHCl_3$).

The experimental data correspond well to the reported data.[55,205,219]

Significant data for (6.5):

Mw =284.393 ($C_{19}H_{24}O_2$).

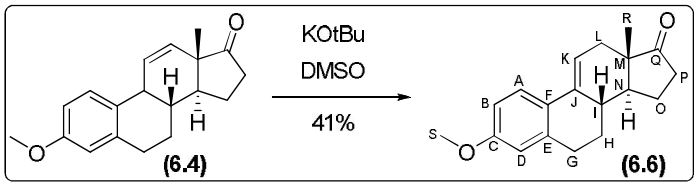
Rf = 0.45 (Hexane/Acetone 80:20).

^{1}H NMR (400 MHz; $CDCl_3$): ***Characteristic peaks*** δ 7.25 (1H, d, *J = 8.5 Hz*, H_A), 6.73 (1H, dd, *J = 8.6, 2.6 Hz*, H_B), 6.63 (1H, d, *J = 3.0 Hz*, H_D), 3.78 (3H, s, H_G), 3.03 (1H, m), 2.82 (1H, m), 2.70 (1H, dt, *J = 17.1, 4.5 Hz*), 0.98 (3H, s, H_P) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 220.8 (Q, C_N), 157.5 (Q, C_C), 138.5 (Q, C_E), 130.0 (Q, C_F), 127.5 (CH, C_A), 114.0 (CH, C_D), 112.2 (CH, C_B), 55.3 (CH_3, C_G), 48.0 (Q, C_O), 42.5 (CH), 37.5 (CH), 35.5 (CH_2), 34.0 (CH), 27.5 (CH_2), 26.1 (CH_2), 24.9 (CH_2), 24.3 (CH_2), 21.9 (CH_2), 13.5 (CH_3, C_P) ppm.

The experimental data correspond well to the reported data.[242,243]

<u>The Δ9,11-steroid (6.6):</u>



A solution of steroid **(6.4)** (49 mg, 0.177 mmol, 1.0 equiv) in dry DMSO (5 mL) was treated with KO*t*Bu (52 mg, 0.460 mmol, 2.5 equiv) with stirring for 1 h at room temperature. Water (5 mL) and brine (2.5 mL) were added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and purification of the resulting residue by column chromatography (Hexane/Acetone 70:30) afforded steroid **(6.6)** (20 mg, 41%) as an orange oil.

MW = 282.377 ($C_{19}H_{22}O_2$).

Rf = 0.29 (Hexane/Acetone 80:20).

IR (film): 2905 (m), 1723 (s), 1600 (m), 1492 (s), 1208 (m), 1036 (s) cm^{-1}.

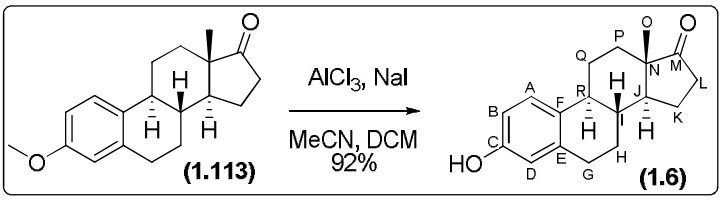
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.55 (1H, d, *J = 8.8 Hz*, H_A), 6.77 (1H, dd, *J = 8.8, 2.5 Hz*, H_B), 6.64 (1H, d, *J = 2.3 Hz*, H_D), 6.22 (1H, m, H_K), 3.81 (3H, s, H_S), 3.01-2.88 (2H, m), 2.81 (1H, dd, *J = 18.6, 6.9 Hz*, H_N), 2.56 (1H, m), 2.46-2.38 (2H, m), 2.31 (1H, dd, *J = 18.6, 13.6 Hz*), 2.12-1.97 (3H, m), 1.61-1.50 (2H, m), 1.12 (3H, s, H_R) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 203.6 (Q, C_Q), 158.9 (Q, C_C), 137.2 (Q, C_E), 135.2 (Q, C_F), 126.5 (Q, C_J), 125.3 (CH, C_A), 115.9 (CH, C_K), 113.4 (CH, $C_{B/D}$), 113.0 (CH, $C_{B/D}$),

55.3 (CH_3, C_S), 46.4 (Q, C_M), 40.4 (CH, C_N), 37.7 (CH, C_I), 37.0 (CH_2, C_P), 33.0 (CH_2, C_L), 29.7 (CH_2), 27.94 (CH_2), 27.86 (CH_2), 14.7 (CH_3, C_R) ppm.

The NMR data correspond to literature data.[205,221-223]

Estrone (1.6)



To a cooled (0 °C) solution of MeCN (2 mL) and DCM (1 mL) was added $AlCl_3$ (0.070 g, 0.53 mmol, 10.0 equiv) followed by NaI (0.078 g, 0.125 mmol, 2.4 equiv) and finally methyl-estrone **(1.113)** (0.015 g, 0.053 mmol, 1.0 equiv). The mixture was stirred for 5 h at room temperature, diluted with DCM (5 mL), poured onto 2 N HCl solution (5 mL), extracted with DCM (3 x 5 mL), dried over $MgSO_4$ and finally concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 70:30) to afford estrone **(1.6)** (0.014 g, 92 %) as a white solid.

Mw = 270.366 ($C_{18}H_{22}O_2$).

m.p. = 248-252 °C.

Rf = 0.36 (Hexane/Acetone 80:20).

IR (film): 3271 (br, m), 2924 (m), 2860 (m), 1716 (s), 1704 (s) 1621 (m), 1579 (m), 1496 (m), 1287 (s), 1246 (s), 1055 (s), 816 (s) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.16 (1H, d, *J = 8.4 Hz*, H_A), 6.65 (1H, dd, *J = 8.4, 2.3 Hz*, H_B), 6.60 (1H, d, *J = 2.4 Hz*, H_D), 4.70 (1H, br s, OH), 2.88 (2H, m, H_G), 2.52 (1H, dd, *J = 18.8, 8.5 Hz*, H_J), 2.39 (1H, m), 2.25 (1H, m), 2.20-1.93 (4H, m), 1.69-1.39 (6H, m), 0.92 (3H, s, H_O) ppm.

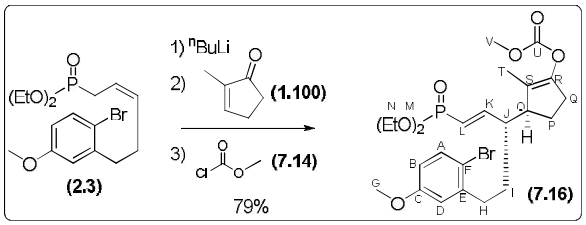
^{13}C NMR (100 MHz; $CDCl_3$): δ 221.0 (Q, C_M), 153.4 (Q, C_C), 138.1 (Q, C_E), 132.1 (Q, C_F), 126.5 (CH, C_A), 115.3 (CH, C_D), 112.8 (CH, C_B), 50.4 (CH, C_R), 48.0 (Q, C_N), 44.0 (CH, C_J), 38.4 (CH, C_I), 35.9 (CH_2, C_L), 31.6 (CH_2, C_P), 29.5 (CH_2, C_H), 26.5 (CH_2, $C_{H/Q}$), 25.9 (CH_2, $C_{H/Q}$), 21.6 (CH_2, C_K), 13.9 (CH_3, C_O) ppm.

CIMS m/z (%): 271 ($M+H^+$, 100).

The experimental data correspond well will literature data.[244]

9.6 Experimental data for Chapter 7

The carbonate (7.16)



To a solution of the *Z*-allylic phosphonate **(2.3)** (1.03 g, 2.63 mmol, 1.0 equiv) in THF (20 mL), cooled to -78 °C, ^{n}BuLi (2.5 M in Hexane, 1.15 mL, 2.89 mmol, 1.1 equiv) was added slowly and the mixture was stirred for 15 min at -78 °C. After warming to 0 °C, a solution of 2-methyl-2-cyclopentenone **(1.100)** (0.333 mL, 2.89 mmol, 1.3 equiv) in THF (10 mL) was immediately added over 2 min. via cannula. The solution was stirred for 1 h at 0 °C and then quenched with methyl cyanoformate **(7.14)** (2.02 mL, 26.3 mmol, 10 equiv). The solution was warmed to room temperature and stirred for 1 h. Water (50 mL) was added and the reaction was extracted with DCM (3 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 70:30) to afford **(7.16)** as a light yellow oil (1.08 g, 79%).

MW = 544.123 ($C_{24}H_{34}BrO_7P$).

Rf = 0.54 (Hexane/Acetone 65:35).

IR (neat): 2956 (w), 1758 (s), 1572 (w), 1472 (m), 1236 (s), 1050 (s), 1020 (s), 957 (s), 784 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.39 (1H, d, *J = 8.7 Hz*, H_A), 6.78 (1H, ddd, *J = 22.1, 17.2, 7.6 Hz*, H_K), 6.74 (1H, d, *J = 3.0 Hz*, H_B), 6.63 (1H, dd, *J = 8.7, 3.0 Hz*, H_D), 5.80 (1H, dd, *J = 20.4, 17.2 Hz*, H_L), 4.16-4.04 (4H, m, H_M), 3.81 (3H, s, $H_{G/V}$), 3.78 (3H, s, $H_{G/V}$), 2.79-2.66 (2H, m, H_O+H_H), 2.54 (1H, m, $H_{H'}$), 2.48-2.42 (3H, m, H_J+H_Q+$H_{Q'}$), 1.97 (1H, ddd, *J = 16.5, 13.3, 7.7 Hz*, H_P), 1.82-1.66 (2H, m, H_I+$H_{P'}$), 1.60 (1H, dtd, *J = 15.3, 10.5, 5.0 Hz*, $H_{I'}$), 1.50 (3H, s, H_T), 1.35 (6H, t, *J = 7.1 Hz*, H_N) ppm.

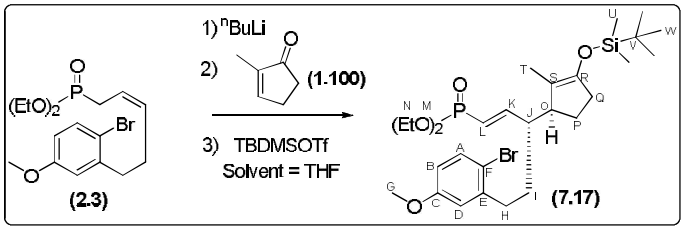
^{13}C NMR (100 MHz; $CDCl_3$): δ 159.0 (Q, C_C), 155.3 (d, *J = 4.2 Hz*, CH, C_K), 153.0 (Q, C_U), 145.9 (Q, C_R), 142.0 (Q, C_E), 133.3 (CH, C_A), 123.3 (Q, C_S), 118.2 (d, *J = 186.1 Hz*, CH, C_L), 115.9 (CH, C_D), 114.7 (Q, C_F), 113.4 (CH, C_B), 61.7 (d, *J = 5.2 Hz*, CH_2, C_M), 61.7 (d, *J = 5.3 Hz*, CH_2, $C_{M'}$), 55.4 (CH_3, $C_{G/V}$), 55.1 (CH_3, $C_{G/V}$), 48.9 (CH, C_O), 45.9 (d, *J = 20.3 Hz*, CH, C_J), 34.6 (CH_2, C_H), 29.7 (CH_2, C_Q), 28.0 (CH_2, C_I), 22.1 (CH_2, C_P), 16.4 (d, *J = 5.0 Hz*, 2 x CH_3, C_N), 10.6 (CH_3, C_T) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 18.85 ppm.

ES$^+$MS m/z (%): 569/567 (1:1, $(M+Na)^+$, 37), 547/545 (1:1, $(M+H)^+$, 13).

HRES$^+$MS for $C_{24}H_{34}O_7{}^{79}BrP$ $(M+H)^+$: calcd 545.1298, found 545.1300.

The silyl enol ether (7.17)



To a solution of the *Z*-allylic phosphonate **(2.3)** (1.03 g, 2.63 mmol, 1.0 equiv) in THF (20 mL), cooled to -78 °C, ^{n}BuLi (1.6 M in Hexane, 1.81 mL, 2.89 mmol, 1.1 equiv) was added slowly and the mixture was stirred for 15 min at -78 °C. After warming to 0 °C, a solution of 2-methyl-2-cyclopentenone **(1.100)** (0.334 mL, 3.42 mmol, 1.3 equiv) in THF (10 mL) was immediately added over 2 min. via cannula. The solution was stirred for 1 h at 0 °C and then quenched with TBDMSOTf (1.21 mL, 5.26 mmol, 2.0 equiv). The solution was warmed to room temperature and stirred for 1 h. Water (10 mL) was added and the reaction was extracted with DCM (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 70:30) using pre-neutralized silica gel to afford **(7.17)** as a light yellow oil (1.27 g, 84%).

Mw = 601,625 ($C_{28}H_{46}BrO_5PSi$).

Rf = 0.48 (Hexane/Acetone 65:35).

IR (film): 2936 (m), 2855 (m), 1727 (m), 1471 (w), 1242 (m), 1101 (m), 1052 (s), 1022 (s), 959 (m) cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.39 (1H, d, *J = 8.7 Hz*, H_A), 6.79 (1H, ddd, *J = 22.1, 17.2, 8.5 Hz*, H_K), 6.72 (1H, d, *J = 3.0 Hz*, H_D), 6.63 (1H, dd, *J = 8.7, 3.0 Hz*, H_B), 5.77 (1H, dd, *J = 20.9, 17.2 Hz*, H_L), 4.16-4.05 (4H, m, H_M), 3.78 (3H, s, H_G), 2.78-2.59 (2H, m, H_O+H_H), 2.51 (1H, ddd, *J = 13.5, 10.4, 6.3 Hz*, $H_{H'}$), 2.43 (1H, m, H_J), 2.27-2.12 (2H, m, H_Q), 1.90-1.80 (1H, m, H_P), 1.75-1.66 (1H, m, H_I), 1.62-1.51 (2H, m, $H_{I'}$+$H_{P'}$), 1.47 (3H, s, H_T), 1.35 (6H, t, *J = 7.1 Hz*, H_N), 0.93 (9H, s, H_W), 0.10 (3H, s, H_U) ppm.

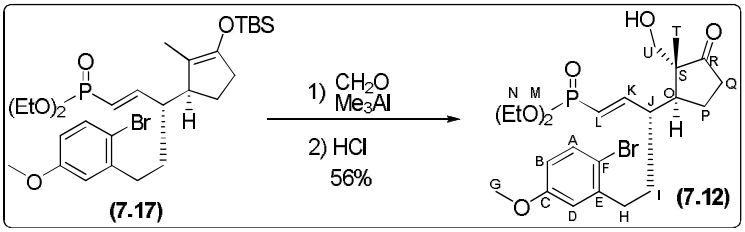
^{13}C NMR (100 MHz; $CDCl_3$): δ 158.9 (Q, C_C), 156.5 (d, *J = 4.1 Hz*, CH, C_H), 148.9 (Q, C_R), 142.4 (Q, C_E), 133.3 (CH, C_A), 117.5 (d, *J = 186.0 Hz*, CH, C_L), 116.0 (CH, C_D), 114.7 (Q, C_F), 113.2 (CH, C_B), 113.1 (Q, C_S), 61.6 (d, *J = 3.9 Hz*, 2 x CH_2, C_M), 55.4 (CH_3, C_G), 49.3 (CH, C_O), 46.6 (d, *J = 20.1 Hz*, CH, C_J), 34.9 (CH_2, C_H), 32.8 (CH_2, C_Q), 28.1 (CH_2, C_I), 25.7 (3 x CH_3, C_W), 22.0 (CH_2, C_P), 18.1 (Q, C_V), 16.4 (d, *J = 5.1 Hz*, 2 x CH_3, C_N), 10.7 (CH_3, C_T), -4.0 (CH_3, C_U) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 19.22 ppm.

ES^{+}MS m/z (%): 626/623 (1:1, $(M+Na)^+$, 100), 603/601 (1:1, $(M+H)^+$, 30).

HRES^{+}MS For $C_{28}H_{46}{}^{79}BrO_5PSiNa$ $(M+Na)^+$: calcd 623.1928, found 623.1942.

The alcohol (7.12)



To a stirred solution of silyl enol ether **(7.17)** (0.133 g, 0.221 mmol, 1.0 equiv) and paraformaldehyde (0.066 g, 2.21 mmol, 10 equiv) in DCM (3 mL) was slowly added $AlMe_3$ (2 M in Hexane, 0.221 mL, 2.0 equiv). The mixture was stirred at room temperature for 5 h, then water was added (2 mL). The reaction was extracted with DCM (3 x 5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was dissolved in THF (3 mL), treated with HCl 2 M (2 mL) and stirred at room temperature for 1 h. After usual work-up, the crude product was purified by column chromatography (Hexane/Acetone 60:40) to afford alcohol **(7.12)** as a light yellow oil (0.064 g, 56%).

Mw = 517,390 ($C_{23}H_{34}BrO_6P$).

Rf = 0.27 (Hexane/Acetone 65:35).

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.40 (1H, d, *J = 8.7 Hz*, H_A), 6.73 (1H, d, *J = 3.0 Hz*, H_D), 6.71 (1H, m, H_K), 6.64 (1H, dd, *J = 8.8, 3.0 Hz*, H_B), 5.78 (1H, dd, *J = 20.6, 17.3 Hz*, H_L), 4.21-4.05 (4H, m, H_M), 3.78 (3H, s, H_G), 3.77 (1H, d, *J = 9.7 Hz*, H_U), 3.44 (1H, d, *J = 9.7 Hz*, $H_{U'}$), 2.71 (1H, ddd, *J = 13.2, 11.8, 5.0 Hz*, H_Q), 2.58-2.45 (2H, m, $H_{Q'}$+H_O), 2.44-2.32 (2H, m, H_J+H_I), 2.28-2.06 (2H, m, H_P+$H_{I'}$), 1.99 (1H, m, H_H), 1.69-1.41 (2H, m, $H_{P'}$+$H_{H'}$), 1.35 (6H, t, *J = 7.1 Hz*, H_N), 0.83 (3H, s, H_T) ppm.

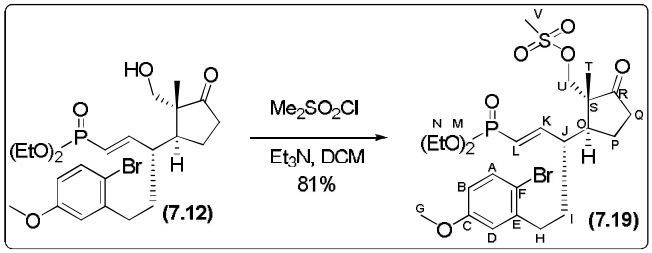
^{13}C NMR (100 MHz; $CDCl_3$): δ 222.8 (Q, C_R), 159.1 (Q, C_C), 155.4 (d, *J = 3.8 Hz*, CH, C_K), 142.0 (Q, C_E), 133.4 (CH, C_A), 119.0 (d, *J = 186.7 Hz*, CH, C_L), 116.0 (CH, C_D), 114.6 (Q, C_F), 113.2 (CH, C_B), 65.4 (CH_2, C_U), 61.8 (d, *J = 5.5 Hz*, 2 x CH_2, C_M), 55.4 (CH_3, C_G), 53.7 (Q, C_S), 46.6 (d, *J = 20.9 Hz*, CH, C_J), 42.5 (CH, C_O), 37.0 (CH_2, C_I), 34.0 (CH_2, C_Q), 32.0 (CH_2, C_H), 23.5 (CH_2, C_P), 16.4 (d, *J = 6.2 Hz*, 2 x CH_3, C_N), 13.7 (CH_3, C_T) ppm.

^{31}P NMR (121 MHz; $CDCl_3$): δ 17.97 ppm.

ES$^+$MS m/z (%): 541/539 (1:1, $(M+Na)^+$, 100), 519/517 (1:1, $(M+H)^+$, 10).

HRES$^+$MS For $C_{23}H_{34}{}^{79}BrO_6PNa$ $(M+Na)^+$: calcd 539.1174, found 539.1176.

<u>The mesylate (7.19)</u>



Triethylamine (45 µL, 0.33 mmol, 2.5 equiv) in DCM (1 mL) was added dropwise to alcohol **(7.12)** (67 mg, 0.13 mmol, 1.0 equiv) and methanesulfonyl chloride (20 µL, 0.26 mmol, 2.0 equiv) in DCM (2 mL) at -20 °C. After 20 min, the mixture was allowed to warm to room temperature. After an additional 40 min, the mixture was poured into water (5 mL), and the organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (Hexane/Acetone 60:40) to afford **(7.19)** as a colourless oil (62 mg, 81%).

Mw = 595.481 ($C_{24}H_{36}O_8PS$).

Rf = 0.29 (Hexane/Acetone 65:35).

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41 (1H, d, *J* = 8.7 Hz, H_A), 6.73 (1H, d, *J* = 3.0 Hz, H_D), 6.63 (1H, ddd, *J* = 21.8, 17.3, 9.7 Hz, H_K), 6.65 (1H, dd, *J* = 8.8, 2.8 Hz, H_B), 5.84 (1H, dd, *J* = 20.4, 17.3 Hz, H_L), 4.31 (1H, d, *J* = 9.8 Hz, H_U), 4.21-4.06 (4H, m, H_M), 4.02 (1H, d, *J* = 9.8 Hz, $H_{U'}$), 3.79 (3H, s, H_G), 3.01 (3H, s, H_V), 2.70 (1H, m, H_Q), 2.57-2.08 (6H, m, H_I+$H_{I'}$+H_J+H_O+H_P+$H_{Q'}$), 2.01 (1H, m, H_H), 1.67-1.48 (2H, m, $H_{H'}$+$H_{P'}$), 1.36 (6H, t, *J* = 7.0 Hz, H_N), 0.89 (3H, s, H_T) ppm.

^{13}C NMR (100 MHz; $CDCl_3$): δ 218.4 (Q, C_R), 159.0 (Q, C_C), 153.4 (d, *J = 3.1 Hz*, CH, C_K), 141.7 (Q, C_E), 133.4 (CH, C_A), 120.4 (d, *J = 187.3 Hz*, CH, C_L), 116.0 (CH, C_D), 114.6 (Q, C_F), 113.3 (CH, C_B), 71.5 (CH_2, C_U), 62.0 (d, *J = 5.6 Hz*, CH_2, C_M), 62.0 (d, *J = 5.5 Hz*, CH_2, $C_{M'}$), 55.4 (CH_3, C_G), 51.9 (Q, C_S), 46.6 (d, *J = 20.8 Hz*, CH, C_J), 42.2 (CH, C_O), 36.7 (CH_3, C_V), 36.3 (CH_2, C_I), 34.0 (CH_2, C_Q), 31.9 (CH_2, C_H), 23.2 (CH_2, C_P), 16.4 (d, *J = 6.1 Hz*, 2 x CH_3, C_N), 13.5 (CH_3, C_T) ppm.

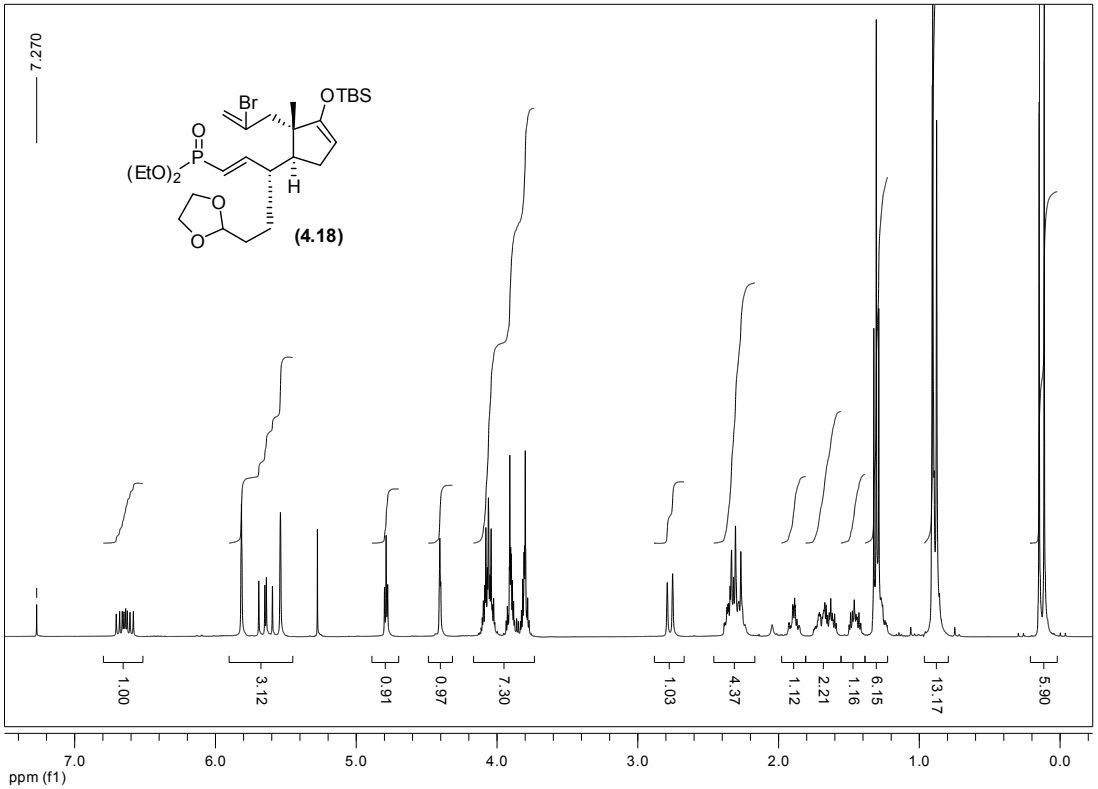
^{31}P NMR (121 MHz; $CDCl_3$): δ 16.89 ppm.

ES$^+$MS m/z (%): 619/617 (1:1, $(M+Na)^+$, 100), 597/595 (1:1, $(M+H)^+$, 65).

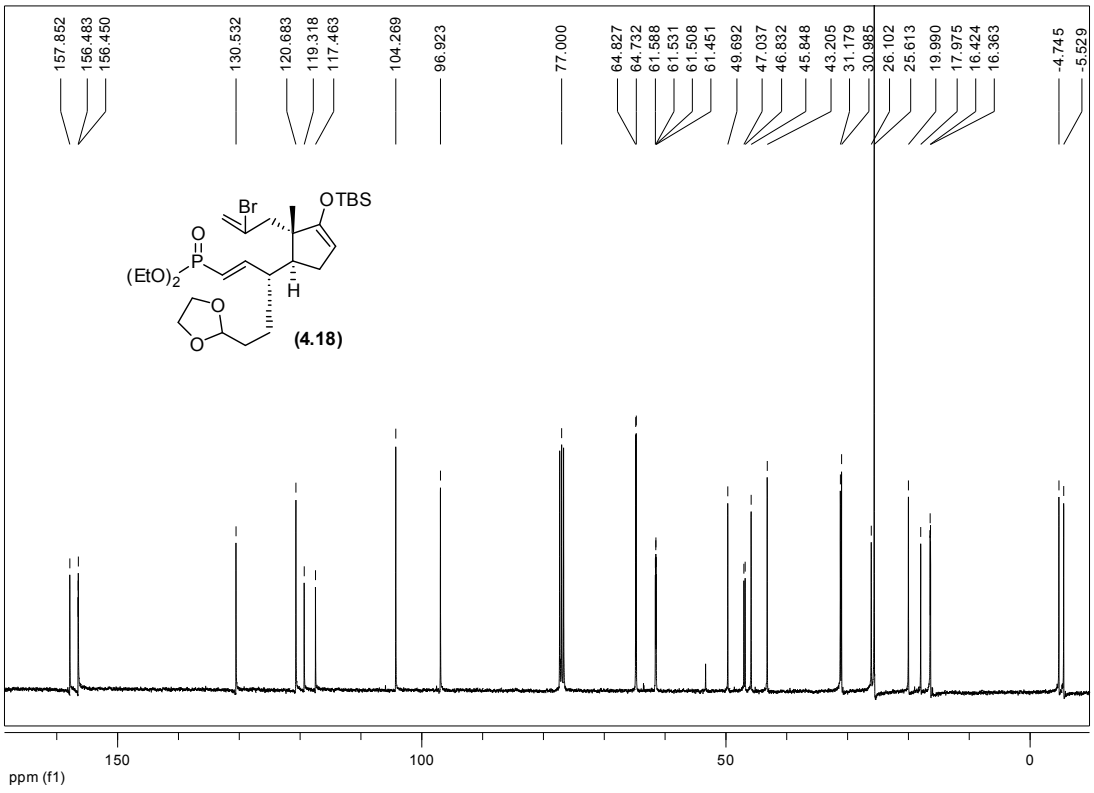
HRES+MS For $C_{24}H_{36}O_8PS^{79}BrNa$ $(M+Na)^+$: calcd 617.0944, found 617.0954.

Appendix I : Copies of ^{1}H and ^{13}C NMR spectra

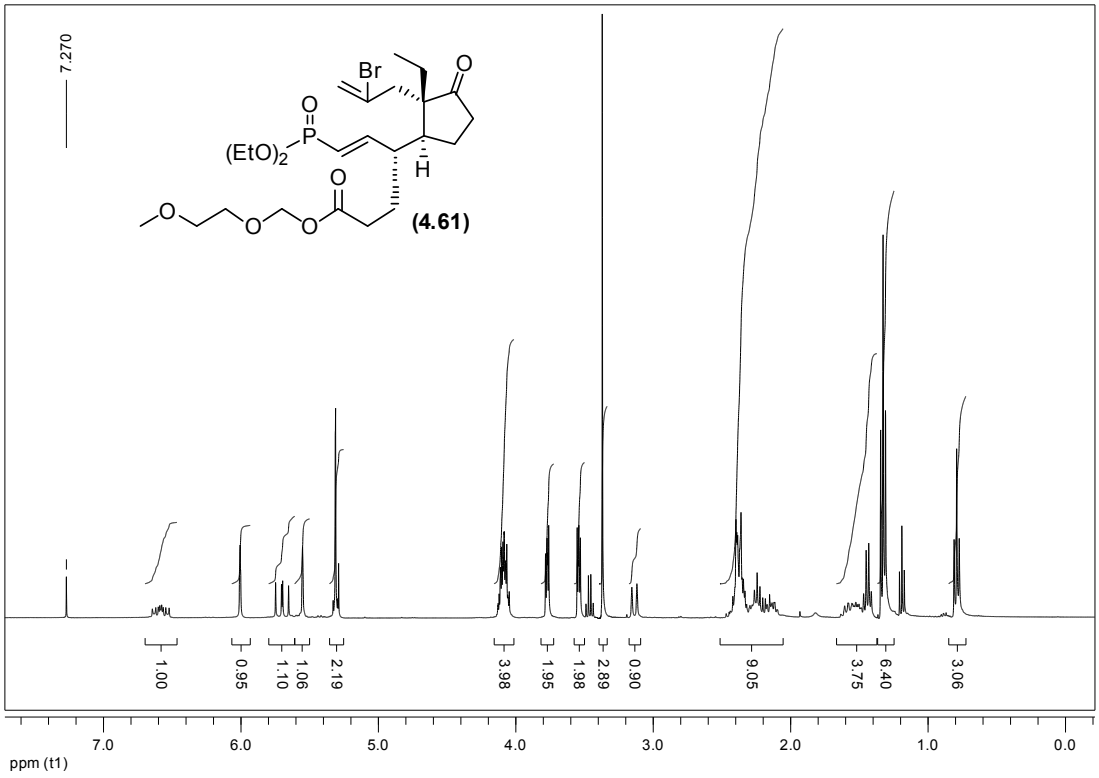
^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **(4.18)**.



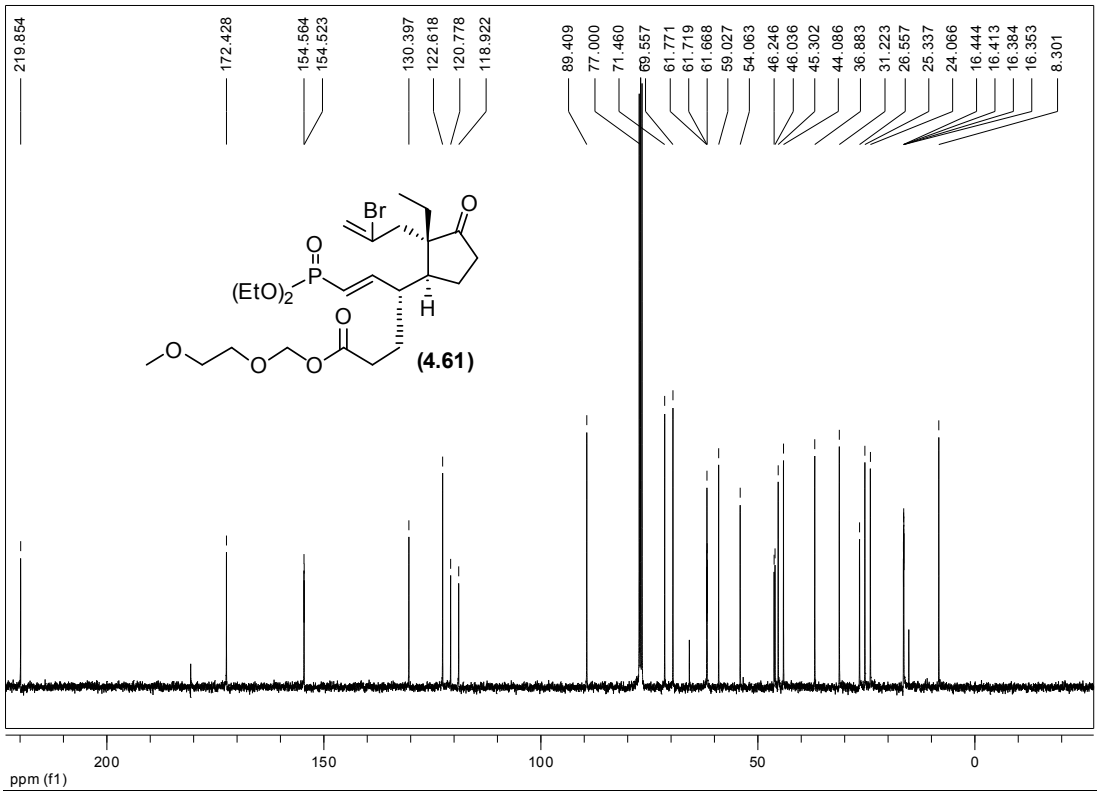
^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **(4.18)**.



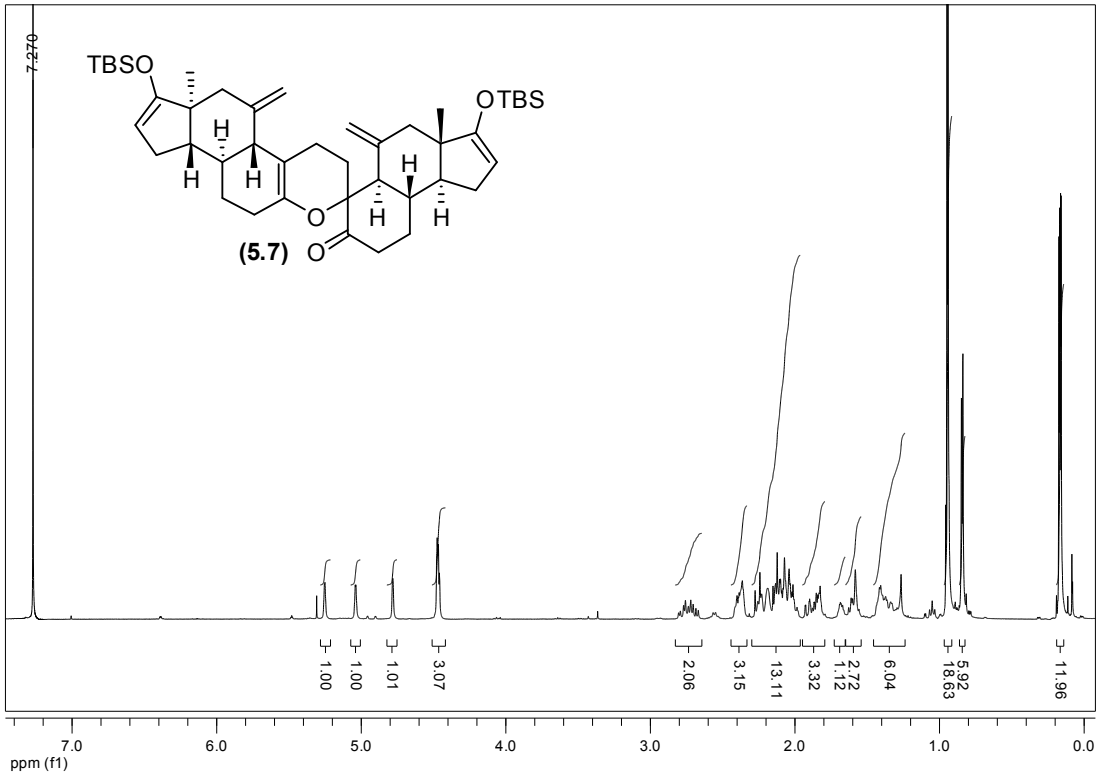
^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **(4.61)**.



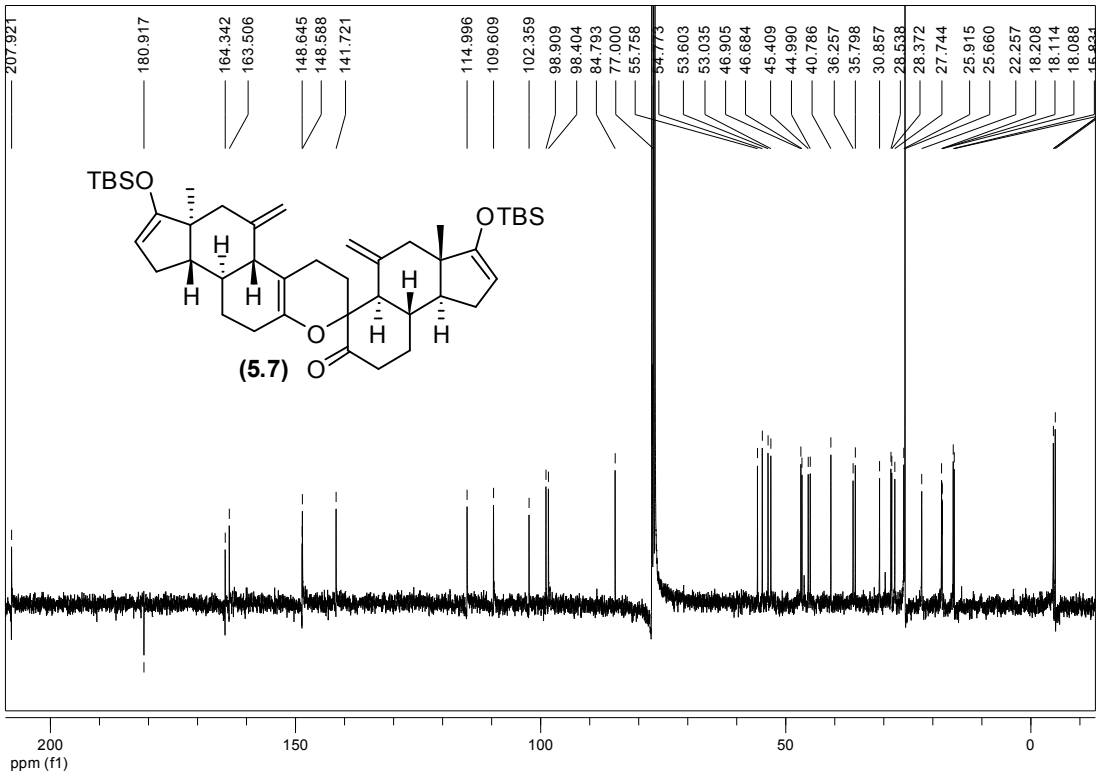
^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **(4.61)**.



^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **(5.7)**.



^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **(5.7)**.



Appendix II: X-ray data

X-ray data for (3.3)

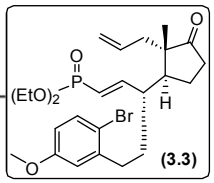


Table 1. Crystal data and structure refinement details.

Identification code	2008sotl297
Empirical formula	$C_{25}H_{36}BrO_3P$
Formula weight	527.42
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*C2/c*
Unit cell dimensions	$a = 35.9751(6)$ Å $b = 11.4216(2)$ Å $\beta = 102.2390(10)°$ $c = 13.0400(2)$ Å
Volume	5236.27(15) Å^3
Z	8
Density (calculated)	1.338 Mg / m^3
Absorption coefficient	1.663 mm^{-1}
F(000)	2208
Crystal	Fragment; Colourless
Crystal size	0.2 × 0.14 × 0.05 mm^3
θ range for data collection	3.15 – 25.03°
Index ranges	$-42 \le h \le 41, 0 \le k \le 13, 0 \le l \le 15$
Reflections collected	6233
Independent reflections	6233 [$R_{int} = 0.0000$]
Completeness to $\theta = 25.03°$	99.5 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9215 and 0.7221
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6233 / 0 / 294
Goodness-of-fit on F^2	3.145
Final *R* indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0875$, $wR2 = 0.1519$
R indices (all data)	$R1 = 0.1068$, $wR2 = 0.1587$
Largest diff. peak and hole	1.161 and –1.122 e Å^{-3}

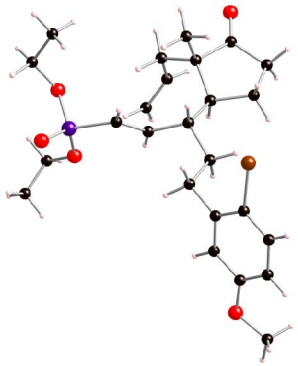


Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Br1	262(1)	6728(1)	4792(1)	38(1)	1
P1	–1743(1)	8996(1)	4497(1)	29(1)	1
O1	580(1)	11108(3)	7405(3)	34(1)	1
O2	–1385(1)	3664(3)	7649(3)	35(1)	1
O3	–1771(1)	9647(3)	3527(3)	46(1)	1
O4	–2104(1)	8225(3)	4539(3)	43(1)	1
O5	–1705(1)	9733(3)	5530(3)	46(1)	1
C1	953(2)	11309(5)	8021(4)	42(1)	1
C2	534(1)	10124(4)	6796(3)	26(1)	1
C3	826(1)	9461(4)	6554(4)	27(1)	1
C4	737(1)	8472(4)	5943(3)	26(1)	1
C5	364(1)	8139(4)	5597(3)	24(1)	1
C6	62(1)	8792(4)	5819(3)	19(1)	1
C7	160(1)	9793(4)	6409(3)	21(1)	1
C8	–344(1)	8408(4)	5517(3)	21(1)	1
C9	–438(1)	7558(4)	6332(3)	20(1)	1
C10	–826(1)	6952(4)	6008(3)	18(1)	1
C11	–900(1)	6138(4)	6890(3)	19(1)	1
C12	–569(1)	5288(4)	7316(3)	24(1)	1
C13	–739(1)	4396(4)	7955(4)	30(1)	1
C14	–1157(1)	4362(4)	7438(4)	26(1)	1
C15	–1255(1)	5334(4)	6626(3)	21(1)	1
C16	–1301(1)	4745(4)	5543(3)	28(1)	1
C17	–1636(1)	5905(4)	6707(3)	22(1)	1
C18	–1637(1)	6476(5)	7743(4)	31(1)	1
C19	–1702(1)	7588(5)	7871(5)	42(1)	1
C20	–1138(1)	7844(4)	5734(3)	19(1)	1
C21	–1351(1)	8031(4)	4789(3)	21(1)	1
C22	–2372(2)	7844(5)	3624(5)	50(2)	1
C23	–2264(2)	6709(6)	3222(6)	73(2)	1
C24	–2012(2)	10394(6)	5801(7)	79(2)	1
C25	–2001(3)	11576(7)	5648(8)	112(4)	1

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

Br1–C5	1.916(5)	C8–C9	1.530(6)
P1 O3	1.452(4)	C9 C10	1.534(6)
P1 O5	1.570(4)	C10 C20	1.502(6)
P1 O4	1.580(4)	C10 C11	1.545(6)
P1 C21	1.767(4)	C11 C12	1.546(6)
O1 C2	1.366(6)	C11 C15	1.552(6)
O1 C1	1.431(6)	C12 C13	1.526(6)
O2 C14	1.215(6)	C13 C14	1.512(7)
O4 C22	1.433(6)	C14 C15	1.524(6)
O5 C24	1.442(7)	C15 C17	1.539(6)
C2–C3	1.383(7)	C15–C16	1.541(6)
C2 C7	1.387(6)	C17 C18	1.501(6)
C3 C4	1.380(7)	C18 C19	1.308(7)
C4 C5	1.374(6)	C20 C21	1.324(6)
C5–C6	1.399(6)	C22–C23	1.482(8)
C6–C7	1.382(6)	C24–C25	1.366(10)
C6–C8	1.493(6)		
O3 P1 O5	116.8(2)	C20 C10 C9	110.5(4)
O3 P1 O4	114.3(2)	C20 C10 C11	110.3(3)
O5 P1 O4	101.1(2)	C9 C10 C11	110.9(3)
O3–P1–C21	114.2(2)	C10–C11–C12	113.8(4)
O5–P1–C21	103.2(2)	C10–C11–C15	117.1(3)
O4 P1 C21	105.6(2)	C12 C11 C15	104.1(3)
C2 O1 C1	116.1(4)	C13 C12 C11	104.3(4)
C22 O4 P1	123.6(4)	C14 C13 C12	104.5(4)
C24–O5–P1	123.9(4)	O2–C14–C13	124.7(4)
O1–C2–C3	125.4(4)	O2–C14–C15	124.5(4)
O1 C2 C7	115.0(4)	C13 C14 C15	110.7(4)
C3 C2 C7	119.6(4)	C14 C15 C17	109.9(4)
C4 C3 C2	118.9(4)	C14 C15 C16	106.4(4)
C5 C4 C3	120.5(4)	C17 C15 C16	108.9(4)
C4–C5–C6	122.1(4)	C14–C15–C11	102.6(3)
C4 C5 Br1	118.2(4)	C17 C15 C11	115.9(4)
C6 C5 Br1	119.7(3)	C16 C15 C11	112.6(4)
C7 C6 C5	116.0(4)	C18 C17 C15	114.7(4)
C7 C6 C8	120.7(4)	C19 C18 C17	124.9(5)
C5–C6–C8	123.2(4)	C21–C20–C10	125.9(4)
C6–C7–C2	122.8(4)	C20–C21–P1	125.4(4)
C6 C8 C9	110.6(3)	O4 C22 C23	112.3(5)
C8 C9 C10	114.7(3)	C25 C24 O5	115.8(7)

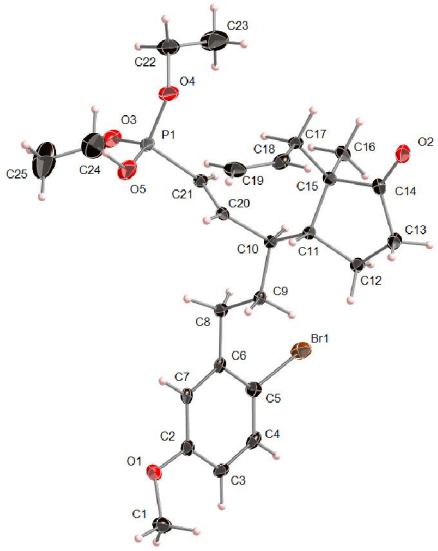
Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br1	36(1)	42(1)	36(1)	12(1)	7(1)	8(1)
P1	19(1)	29(1)	39(1)	10(1)	3(1)	1(1)
O1	38(2)	24(2)	36(2)	2(2)	2(2)	6(2)
O2	31(2)	29(2)	46(2)	12(2)	13(2)	0(2)
O3	34(2)	48(2)	56(2)	27(2)	6(2)	6(2)
O4	23(2)	51(2)	52(2)	9(2)	2(2)	4(2)
O5	44(2)	39(2)	56(2)	9(2)	13(2)	13(2)
C1	41(3)	37(3)	42(3)	2(3)	−6(3)	−11(3)
C2	30(3)	23(3)	23(2)	9(2)	5(2)	−1(2)
C3	19(2)	33(3)	27(3)	15(2)	2(2)	4(2)
C4	20(2)	38(3)	22(2)	13(2)	9(2)	6(2)
C5	27(3)	30(3)	16(2)	4(2)	5(2)	2(2)
C6	22(2)	24(2)	12(2)	10(2)	5(2)	4(2)
C7	26(3)	20(2)	18(2)	9(2)	6(2)	4(2)
C8	21(2)	24(3)	17(2)	4(2)	4(2)	0(2)
C9	21(2)	20(2)	18(2)	3(2)	4(2)	3(2)
C10	18(2)	20(2)	16(2)	2(2)	6(2)	1(2)
C11	21(2)	19(2)	16(2)	1(2)	5(2)	2(2)
C12	22(2)	24(3)	26(2)	2(2)	5(2)	1(2)
C13	33(3)	24(3)	32(3)	5(2)	3(2)	3(2)
C14	31(3)	20(3)	28(3)	1(2)	12(2)	1(2)
C15	21(2)	20(2)	24(2)	2(2)	8(2)	1(2)
C16	29(3)	25(3)	27(3)	7(2)	4(2)	5(2)
C17	17(2)	26(3)	23(2)	3(2)	3(2)	3(2)
C18	23(3)	41(3)	30(3)	2(2)	8(2)	6(2)
C19	26(3)	51(4)	49(3)	20(3)	11(3)	3(3)

C20	21(2)	17(2)	19(2)	0(2)	8(2)	2(2)
C21	18(2)	23(3)	22(2)	1(2)	6(2)	−1(2)
C22	31(3)	59(4)	56(4)	2(3)	−1(3)	−7(3)
C23	40(4)	91(6)	88(5)	22(5)	16(4)	7(4)
C24	60(5)	62(5)	121(7)	24(5)	34(5)	18(4)
C25	131(9)	77(6)	146(9)	11(6)	70(7)	52(6)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	1040	10613	8443	64	1
H1B	948	11981	8485	64	1
H1C	1128	11472	7556	64	1
H3	1084	9684	6805	32	1
H4	934	8019	5761	31	1
H7	38	10275	6557	25	1
H8A	−389	8020	4822	25	1
H8B	−513	9100	5461	25	1
H9A	431	7993	6993	23	1
H9B	238	6950	6478	23	1
H10	824	6465	5372	21	1
H11	−932	6650	7487	22	1
H12A	−479	4903	6734	29	1
H12B	353	5708	7763	29	1
H13A	621	3617	7930	36	1
H13B	−703	4646	8697	36	1
H16A	−1063	4357	5493	41	1
H16B	−1364	5340	4992	41	1
H16C	1506	4165	5456	41	1
H17A	1702	6501	6147	26	1
H17B	−1837	5298	6575	26	1
H18	−1586	5994	8350	38	1
H19A	1753	8097	7282	50	1
H19B	1698	7886	8554	50	1
H20	1187	8317	6290	22	1
H21	1288	7611	4220	25	1
H22A	2390	8444	3068	60	1
H22B	2626	7768	3797	60	1
H23A	2026	6802	2977	109	1
H23B	2465	6449	2638	109	1
H23C	2228	6124	3785	109	1
H24A	−2255	10091	5383	95	1
H24B	−2012	10250	6549	95	1
H25A	1754	11884	6014	168	1
H25B	2205	11952	5924	168	1
H25C	2037	11741	4896	168	1



Thermal ellipsoids drawn at the 35% probability level

X-ray data for (4.26)

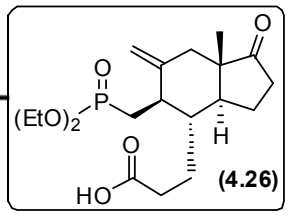


Table 1. Crystal data and structure refinement details.

Identification code	2007sot1091 (VF/4946/24)	
Empirical formula	$C_{19}H_{31}O_6P$	
Formula weight	386.41	
Temperature	120(2) K	
Wavelength	0.71069 Å	
Crystal system	Triclinic	
Space group	*P* 1	
Unit cell dimensions	*a* = 8.942(5) Å	α = 108.282(5)°
	b = 14.765(5) Å	β = 90.978(5)°
	c = 15.794(5) Å	γ = 90.370(5)°
Volume	1979.6(14) Å^3	
Z	4	
Density (calculated)	1.297 Mg / m^3	
Absorption coefficient	0.170 mm^{-1}	
F(000)	832	
Crystal	Block; Colourless	
Crystal size	0.2 × 0.05 × 0.05 mm^3	
θ range for data collection	3.19 25.02°	
Index ranges	10 ≤ *h* ≤ 10, 17 ≤ *k* ≤ 17, 18 ≤ *l* ≤ 18	
Reflections collected	25253	
Independent reflections	6931 [R_{int} = 0.2139]	
Completeness to θ = 25.02°	98.9 %	
Absorption correction	Semi empirical from equivalents	
Max. and min. transmission	0.9915 and 0.9567	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6931 / 338 / 491	
Goodness-of-fit on F^2	1.066	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R*1 = 0.1893, *wR*2 = 0.3504	
R indices (all data)	*R*1 = 0.3500, *wR*2 = 0.4365	
Largest diff. peak and hole	1.045 and -0.516 e Å^{-3}	

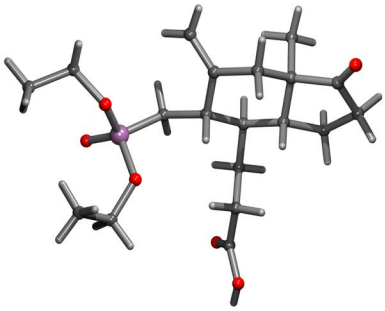


Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	S.o.f.
P1	6863(3)	-1621(2)	7058(2)	29(1)	1
O1	7003(8)	1162(6)	8098(5)	40(2)	1
O2	5296(7)	1693(5)	6729(4)	26(2)	1
O3	7924(8)	952(5)	6711(5)	38(2)	1
O4	14885(7)	3594(5)	7622(5)	32(2)	1
O5	8885(10)	-2991(7)	3591(6)	59(3)	1
O6	10615(8)	1869(5)	3793(5)	38(2)	1
C1	4727(16)	471(11)	8830(10)	70(4)	1
C2	5852(14)	1238(10)	8693(9)	50(4)	1
C3A	7130(30)	660(16)	7277(15)	73(5)	0.562(18)
C4A	7470(30)	160(11)	6447(12)	47(4)	0.562(18)
C3B	7180(40)	20(20)	5727(14)	73(5)	0.438(18)
C4B	7340(40)	58(13)	6676(15)	47(4)	0.438(18)
C5	7731(9)	-2714(7)	6698(4)	29(3)	1
C6	9502(10)	-2752(7)	6820(6)	20(2)	1
C7	9985(11)	2832(8)	7708(7)	29(3)	1
C8	11698(10)	2866(8)	7833(7)	27(3)	1
C9	12283(11)	3694(7)	7087(7)	24(3)	1
C10	13980(11)	-3812(7)	7014(7)	23(2)	1
C11	14313(11)	-4249(8)	6031(7)	28(3)	1
C12	12869(11)	4295(8)	5507(7)	27(3)	1
C13	11875(10)	3565(8)	6190(7)	25(3)	1
C14	10233(9)	3565(7)	6017(6)	17(2)	1
C15	11711(11)	4652(7)	7185(7)	28(3)	1
C16	9138(12)	-2944(8)	8361(6)	39(3)	1
C17	9859(9)	3482(7)	5059(5)	20(2)	1
C18	10335(11)	2553(8)	4941(7)	28(3)	1
C19	9871(12)	2511(8)	4051(8)	32(3)	1
P2	8041(3)	1618(2)	1970(2)	37(1)	1
O7	7957(10)	-1218(8)	1173(7)	71(3)	1
O8	9597(7)	1658(5)	2293(5)	28(2)	1
O9	7021(9)	902(6)	2716(7)	67(3)	1
O10	89(8)	3521(6)	314(5)	40(2)	1
O11	5830(8)	3248(6)	4647(5)	38(2)	1
O12	4453(9)	-1940(6)	5078(5)	44(2)	1
C20	9860(20)	-162(12)	1081(12)	88(5)	1

C21	9233(14)	1113(9)	681(9)	47(3)	1
C22A	7710(30)	0(16)	4302(11)	102(6)	0.84(2)
C23A	7510(20)	19(11)	3342(10)	73(4)	0.84(2)
C22B	6320(30)	166(16)	4130(20)	102(6)	0.16(2)
C23B	7490(50)	−120(30)	3440(20)	73(4)	0.16(2)
C24	7103(9)	−2724(6)	1713(5)	28(3)	1
C25	5358(11)	−2763(8)	1593(7)	26(3)	1
C26	4853(12)	2799(9)	677(8)	38(3)	1
C27	3122(11)	2787(9)	550(8)	36(3)	1
C28	2507(11)	−3661(8)	767(8)	32(3)	1
C29	784(12)	−3746(9)	803(8)	34(3)	1
C30	443(11)	4209(8)	1490(8)	35(3)	1
C31	1962(11)	4332(8)	1940(7)	30(3)	1
C32	2953(10)	3584(7)	1725(7)	20(2)	1
C33	4647(10)	3604(7)	1860(7)	21(2)	1
C34	2943(7)	−4588(7)	42(8)	38(3)	1
C35	5679(13)	2891(9)	51(7)	52(4)	1
C36	5019(10)	3591(7)	2839(6)	29(3)	1
C37	4633(12)	2676(8)	3535(7)	32(3)	1
C38	5059(10)	2675(8)	4459(7)	25(3)	1

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

P1–O2	1.478(7)	P2–O8	1.482(7)
P1 O1	1.571(8)	P2 O7	1.550(11)
P1 O3	1.587(8)	P2 O9	1.614(9)
P1 C5	1.728(10)	P2 C24	1.758(9)
O1 C2	1.433(15)	O7 C21	1.425(15)
O3–C4A	1.419(15)	O5–C23B	1.403(19)
O3 C4B	1.440(16)	O5 C23A	1.468(14)
O4 C10	1.207(12)	O10 C29	1.209(14)
O5 C19	1.206(13)	O11 C38	1.199(13)
O6 C19	1.323(14)	O12 C38	1.336(12)
C1–C2	1.487(19)	C20–C21	1.452(19)
C3A–C4A	1.516(17)	C22A–C23A	1.533(16)
C3B C4B	1.543(18)	C22B C23B	1.54(2)
C5 C6	1.596(12)	C24 C25	1.567(13)
C6–C7	1.500(15)	C25–C26	1.492(16)
C6–C14	1.600(13)	C25–C33	1.566(15)
C7–C16	1.340(15)	C26–C35	1.348(16)
C7 C8	1.544(14)	C26 C27	1.558(15)
C8 C9	1.511(14)	C27 C28	1.536(17)
C9–C13	1.527(15)	C28–C32	1.526(15)
C9–C10	1.531(13)	C28–C34	1.542(14)
C9–C15	1.555(15)	C28–C29	1.548(15)
C10 C11	1.518(14)	C29 C30	1.487(17)
C11 C12	1.511(14)	C30 C31	1.560(15)
C12–C13	1.559(14)	C31–C32	1.534(15)
C13–C14	1.489(13)	C32–C33	1.528(13)
C14 C17	1.586(13)	C33 C36	1.571(14)
C17 C18	1.502(15)	C36 C37	1.496(14)
C18 C19	1.478(16)	C37 C38	1.502(15)

O2 P1 O1	112.5(4)	C8 C9 C10	117.8(8)
O2 P1 O3	115.3(5)	C13 C9 C10	101.4(8)
O1–P1–O3	102.4(4)	C8–C9–C15	110.0(9)
O2 P1 C5	111.2(4)	C13 C9 C15	113.8(8)
O1 P1 C5	111.6(4)	C10 C9 C15	104.2(8)
O3 P1 C5	103.2(4)	O4 C10 C11	126.4(9)
C2 O1 P1	123.1(7)	O4 C10 C9	126.5(9)
C4A–O3–C4B	14.7(13)	C11–C10–C9	107.1(8)
C4A–O3–P1	126.1(11)	C12–C11–C10	108.0(8)
C4B O3 P1	118.0(14)	C11 C12 C13	102.4(8)
O1 C2 C1	112.4(12)	C14 C13 C9	113.4(8)
O3 C4A C3A	108.5(16)	C14 C13 C12	119.3(8)
O3–C4B–C3B	114(2)	C9–C13–C12	104.4(8)
C6–C5–P1	118.8(7)	C13–C14–C17	111.8(8)
C7 C6 C5	113.5(7)	C13 C14 C6	108.5(7)
C7 C6 C14	111.4(8)	C17 C14 C6	114.2(8)
C5 C6 C14	111.9(7)	C18 C17 C14	114.3(7)
C16–C7–C6	128.8(9)	C19–C18–C17	110.9(8)
C16–C7–C8	117.2(10)	O5–C19–O6	121.2(12)
C6 C7 C8	113.9(9)	O5 C19 C18	124.7(11)
C9 C8 C7	108.2(8)	O4 C19 C18	114.1(9)
C8 C9 C13	109.6(9)	O8 P2 O7	112.4(5)

O8 P2 O9	112.3(5)	C32 C28 C34	116.3(9)
O7–P2–O9	104.1(6)	C27–C28–C34	110.4(9)
O8–P2–C24	112.4(4)	C32–C28–C29	100.8(9)
O7 P2 C24	111.0(5)	C27 C28 C29	116.5(10)
O9 P2 C24	104.1(4)	C34 C28 C29	103.5(8)
C21 O7 P2	123.2(9)	O10 C29 C30	127.7(10)
C23B–O9–C23A	11(2)	O10–C29–C28	124.7(11)
C23B–O9–P2	128.0(19)	C30–C29–C28	107.5(9)
C23A O9 P2	125.7(9)	C29 C30 C31	107.0(9)
O7 C21 C20	108.6(12)	C32 C31 C30	101.7(9)
O9–C23A–C22A	113.1(14)	C28–C32–C33	112.4(8)
O9–C23B–C22B	100(2)	C28–C32–C31	104.1(8)
C25 C24 P2	119.2(7)	C33 C32 C31	119.5(9)
C26 C25 C33	110.8(8)	C32 C33 C25	108.2(8)
C26 C25 C24	113.0(8)	C32 C33 C36	109.6(8)
C33 C25 C24	111.8(8)	C25 C33 C36	114.9(8)
C35–C26–C25	128.9(10)	C37–C36–C33	113.8(9)
C35 C26 C27	116.8(11)	C36 C37 C38	112.4(10)
C25 C26 C27	114.2(9)	O11 C38 O12	122.4(10)
C28 C27 C26	106.3(10)	O11 C38 C37	126.3(10)
C32 C28 C27	109.1(9)	O12 C38 C37	111.3(9)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

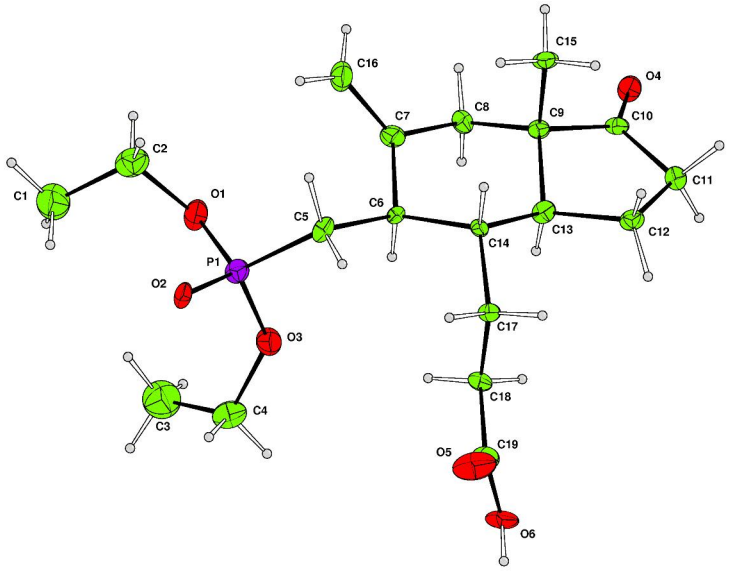
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P1	23(1)	34(2)	29(2)	11(1)	0(1)	−2(1)
O1	32(4)	50(5)	33(4)	7(4)	5(3)	7(3)
O2	19(3)	38(4)	17(4)	2(3)	3(3)	5(3)
O3	35(4)	32(4)	50(5)	16(3)	8(3)	2(3)
O4	25(3)	44(4)	24(4)	9(3)	2(3)	3(3)
O5	66(5)	71(5)	48(5)	31(4)	16(4)	28(4)
O6	40(4)	49(4)	35(4)	30(3)	13(3)	4(3)
C1	69(7)	85(7)	56(7)	23(6)	4(6)	21(6)
C2	49(6)	65(7)	41(6)	21(5)	−3(5)	−4(5)
C3A	72(7)	71(7)	77(7)	25(5)	2(5)	−1(5)
C4A	52(5)	50(6)	44(6)	21(5)	0(5)	−10(4)
C3B	72(7)	71(7)	77(7)	25(5)	2(5)	1(5)
C4B	52(5)	50(6)	44(6)	21(5)	0(5)	10(4)
C5	23(4)	35(5)	26(5)	8(4)	7(4)	−2(4)
C6	18(4)	24(5)	20(5)	11(4)	5(4)	2(4)
C7	26(5)	38(5)	24(5)	13(4)	−6(4)	2(4)
C8	22(4)	31(5)	30(5)	11(4)	−1(4)	5(4)
C9	28(5)	28(5)	16(5)	9(4)	0(4)	5(4)
C10	23(4)	26(5)	25(5)	15(4)	−2(4)	−3(4)
C11	29(5)	27(5)	30(5)	9(4)	4(4)	5(4)
C12	27(5)	34(5)	20(5)	11(4)	−2(4)	−1(4)
C13	18(4)	34(5)	23(5)	9(4)	4(4)	5(4)
C14	15(4)	14(4)	26(5)	11(4)	3(4)	0(3)
C15	31(5)	36(5)	23(5)	18(4)	0(4)	0(4)
C16	29(5)	51(6)	37(6)	11(5)	6(4)	11(4)
C17	15(4)	26(5)	23(5)	12(4)	−4(4)	−5(4)
C18	30(5)	34(5)	25(5)	16(4)	−3(4)	7(4)
C19	26(5)	37(5)	39(6)	21(4)	−4(4)	−4(4)
P2	18(1)	55(2)	50(2)	36(2)	2(1)	2(1)
O7	51(5)	101(6)	83(6)	62(5)	12(4)	16(4)
O8	17(3)	40(4)	32(4)	17(3)	−1(3)	−3(3)
O9	34(4)	51(5)	109(6)	14(5)	13(4)	−1(4)
O10	29(4)	55(5)	41(4)	21(4)	0(3)	−1(3)
O11	43(4)	49(4)	24(4)	15(3)	7(3)	8(3)
O12	45(4)	61(5)	28(4)	17(4)	7(3)	8(4)
C20	96(8)	91(8)	82(8)	37(6)	0(6)	−21(6)
C21	57(6)	57(6)	37(6)	31(5)	−5(5)	−2(5)
C22A	101(7)	101(7)	104(8)	30(5)	−1(6)	5(5)
C23A	74(6)	84(6)	61(6)	23(5)	9(5)	24(5)
C22B	101(7)	101(7)	104(8)	30(5)	1(6)	5(5)
C23B	74(6)	84(6)	61(6)	23(5)	9(5)	24(5)
C24	26(5)	34(5)	29(5)	16(4)	3(4)	2(4)
C25	24(4)	32(5)	24(5)	10(4)	3(4)	0(4)
C26	29(5)	45(6)	41(6)	15(5)	−3(4)	−1(4)
C27	28(5)	58(6)	29(5)	23(5)	1(4)	4(4)
C28	28(5)	36(5)	35(5)	18(4)	7(4)	5(4)
C29	28(5)	45(6)	28(5)	9(5)	8(4)	3(4)
C30	26(5)	42(6)	43(6)	22(5)	1(4)	−2(4)

C31	27(5)	40(5)	26(5)	15(4)	1(4)	5(4)
C32	17(4)	27(5)	19(5)	12(4)	5(4)	4(4)
C33	19(4)	28(5)	19(5)	10(4)	1(4)	−4(4)
C34	33(5)	52(6)	31(5)	16(5)	1(4)	1(5)
C35	38(6)	71(7)	54(6)	29(5)	−4(5)	−2(5)
C36	22(4)	36(5)	31(5)	13(4)	1(4)	−1(4)
C37	28(5)	46(6)	22(5)	9(4)	−2(4)	−1(4)
C38	17(4)	36(5)	25(5)	13(4)	4(4)	6(4)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H906	10296	−1876	3287	57	1
H1A	5232	152	9044	105	1
H1B	4005	−526	9272	105	1
H1C	4201	535	8264	105	1
H2A	6314	1206	9276	60	1
H2B	5343	1866	8449	60	1
H3A1	6419	447	7640	110	0.562(18)
H3A2	6707	1188	7104	110	0.562(18)
H3A3	8062	876	7623	110	0.562(18)
H4A1	6566	−330	6056	57	0.562(18)
H4A2	8275	27	6110	57	0.562(18)
H3B1	8146	205	5543	110	0.438(18)
H3B2	6434	500	5722	110	0.438(18)
H3B3	6862	−600	5312	110	0.438(18)
H4B1	8007	464	7035	57	0.438(18)
H4B2	6346	37	6955	57	0.438(18)
H5A	7274	3128	7012	34	1
H5B	7486	3004	6056	34	1
H6	9911	−2130	6794	23	1
H8A	12165	2262	7817	33	1
H8B	11944	2951	8417	33	1
H11A	15064	3855	5849	34	1
H11B	14719	4898	5917	34	1
H12A	12420	−4943	5328	32	1
H12B	13028	−4102	4968	32	1
H13	12254	2917	6218	30	1
H14	9823	4192	6030	21	1
H15A	12100	5185	6701	42	1
H15B	10615	−4671	7157	42	1
H15C	12057	−4705	7760	42	1
H16A	8080	2982	8290	47	1
H16B	9596	2984	8895	47	1
H17A	10356	4009	4606	24	1
H17B	8766	−3567	4946	24	1
H18A	9881	−2019	5407	33	1
H18B	11436	2482	5010	33	1
H12	4709	1954	5587	67	1
H20A	9066	310	1145	131	1
H20B	10638	45	698	131	1
H20C	10292	108	1669	131	1
H21A	8939	−1208	51	57	1
H21B	9988	−1597	693	57	1
H22A	6891	348	4664	153	0.84(2)
H22B	8666	302	4551	153	0.84(2)
H22C	7694	−663	4306	153	0.84(2)
H23A	6771	509	3330	87	0.84(2)
H23B	8478	206	3142	87	0.84(2)
H22D	5371	86	3991	153	0.16(2)
H22E	6676	214	4726	153	0.16(2)
H22F	6180	831	4109	153	0.16(2)
H23C	7426	488	3292	87	0.16(2)
H23D	8520	193	3641	87	0.16(2)
H24A	7525	3148	1155	34	1
H24B	7356	3003	2191	34	1
H25	4968	2158	2013	32	1
H27A	2706	−2193	958	43	1
H27B	2855	2826	71	43	1
H30A	46	4838	1209	42	1
H30B	236	3807	1939	42	1
H31A	1864	4195	2591	36	1
H31B	2357	−4983	1677	36	1
H32	2613	2946	2110	24	1
H33	5022	4216	1443	26	1

H34A	2603	5139	210	57	1
H34B	4033	−4607	−18	57	1
H34C	2472	−4607	−528	57	1
H35A	6735	2943	17	63	1
H35B	5206	2904	597	63	1
H36A	4467	4120	2957	35	1
H36B	6101	−3706	2891	35	1
H37A	3544	−2572	3505	39	1
H37B	5155	2141	3408	39	1



One of the 2 independent molecules in the asymmetric unit. Thermal ellipsoids drawn at the 35% probability level, disorder omitted for clarity.

X-ray data for (4.29)

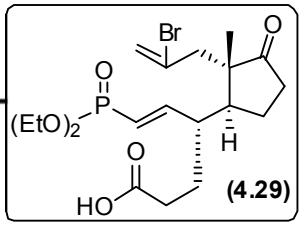


Table 1. Crystal data and structure refinement details.

Identification code	2006sotl373 (VF/4726/23)
Empirical formula	$C_{19}H_{30}BrO_6P$
Formula weight	465.31
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 7.27800(10) Å
	b = 15.0888(4) Å β = 95.0070(10)°
	c = 19.8599(5) Å
Volume	2172.62(8) Å^3
Z	4
Density (calculated)	1.423 Mg / m^3
Absorption coefficient	1.996 mm^{-1}
$F(000)$	968
Crystal	Block; Colourless
Crystal size	0.6 × 0.4 × 0.2 mm^3
θ range for data collection	3.12 – 27.48°
Index ranges	$-9 \le h \le 9$, $-19 \le k \le 19$, $-25 \le l \le 25$
Reflections collected	31411
Independent reflections	4976 [R_{int} = 0.0535]
Completeness to θ = 27.48°	99.5 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.6909 and 0.3705
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4976 / 0 / 247
Goodness-of-fit on F^2	1.032
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0399, $wR2$ = 0.0890
R indices (all data)	$R1$ = 0.0589, $wR2$ = 0.0966
Largest diff. peak and hole	0.529 and –0.793 e Å^{-3}

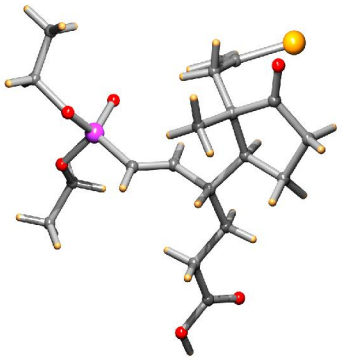


Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	$S.o.f.$
C1	1198(4)	8315(2)	1946(2)	32(1)	1
C2	2747(4)	8083(2)	1701(1)	25(1)	1
C3	4239(3)	7501(2)	2025(1)	20(1)	1
C4	4617(3)	6629(2)	1662(1)	17(1)	1
C5	5823(3)	6780(2)	1074(1)	23(1)	1
C6	5084(4)	6252(2)	468(1)	30(1)	1
C7	3618(3)	5648(2)	717(1)	23(1)	1
C8	2912(3)	6126(2)	1331(1)	16(1)	1
C9	5847(3)	6049(2)	2154(1)	21(1)	1
C10	1960(3)	5495(2)	1798(1)	16(1)	1
C11	254(3)	5065(2)	1426(1)	18(1)	1
C12	–466(3)	4311(2)	1833(1)	22(1)	1
C13	–2160(3)	3870(2)	1503(1)	18(1)	1
C14	1427(3)	5975(2)	2410(1)	16(1)	1
C15	1839(3)	5732(2)	3049(1)	18(1)	1
C16	–1953(3)	5850(2)	3985(2)	36(1)	1
C17	–2747(4)	5036(2)	4265(2)	36(1)	1
C18	4256(4)	7828(2)	4646(2)	35(1)	1
C19	3386(4)	6962(2)	4789(1)	24(1)	1
O1	7214(2)	7217(1)	1122(1)	33(1)	1
O2	–2613(3)	3166(1)	1844(1)	40(1)	1
O3	–3000(3)	4114(1)	995(1)	31(1)	1
O4	585(2)	7278(1)	3521(1)	24(1)	1
O5	3188(2)	6413(1)	4180(1)	21(1)	1
O6	18(2)	5871(1)	4181(1)	22(1)	1
P1	1319(1)	6404(1)	3732(1)	17(1)	1
Br1	3211(1)	8537(1)	833(1)	38(1)	1

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

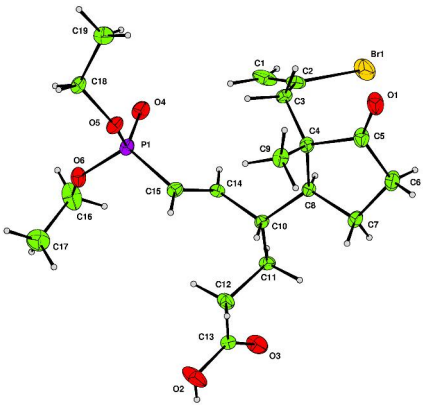
C1 C2	1.314(4)	C11 C12	1.515(3)
C2 C3	1.499(3)	C12 C13	1.501(3)
C2–Br1	1.911(3)	C13–O3	1.191(3)
C3–C4	1.537(3)	C13–O2	1.317(3)
C4 C5	1.538(3)	C14 C15	1.329(3)
C4 C9	1.540(3)	C15 P1	1.762(2)
C4–C8	1.550(3)	C16–O6	1.454(3)
C5–O1	1.205(3)	C16–C17	1.485(4)
C5 C6	1.503(3)	C18 C19	1.489(4)
C6 C7	1.519(3)	C19 O5	1.463(3)
C7 C8	1.544(3)	O4 P1	1.4701(17)
C8–C10	1.535(3)	O5–P1	1.5589(16)
C10–C14	1.494(3)	O6–P1	1.5762(17)
C10 C11	1.533(3)		
C1 C2 C3	127.6(3)	C11 C10 C8	111.08(18)
C1 C2 Br1	117.6(2)	C12 C11 C10	111.34(18)
C3 C2 Br1	114.82(18)	C13 C12 C11	114.18(19)
C2 C3 C4	116.90(19)	O3 C13 O2	123.5(2)
C3–C4–C5	111.5(2)	O3–C13–C12	125.0(2)
C3 C4 C9	107.81(18)	O2 C13 C12	111.5(2)
C5 C4 C9	103.13(18)	C15 C14 C10	126.1(2)
C3 C4 C8	116.65(19)	C14 C15 P1	122.02(18)
C5 C4 C8	103.92(18)	O6 C16 C17	109.0(2)
C9–C4–C8	112.96(19)	O5–C19–C18	110.6(2)
O1–C5–C6	126.3(2)	C19–O5–P1	119.64(15)
O1 C5 C4	123.6(2)	C16 O6 P1	119.15(15)
C6 C5 C4	109.9(2)	O4 P1 O5	115.61(10)
C5 C6 C7	105.7(2)	O4 P1 O6	113.42(10)
C6–C7–C8	105.60(19)	O5–P1–O6	102.66(9)
C10–C8–C7	112.79(19)	O4–P1–C15	113.22(11)
C10 C8 C4	115.72(18)	O5 P1 C15	102.04(10)
C7 C8 C4	104.69(18)	O6 P1 C15	108.80(10)
C14 C10 C11	109.94(18)		
C14–C10–C8	110.74(18)		

Table 4. Anisotropic displacement parameters [$Å^2 \cdot 10^3$]. The anisotropic displacement factor exponent takes the form: $2\pi^2[h^2a^{*2}U^{11} + \ldots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	29(1)	13(1)	53(2)	4(1)	7(1)	0(1)
C2	32(1)	16(1)	26(1)	0(1)	4(1)	8(1)
C3	23(1)	18(1)	16(1)	−3(1)	−2(1)	−4(1)
C4	16(1)	22(1)	14(1)	1(1)	1(1)	4(1)
C5	20(1)	32(1)	17(1)	1(1)	1(1)	3(1)
C6	31(1)	42(2)	18(1)	6(1)	7(1)	12(1)
C7	26(1)	26(1)	16(1)	5(1)	4(1)	5(1)
C8	17(1)	17(1)	13(1)	0(1)	0(1)	−1(1)
C9	16(1)	29(1)	18(1)	0(1)	−1(1)	2(1)
C10	18(1)	15(1)	14(1)	1(1)	0(1)	0(1)
C11	20(1)	15(1)	18(1)	1(1)	2(1)	1(1)
C12	23(1)	22(1)	20(1)	5(1)	3(1)	6(1)
C13	20(1)	16(1)	18(1)	−2(1)	2(1)	−1(1)
C14	16(1)	14(1)	19(1)	0(1)	2(1)	−2(1)
C15	19(1)	16(1)	19(1)	2(1)	1(1)	2(1)
C16	18(1)	55(2)	34(2)	14(1)	0(1)	2(1)
C17	28(1)	38(2)	43(2)	1(1)	2(1)	3(1)
C18	41(2)	30(2)	35(2)	6(1)	9(1)	10(1)
C19	31(1)	28(1)	14(1)	4(1)	0(1)	6(1)
O1	26(1)	51(1)	22(1)	0(1)	3(1)	−16(1)
O2	39(1)	41(1)	38(1)	19(1)	−18(1)	−25(1)
O3	33(1)	31(1)	26(1)	7(1)	12(1)	11(1)
O4	27(1)	22(1)	22(1)	0(1)	1(1)	9(1)
O5	20(1)	24(1)	18(1)	4(1)	2(1)	3(1)
O6	18(1)	31(1)	17(1)	3(1)	1(1)	1(1)
P1	19(1)	19(1)	14(1)	0(1)	0(1)	5(1)
Br1	48(1)	33(1)	31(1)	12(1)	4(1)	4(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	S.o.f.
H1A	926	8107	2378	38	1
H1B	351	8691	1692	38	1
H3A	3921	7354	2487	23	1
H3B	5399	7847	2072	23	1
H6A	6079	5899	288	36	1
H6B	4541	6649	106	36	1
H7A	4151	5064	851	27	1
H7B	2601	5557	359	27	1
H8	1983	6577	1156	19	1
H9A	6156	5498	1927	32	1
H9B	5186	5908	2549	32	1
H9C	6983	6370	2298	32	1
H10	2851	5016	1949	19	1
H11A	724	5517	1340	21	1
H11B	576	4836	984	21	1
H12A	518	3861	1913	26	1
H12B	749	4543	2279	26	1
H14	729	6503	2335	19	1
H15	2433	5178	3139	22	1
H16A	2177	5851	3486	43	1
H16B	2549	6381	4161	43	1
H17A	2224	4513	4060	55	1
H17B	4089	5039	4163	55	1
H17C	-2451	5021	4755	55	1
H02A	5444	7723	4462	53	1
H02B	4452	8170	5065	53	1
H02C	3445	8159	4316	53	1
H18A	4156	6648	5148	29	1
H18B	2158	7067	4952	29	1
H2	3562	2932	1649	60	1

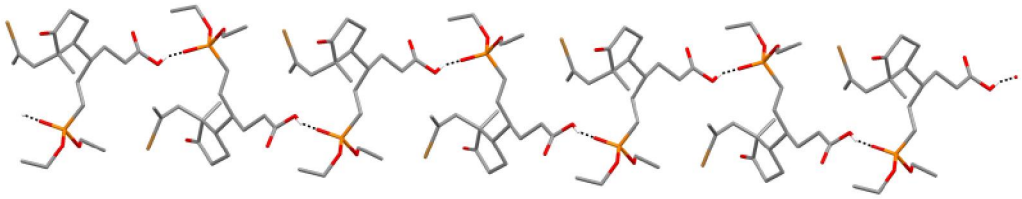


Thermal ellipsoids drawn at the 50%

Table 6. Hydrogen bonds [Å and °].

D H···A	d(D H)	d(H···A)	d(D···A)	(DHA)
O2 H2···O4^{i}	0.84	1.78	2.593(2)	162.5

Symmetry transformations used to generate equivalent atoms:
(i) x 1/2,y 1/2, z+1/2



Hydrogen bonded chains extend along the b axis

X-ray data for (4.40α)

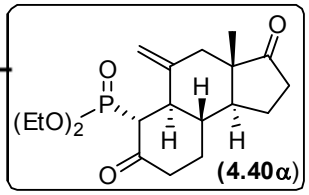


Table 1. Crystal data and structure refinement details.

Identification code	2007sotl320 (VF/4726/56–2))
Empirical formula	$C_{19}H_{29}O_3P$
Formula weight	368.39
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 6.85160(10) Å b = 15.0754(4) Å β = 100.174(2)° c = 18.4301(5) Å
Volume	1873.72(8) Å^3
Z	4
Density (calculated)	1.306 Mg / m^3
Absorption coefficient	0.173 mm^{-1}
$F(000)$	792
Crystal	Block; Colourless
Crystal size	0.4 × 0.2 × 0.15 mm^3
θ range for data collection	2.93 – 27.48°
Index ranges	$-8 \le h \le 8$, $-19 \le k \le 19$, $-23 \le l \le 23$
Reflections collected	26827
Independent reflections	4285 [R_{int} = 0.0673]
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9746 and 0.9241
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4285 / 0 / 230
Goodness-of-fit on F^2	1.049
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0494, $wR2$ = 0.1174
R indices (all data)	$R1$ = 0.0727, $wR2$ = 0.1308
Extinction coefficient	0.018(2)
Largest diff. peak and hole	0.474 and –0.405 e Å^{-3}

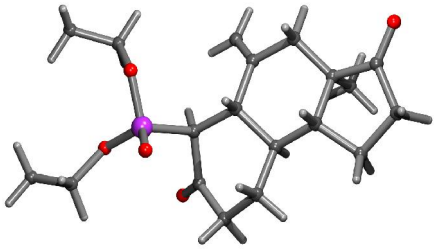


Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	$S.o.f.$
P1	254(1)	3602(1)	1540(1)	25(1)	1
O1	–237(2)	3405(1)	691(1)	43(1)	1
O2	–860(2)	4496(1)	1635(1)	37(1)	1
O3	–266(2)	2912(1)	2030(1)	31(1)	1
O4	4272(3)	3097(1)	791(1)	52(1)	1
C19	4020(3)	5762(1)	2134(1)	28(1)	1
O5	7158(2)	5485(1)	5008(1)	29(1)	1
C1	–2355(3)	2857(2)	–380(1)	39(1)	1
C2	–1330(3)	2640(1)	379(1)	31(1)	1
C3	–2806(4)	5356(2)	659(2)	58(1)	1
C4	–850(4)	5235(2)	1119(2)	49(1)	1
C5	2880(3)	3882(1)	1693(1)	20(1)	1
C6	3983(3)	3103(1)	1421(1)	27(1)	1
C7	4645(3)	2347(1)	1940(1)	28(1)	1
C8	4765(3)	2586(1)	2751(1)	25(1)	1
C9	5368(3)	3557(1)	2875(1)	20(1)	1
C10	3611(3)	4155(1)	2511(1)	20(1)	1
C11	4094(3)	5137(1)	2644(1)	21(1)	1
C12	4744(3)	5373(1)	3454(1)	23(1)	1
C13	6493(3)	4791(1)	3787(1)	21(1)	1
C14	5892(3)	3809(1)	3685(1)	20(1)	1
C15	7539(3)	3310(1)	4199(1)	27(1)	1
C16	7947(3)	3917(1)	4881(1)	28(1)	1
C17	7180(3)	4833(1)	4618(1)	23(1)	1
C18	8358(3)	5031(1)	3461(1)	27(1)	1

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

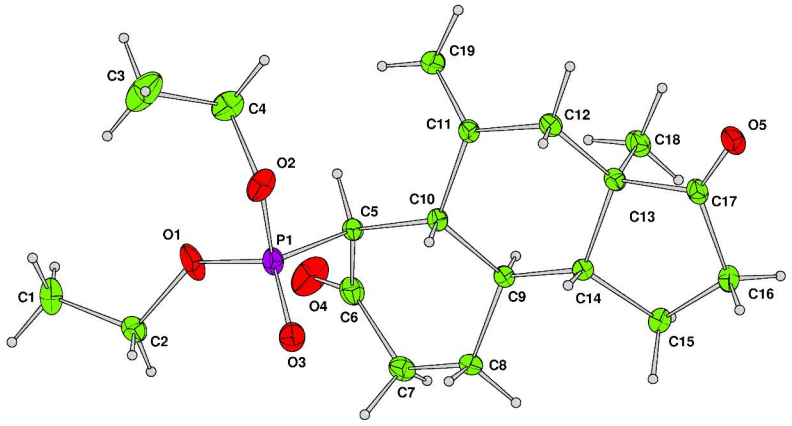
P1 O3	1.4625(15)	C7 C8	1.527(3)
P1 O1	1.5697(15)	C8 C9	1.527(3)
P1–O2	1.5734(16)	C9–C14	1.520(2)
P1 C5	1.8212(18)	C9 C10	1.558(2)
O1 C2	1.439(2)	C10 C11	1.527(3)
O2 C4	1.466(3)	C11 C12	1.523(2)
O4 C6	1.212(2)	C12 C13	1.525(3)
C19–C11	1.326(3)	C13–C17	1.521(3)
O5 C17	1.219(2)	C13 C14	1.539(2)
C1 C2	1.487(3)	C13 C18	1.548(3)
C3 C4	1.466(3)	C14 C15	1.536(2)
C5 C6	1.528(3)	C15 C16	1.540(3)
C5–C10	1.558(2)	C16–C17	1.526(3)
C6–C7	1.505(3)		
O3–P1–O1	116.66(9)	C11–C10–C5	115.79(15)
O3 P1 O2	111.37(9)	C11 C10 C9	111.27(14)
O1 P1 O2	104.51(9)	C5 C10 C9	110.83(14)
O3–P1–C5	114.27(8)	C19–C11–C12	119.84(17)
O1–P1–C5	103.29(8)	C19–C11–C10	126.49(17)
O2–P1–C5	105.65(9)	C12–C11–C10	113.66(15)
C2 O1 P1	123.64(14)	C11 C12 C13	109.46(15)
C4 O2 P1	121.42(15)	C17 C13 C12	117.54(15)
O1–C2–C1	108.93(18)	C17–C13–C14	101.11(14)
O2–C4–C3	111.2(2)	C12–C13–C14	109.27(14)
C6–C5–C10	115.34(15)	C17–C13–C18	104.54(14)
C6 C5 P1	107.65(13)	C12 C13 C18	110.67(16)
C10 C5 P1	110.54(12)	C14 C13 C18	113.50(15)
O4 C6 C7	121.49(18)	C9 C14 C15	120.27(15)
O4–C6–C5	119.56(19)	C9–C14–C13	111.86(15)
C7 C6 C5	118.94(17)	C15 C14 C13	104.07(14)
C6 C7 C8	113.73(16)	C14 C15 C16	102.76(15)
C7 C8 C9	109.83(16)	C17 C16 C15	105.99(15)
C14 C9 C8	113.39(15)	O5 C17 C13	126.36(17)
C14–C9–C10	108.00(14)	O5–C17–C16	125.59(17)
C8 C9 C10	108.80(14)	C13 C17 C16	108.04(15)

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P1	24(1)	30(1)	18(1)	1(1)	1(1)	4(1)
O1	51(1)	58(1)	19(1)	7(1)	2(1)	31(1)
O2	33(1)	43(1)	33(1)	5(1)	2(1)	13(1)
O3	30(1)	38(1)	26(1)	5(1)	4(1)	7(1)
O4	78(1)	58(1)	24(1)	2(1)	15(1)	28(1)
C19	36(1)	20(1)	26(1)	1(1)	2(1)	0(1)
O5	33(1)	30(1)	24(1)	−6(1)	3(1)	−7(1)
C1	31(1)	55(2)	28(1)	−3(1)	−4(1)	−4(1)
C2	39(1)	25(1)	26(1)	5(1)	1(1)	4(1)
C3	39(1)	71(2)	62(2)	28(2)	4(1)	15(1)
C4	49(1)	35(1)	56(2)	8(1)	6(1)	6(1)
C5	25(1)	19(1)	16(1)	1(1)	2(1)	2(1)
C6	30(1)	29(1)	23(1)	7(1)	4(1)	0(1)
C7	32(1)	21(1)	30(1)	−7(1)	4(1)	1(1)
C8	30(1)	17(1)	26(1)	−2(1)	−1(1)	−1(1)
C9	19(1)	18(1)	20(1)	1(1)	1(1)	1(1)
C10	22(1)	19(1)	17(1)	2(1)	1(1)	0(1)
C11	23(1)	19(1)	20(1)	−3(1)	0(1)	2(1)
C12	29(1)	19(1)	21(1)	−5(1)	2(1)	1(1)
C13	23(1)	20(1)	19(1)	−2(1)	2(1)	−2(1)
C14	20(1)	18(1)	21(1)	0(1)	2(1)	0(1)
C15	26(1)	25(1)	27(1)	2(1)	−3(1)	1(1)
C16	26(1)	30(1)	24(1)	2(1)	4(1)	4(1)
C17	20(1)	27(1)	22(1)	0(1)	2(1)	7(1)
C18	27(1)	29(1)	26(1)	0(1)	4(1)	8(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	S.o.f.
H19A	4372	6355	2273	34	1
H19B	3615	5616	1628	34	1
H1A	3347	3320	357	58	1
H1B	3010	2325	612	58	1
H1C	1383	3070	671	58	1
H2A	-2316	2468	687	37	1
H2B	-415	2134	365	37	1
H3A	3174	4818	369	87	1
H3B	2763	5860	326	87	1
H3C	3790	5472	974	87	1
H4A	142	5118	800	58	1
H4B	461	5787	1400	58	1
H5	3046	4406	1377	24	1
H7A	5967	2144	1862	33	1
H7B	3710	1846	1818	33	1
H8A	5750	2201	3060	30	1
H8B	3460	2487	2898	30	1
H9	6539	3677	2634	24	1
H10	2490	4024	2776	23	1
H12A	3629	5280	3722	28	1
H12B	5134	6006	3501	28	1
H14	4654	3735	3896	24	1
H15A	8736	3243	3972	32	1
H15B	7084	2716	4328	32	1
H16A	7244	3696	5271	33	1
H16B	9385	3940	5082	33	1
H18A	8724	5649	3578	41	1
H18B	8075	4953	2925	41	1
H18C	9457	4641	3674	41	1



Thermal ellipsoids drawn at the 35%

X-ray data for (4.43β)

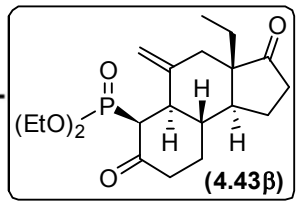


Table 1. Crystal data and structure refinement.

Identification code	2007sotl258	
Empirical formula	$C_{20}H_{31}O_3P$	
Formula weight	382.42	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C*2/*c*	
Unit cell dimensions	$a = 26.5072(12)$ Å	$\alpha = 90°$
	$b = 8.2021(3)$ Å	$\beta = 112.458(2)°$
	$c = 19.1753(10)$ Å	$\gamma = 90°$
Volume	3852.8(3) Å^3	
Z	8	
Density (calculated)	1.319 Mg / m^3	
Absorption coefficient	0.171 mm^{-1}	
F(000)	1648	
Crystal	Fragment; Colourless	
Crystal size	0.07 × 0.05 × 0.02 mm^3	
θ range for data collection	2.99 – 27.48°	
Index ranges	$-34 \le h \le 34, -10 \le k \le 9, -24 \le l \le 23$	
Reflections collected	15078	
Independent reflections	4400 [$R_{int} = 0.0817$]	
Completeness to $\theta = 27.48°$	99.5 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9966 and 0.9882	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4400 / 0 / 238	
Goodness-of-fit on F^2	1.123	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0961$, $wR2 = 0.1628$	
R indices (all data)	$R1 = 0.1553$, $wR2 = 0.1920$	
Largest diff. peak and hole	0.414 and –0.442 e Å^{-3}	

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
P1	794(1)	8365(1)	4222(1)	20(1)	1
O1	3253(1)	7931(4)	7748(2)	27(1)	1
O2	252(1)	12004(4)	4624(2)	32(1)	1
O3	1207(1)	7083(4)	4374(2)	28(1)	1
O4	185(1)	7742(4)	3873(2)	30(1)	1
O5	790(1)	9671(4)	3613(2)	25(1)	1
C1	827(2)	9657(5)	5022(2)	17(1)	1
C2	1366(2)	9600(5)	5731(2)	18(1)	1
C3	1493(2)	7974(5)	6156(2)	17(1)	1
C4	2039(2)	7906(5)	6806(2)	19(1)	1
C5	2490(2)	8413(5)	6541(2)	16(1)	1
C6	3061(2)	8645(5)	7141(2)	20(1)	1
C7	3352(2)	9940(6)	6871(2)	21(1)	1
C8	2909(2)	10708(5)	6167(2)	19(1)	1
C9	2376(2)	10168(5)	6235(2)	18(1)	1
C10	1843(2)	10341(5)	5552(2)	17(1)	1
C11	1717(2)	12136(5)	5358(2)	21(1)	1
C12	1165(2)	12450(5)	4717(2)	21(1)	1
C13	706(2)	11447(5)	4766(2)	19(1)	1
C14	1151(2)	6720(6)	6006(2)	26(1)	1
C15	2543(2)	7200(5)	5954(2)	21(1)	1
C16	2685(2)	5457(5)	6264(3)	24(1)	1
C17	24(2)	6117(6)	4032(3)	37(1)	1
C18	–123(3)	5071(7)	3367(3)	52(2)	1
C19	771(2)	9161(6)	2882(3)	28(1)	1
C20	749(2)	10650(6)	2417(3)	36(1)	1

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

P1 O3	1.466(3)	C19 O5 P1	120.5(3)	C12 C13 C1	117.9(3)
P1 O4	1.577(3)	C13 C1 C2	108.5(3)	C3 C14 H14A	120.0
P1-O5	1.583(3)	C13-C1-P1	110.2(3)	C3-C14-H14B	120.0
P1-C1	1.839(4)	C2-C1-P1	116.6(3)	H14A-C14-H14B	120.0
O1 C6	1.225(3)	C13 C1 H1	107.1	C16-C15-C5	113.2(4)
O2 C13	1.217(3)	C2 C1 H1	107.1	C16 C15 H15A	108.9
O4 C17	1.467(6)	P1 C1 H1	107.1	C5 C15 H15A	108.9
O5-C19	1.444(3)	C3-C2-C1	115.7(3)	C16 C15 H15B	108.9
C1-C13	1.542(6)	C3-C2-C10	115.2(3)	C5-C15-H15B	108.9
C1 C2	1.552(6)	C1 C2 C10	110.5(3)	H15A C15 H15B	107.8
C1 H1	1.0000	C3 C2 H2	104.7	C15 C16 H16A	109.5
C2 C3	1.532(6)	C1 C2 H2	104.7	C15 C16 H16B	109.5
C2-C10	1.553(3)	C10 C2 H2	104.7	H16A C16 H16B	109.5
C2-H2	1.0000	C14-C3-C4	120.7(4)	C15-C16-H16C	109.5
C3 C14	1.329(6)	C14 C3 C2	124.4(4)	H16A C16 H16C	109.5
C3 C4	1.508(6)	C4 C3 C2	114.8(3)	H16B C16 H16C	109.5
C4 C5	1.524(3)	C3 C4 C5	109.9(3)	C18 C17 O4	110.7(4)
C4-H4A	0.9900	C3 C4 H4A	109.7	C18 C17 H17A	109.5
C4-H4B	0.9900	C5-C4-H4A	109.7	O4-C17-H17A	109.5
C5 C6	1.522(3)	C3 C4 H4B	109.7	C18-C17-H17B	109.5
C5 C9	1.540(6)	C5 C4 H4B	109.7	O4 C17 H17B	109.5
C5 C15	1.548(6)	H4A C4 H4B	108.2	H17A C17 H17B	108.1
C6 C7	1.518(6)	C6 C5 C4	117.4(3)	C17 C18 H18A	109.5
C7-C8	1.545(6)	C6-C5-C9	99.5(3)	C17-C18-H18B	109.5
C7 H7A	0.9900	C4-C5-C9	108.4(3)	H18A-C18-H18B	109.5
C7 H7B	0.9900	C6 C5 C15	106.9(3)	C17 C18 H18C	109.5
C8 C9	1.534(6)	C4 C5 C15	111.5(3)	H18A C18 H18C	109.5
C8 H8A	0.9900	C9 C5 C15	112.5(3)	H18B C18 H18C	109.5
C8-H8B	0.9900	O1-C6-C7	125.2(4)	O5-C19-C20	108.7(4)
C9 C10	1.523(3)	O1-C6-C5	126.3(4)	O5-C19-H19A	110.0
C9 H9	1.0000	C7 C6 C5	108.5(3)	C20 C19 H19A	110.0
C10 C11	1.523(6)	C6 C7 C8	105.5(3)	O5 C19 H19B	110.0
C10 H10	1.0000	C6 C7 H7A	110.6	C20 C19 H19B	110.0
C11-C12	1.531(6)	C8-C7-H7A	110.6	H19A-C19-H19B	108.3
C11-H11A	0.9900	C6-C7-H7B	110.6	C19-C20-H20A	109.5
C11 H11B	0.9900	C8 C7 H7B	110.6	C19 C20 H20B	109.5
C12 C13	1.501(6)	H7A C7 H7B	108.8	H20A C20 H20B	109.5
C12-H12A	0.9900	C9-C8-C7	103.1(3)	C19 C20 H20C	109.5
C12-H12B	0.9900	C9-C8-H8A	111.1	H20A-C20-H20C	109.5
C14-H14A	0.9500	C7-C8-H8A	111.1	H20B-C20-H20C	109.5
C14 H14B	0.9500	C9 C8 H8B	111.1		
C15 C16	1.539(6)	C7 C8 H8B	111.1		
C15-H15A	0.9900	H8A C8 H8B	109.1		
C15-H15B	0.9900	C10-C9-C8	118.8(3)		
C16 H16A	0.9800	C10 C9 C5	113.5(3)		
C16 H16B	0.9800	C8 C9 C5	104.4(3)		
C16 H16C	0.9800	C10 C9 H9	106.5		
C17-C18	1.461(7)	C8 C9 H9	106.5		
C17-H17A	0.9900	C5 C9 H9	106.5		
C17 H17B	0.9900	C11 C10 C9	110.1(3)		
C18 H18A	0.9800	C11 C10 C2	108.2(3)		
C18 H18B	0.9800	C9 C10 C2	109.8(3)		
C18 H18C	0.9800	C11 C10 H10	109.6		
C19-C20	1.500(7)	C9-C10-H10	109.6		
C19 H19A	0.9900	C2-C10-H10	109.6		
C19 H19B	0.9900	C10 C11 C12	114.3(3)		
C20 H20A	0.9800	C10 C11 H11A	108.7		
C20 H20B	0.9800	C12 C11 H11A	108.7		
C20-H20C	0.9800	C10-C11-H11B	108.7		
		C12-C11-H11B	108.7		
O3-P1-O4	114.74(19)	H11A-C11-H11B	107.6		
O3-P1-O5	115.17(19)	C13 C12 C11	114.0(4)		
O4 P1 O5	100.91(17)	C13 C12 H12A	108.8		
O3 P1 C1	117.01(19)	C11-C12-H12A	108.8		
O4 P1 C1	104.82(19)	C13-C12-H12B	108.8		
O5-P1-C1	102.15(18)	C11 C12 H12B	108.8		
C17-O4-P1	122.6(3)	H12A C12 H12B	107.6		
		O2 C13 C12	122.4(4)		
		O2-C13-C1	119.7(4)		

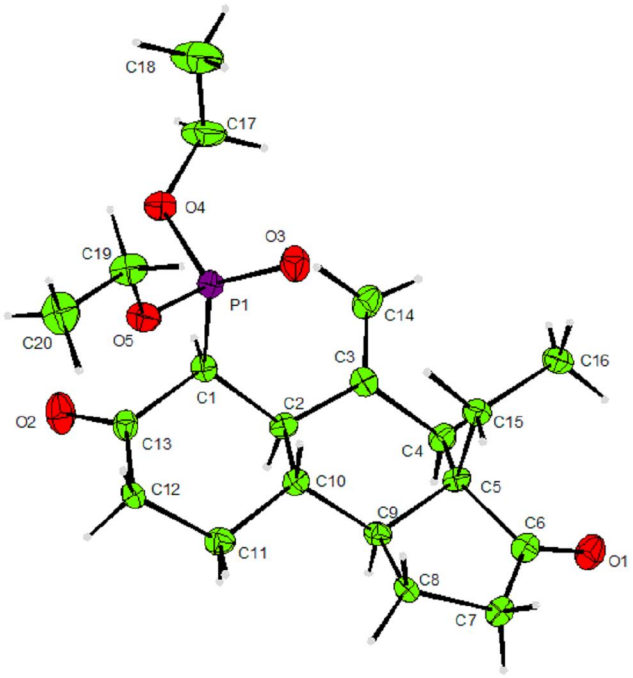
Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P1	21(1)	18(1)	17(1)	1(1)	5(1)	0(1)
O1	26(2)	34(2)	20(2)	5(1)	6(1)	1(1)
O2	25(2)	34(2)	40(2)	9(2)	15(2)	10(2)
O3	30(2)	29(2)	23(2)	1(1)	10(1)	9(1)
O4	26(2)	24(2)	34(2)	0(2)	6(2)	-5(1)
O5	36(2)	24(2)	17(2)	0(1)	10(1)	5(1)
C1	17(2)	18(2)	18(2)	2(2)	9(2)	0(2)
C2	18(2)	19(2)	16(2)	2(2)	7(2)	2(2)
C3	22(2)	20(2)	15(2)	2(2)	12(2)	1(2)
C4	19(2)	23(2)	16(2)	1(2)	7(2)	-1(2)
C5	18(2)	19(2)	11(2)	1(2)	7(2)	3(2)
C6	20(2)	24(2)	17(2)	-6(2)	9(2)	4(2)
C7	18(2)	26(2)	18(2)	1(2)	6(2)	0(2)
C8	22(2)	13(2)	22(2)	1(2)	6(2)	1(2)
C9	22(2)	15(2)	16(2)	2(2)	8(2)	2(2)
C10	17(2)	20(2)	15(2)	2(2)	8(2)	2(2)
C11	24(2)	22(2)	17(2)	3(2)	8(2)	2(2)
C12	22(2)	14(2)	23(2)	3(2)	3(2)	1(2)
C13	21(2)	22(2)	16(2)	2(2)	7(2)	4(2)
C14	26(2)	32(3)	18(2)	4(2)	6(2)	0(2)
C15	22(2)	19(2)	21(2)	0(2)	7(2)	-2(2)
C16	28(2)	18(2)	24(2)	1(2)	8(2)	3(2)
C17	46(3)	29(3)	34(3)	5(2)	14(3)	19(2)
C18	80(5)	40(3)	29(3)	-2(3)	13(3)	-28(3)
C19	32(3)	33(3)	22(2)	3(2)	14(2)	7(2)
C20	45(3)	42(3)	24(3)	7(2)	17(2)	3(3)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

Atom	x	y	z	U_{eq}	$S.o.f.$
H1	528	9290	5183	20	1
H2	1308	10386	6092	21	1
H4A	2109	6784	7012	23	1
H4B	2037	8646	7213	23	1
H7A	3645	9447	6739	25	1
H7B	3516	10774	7267	25	1
H8A	2940	11912	6176	23	1
H8B	2933	10289	5697	23	1
H9	2336	10844	6646	21	1
H10	1873	9760	5111	20	1
H11A	2009	12603	5216	25	1
H11B	1725	12716	5815	25	1
H12A	1073	13619	4721	25	1
H12B	1199	12220	4230	25	1
H14A	1248	5768	6310	31	1
H14B	808	6777	5595	31	1
H15A	2194	7177	5510	25	1
H15B	2830	7594	5784	25	1
H16A	3016	5480	6726	36	1
H16B	2748	4772	5886	36	1
H16C	2382	5008	6377	36	1
H17A	330	5618	4455	44	1
H17B	-292	6215	4185	44	1
H18A	423	5570	2947	78	1
H18B	-237	4000	3480	78	1
H18C	194	4941	3226	78	1
H19A	445	8475	2629	33	1
H19B	1100	8510	2942	33	1
H20A	424	11291	2363	54	1
H20B	731	10319	1917	54	1
H20C	1076	11311	2666	54	1



N.B. As well as the enantiomer illusrated, the crystal structure also contains the opposite enantiomer and thus is a racemic mixture

X-ray data for (4.45)

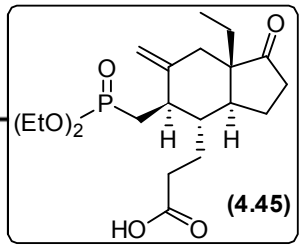


Table 1. Crystal data and structure refinement.

Identification code	2007sot1256y	
Empirical formula	$C_{20}H_{33}O_4P$	
Formula weight	400.43	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 16.1492(12) Å	α = 90°
	b = 14.4787(11) Å	β = 91.615(4)°
	c = 8.9388(6) Å	γ = 90°
Volume	2089.2(3) Å^3	
Z	4	
Density (calculated)	1.273 Mg / m^3	
Absorption coefficient	0.164 mm^{-1}	
$F(000)$	864	
Crystal	Lath; colourless	
Crystal size	0.14 × 0.05 × 0.01 mm^3	
θ range for data collection	2.93 – 27.48°	
Index ranges	$-20 \le h \le 20$, $-18 \le k \le 18$, $-11 \le l \le 11$	
Reflections collected	17897	
Independent reflections	4754 [R_{int} = 0.1220]	
Completeness to θ = 27.48°	99.4 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9984 and 0.9774	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4754 / 0 / 248	
Goodness-of-fit on F^2	1.154	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.1317, $wR2$ = 0.2662	
R indices (all data)	$R1$ = 0.2336, $wR2$ = 0.3254	
Largest diff. peak and hole	0.412 and –0.439 e Å^{-3}	

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	$S.o.f.$
P1	7583(1)	9002(1)	10665(2)	24(1)	1
O1	6384(3)	10751(3)	2501(5)	30(1)	1
O2	10567(3)	9472(4)	8566(5)	36(1)	1
O3	10622(3)	10563(3)	6803(5)	31(1)	1
O4	7861(3)	9098(3)	12263(5)	26(1)	1
O5	6708(3)	8532(4)	10502(5)	36(1)	1
O6	8163(3)	8394(3)	9682(5)	35(1)	1
C1	7435(4)	10054(4)	7959(7)	20(1)	1
C2	6525(4)	10073(4)	7418(7)	24(1)	1
C3	6406(4)	10094(5)	5722(7)	26(2)	1
C4	6864(4)	10920(5)	5104(7)	22(1)	1
C5	6906(4)	10996(5)	3413(7)	28(2)	1
C6	7744(4)	11421(4)	3041(7)	24(2)	1
C7	8227(4)	11533(4)	4548(7)	24(1)	1
C8	7788(4)	10833(4)	5540(6)	18(1)	1
C9	7951(4)	10847(4)	7240(6)	18(1)	1
C10	5882(4)	10085(5)	8316(8)	30(2)	1
C11	6484(4)	11849(4)	5630(7)	24(2)	1
C12	5607(5)	12020(6)	5073(9)	40(2)	1
C13	8876(4)	10825(5)	7632(7)	25(2)	1
C14	9308(4)	9906(5)	7228(7)	27(2)	1
C15	10225(4)	9944(5)	7627(7)	25(2)	1
C16	7569(4)	10067(4)	9673(6)	22(1)	1
C17	6165(4)	8371(5)	11736(9)	35(2)	1
C18	6265(5)	7409(6)	12264(10)	50(2)	1
C19	8478(5)	7507(5)	10211(9)	34(2)	1
C20	9396(5)	7544(6)	10299(10)	48(2)	1

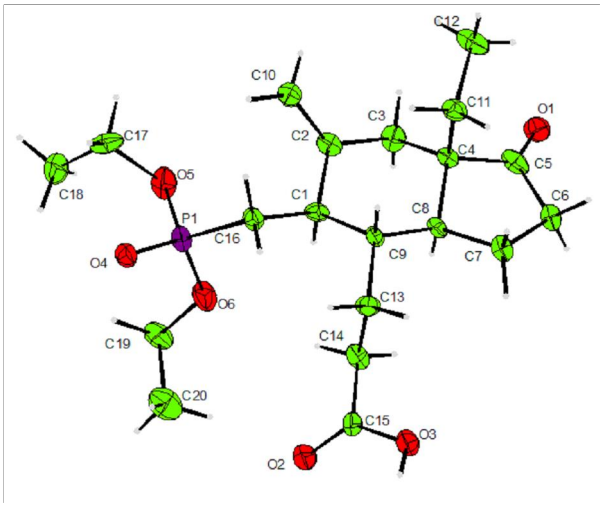
Table 3. Bond lengths [Å] and angles [°].

P1 O4	1.492(4)	O6 P1 C16	101.9(3)	C14 C13 H13A	108.7		
P1 O5	1.572(3)	C15–O3–H3	109.5	C9 C13 H13B	108.7		
P1–O6	1.572(3)	C17–O5–P1	124.1(4)	C14–C13–H13B	108.7		
P1–C16	1.778(6)	C19 O6 P1	121.4(4)	H13A–C13–H13B	107.6		
O1 C5	1.209(8)	C2 C1 C16	114.7(5)	C15 C14 C13	110.9(5)		
O2 C15	1.204(7)	C2 C1 C9	112.0(5)	C15 C14 H14A	109.5		
O3 C15	1.335(8)	C16–C1–C9	109.8(5)	C13 C14 H14A	109.5		
O3–H3	0.8400	C2–C1–H1	106.6	C15–C14–H14B	109.5		
O5–C17	1.447(8)	C16 C1 H1	106.6	C13–C14–H14B	109.5		
O6 C19	1.456(8)	C9 C1 H1	106.6	H14A C14 H14B	108.0		
C1 C2	1.535(9)	C10 C2 C3	121.5(6)	O2 C15 O3	123.2(6)		
C1 C16	1.542(8)	C10 C2 C1	124.6(6)	O2 C15 C14	124.7(6)		
C1–C9	1.566(8)	C3 C2 C1	114.0(6)	O3–C15–C14	112.1(5)		
C1–H1	1.0000	C4 C3 C2	109.2(5)	C1–C16–P1	119.0(5)		
C2 C10	1.330(9)	C4 C3 H3A	109.8	C1 C16 H16A	107.6		
C2 C3	1.523(9)	C2 C3 H3A	109.8	P1 C16 H16A	107.6		
C3 C4	1.519(9)	C4 C3 H3B	109.8	C1 C16 H16B	107.6		
C3–H3A	0.9900	C2–C3–H3B	109.8	P1–C16–H16B	107.6		
C3–H3B	0.9900	H3A C3 H3B	108.3	H16A–C16–H16B	107.0		
C4 C5	1.519(9)	C3 C4 C5	117.0(5)	O5 C17 C18	109.4(6)		
C4 C8	1.536(8)	C3 C4 C8	108.8(5)	O5 C17 H17A	109.8		
C4 C11	1.556(9)	C5–C4–C8	100.9(5)	C18 C17 H17A	109.8		
C5 C6	1.531(10)	C3–C4–C11	111.7(5)	O5–C17–H17B	109.8		
C6–C7	1.546(8)	C5–C4–C11	105.5(5)	C18–C17–H17B	109.8		
C6 H6A	0.9900	C8 C4 C11	112.5(5)	H17A C17 H17B	108.2		
C6 H6B	0.9900	O1 C5 C4	126.8(7)	C17 C18 H18A	109.5		
C7 C8	1.534(9)	O1–C5–C6	125.1(6)	C17 C18 H18B	109.5		
C7 H7A	0.9900	C4–C5–C6	108.0(5)	H18A C18 H18B	109.5		
C7–H7B	0.9900	C5 C6 C7	106.3(5)	C17 C18 H18C	109.5		
C8 C9	1.536(8)	C5 C6 H6A	110.5	H18A C18 H18C	109.5		
C8 H8	1.0000	C7 C6 H6A	110.5	H18B C18 H18C	109.5		
C9 C13	1.525(9)	C5–C6–H6B	110.5	O6 C19 C20	108.9(6)		
C9 H9	1.0000	C7–C6–H6B	110.5	O6 C19 H19A	109.9		
C10–H10A	0.9500	H6A C6 H6B	108.7	C20–C19–H19A	109.9		
C10–H10B	0.9500	C8 C7 C6	101.8(5)	O6 C19 H19B	109.9		
C11 C12	1.509(9)	C8 C7 H7A	111.4	C20 C19 H19B	109.9		
C11 H11A	0.9900	C6–C7–H7A	111.4	H19A C19 H19B	108.3		
C11–H11B	0.9900	C8–C7–H7B	111.4	C19–C20–H20A	109.5		
C12–H12A	0.9800	C6 C7 H7B	111.4	C19–C20–H20B	109.5		
C12–H12B	0.9800	H7A C7 H7B	109.3	H20A–C20–H20B	109.5		
C12 H12C	0.9800	C7 C8 C9	119.6(5)	C19 C20 H20C	109.5		
C13 C14	1.549(9)	C7 C8 C4	105.1(5)	H20A C20 H20C	109.5		
C13–H13A	0.9900	C9–C8–C4	112.9(5)	H20B–C20–H20C	109.5		
C13–H13B	0.9900	C7 C8 H8	106.1				
C14 C15	1.515(9)	C9 C8 H8	106.1				
C14 H14A	0.9900	C4 C8 H8	106.1				
C14 H14B	0.9900	C13 C9 C8	111.5(5)				
C16–H16A	0.9900	C13–C9–C1	114.8(5)				
C16–H16B	0.9900	C8 C9 C1	108.5(5)				
C17 C18	1.478(11)	C13 C9 H9	107.2				
C17 H17A	0.9900	C8 C9 H9	107.2				
C17 H17B	0.9900	C1 C9 H9	107.2				
C18 H18A	0.9800	C2–C10–H10A	120.0				
C18–H18B	0.9800	C2–C10–H10B	120.0				
C18 H18C	0.9800	H10A C10 H10B	120.0				
C19 C20	1.483(11)	C12 C11 C4	114.7(6)				
C19 H19A	0.9900	C12 C11 H11A	108.6				
C19 H19B	0.9900	C4–C11–H11A	108.6				
C20–H20A	0.9800	C12–C11–H11B	108.6				
C20 H20B	0.9800	C4 C11 H11B	108.6				
C20 H20C	0.9800	H11A C11 H11B	107.6				
		C11 C12 H12A	109.5				
O4 P1 O5	112.0(3)	C11–C12–H12B	109.5				
O4 P1 O6	114.8(3)	H12A–C12–H12B	109.5				
O5 P1 O6	104.7(3)	C11 C12 H12C	109.5				
O4–P1–C16	113.3(3)	H12A C12 H12C	109.5				
O5–P1–C16	109.3(3)	H12B–C12–H12C	109.5				

Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P1	29(1)	24(1)	19(1)	3(1)	2(1)	2(1)
O1	26(3)	42(3)	22(2)	3(2)	4(2)	0(2)
O2	29(3)	42(3)	37(3)	16(2)	1(2)	1(2)
O3	26(3)	33(3)	32(3)	11(2)	5(2)	5(2)
O4	25(3)	30(3)	22(2)	4(2)	3(2)	1(2)
O5	36(3)	43(3)	27(3)	4(2)	8(2)	16(3)
O6	50(3)	26(3)	31(3)	5(2)	4(2)	12(2)
C1	18(3)	15(3)	26(3)	1(3)	1(3)	3(3)
C2	24(4)	18(3)	29(3)	−2(3)	−4(3)	0(3)
C3	28(4)	29(4)	21(3)	5(3)	6(3)	8(3)
C4	18(3)	25(3)	22(3)	3(3)	2(2)	3(3)
C5	32(4)	21(3)	30(4)	2(3)	10(3)	7(3)
C6	33(4)	20(3)	20(3)	1(3)	2(3)	0(3)
C7	31(4)	19(3)	21(3)	−1(3)	−4(3)	−1(3)
C8	22(3)	15(3)	17(3)	0(2)	−4(2)	5(3)
C9	18(3)	19(3)	18(3)	6(2)	3(2)	1(3)
C10	23(4)	40(4)	27(4)	5(3)	2(3)	1(3)
C11	25(4)	21(3)	24(3)	3(3)	1(3)	6(3)
C12	35(5)	43(5)	41(4)	−3(4)	−13(4)	15(4)
C13	20(3)	28(4)	26(3)	−1(3)	0(3)	4(3)
C14	28(4)	24(4)	27(3)	5(3)	7(3)	1(3)
C15	27(4)	25(4)	22(3)	7(3)	4(3)	2(3)
C16	24(4)	24(3)	18(3)	2(3)	2(3)	0(3)
C17	16(4)	45(5)	45(4)	9(4)	3(3)	4(3)
C18	38(5)	62(6)	51(5)	31(5)	6(4)	−6(4)
C19	39(5)	22(4)	41(4)	1(3)	−5(3)	11(3)
C20	54(6)	32(4)	58(5)	4(4)	−4(4)	9(4)



N.B. As well as the enantiomer illusrated, the crystal structure also contains the opposite enantiomer and thus is a racemic mixture

X-ray data for (1.71)

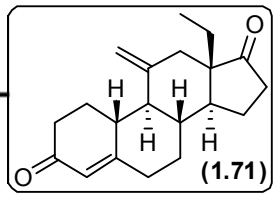


Table 1. Crystal data and structure refinement details.

Identification code	2008sor0073 (VF/4946/36)
Empirical formula	$C_{20}H_{26}O_2$
Formula weight	298.41
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 15.0183(5) Å
	b = 10.3738(3) Å β = 93.9
	c = 20.8833(7) Å
Volume	3245.73(18) Å^3
Z	8 (2 molecules)
Density (calculated)	1.221 Mg / m^3
Absorption coefficient	0.077 mm^{-1}
$F(000)$	1296
Crystal	Fragment; Colourless
Crystal size	0.11 × 0.08 × 0.03 mm^3
θ range for data collection	3.03 – 25.03°
Index ranges	$-17 \le h \le 17$, $-12 \le k \le 12$, $-24 \le l \le 24$
Reflections collected	24995
Independent reflections	5724 [R_{int} = 0.0849]
Completeness to θ = 25.03°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9977 and 0.9816
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5724 / 0 / 399
Goodness-of-fit on F^2	1.073
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0889, $wR2$ = 0.1664
R indices (all data)	$R1$ = 0.1391, $wR2$ = 0.1922
Largest diff. peak and hole	0.252 and −0.240 e Å^{-3}

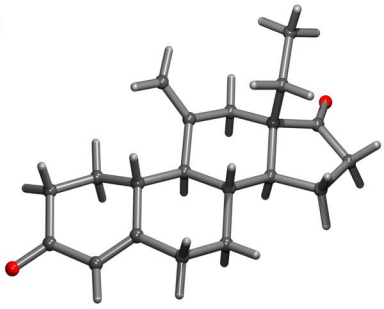


Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	S.o.f.
O1	2302(2)	8910(3)	4268(2)	64(1)	1
O2	−943(2)	43(3)	2853(1)	49(1)	1
C1	1883(3)	7898(4)	4208(2)	46(1)	1
C2	2249(3)	6650(4)	4478(2)	41(1)	1
C3	1840(2)	5493(3)	4122(2)	32(1)	1
C4	823(2)	5495(3)	4115(2)	28(1)	1
C5	406(2)	4350(3)	3726(2)	25(1)	1
C6	−617(2)	4471(3)	3583(2)	28(1)	1
C7	−841(3)	5744(3)	3244(2)	35(1)	1
C8	−506(2)	6876(3)	3651(2)	36(1)	1
C9	461(2)	6788(3)	3879(2)	30(1)	1
C10	980(3)	7851(4)	3899(2)	41(1)	1
C11	1042(3)	2807(4)	4579(2)	37(1)	1
C12	644(2)	3022(3)	4003(2)	27(1)	1
C13	313(2)	1914(3)	3579(2)	33(1)	1
C14	−704(2)	2007(3)	3487(2)	29(1)	1
C15	−1186(3)	1116(4)	3001(2)	39(1)	1
C16	−2011(3)	1800(4)	2717(2)	48(1)	1
C17	−1939(3)	3201(4)	2961(2)	43(1)	1
C18	−945(2)	3325(3)	3179(2)	31(1)	1
C19	−1153(3)	1787(3)	4123(2)	30(1)	1
C20	−1007(3)	433(4)	4400(2)	43(1)	1
O3	7150(2)	−4307(3)	3894(2)	96(2)	1
O4	3794(2)	4630(2)	2890(1)	45(1)	1
C21	6733(3)	−3300(4)	3898(3)	63(2)	1
C22	7159(3)	−2082(4)	4162(2)	57(1)	1
C23	6707(3)	−873(4)	3879(2)	42(1)	1
C24	5701(2)	−868(3)	3973(2)	32(1)	1
C25	5237(2)	287(3)	3626(2)	28(1)	1
C26	4208(2)	197(3)	3584(2)	26(1)	1
C27	3907(3)	−1070(3)	3265(2)	37(1)	1
C28	4302(3)	−2210(3)	3646(2)	41(1)	1
C29	5297(3)	−2143(3)	3754(2)	36(1)	1

C30	5788(3)	3209(4)	3693(2)	49(1)	1
C31	6019(3)	1826(4)	4425(2)	46(1)	1
C32	5532(2)	1609(3)	3881(2)	32(1)	1
C33	5140(3)	2725(3)	3491(2)	36(1)	1
C34	4123(2)	2659(3)	3500(2)	27(1)	1
C35	3576(3)	3568(4)	3060(2)	36(1)	1
C36	2690(3)	2897(4)	2863(2)	42(1)	1
C37	2797(3)	1494(3)	3105(2)	37(1)	1
C38	3811(2)	1349(3)	3215(2)	30(1)	1
C39	3807(3)	2884(3)	4181(2)	32(1)	1
C40	4106(3)	4175(4)	4476(2)	43(1)	1

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

O1 C1	1.226(3)	O3 C21	1.218(3)
O2–C15	1.217(3)	O4–C35	1.210(4)
C1 C10	1.461(6)	C21 C30	1.457(6)
C1 C2	1.501(6)	C21 C22	1.504(7)
C2 C3	1.519(3)	C22 C23	1.525(5)
C3 C4	1.527(5)	C23 C24	1.537(5)
C4–C9	1.517(3)	C24–C29	1.513(5)
C4–C5	1.546(5)	C24–C25	1.542(5)
C5 C12	1.526(5)	C25 C32	1.526(5)
C5 C6	1.551(5)	C25 C26	1.544(5)
C6 C18	1.519(3)	C26 C38	1.522(5)
C6–C7	1.524(5)	C26–C27	1.528(5)
C7–C8	1.516(5)	C27–C28	1.523(5)
C8 C9	1.500(5)	C28 C29	1.496(5)
C9 C10	1.350(5)	C29 C30	1.340(5)
C11 C12	1.324(5)	C31 C32	1.327(5)
C12–C13	1.514(5)	C32–C33	1.512(5)
C13–C14	1.529(5)	C33–C34	1.531(5)
C14 C15	1.518(5)	C34 C35	1.516(5)
C14 C18	1.543(5)	C34 C38	1.543(5)
C14 C19	1.548(5)	C34 C39	1.548(5)
C15–C16	1.513(6)	C35–C36	1.532(6)
C16–C17	1.542(5)	C36–C37	1.546(5)
C17 C18	1.536(5)	C37 C38	1.532(5)
C19 C20	1.529(5)	C39 C40	1.529(5)

O1 C1 C10	121.8(4)	O2 C15 C16	125.5(4)
O1 C1 C2	121.9(4)	O2 C15 C14	126.1(4)
C10 C1 C2	116.3(3)	C16 C15 C14	108.4(3)
C1–C2–C3	111.8(3)	C15–C16–C17	106.0(3)
C2 C3 C4	112.0(3)	C18 C17 C16	102.8(3)
C9 C4 C3	109.8(3)	C6 C18 C17	120.0(3)
C9 C4 C5	112.7(3)	C6 C18 C14	113.9(3)
C3 C4 C5	111.8(3)	C17 C18 C14	104.1(3)
C12–C5–C4	114.8(3)	C20–C19–C14	113.6(3)
C12 C5 C6	110.4(3)	O3 C21 C30	123.0(5)
C4 C5 C6	113.5(3)	O3 C21 C22	121.1(5)
C18 C6 C7	111.6(3)	C30 C21 C22	115.7(4)
C18 C6 C5	108.8(3)	C21 C22 C23	112.5(4)
C7–C6–C5	110.1(3)	C22–C23–C24	111.6(3)
C8–C7–C6	110.9(3)	C29–C24–C23	109.6(3)
C9 C8 C7	114.0(3)	C29 C24 C25	112.3(3)
C10 C9 C8	120.4(3)	C23 C24 C25	111.0(3)
C10–C9–C4	121.3(3)	C32–C25–C24	115.1(3)
C8–C9–C4	118.3(3)	C32–C25–C26	109.8(3)
C9–C10–C1	123.9(4)	C24–C25–C26	113.4(3)
C11 C12 C13	120.8(3)	C38 C26 C27	111.1(3)
C11 C12 C5	125.1(3)	C38 C26 C25	109.6(3)
C13–C12–C5	113.9(3)	C27–C26–C25	110.0(3)
C12–C13–C14	108.1(3)	C28–C27–C26	110.3(3)
C15–C14–C13	118.1(3)	C29–C28–C27	113.1(3)
C15 C14 C18	100.1(3)	C30 C29 C28	119.9(4)
C13 C14 C18	108.1(3)	C30 C29 C24	122.6(4)
C15–C14–C19	105.6(3)	C28–C29–C24	117.5(3)
C13–C14–C19	111.9(3)	C29–C30–C21	123.9(4)
C18 C14 C19	112.6(3)	C31 C32 C33	120.2(3)

C31 C32 C25	125.5(4)	O4 C35 C34	126.6(4)
C33 C32 C25	114.0(3)	O4 C35 C36	125.6(4)
C32 C33 C34	108.1(3)	C34 C35 C36	107.7(3)
C35–C34–C33	117.7(3)	C35–C36–C37	105.7(3)
C35 C34 C38	100.2(3)	C38 C37 C36	102.8(3)
C33 C34 C38	108.1(3)	C26 C38 C37	120.2(3)
C35 C34 C39	106.0(3)	C26 C38 C34	113.5(3)
C33 C34 C39	112.0(3)	C37 C38 C34	104.1(3)
C38–C34–C39	112.5(3)	C40–C39–C34	113.7(3)

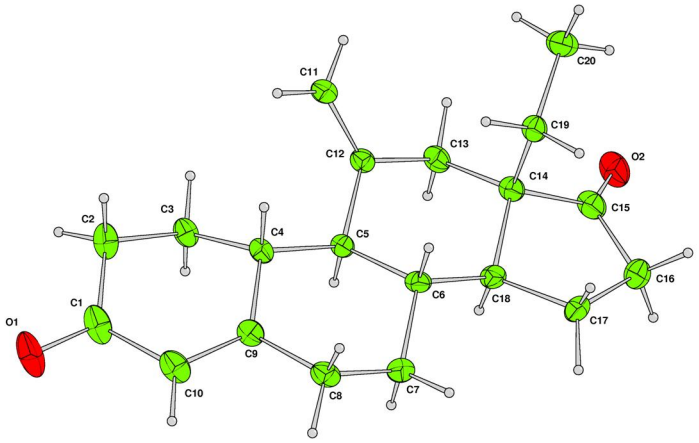
Table 4. Anisotropic displacement parameters [Å^2 × 10^3]. The anisotropic displacement factor exponent takes the form: $2\pi^2[h^2a^{*2}U^{11} + \ldots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	52(2)	34(2)	107(3)	-19(2)	20(2)	-15(2)
O2	65(2)	37(2)	45(2)	14(1)	8(2)	13(1)
C1	38(2)	33(2)	67(3)	15(2)	19(2)	5(2)
C2	31(2)	37(2)	55(3)	13(2)	8(2)	4(2)
C3	33(2)	26(2)	38(2)	4(2)	8(2)	3(2)
C4	32(2)	23(2)	29(2)	1(2)	6(2)	3(2)
C5	30(2)	23(2)	22(2)	2(1)	3(2)	2(2)
C6	37(2)	25(2)	22(2)	2(2)	1(2)	0(2)
C7	36(2)	32(2)	37(2)	5(2)	3(2)	2(2)
C8	39(2)	25(2)	44(2)	4(2)	6(2)	6(2)
C9	35(2)	23(2)	32(2)	5(2)	6(2)	3(2)
C10	42(3)	26(2)	58(3)	4(2)	15(2)	3(2)
C11	44(2)	25(2)	41(2)	7(2)	6(2)	4(2)
C12	27(2)	25(2)	31(2)	2(2)	5(2)	1(2)
C13	39(2)	21(2)	38(2)	3(2)	4(2)	0(2)
C14	37(2)	25(2)	26(2)	-2(2)	3(2)	-2(2)
C15	55(3)	33(2)	29(2)	-3(2)	5(2)	-10(2)
C16	61(3)	47(3)	33(2)	2(2)	14(2)	18(2)
C17	45(3)	38(2)	43(2)	5(2)	19(2)	6(2)
C18	39(2)	29(2)	23(2)	1(2)	3(2)	1(2)
C19	37(2)	27(2)	27(2)	-5(2)	1(2)	-3(2)
C20	51(3)	38(2)	40(2)	9(2)	3(2)	-1(2)
O3	66(3)	46(2)	181(4)	32(2)	46(3)	32(2)
O4	63(2)	26(2)	46(2)	5(1)	-4(1)	5(1)
C21	55(3)	41(3)	96(4)	27(3)	35(3)	23(2)
C22	34(3)	58(3)	81(3)	24(3)	17(2)	16(2)
C23	35(2)	36(2)	55(3)	8(2)	12(2)	9(2)
C24	29(2)	34(2)	33(2)	7(2)	5(2)	6(2)
C25	32(2)	24(2)	29(2)	4(2)	4(2)	3(2)
C26	28(2)	23(2)	26(2)	2(1)	2(2)	0(2)
C27	42(2)	25(2)	43(2)	5(2)	1(2)	0(2)
C28	49(3)	24(2)	49(2)	3(2)	5(2)	0(2)
C29	45(2)	28(2)	38(2)	11(2)	12(2)	8(2)
C30	53(3)	28(2)	68(3)	7(2)	22(2)	9(2)
C31	44(3)	38(2)	55(3)	5(2)	12(2)	6(2)
C32	29(2)	28(2)	39(2)	0(2)	4(2)	1(2)
C33	43(2)	22(2)	42(2)	2(2)	3(2)	1(2)
C34	30(2)	23(2)	28(2)	0(2)	-4(2)	1(2)
C35	52(3)	28(2)	29(2)	2(2)	5(2)	4(2)
C36	48(3)	36(2)	39(2)	3(2)	12(2)	8(2)
C37	41(2)	28(2)	39(2)	6(2)	10(2)	6(2)
C38	34(2)	25(2)	29(2)	3(2)	3(2)	2(2)
C39	35(2)	28(2)	34(2)	-3(2)	-5(2)	2(2)
C40	49(3)	39(2)	38(2)	-13(2)	-4(2)	3(2)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

Atom	x	y	z	U_{eq}	S.o.f.
H2A	2129	6591	4937	49	1
H2B	2905	6637	4449	49	1
H3A	2074	4693	4330	39	1
H3B	2020	5500	3675	39	1
H4	662	5390	4569	33	1
H5	669	4383	3299	30	1

H6	911	4454	3998	34	1
H7A	563	5764	2828	42	1
H7B	1495	5814	3156	42	1
H8A	−602	7678	3398	43	1
H8B	866	6939	4030	43	1
H10	745	8614	3701	50	1
H11A	1123	1948	4730	44	1
H11B	1247	3510	4840	44	1
H13A	489	1082	3782	39	1
H13B	577	1965	3158	39	1
H16A	2557	1385	2860	58	1
H16B	2033	1777	2242	58	1
H17A	−2111	3822	2614	52	1
H17B	−2319	3343	3324	52	1
H18	621	3367	2777	37	1
H19A	914	2425	4444	36	1
H19B	1802	1943	4049	36	1
H20A	1223	207	4081	65	1
H20B	−1336	341	4787	65	1
H20C	369	296	4510	65	1
H22A	7796	2074	4068	69	1
H22B	7130	2072	4634	69	1
H23A	6799	825	3415	50	1
H23B	6985	−102	4089	50	1
H24	5623	777	4443	38	1
H25	5414	251	3173	34	1
H26	4002	215	4029	31	1
H27A	3247	−1123	3241	44	1
H27B	4102	−1098	2822	44	1
H28A	4038	2243	4067	49	1
H28B	4138	3017	3413	49	1
H30	5503	−3949	3506	59	1
H31A	6122	2685	4570	55	1
H31B	6264	1123	4670	55	1
H33A	5318	2669	3044	43	1
H33B	5362	3551	3677	43	1
H36A	2572	2916	2391	50	1
H36B	2190	3328	3062	50	1
H37A	2499	1366	3509	44	1
H37B	2549	874	2779	44	1
H38	4045	1305	2779	35	1
H39A	3147	2841	4160	39	1
H39B	4039	2180	4465	39	1
H40A	4754	4165	4572	64	1
H40B	3808	4315	4874	64	1
H40C	3947	4872	4173	64	1



Residue 1; thermal ellipsoids drawn at the 35% probability level.

X-ray data for (5.13)

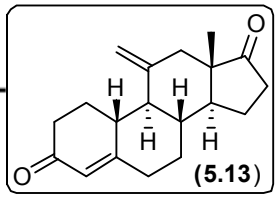


Table 1. Crystal data and structure refinement details.

Identification code	2007sot1763 (VF/4946/14–1)	
Empirical formula	$C_{19}H_{24}O_2$	
Formula weight	284.38	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 7.1647(3) Å	α = 96.669(2)°
	b = 9.4880(3) Å	β = 98.612(2)°
	c = 11.8099(5) Å	γ = 102.413(2)°
Volume	766.01(5) Å^3	
Z	2	
Density (calculated)	1.233 Mg / m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	308	
Crystal	Block; Colourless	
Crystal size	0.6 × 0.3 × 0.12 mm^3	
θ range for data collection	3.05 – 27.48°	
Index ranges	$-9 \le h \le 9$, $-12 \le k \le 12$, $-15 \le l \le 15$	
Reflections collected	14508	
Independent reflections	3490 [R_{int} = 0.0306]	
Completeness to θ = 27.48°	99.3 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9907 and 0.9447	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3490 / 0 / 192	
Goodness-of-fit on F^2	1.159	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0550, $wR2$ = 0.1379	
R indices (all data)	$R1$ = 0.0613, $wR2$ = 0.1430	
Extinction coefficient	0.34(2)	
Largest diff. peak and hole	0.563 and –0.548 e Å^{-3}	

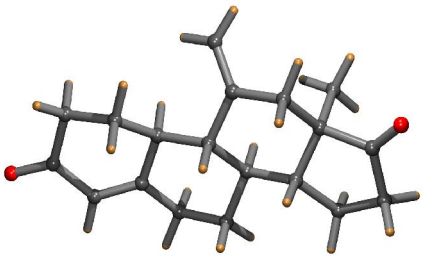


Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	–2842(2)	14539(1)	8723(1)	36(1)	1
O2	810(1)	4151(1)	6630(1)	24(1)	1
C1	–2373(2)	13414(1)	8383(1)	21(1)	1
C2	–3435(2)	12416(1)	7286(1)	21(1)	1
C3	–3125(2)	10871(1)	7290(1)	20(1)	1
C4	–948(2)	10884(1)	7470(1)	16(1)	1
C5	93(2)	11956(1)	8552(1)	16(1)	1
C6	–655(2)	13039(1)	8990(1)	18(1)	1
C7	–607(2)	9331(1)	7508(1)	15(1)	1
C8	1543(2)	9342(1)	7981(1)	15(1)	1
C9	2270(2)	10304(1)	9158(1)	19(1)	1
C10	2099(2)	11871(1)	9087(1)	20(1)	1
C11	–1303(2)	8290(1)	6356(1)	17(1)	1
C12	–1104(2)	6732(1)	6412(1)	19(1)	1
C13	1032(2)	6784(1)	6864(1)	16(1)	1
C14	1672(2)	7768(1)	8047(1)	15(1)	1
C15	1541(2)	5374(1)	7159(1)	19(1)	1
C16	3157(2)	5749(1)	8218(1)	23(1)	1
C17	3586(2)	7419(1)	8569(1)	20(1)	1
C18	–1904(2)	8677(1)	5344(1)	23(1)	1
C19	2312(2)	7255(1)	5963(1)	22(1)	1

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

O1–C1	1.2277(15)	C8–C9	1.5235(15)
O2 C15	1.2177(15)	C8 C14	1.5266(15)
C1 C6	1.4627(17)	C9 C10	1.5284(16)
C1–C2	1.5055(17)	C11–C18	1.3287(17)
C2–C3	1.5294(16)	C11–C12	1.5229(16)
C3 C4	1.5392(16)	C12 C13	1.5320(16)
C4 C5	1.5202(15)	C13 C15	1.5244(16)
C4 C7	1.5491(15)	C13 C14	1.5350(15)
C5–C6	1.3439(16)	C13–C19	1.5489(16)
C5–C10	1.5033(16)	C14–C17	1.5354(16)
C7 C11	1.5325(15)	C15 C16	1.5222(17)
C7 C8	1.5557(15)	C16 C17	1.5421(16)

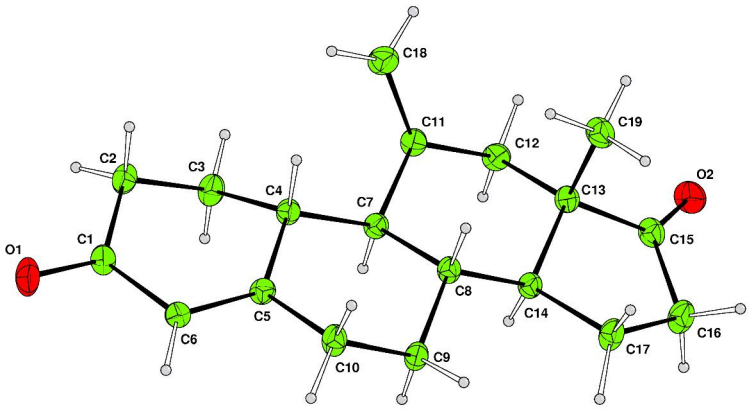
O1 C1 C6	121.00(11)	C5 C10 C9	112.80(9)
O1 C1 C2	122.14(11)	C18 C11 C12	119.91(10)
C6 C1 C2	116.71(10)	C18 C11 C7	125.06(11)
C1–C2–C3	111.46(10)	C12–C11–C7	114.84(9)
C2 C3 C4	111.09(9)	C11 C12 C13	108.23(9)
C5 C4 C3	108.86(9)	C15 C13 C12	117.74(9)
C5 C4 C7	112.81(9)	C15 C13 C14	101.25(9)
C3 C4 C7	111.74(9)	C12 C13 C14	108.84(9)
C6–C5–C10	119.15(10)	C15–C13–C19	104.19(9)
C6–C5–C4	122.21(10)	C12–C13–C19	110.96(10)
C10 C5 C4	118.43(10)	C14 C13 C19	113.65(9)
C5 C6 C1	122.98(11)	C8 C14 C13	112.70(9)
C11 C7 C4	114.70(9)	C8 C14 C17	120.81(9)
C11–C7–C8	109.29(9)	C13–C14–C17	104.64(9)
C4–C7–C8	112.94(9)	O2–C15–C16	125.28(11)
C9 C8 C14	111.43(9)	O2 C15 C13	126.15(11)
C9 C8 C7	111.24(9)	C16 C15 C13	108.56(9)
C14–C8–C7	108.07(9)	C15–C16–C17	105.89(10)
C8–C9–C10	111.01(9)	C14–C17–C16	102.29(9)

Table 4. Anisotropic displacement parameters [Å^2⁄ 10^3]. The anisotropic displacement factor exponent takes the form: $2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	40(1)	34(1)	36(1)	−7(1)	−3(1)	26(1)
O2	34(1)	14(1)	24(1)	0(1)	4(1)	4(1)
C1	23(1)	21(1)	22(1)	4(1)	6(1)	10(1)
C2	19(1)	22(1)	23(1)	4(1)	2(1)	9(1)
C3	17(1)	19(1)	25(1)	3(1)	2(1)	5(1)
C4	16(1)	15(1)	17(1)	2(1)	2(1)	5(1)
C5	18(1)	14(1)	17(1)	4(1)	3(1)	3(1)
C6	22(1)	18(1)	16(1)	2(1)	3(1)	7(1)
C7	16(1)	13(1)	16(1)	2(1)	1(1)	3(1)
C8	15(1)	13(1)	17(1)	0(1)	1(1)	4(1)
C9	19(1)	17(1)	20(1)	2(1)	3(1)	8(1)
C10	18(1)	15(1)	24(1)	3(1)	1(1)	5(1)
C11	16(1)	15(1)	19(1)	1(1)	1(1)	3(1)
C12	21(1)	14(1)	18(1)	0(1)	1(1)	3(1)
C13	19(1)	12(1)	17(1)	2(1)	3(1)	4(1)
C14	17(1)	13(1)	16(1)	1(1)	1(1)	4(1)
C15	21(1)	15(1)	21(1)	3(1)	7(1)	5(1)
C16	24(1)	16(1)	28(1)	2(1)	1(1)	7(1)
C17	19(1)	16(1)	25(1)	2(1)	1(1)	6(1)
C18	28(1)	20(1)	20(1)	0(1)	2(1)	6(1)
C19	28(1)	18(1)	22(1)	3(1)	8(1)	7(1)

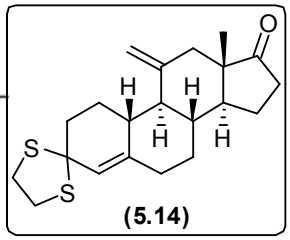
Table 5. Hydrogen coordinates [/ 10^4] and isotropic displacement parameters [$Å^2$ \ 10^3].

Atom	x	y	z	U_{eq}	S.o.f.
H2A	2967	12811	6612	25	1
H2B	4841	12379	7202	25	1
H3A	-3793	10255	6544	25	1
H3B	-3704	10439	7918	25	1
H4	424	11254	6793	19	1
H6	39	13585	9727	22	1
H7	1390	8898	8070	18	1
H8	2366	9735	7423	19	1
H9A	3644	10301	9431	23	1
H9B	1499	9902	9726	23	1
H10A	2446	12440	9877	24	1
H10B	3040	12322	8622	24	1
H12A	1527	6140	5631	22	1
H12B	-1930	6281	6936	22	1
H14	708	7381	8533	18	1
H16A	4330	5452	8027	27	1
H16B	2734	5244	8857	27	1
H17A	3881	7698	9422	25	1
H17B	4685	7923	8233	25	1
H18A	-2208	7983	4656	28	1
H18B	2028	9649	5308	28	1
H19A	3669	7281	6271	33	1
H19B	2204	8228	5803	33	1
H19C	1871	6554	5244	33	1



Thermal ellipsoids drawn at the 50% probability level

X-ray data for (5.14)



(5.14)

Table 1. Crystal data and structure refinement details.

Identification code	2008sot0074 (VF/4946/84)
Empirical formula	$C_{21}H_{28}OS_2$
Formula weight	360.55
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 9.4754(2) Å
	b = 14.9177(4) Å β = 100.5860(10)°
	c = 13.5116(3) Å
Volume	1877.37(8) Å^3
Z	4
Density (calculated)	1.276 Mg / m^3
Absorption coefficient	0.289 mm^{-1}
$F(000)$	776
Crystal	Fragment; Colourless
Crystal size	0.4 × 0.35 × 0.12 mm^3
θ range for data collection	3.07 – 27.48°
Index ranges	$-11 \le h \le 12$, $-19 \le k \le 19$, $-17 \le l \le 17$
Reflections collected	24931
Independent reflections	4302 [R_{int} = 0.0474]
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9662 and 0.8832
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4302 / 0 / 218
Goodness-of-fit on F^2	0.864
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0411, $wR2$ = 0.1146
R indices (all data)	$R1$ = 0.0582, $wR2$ = 0.1284
Largest diff. peak and hole	0.342 and –0.382 e Å^{-3}

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	$S.o.f.$
C1	4387(3)	234(2)	6144(2)	41(1)	1
C2	5784(2)	58(2)	6870(2)	43(1)	1
C3	4149(2)	1155(1)	7856(1)	21(1)	1
C4	3827(2)	2149(1)	7669(1)	22(1)	1
C5	2379(2)	2389(1)	7942(1)	23(1)	1
C6	2351(2)	2227(1)	9060(1)	17(1)	1
C7	3076(2)	1347(1)	9410(1)	18(1)	1
C8	3847(2)	874(1)	8863(1)	20(1)	1
C9	782(2)	2247(1)	9244(1)	16(1)	1
C10	604(2)	1899(1)	10301(1)	17(1)	1
C11	1316(2)	986(1)	10520(1)	21(1)	1
C12	2899(2)	1024(1)	10434(1)	22(1)	1
C13	696(2)	3923(1)	8968(2)	30(1)	1
C14	37(2)	3153(1)	9051(1)	21(1)	1
C15	–1555(2)	3127(1)	9080(1)	23(1)	1
C16	–1714(2)	2800(1)	10126(1)	20(1)	1
C17	–1001(2)	1875(1)	10325(1)	19(1)	1
C18	–1563(2)	1517(1)	11246(1)	26(1)	1
C19	–3152(2)	1814(1)	11022(2)	28(1)	1
C20	–3226(2)	2604(1)	10302(1)	22(1)	1
C21	–1137(2)	3509(1)	10936(2)	28(1)	1
O1	–4305(1)	3016(1)	9940(1)	29(1)	1
S1	3050(1)	432(1)	6909(1)	35(1)	1
S2	6048(1)	962(1)	7769(1)	28(1)	1

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

C1 C2	1.519(4)	C9 C10	1.558(2)
C1 S1	1.800(2)	C10 C11	1.525(2)
C2 S2	1.802(2)	C10 C17	1.527(2)
C3–C8	1.501(2)	C11–C12	1.527(2)
C3–C4	1.527(2)	C13–C14	1.321(3)
C3 S1	1.8423(17)	C14 C15	1.517(2)
C3 S2	1.8465(17)	C15 C16	1.528(2)
C4 C5	1.527(2)	C16 C20	1.523(2)
C5–C6	1.535(2)	C16–C17	1.539(2)
C6–C7	1.517(2)	C16–C21	1.548(2)
C6 C9	1.551(2)	C17 C18	1.536(2)
C7 C8	1.333(2)	C18 C19	1.545(2)
C7 C12	1.503(2)	C19 C20	1.522(3)
C9–C14	1.525(2)	C20–O1	1.216(2)
C2–C1–S1	106.22(14)	C10–C11–C12	110.97(14)
C1–C2–S2	107.59(14)	C7–C12–C11	111.08(13)
C8 C3 C4	110.81(14)	C13 C14 C15	120.80(16)
C8 C3 S1	106.79(12)	C13 C14 C9	124.98(15)
C4 C3 S1	112.57(12)	C15 C14 C9	113.85(14)
C8 C3 S2	111.38(12)	C14 C15 C16	107.46(13)
C4–C3–S2	107.95(12)	C20–C16–C15	117.49(13)
S1 C3 S2	107.33(9)	C20 C16 C17	101.34(13)
C3 C4 C5	110.42(14)	C15 C16 C17	109.48(14)
C4 C5 C6	112.32(13)	C20 C16 C21	103.92(14)
C7 C6 C5	110.75(13)	C15 C16 C21	110.67(15)
C7–C6–C9	111.07(13)	C17–C16–C21	113.73(14)
C5–C6–C9	110.16(13)	C10–C17–C18	121.33(13)
C8 C7 C12	120.42(15)	C10 C17 C16	112.48(13)
C8 C7 C6	123.26(15)	C18 C17 C16	104.26(14)
C12–C7–C6	116.32(14)	C17–C18–C19	102.27(14)
C7–C8–C3	124.80(15)	C20–C19–C18	106.03(14)
C14–C9–C6	114.63(13)	O1–C20–C19	125.86(16)
C14 C9 C10	109.13(13)	O1 C20 C16	125.83(17)
C6 C9 C10	114.10(12)	C19 C20 C16	108.31(14)
C11–C10–C17	112.44(13)	C1–S1–C3	97.30(9)
C11–C10–C9	110.92(13)	C2–S2–C3	98.23(9)
C17–C10–C9	107.63(12)		

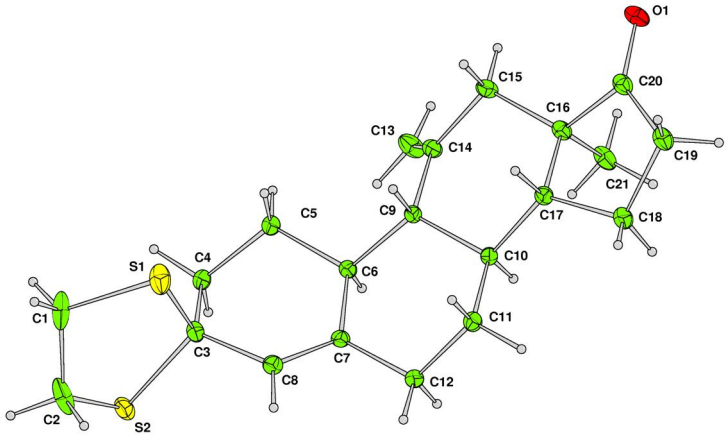
Table 4. Anisotropic displacement parameters [Å² 10³]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	57(1)	39(1)	35(1)	−16(1)	31(1)	−19(1)
C2	47(1)	29(1)	64(2)	−8(1)	40(1)	−1(1)
C3	19(1)	23(1)	21(1)	2(1)	7(1)	0(1)
C4	23(1)	26(1)	19(1)	5(1)	7(1)	1(1)
C5	23(1)	27(1)	20(1)	5(1)	7(1)	5(1)
C6	16(1)	19(1)	18(1)	1(1)	4(1)	1(1)
C7	15(1)	20(1)	18(1)	1(1)	2(1)	0(1)
C8	20(1)	19(1)	22(1)	2(1)	4(1)	0(1)
C9	15(1)	18(1)	16(1)	1(1)	3(1)	0(1)
C10	16(1)	20(1)	16(1)	1(1)	3(1)	0(1)
C11	22(1)	22(1)	21(1)	5(1)	7(1)	3(1)
C12	21(1)	26(1)	20(1)	5(1)	5(1)	7(1)
C13	25(1)	20(1)	48(1)	5(1)	13(1)	4(1)
C14	18(1)	22(1)	23(1)	2(1)	4(1)	3(1)
C15	18(1)	22(1)	28(1)	5(1)	4(1)	4(1)
C16	15(1)	21(1)	24(1)	3(1)	4(1)	1(1)
C17	16(1)	21(1)	19(1)	0(1)	4(1)	−1(1)
C18	21(1)	33(1)	27(1)	5(1)	10(1)	1(1)
C19	20(1)	36(1)	32(1)	3(1)	10(1)	−1(1)
C20	17(1)	26(1)	24(1)	7(1)	4(1)	1(1)
C21	20(1)	28(1)	36(1)	12(1)	7(1)	0(1)
O1	16(1)	33(1)	37(1)	2(1)	3(1)	3(1)

S1	32(1)	42(1)	31(1)	17(1)	12(1)	12(1)
S2	21(1)	31(1)	33(1)	3(1)	12(1)	3(1)

Table 5. Hydrogen coordinates [× 10⁴] and isotropic displacement parameters [Å² × 10³].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	4120	290	5699	49	1
H1B	4483	764	5720	49	1
H2A	6594	32	6500	52	1
H2B	5732	−521	7219	52	1
H4A	3812	2291	6951	27	1
H4B	4593	2512	8081	27	1
H5A	1618	2025	7528	28	1
H5B	2166	3028	7782	28	1
H6	2894	2722	9459	21	1
H8	4235	319	9130	24	1
H9	230	1823	8744	20	1
H10	1076	2334	10822	21	1
H11A	816	539	10038	26	1
H11B	1232	792	11208	26	1
H12A	3415	1433	10955	27	1
H12B	3328	420	10555	27	1
H13A	172	4468	8927	36	1
H13B	1694	3930	8951	36	1
H15A	2056	2714	8557	27	1
H15B	1978	3732	8953	27	1
H17	1444	1487	9747	22	1
H18A	−1043	1790	11877	31	1
H18B	−1477	857	11295	31	1
H19A	3772	1319	10708	34	1
H19B	3471	1995	11650	34	1
H21A	1673	4070	10784	41	1
H21B	−117	3617	10936	41	1
H21C	−1256	3290	11599	41	1



Thermal ellipsoids drawn at the 35% probability level

X-ray data for (5.15)

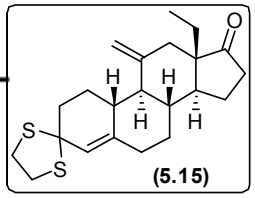


Table 1. Crystal data and structure refinement details.

Identification code	2008sot0127 (VF4946/85)
Empirical formula	$C_{22}H_{30}OS_2$
Formula weight	374.58
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 10.0365(4) Å
	b = 18.7175(6) Å β = 93.356(2)°
	c = 10.1806(2) Å
Volume	1909.23(10) Å^3
Z	4
Density (calculated)	1.303 Mg / m^3
Absorption coefficient	0.287 mm^{-1}
$F(000)$	808
Crystal	Slab; Colourless
Crystal size	0.42 × 0.2 × 0.04 mm^3
θ range for data collection	2.98 – 27.53°
Index ranges	$-13 \le h \le 12$, $-24 \le k \le 24$, $-13 \le l \le 12$
Reflections collected	21175
Independent reflections	4365 [R_{int} = 0.0578]
Completeness to θ = 27.50°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9886 and 0.8791
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4365 / 0 / 228
Goodness-of-fit on F^2	0.968
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0447, $wR2$ = 0.1030
R indices (all data)	$R1$ = 0.0664, $wR2$ = 0.1138
Extinction coefficient	0.0121(15)
Largest diff. peak and hole	0.355 and –0.447 e Å^{-3}

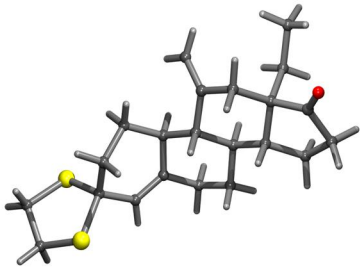


Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	$S.o.f.$
C1	2015(2)	1138(1)	4539(2)	27(1)	1
C2	2982(2)	1457(1)	5580(2)	27(1)	1
C3	4363(2)	1210(1)	3343(2)	19(1)	1
C4	5633(2)	785(1)	3384(2)	20(1)	1
C5	6308(2)	632(1)	2328(2)	18(1)	1
C6	5848(2)	845(1)	933(2)	19(1)	1
C7	4446(2)	1179(1)	875(2)	22(1)	1
C8	4212(2)	1646(1)	2070(2)	20(1)	1
C9	7633(2)	260(1)	2456(2)	20(1)	1
C10	8702(2)	741(1)	1905(2)	20(1)	1
C11	8324(2)	943(1)	476(2)	17(1)	1
C12	6929(2)	1308(1)	322(2)	18(1)	1
C13	9347(2)	1440(1)	–86(2)	18(1)	1
C14	9030(2)	1644(1)	–1539(2)	17(1)	1
C15	7661(2)	2013(1)	–1654(2)	21(1)	1
C16	6658(2)	1496(1)	–1128(2)	19(1)	1
C17	5745(2)	1180(1)	–1927(2)	26(1)	1
C18	10822(2)	1224(1)	–17(2)	20(1)	1
C19	11434(2)	1780(1)	–925(2)	25(1)	1
C20	10265(2)	2077(1)	–1792(2)	21(1)	1
C21	9088(2)	997(1)	–2496(2)	21(1)	1
C22	8744(2)	1182(1)	–3944(2)	29(1)	1
O1	10353(2)	2574(1)	–2551(2)	32(1)	1
S1	2994(1)	574(1)	3528(1)	24(1)	1
S2	4355(1)	1841(1)	4740(1)	23(1)	1

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

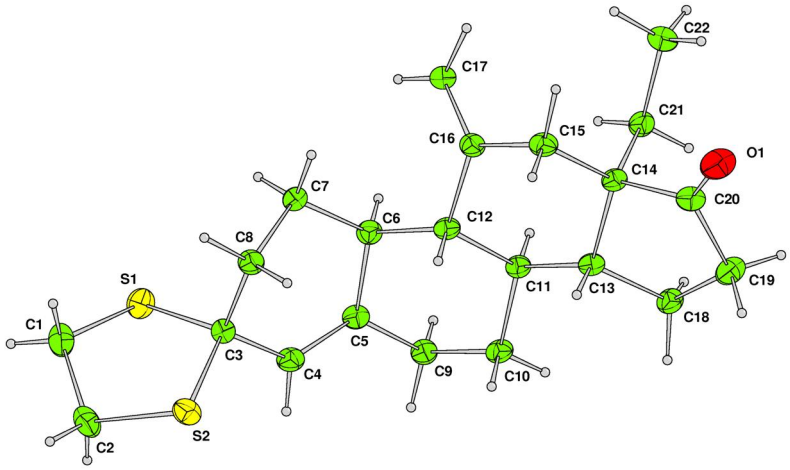
C1 C2	1.517(3)	C11 C13	1.522(3)
C1–S1	1.805(2)	C11–C12	1.557(3)
C2–S2	1.813(2)	C12–C16	1.526(2)
C3 C4	1.501(3)	C13 C18	1.532(3)
C3 C8	1.532(2)	C13 C14	1.544(2)
C3 S1	1.836(2)	C14 C20	1.515(3)
C3–S2	1.8495(19)	C14–C15	1.536(3)
C4–C5	1.335(3)	C14–C21	1.556(3)
C5 C9	1.500(3)	C15 C16	1.516(3)
C5 C6	1.520(2)	C16 C17	1.328(3)
C6 C7	1.538(3)	C18 C19	1.543(3)
C6–C12	1.547(3)	C19–C20	1.532(3)
C7–C8	1.528(3)	C20–O1	1.216(2)
C9 C10	1.532(3)	C21 C22	1.534(3)
C10 C11	1.529(2)		
C2 C1 S1	106.35(15)	C16 C12 C11	107.88(15)
C1 C2 S2	107.40(14)	C6 C12 C11	111.18(15)
C4–C3–C8	110.35(15)	C11–C13–C18	119.50(15)
C4–C3–S1	107.09(13)	C11–C13–C14	113.94(15)
C8 C3 S1	113.28(13)	C18 C13 C14	104.69(15)
C4 C3 S2	111.00(13)	C20 C14 C15	118.96(16)
C8 C3 S2	107.74(13)	C20 C14 C13	99.81(14)
S1–C3–S2	107.38(10)	C15–C14–C13	108.51(15)
C5–C4–C3	124.15(17)	C20–C14–C21	104.39(15)
C4 C5 C9	121.26(17)	C15 C14 C21	111.58(15)
C4 C5 C6	123.74(18)	C13 C14 C21	113.21(15)
C9 C5 C6	114.94(16)	C16 C15 C14	107.21(15)
C5 C6 C7	111.72(15)	C17 C16 C15	121.04(17)
C5–C6–C12	109.94(15)	C17–C16–C12	124.55(18)
C7 C6 C12	114.72(16)	C15 C16 C12	113.89(16)
C8 C7 C6	112.62(15)	C13 C18 C19	102.24(15)
C7 C8 C3	110.85(16)	C20 C19 C18	105.77(16)
C5–C9–C10	109.39(15)	O1–C20–C14	127.43(18)
C11–C10–C9	110.64(15)	O1–C20–C19	124.22(19)
C13–C11–C10	111.87(15)	C14–C20–C19	108.35(15)
C13 C11 C12	108.41(14)	C22 C21 C14	114.34(16)
C10 C11 C12	112.07(15)	C1 S1 C3	96.59(9)
C16 C12 C6	115.39(15)	C2 S2 C3	98.45(9)

Table 4. Anisotropic displacement parameters [Å² 10³]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	23(1)	29(1)	30(1)	4(1)	7(1)	2(1)
C2	29(1)	32(1)	22(1)	4(1)	9(1)	2(1)
C3	18(1)	21(1)	18(1)	0(1)	1(1)	0(1)
C4	21(1)	20(1)	18(1)	4(1)	2(1)	1(1)
C5	21(1)	16(1)	18(1)	2(1)	-1(1)	-1(1)
C6	19(1)	20(1)	18(1)	2(1)	0(1)	1(1)
C7	16(1)	30(1)	18(1)	0(1)	1(1)	2(1)
C8	20(1)	22(1)	18(1)	2(1)	0(1)	4(1)
C9	20(1)	20(1)	19(1)	3(1)	0(1)	3(1)
C10	19(1)	21(1)	19(1)	3(1)	-3(1)	3(1)
C11	18(1)	16(1)	16(1)	0(1)	1(1)	1(1)
C12	19(1)	17(1)	17(1)	1(1)	2(1)	2(1)
C13	19(1)	16(1)	17(1)	1(1)	2(1)	0(1)
C14	17(1)	18(1)	17(1)	2(1)	-2(1)	1(1)
C15	23(1)	21(1)	18(1)	4(1)	2(1)	3(1)
C16	19(1)	22(1)	16(1)	2(1)	0(1)	5(1)
C17	19(1)	41(1)	17(1)	1(1)	1(1)	0(1)
C18	18(1)	22(1)	21(1)	4(1)	2(1)	0(1)
C19	21(1)	26(1)	28(1)	5(1)	4(1)	4(1)
C20	25(1)	20(1)	19(1)	-1(1)	-2(1)	-1(1)
C21	19(1)	22(1)	21(1)	-4(1)	0(1)	-1(1)
C22	29(1)	40(1)	18(1)	-4(1)	0(1)	-3(1)
O1	32(1)	30(1)	32(1)	14(1)	6(1)	9(1)
S1	23(1)	22(1)	28(1)	0(1)	2(1)	3(1)
S2	27(1)	23(1)	19(1)	3(1)	2(1)	1(1)

Table 5. Hydrogen coordinates [10^4] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	S.o.f.
H1A	1572	1520	4002	32	1
H1B	1321	854	4954	32	1
H2A	3314	1081	6202	33	1
H2B	2532	1830	6082	33	1
H4	5979	615	4215	24	1
H6	5777	394	408	23	1
H7A	4323	1473	67	26	1
H7B	3771	793	819	26	1
H8A	3304	1854	1979	24	1
H8B	4863	2045	2112	24	1
H9A	7583	197	1965	24	1
H9B	7869	153	3393	24	1
H10A	8800	1181	2444	24	1
H10B	9570	489	1954	24	1
H11	8289	494	−60	20	1
H12	6990	1767	824	21	1
H13	9302	1895	425	21	1
H15A	7684	2460	1135	25	1
H15B	7413	2131	−2584	25	1
H17A	5713	1277	−2844	31	1
H17B	5124	857	1581	31	1
H18A	10939	732	348	24	1
H18B	11222	1258	894	24	1
H19A	11878	2166	400	30	1
H19B	12099	1552	1471	30	1
H21A	9997	791	−2416	25	1
H21B	8460	626	−2219	25	1
H22A	7797	1308	4061	43	1
H22B	8925	767	4495	43	1
H22C	9289	1586	4202	43	1



Thermal ellipsoids drawn at the 50% probability level

List of references

(1) Fieser, L. F.; Fieser, M. *Steroids*; Chapman and Hall, Ltd: London, 1959.
(2) Blickenstaff, R. T.; Ghosh, A. C.; Wolf, C. *Total synthesis of steroids*; Academic press: New York and London, 1974.
(3) Chinn, L. J.; Klimstra, P. D.; Baran, J. S.; Pappo, R. *The chemistry and biochemistry of steroids*; Intra-Science Research Associate: Santa Monica, 1969.
(4) Fried, J.; Edwards, J. A. *Organic reactions in steroid chemistry*; Van Nostrand Reinhold company: London, 1972.
(5) Capek, A.; Hanc, O.; Tadra, M. *Microbial transformations of steroids*; Academia publishing house of the Czechoslovak academy of sciences: Prague, 1966.
(6) Barton, D.; Nakanisi, K.; Meth-Cohn, O. *Comprehensive natural product chemistry*; Elsevier science, 1999; Vol. 2.
(7) Djerassi, C. *Steroid reactions an outline for organic chemists*; Holden-Day inc.: San Francisco, 1963.
(8) Loewenthal, H. J. E. *Tetrahedron* **1959**, *6*, 269-303.
(9) Stryer, L. *Biochemistry*; 4th ed.; W. H. Freeman and Company: New York, 1999.
(10) Olsen, J. R.; Lindberg, M.; Bloch, K. *J. Biol. Chem.* **1957**, *226*, 941-956.
(11) Campbell, N. A. *Biology*; 3rd ed.; Benjamin/Cummings Publishing Company, Inc: Wokingham, 1993.
(12) Johnson, M. F.; Everitt, B. J. *Essential Reproduction*; fifth ed.; Blackwell Science Ltd, 2000.
(13) McLaren, A. *A history of contraception: from antiquity to the present day*; Blackwell: Oxford, 1990.
(14) Hedon, B. *Acta Obstet. Gyn. Scan. Suppl.* **1990**, *152*, 7-12.
(15) Lewis, M. A. *Hum. Reprod. Update* **1999**, *5*, 707-720.
(16) Farley, T. M. M.; Meirik, O.; Collins, J. *Hum. Reprod. Update* **1998**, *5*, 721-735.
(17) Lammers, P.; Blumenthal, P. D.; Huggins, G. R. *Contraception* **1998**, *57*, 1S-27S.
(18) Bursi, R.; Groen, M. B. *Eur. J. Med. Chem.* **2000**, *35*, 787-796.
(19) Tuba, Z.; Bardin, C. W.; Dancsi, A.; Francsicics-Czinege, E.; Molnar, C.; Csorgei, J.; Falkay, G.; Koide, S. S.; Kumar, N.; Sundarum, K.; Dukat-Abrok, V.; Balogh, G. *Steroids* **2000**, *65*, 266-274.
(20) Kloosterboer, H. J.; Vonk-Noordegraaf, C. A.; Turpijn, E. W. *Contraception* **1988**, *38*, 325-332.
(21) Clarkson, R. A. Towards the total synthesis of desogestrel, PhD thesis, 2004.
(22) Smith, H.; Hughs, G. A.; Douglas, G. H.; Wendt, G. R.; al., e. *J. Chem. Soc.* **1964**, 4472-4492.
(23) Corey, E. J.; Huang, A. X. *J. Am. Chem. Soc.* **1999**, *121*, 710-714.
(24) Cohen, N.; Banner, B.; Borer, R.; Mueller, R.; Yang, R.; Rosenburger, M.; Saucy, G. *J. Org. Chem.* **1972**, *37*, 3385-3392.
(25) Rosenburger, M.; Frasher, T. P.; Saucy, G. *Helv. Chim. Acta* **1971**, *54*, 2857-2870.
(26) Tietze, L. F.; Krimmelbein, I. K. *Chem. Eur. J.* **2008**, *14*, 1541-1551.
(27) Gao, H.; Su, X.; Li, Z. *Steroids* **1997**, *62*, 398-402.
(28) Baier, H.; Durner, G.; Quinkert, G. *Helv. Chim. Acta* **1985**, *68*, 1054-1068.
(29) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1612-1615.
(30) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621.

(31) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W. *J. Org. Chem.* **1975**, *40*, 675-681.
(32) Cohen, N.; Banner, B. L.; Eichel, W. F.; Parrish, D. R.; Portland, L. A.; Sciamanna, W. *J. Org. Chem.* **1975**, *40*, 681-685.
(33) Nassim, B.; Schlemper, E. O.; Crabbe, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2337-2347.
(34) Tietze, L. F.; Nöbel, T.; Spescha, M. *J. Am. Chem. Soc.* **1999**, *120*, 8971-8977.
(35) Hu, Q. Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984-5986.
(36) Corey, E. J. *Ang. Chem. Int. Ed.* **2009**, *48*, 2-20.
(37) Dane, E. *Ang. Chem.* **1939**, *52*, 655.
(38) Dane, E.; Schmitt, L. *Liebigs Ann. Chem* **1938**, 536.
(39) Schwartz, S.; Ring, S.; Weber, G.; Teichmuller, G.; Palme, H.-J.; Pfeiffer, C.; Undeutsch, B.; Erhart, B.; Grawe, D. *Tetrahedron* **1994**, *50*, 10709-10720.
(40) Gao, H. *Org. Prep. Proced. Int.* **1997**, *29*, 499-539.
(41) Stephan; Zen, R.; Authier, L.; Jaouen, G. *Steroids* **1995**, *60*, 809-811.
(42) de Flines, J.; van der Waard, W. F.; Mijs, W. J.; Szpilfogel, S. *Recl. Trav. Pays-Bas* **1963**, *82*, 121-128.
(43) Gao, H.; Su, X.; Zhou, L.; Li, Z. *Org. Prep. Proced. Int.* **1997**, *29*, 572-579.
(44) Liu, L.-G.; Su, X.-D.; Li, Z.-S. *Synth. Commun.* **1995**, *25*, 3113-3124.
(45) Liu, L.-G.; Zhang, T.; Li, Z.-S. **1996**, *52*, 4495-4504.
(46) Liang, C. D.; Batran, J. S.; Allinger, N. L.; Yuh, Y. *Tetrahedron* **1976**, *32*, 2067-2069.
(47) van den Broek, A. J.; van Bokhoven, C.; Hobbelen, P. M.; Leemhuis, J. *Recl. Trav. Pays-Bas* **1975**, *94*, 35-39.
(48) Gao, H.; Su, X.; Huang, L.; Li, Z. *Synth. Commun.* **1997**, *27*, 1981-1987.
(49) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.
(50) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717.
(51) Akhrem, A. A.; Titov, Y. A. *Total steroid synthesis*; Plenum Press ed. New York-London, 1970.
(52) Anner, G.; Miescher, K. *Helv. Chim. Acta* **1948**, *31*, 2173.
(53) Tanada, K.; Nakashima, H.; Tanigushi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 1915-1917.
(54) Anachenko, S. N.; Torgov, I. V. *Tetrahedron Lett.* **1963**, 1553-1558.
(55) Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 7403.
(56) Quinkert, G.; del Grosso, M.; Doring, A.; Doring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Durner, G. *Helv. Chim. Acta* **1995**, *78*, 1345-1391.
(57) Canales, E.; Corey, E. J. *Org. Lett.* **2008**, *10*, 3271-3273.
(58) Soorukram, D.; Knochel, P. *Org. Lett.* **2007**, *9*, 1021-1023.
(59) Anachenko, S. N.; Limanov, V. Y.; Leonov, V. N.; Rzheznikov, V. N.; Torgov, I. V. *Tetrahedron* **1962**, *18*, 1355-1367.
(60) Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346-10347.
(61) Pattenden, G.; Reddy, L. K.; Walter, A. *Tetrahedron Lett.* **2004**, *45*, 4027.
(62) Pattenden, G.; Gonzalez, M. A.; Mcculloch, S.; Walter, A.; Woodhead, S. J. *Proc. Nat. Acad. Sci* **2004**, *101*, 12024.
(63) Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665-722.
(64) Guizzardi, B. Total synthesis of 3-O-methyl-estrone, PhD thesis, 2005.
(65) Meyers, A. I.; Mihelich, E. D. *Angew. Chem. Int. Ed.* **1976**, *15*, 270.

(66) Golding, B. T.; Atkins, M. P.; Howes, D. A. *J. Chem. Soc. Chem. Comm.* **1980**, 207-208.
(67) Ueno, H.; Maruyama, A.; Miyake, M.; Nakao, E.; Nakao, K.; Umezu, K.; Nitta, I. *J. Med. Chem.* **1991**, *34*, 2468-2473.
(68) Pinner, A. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 325.
(69) Marko, I. E.; Ates, A. *Synlett.* **1999**, *7*, 1033-1036.
(70) DeWolf, R. H. *Synthesis* **1974**, 153-172.
(71) Casy, G.; Furber, M.; Richardson, K. A.; Stephenson, G.; Taylor, R. J. K. *Tetrahedron* **1986**, *21*, 5849-5856.
(72) Yus, M.; Torregrosa, R.; Pastor, I. M. *Molecules* **2004**, *9*, 330-348.
(73) Jones, R. C. F.; Schofield, J. *J. Chem. Soc. Perkin Trans. 1* **1990**, 375-380.
(74) Cano, M.; Ladlow, M.; Balasubramanian, S. *J. Org. Chem.* **2002**, *67*, 129-135.
(75) Larock, R. C. *Comprehensive Organic Transformations*; VCH publication: New York, 1989.
(76) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113-4114.
(77) Das, S.; Panigrahi, A. K.; Maikap, G. C. *Tetrahedron Lett.* **2003**, *44*, 1375-1377.
(78) Ganem, B.; Godfrey, A. G. *Tetrahedron Lett.* **1990**, *34*, 4825-4826.
(79) Soderquist, J. A.; Anderson, C. A. *Tetrahedron Lett.* **1986**, *27*, 3961.
(80) Shen, Y.; Yao, J. *J. Chem. Research* **1996**, 428-429.
(81) Minami, T.; Harui, N.; Tanigushi, Y. *J. Org. Chem.* **1986**, *51*, 3572-3576.
(82) Kiddle, J. J.; Babler, J. H. *J. Org. Chem.* **1993**, *58*, 3572-3574.
(83) Just, G.; O'Connor, B. *Tetrahedron Lett.* **1985**, *26*, 1799-1802.
(84) Keinan, E.; C., S. S.; Singh, S. P. *Tetrahedron* **1991**, *47*, 4631-4638.
(85) Clinet, J.-C.; Dunach, E.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6710-6712.
(86) Thijs, L.; Waanders, P. P.; Stokkingreef, E. H. M.; Zwanenburg, B. *Recl. Trav. Pays-Bas* **1986**, *105*, 332-337.
(87) Deslongchamps, P.; Roy, B. L. *Can. J. Chem.* **1986**, *64*, 2068-2075.
(88) Holmes, A. B.; Hughs, A. B.; Smith, A. L.; Williams, S. F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1089-1099.
(89) Mayer, S. F.; Streinreiber, A.; Orru, R. V. A.; Faber, K. *J. Org. Chem.* **2002**, *67*, 9115-9121.
(90) Aerssens, M. H. P. J.; Brandsma, L. *J. Chem. Soc. Chem. Comm.* **1984**, 735-736.
(91) Boland, W.; Schroer, N.; Sieler, C. *Helv. Chim. Acta* **1987**, *70*, 1025-1040.
(92) Chou, W.-N.; Clark, D. L.; White, J. B. *Tetrahedron Lett.* **1991**, *32*, 299-302.
(93) Cossy, J.; Blanchard, N.; Meyer, C. *Tetrahedron Lett.* **2002**, *43*, 1801-1805.
(94) Rieke, R. D.; Li, P. T. J.; Burns, T. P.; Uhm, S. J. *J. Org. Chem.* **1981**, *46*, 4323-4324.
(95) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452-453.
(96) Sondengam, B. L.; Charles, G.; Akam, T. M. *Tetrahedron Lett.* **1980**, *21*, 1069-1070.
(97) Unelius, C. R.; Liblikas, I.; Mozuraitis, R. *Acta Chem. Scand.* **1998**, *52*, 930-934.
(98) Wang, S. S.; Shi, X.-X.; Powell, W. S.; Tiemon, T.; Feinmark, S. J.; Rokach, J. *Tetrahedron Lett.* **1995**, *36*, 513-516.
(99) Magid, R. M.; Fruchey, O. S.; Johnson, W. L. *Tetrahedron. Lett.* **1977**, *35*, 2999-3002.
(100) Magid, R. M.; Fruchey, O. S.; Johnson, W. L. *J. Org. Chem.* **1979**, *44*, 359-363.
(101) Magid, R. M.; Talley, B. G.; Souther, S. K. *J. Org. Chem.* **1981**, *46*, 824-825.
(102) Bahattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.

(103) Megati, S.; Phadtare, S.; Zemlicka, J. *J. Org. Chem.* **1992**, *57*, 2320-2327.
(104) Hoye, R.; Liang, M. *J. Org. Chem.* **1997**, *62*, 8586-8588.
(105) Hopf, H.; Bohm, I.; Kleinschroth, J. *Org. Synth.* **1981**, *60*, 41.
(106) Dotz, K. H.; Gerhardt, A. *J. Organomet. Chem.* **1999**, *578*, 223.
(107) Hubschwerlen, C.; Angehrn, P.; Gubernator, K.; Page, M. G. P.; Specklin, J. *J . Med. Chem.* **1998**, *41*, 3972.
(108) Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677-2678.
(109) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.
(110) Alpegiani, M.; Hanessian, S. *J. Org. Chem.* **1987**, *52*, 278-279.
(111) Porter, N. A.; Wujek, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 2626-2629.
(112) Bennani, Y. L.; Hanessian, S. *Tetrahedron* **1996**, *52*, 13837-13866.
(113) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754-5756.
(114) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939-1942.
(115) Alexakis, A.; Mutti, S.; Normant, J. F.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 437-440.
(116) Binns, M. R.; Haynes, R. K. *J. Org. Chem.* **1981**, *46*, 3790-3795.
(117) Binns, M. R.; Haynes, R. K.; Houston, T. L.; Jackson, W. R. *Tetrahedron Lett.* **1980**, *21*, 573-576.
(118) Binns, M. R.; Haynes, R. K.; Katsifis, A. A.; Schober, P. A.; Vonwiller, S. C. *Tetrahedron Lett.* **1985**, *26*, 1565-1568.
(119) Haynes, R. K.; Katsifis, A. G.; Vonwiller, S. C.; Hambley, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5423-5433.
(120) Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schrober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *1988*, 5411-5423.
(121) Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schrober, P. A.; Vonwiller, S. C. *J. Org. Chem.* **1989**, *54*, 1960-1968.
(122) Hanessian, S.; Gomstyan, A.; Payne, A.; Herve, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032-5034.
(123) Hanessian, S.; Gomstyan, A.; Malek, N. *J. Org. Chem.* **2000**, *65*, 5623-5631.
(124) Denmark, S. E.; Kim, J.-H. *J. Org. Chem.* **1995**, *60*, 7535-7547.
(125) Chattery, P. K.; Lee, H.; Parr, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 1855-1856.
(126) Hanessian, S.; Andreotti, D.; Gomstyan, A. *J. Am. Chem. Soc.* **1995**, *117*, 10393-10394.
(127) Haynes, R. K.; Katsifis, A. G. *Aust. J. Chem.* **1989**, *42*, 1455-1471.
(128) Binns, M. R.; Chai, O. L.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *Tetrahedron Lett.* **1985**, *26*, 1569-1572.
(129) Evans, D. A. *Asymetric Synthesis*; Academic Press: New-York, 1984; Vol. 3.
(130) Hanessian, S.; Gomstyan, A. *Tetrahedron Lett.* **1994**, *35*, 7509-7512.
(131) Dancer, R. J.; Haynes, R. K.; Loughlin, W. A.; Vonwiller, S. C. *Aust. J. Chem.* **1990**, *43*, 1375-1389.
(132) Haynes, R. K.; Stokes, J. P.; Hambley, T. W. *J. Chem. Soc. Chem. Comm.* **1991**, 58-60.
(133) Haynes, R. K.; Vonwiller, S. C.; Hambley, T. W. *J. Org. Chem.* **1989**, *54*, 5162-5170.
(134) Jones, D. N.; Maybury, M. W. J.; Swallow, S.; Tomkinson, N. C. O. *Tetrahedron Lett.* **1993**, *34*, 8553-8556.
(135) Jones, D. N.; Maybury, M. W. J.; Swallow, S.; Tomkinson, N. C. O.; Wood, W. W. *Tetrahedron Lett.* **2001**, *42*, 2193-2195.

(136) Tanaka, K.; Ohta, Y.; Fuji, K. *J. Org. Chem.* **1995**, *60*, 8036-8043.
(137) Geraghty, N. W. A.; Morris, N. M. *Synthesis* **1989**, 603-607.
(138) Burnell, D. J.; Boodbrand, H. B.; Kaiser, S. M.; Valenta, Z. *Can. J. Chem.* **1987**, *65*, 154-165.
(139) Phillips, A. M. M. M.; Modro, T. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1875.
(140) Ayyangar, N. R.; Mehendale, A. R.; Argade, A. B. *Synth. Commun.* **1987**, *17*, 1959-1964.
(141) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-136.
(142) Middleton, S.; Stock, L. E. *Aust. J. Chem.* **1980**, *33*, 2467-2476.
(143) Amri, H.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1989**, *30*, 7381-7382.
(144) Samarat, A.; Fargeas, V.; Villieras, J.; Lebreton, J.; Amri, H. *Tetrahedron Lett.* **2001**, *42*, 1273-1274.
(145) Lin, C.-H.; Aristoff, P. A.; Johnson, P. D.; McGrath, J. P.; Timko, J. M.; Robert, A. *J. Org. Chem.* **1987**, *52*, 5594-5601.
(146) Conolly, P. J.; Heathcock, P. J.; Patel, C. H. *J. Org. Chem.* **1985**, *50*, 4135-4144.
(147) Kraus, G. A.; Shi, J. *J. Org. Chem.* **1991**, *56*, 4147-4151.
(148) Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692-7697.
(149) Heys, L.; Murphy, P. J.; Coles, S. J.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron Lett.* **1999**, *40*, 7151-7152.
(150) Boatman, R. J.; Whitlock, B. J.; Whitlock Jr, H. W. *J. Am. Chem. Soc.* **1977**, *99*, 4822-4824.
(151) Bradsher, C. K.; Edgar, K. J. *J. Org. Chem.* **1981**, *46*, 4600-4602.
(152) Hergrueter, C. N.; Brewer, P. D.; Tagat, J.; Helquist, P. *Tetrahedron Lett.* **1977**, *48*, 4145-4148.
(153) Maezaki, N.; Izumi, M.; Yuyama, S.; Sawamoto, H.; Iwata, C.; Tanaka, T. *Tetrahedron* **2000**, *56*, 7297-7945.
(154) Monti, H.; Charles, P.; Leandri, G. *Synth. Commun.* **1996**, *26*, 4123-4130.
(155) Nevill Jr, C. R.; Braish, T. F.; Jakubowski, J. A.; Fuchs, P. L. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 77-78.
(156) Parham, W. E.; Jones, L. D.; Sayed, Y. *J. Org. Chem.* **1975**, *40*, 2394-2399.
(157) Piers, E.; Harrison, C. L.; Zetina-Rocha, C. *Org. Lett.* **2001**, *3*, 3245-3247.
(158) Piers, E.; Tse, H. L. A. *Tetrahedron Lett.* **1984**, *25*, 3155-3158.
(159) Tada, M.; Chiba, K.; Izumiya, K.; Tamura, M. *Bull. Chem. Soc. Jap.* **1993**, *66*, 3532-3533.
(160) Golinski, M.; Brock, C. P.; Watt, D. S. *J. Org. Chem.* **1993**, *58*, 159-164.
(161) Peters, O.; Debaerdemaeker, T.; Friedrichsen, W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 59-69.
(162) Romo, J.; Rosenkranz, G.; Djerassi, C. *J. Am. Chem. Soc.* **1951**, *73*, 4961-4964.
(163) Mislin, G. L.; Miesch, M. *J. Org. Chem.* **2003**, *68*, 433-441.
(164) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953-5956.
(165) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*; 5th ed.; Butterworth Heinemann, 2003.
(166) Paquette, L. A.; Lin, H.-S.; Gunn, B. P.; Coghlan, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 5818-5826.
(167) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J. M.; Quesnel, Y.; Markó, I. E. *Tetrahedron Lett.* **1999**, *40*, 1799-1802.
(168) Markó, I. E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J. M. *Ang. Chem. Int. Ed.* **1999**, *38*, 3207-3209.
(169) Andrés, J. M.; de Elena, N.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1503-1509.

(170) Bal, B. S.; Childers Jr, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091-2096.
(171) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031-1034.
(172) Matsuura, F.; Hamada, Y.; Shiori, T. *Tetrahedron* **1994**, *50*, 9457-9470.
(173) Amos, R. I. J.; Gourlay, B. S.; Molesworth, P. P.; Smith, J. A.; Sprod, O. R. *Tetrahedron* **2005**, *61*, 8226-8230.
(174) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726-9728.
(175) Liras, J. L.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **1997**, *119*, 9191-8200.
(176) Hays, S. J.; Bigge, C. F.; Novak, P. M.; Drummond, J. T.; Bobovski, T. P.; Rice, M. J.; Johnson, G.; Brahce, L. J.; Coughenour, L. L. *J. Med. Chem.* **1990**, *33*, 2919-2924.
(177) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minova, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318-326.
(178) Ishikawa, T.; Senzaki, M.; Kadoya, R.; Morimoto, T.; Miyake, N.; Izawa, M.; Saito, S. *J. Am. Chem. Soc.* **2001**, *123*, 4607-4608.
(179) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353-2356.
(180) Wong, P. L.; Moeller, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 11434-11445.
(181) Danieli, B.; Lesma, G.; Luzzani, M.; Passarella, D.; Silvani, A. *Tetrahedron* **1996**, *52*, 11291-11296.
(182) Kraus, G. A.; Bougie, D. *Tetrahedron* **1994**, *50*, 2681-2690.
(183) Kende, A. S.; Hernando, J. I.; Milbrank, J. B. J. *Tetrahedron* **2002**, *50*, 61-74.
(184) Rat, S.; Norsikian, S. *Synlett.* **2006**, *7*, 1004-1008.
(185) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495-498.
(186) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533-534.
(187) Honda, T.; Kimura, N. *Org. Lett.* **2002**, *4*, 4567-4570.
(188) Harrowven, D. C.; Poon, H. S. *Tetrahedron* **1996**, *52*, 1389-1398.
(189) Harrowven, D. C.; Poon, H. S. *Tetrahedron Lett.* **1996**, *37*, 4281-4282.
(190) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1994**, *59*, 2304-2313.
(191) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191-198.
(192) Hu, Y.; Zorumski, C. F.; Covey, D. F. *J. Org. Chem.* **1995**, *60*, 3619-3625.
(193) Beji, F.; Besbes, R.; Amri, H. *Synth. Commun.* **2000**, *21*, 3947-3954.
(194) An, J.; Wilson, J. M.; An, Y.; Wiemer, D. *J. Org. Chem.* **1996**, *61*, 4040-4045.
(195) Mikolajczyk, M.; Zatorsky, A. *J. Org. Chem.* **1991**, *56*, 1217-1223.
(196) Fouque, D.; About-Jaudet, E.; Collignon, N.; Savignac, P. *Synth. Commun.* **1992**, *22*, 219-228.
(197) Rocca, J. R.; Tumlinson, J. H.; Glancey, B. M.; Lofgren, C. S. *Tetrahedron Lett.* **1983**, *24*, 1893-1896.
(198) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183-2186.
(199) Chien, C. F.; D., W. J.; Ly, T. W.; Shia, K. S.; Liu, H. J. *Chem. Commun.* **2002**, 248-249.
(200) Lee, S. Y.; Hong, J. E.; Jang, W. B.; Oh, D. Y. *Tetrahedron Lett.* **1997**, *38*, 4567-4570.
(201) Lee, S. Y.; Lee, C. W.; Oh, D. Y. *J. Org. Chem.* **2000**, *65*, 245-248.
(202) Khripach, V. A.; Zhabinskii, V. N.; Tsavlovskii, D. N.; Drachenova, O. A.; Ivanova, G. V.; Konstantinova, O. V.; Zavadskaya, M. I.; Lyakhov, A. S.; Govorova, A. A.; Groen, M. B.; Groot, A. d. *Steroids* **2001**, *66*, 569-580.
(203) Groen, M. B., Personnal communication.

(204) Node, M.; Ohta, K.; Kajimoto, T.; Nishide, K.; Fujita, K. *Chem. Pharm. Bull.* **1983**, *31*, 4178-4180.
(205) Hanada, K.; Miyazawa, N.; Ogasawara, K. *Chem. Pharm. Bull.* **2003**, *51*, 104-106.
(206) Holder, S.; Blechert, S. *Synlett.* **1996**, 505-506.
(207) Borsting, P.; Christensen, M. S.; Steffansen, S. I.; Nielsen, P. *Tetrahedron* **2006**, *62*, 1139-1149.
(208) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1998**, *39*, 3939-3942.
(209) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1999**, *40*, 3297-3300.
(210) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239-2258.
(211) Yet, L. *Chem. Rev.* **2000**, *100*, 2963-3007.
(212) Bienick, M.; Michrowska, A.; Usanov, D. L.; Grela, K. *Chem. Eur. J.* **2008**, *14*, 806-818.
(213) Collins, S. K. *J. Organomet. Chem.* **2006**, *691*, 5122-5128.
(214) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653-5660.
(215) Grela, K.; Bieniek, M. *Tetrahedron Lett.* **2001**, *42*, 6425-6428.
(216) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem* **2004**, *2*, 8-23.
(217) Lelievre, S.; Mercier, F.; Mathey, F. *J. Org. Chem.* **1996**, *61*, 3531-3533.
(218) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, K. P.; Priermeier, M. B.; Fisher, H. *Ang. Chem. Int. Ed.* **1995**, *34*, 1844-1848.
(219) Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28-34.
(220) Hutchinson, J. H.; Money, T. *Can. J. Chem.* **1987**, *65*, 1-6.
(221) Dracht, S.; Charnikova, T.; Saraber, F. C. E.; Jansen, B. J. M.; Groot, A. *Tetrahedron* **2003**, *24*, 4287-4296.
(222) Doussot, J.; Garreau, R.; Dallery, L.; Guette, J.-P.; Guy, A. *Bull. Soc. Chim. Fr.* **1995**, *132*, 59-66.
(223) Posner, G. H.; Mallamo, J. P.; Black, A. Y. *Tetrahedron* **1981**, *37*, 3921-3926.
(224) Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *108*, 1239.
(225) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1992**, *33*, 1909.
(226) Quinkert, G.; Weber, W.-D.; Schwartz, U.; Duerner, G. *Ang. Chem.* **1980**, *12*, 1060-1062.
(227) Brunel, J.-M.; Buono, G. *J. Org. Chem.* **1993**, *58*, 7313-7314.
(228) Ding, K.; Wang, Y.; Zhang, L.; Wu, Y.; Matsuura, T. *Tetrahedron* **1996**, *52*, 1005-1010.
(229) Wang, Y.; Sun, J.; Ding, K. *Tetrahedron* **2000**, *56*, 4447-4451.
(230) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319-6337.
(231) He, Z.; Modro, T. A. *J. Chem. Res.* **1999**, 656.
(232) Snider, B. B.; Kirk, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2364-2368.
(233) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934-946.
(234) Sarabèr, F. C. E.; Baranowsky, A.; Jansen, B. J. M.; Posthumus, M. A.; de Groot, A. *Tetrahedron* **2006**, *62*, 1726-1742.
(235) Mukaiyama, T.; Banno, T.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *24*, 7503-7509.
(236) Snider, B. B.; Phillips, G. B. *J. Org. Chem* **1983**, *48*, 2789-2792.
(237) Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1983**, *105*, 7358-7363.
(238) Gumulka, M.; Ibrahim, I. H.; Boncza-Tomaszewski, Z.; Engel, C. R. *Can. J. Chem.* **1985**, 766-772.
(239) Suginome, H.; Yamada, S.; Wang, J. B. *J. Org. Chem.* **1990**, *55*, 2170-2176.
(240) Pyne, S. G.; Bloem, P.; Chapman, S. L.; Dixon, C. E.; Griffith, R. *J. Org. Chem.* **1990**, *55*, 1086-1093.

(241) Mandai, T.; Ueda, M.; Kashiwagi, K.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1993**, *34*, 111-114.
(242) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J.; Yamamoto, K. *Tetrahedron Lett.* **1989**, *30*, 4999.
(243) Edwards, J. A.; Carpio, H.; Cross, A. D. *Tetrahedron Lett.* **1964**, 3299.
(244) Hakuba, H.; Kitagaki, S.; Mukai, C. T. *Tetrahedron* **2007**, *63*, 12639-12645.