UNIVERSITY OF SOUTHAMPTON

The Preparation of 1,3,6,8-Tetraene Systems for Use as Intramolecular Diels-Alder Substrates in Desymmetrization Reactions

Henry James Seaman Bush

Doctor of Philosophy

Department of Chemistry

September 2003

Preface

The research described in this thesis was carried out by Henry James Seaman Bush under the supervision of Dr Bruno Linclau at the University of Southampton between October 1999 and August 2003. No part of this thesis has been previously submitted at this or any other university.

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

THE PREPARATION OF 1,3,6,8-TETRAENE SYSTEMS FOR USE AS INTRAMOLECULAR DIELS-ALDER SUBSTRATES IN DESYMMETRIZATION REACTIONS

by Henry James Seaman Bush

The synthesis of 1,3,6,8-tetraene systems was undertaken, with the aim of preparing suitable substrates for the study of a desymmetrization process using the intramolecular Diels-Alder reaction.

Secondary alcohol **94**, which contains the 1,3,6,8-tetraene system, was prepared using an organolithium reagent prepared from 1-bromobuta-1,3-diene (**92**). **94** proved highly susceptible to polymerization, and isomerization of the double bond system plagued further reactions. Tertiary alcohol **114** demonstrated greater stability, and subsequent reactions afforded intramolecular Diels-Alder substrate **106**.

1,4-Dialkyne **144** was found to be accessible in good yield via ring opening of terminal epoxide **145**. Attempts to use this to prepare 1,3,6,8-tetraene systems were impeded by the extreme sensitivity of **144** to base, and further reaction generally resulted in π-bond isomerization. Removal of silyl acetylene protecting groups under acidic conditions gave promising results, but in an impractically long timescale.

Wittig reactions on 1,3-dicarbonyl compounds were tested for the synthesis of 1,3,6,8-tetraene systems, as were one-pot oxidation followed by Wittig reactions from 1,3-diols. Neither of these produced the desired polyene system.

Table of Contents

For mum and dad

For providing more love, support, and sympathy than one person could possibly deserve or ever need.

Acknowledgements

Thank you to my supervisor, Bruno Linclau. His knowledge is phenomenal, and his patience commendable. He has been continually supportive through very difficult times.

A special thank you also to Martin Grossel. I have found his approachability and experience in academia indispensable: he has proven invaluable as a source of wisdom and counsel. Thank you also to his group for being consistently helpful and friendly.

At Southampton, we are blessed with outstanding spectroscopic facilities and staff. John and Julie in Mass Spec, and Joan and Neil in NMR are all very forgiving of everyone who takes what they do for granted. On behalf of all the students in the department, thank you.

Yoann Pelois carried out some of our Wittig reaction investigations, and taught me the French for "bless you"; thank you for both.

I could not have got this far without the Linclau group. When I started, the group consisted only of Phil and myself: remember all those Christmases? Then we got the "new guys" in: Martin, the self-confessed "king of smart casual", and Rob, whose sense of humour turned out to be scarily similar to mine. Rob is also, in my opinion, the most dependable person in the group: every team needs a member like him. The next year we got the "new guys" in: Helen and Benedetta, our first girls, both fitted in so well so quickly. Finally, this year we got the "new guys" in: Nadia, who has taken over this project and the lab role of producing litres of black gunk, and finally the incomparable Jimbob, who has been around forever. The facial hair growing contests, the "dancing" to 'Harvey the Wonder Hamster'... life just won't be the same without such a weird group of people around eight hours a day.

In my first two years here, we slowly ousted John Mellor's group from his lab, and I must thank them: John for his generous donations of equipment (most knowingly, some less so), and his group for imparting their experience of research when we didn't have a clue.

I have thoroughly enjoyed my time at Southampton, and that is down in the most part to my friends. In chronological order: Jenny, Jenny, Marianne, Pete and Erica, plus too many others to mention. All my friends have always been there for me, and have made my time here the happiest of my life so far.

Finally, to Helen. For the past nine months you have lit up my life, and helped me through some awful times. One day maybe I'll be the proper boyfriend that you so richly deserve. Until then... well, we could visit Holmfirth.

Il n'y a pour l'homme que trois événements: naître, vivre et mourir. Il ne se sent pas naître, il souffre à mourir, et il oublie de vivre.

Jean de la Bruyère

Abbreviations

The following abbreviations are used in this thesis:

18-crown-6	–	1,4,7,10,13,16-hexaoxacycloctadecane
Ac	–	Acyl
Ar	–	Aryl
CIMS	–	Chemical Ionization Mass Spectrometry
DBU	–	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	–	Dicyclohexylcarbodiimide
DMAP	–	Dimethylaminopyridine
DMSO	–	Dimethylsulfoxide
EIMS	–	Electron Ionization Mass Spectrometry
HMPA	–	Hexamethylphosphoramide
HOMO	–	Highest Occupied Molecular Orbital
HPLC	–	High Performance Liquid Chromatography
HRMS	–	High-Resolution Mass Spectrometry
LDA	–	Lithium diisopropylamide
LUMO	–	Lowest Unoccupied Molecular Orbital
Ms	–	Mesyl, methanesulfonyl
NaHMDS	–	Sodium hexamethyldisilazide
NMR	–	Nuclear Magnetic Resonance
PPTS	–	Pyridinium *p*-toluenesulfonate
TBAF	–	Tetrabutylammonium fluoride
TBS	–	*tert*-Butyldimethylsilyl
TFA	–	Trifluoroacetic acid
THF	–	Tetrahydrofuran
THP	–	Tetrahydropyranyl
TLC	–	Thin Layer Chromatography
TMS	–	Trimethylsilyl
Tris	–	Triisopropylbenzenesulfonyl
Ts	–	Tosyl, *p*-toluenesulfonyl

Chapter One

Introduction

Chapter 1: Introduction

1.1 The Diels-Alder Reaction

The Diels-Alder reaction is one of the most famous, useful, and adaptable carbon–carbon bond forming reactions in modern organic synthesis.[1] The formation of two carbon–carbon σ bonds from two carbon–carbon π bonds acts as a strong driving force for the reaction; as a result, Diels-Alder reactions are generally kinetic, irreversible reactions.

The Diels-Alder reaction is a [4+2] cycloaddition that proceeds readily under thermal conditions. Other cycloadditions, such as [2+2] cycloadditions, have been shown not to proceed under thermal conditions. This phenomenon can be explained using frontier molecular orbital (FMO) theory (Figure 1).[2]

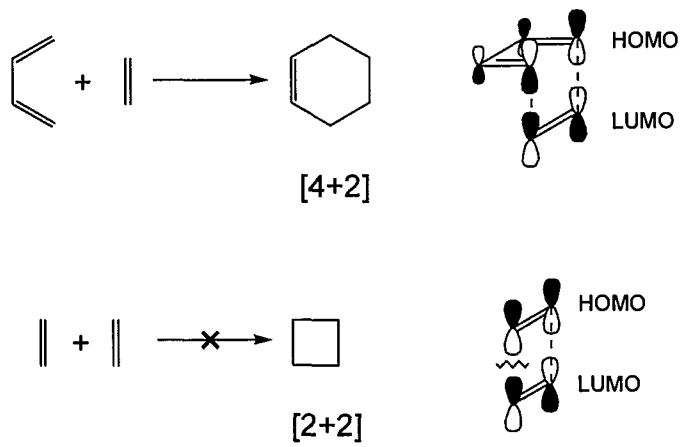


Figure 1

The interacting orbitals are shown on the right of the diagram, with the two colours reflecting the two different signs. The size of the orbital depicts the size of the orbital coefficient, which is a measure of the electron population around an atom.
In the [4+2] reaction, there is a bonding overlap on both of the pairs of reacting centres, resulting in a symmetry allowed reaction. In the symmetry forbidden [2+2] reaction, however, there is one bonding overlap and one anti-bonding.

In the majority of Diels-Alder reactions, the diene is electron rich and the dienophile is electron deficient. This results in the HOMO of the diene and the LUMO of the dienophile being close in energy, which in turn means that these two orbitals interact in the reaction

(as illustrated in Figure 1). The dienophile is rendered electron deficient by the addition of an electron withdrawing substituent, such as a carbonyl or a nitrile.

It is possible to use an electron *deficient* diene in combination with an electron *rich* dienophile, though the number of precedents in the literature is substantially lower. These reactions are known as 'inverse electron demand' Diels-Alder reactions, and FMO theory accounts for them as shown in Figure 2.[2]

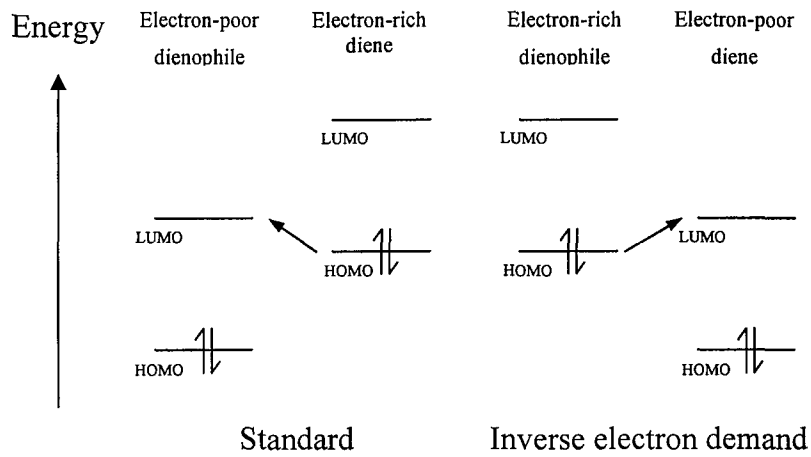


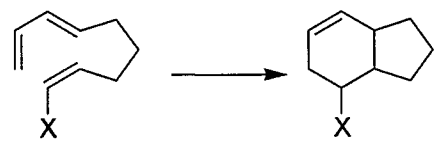
Figure 2

In a "standard" Diels-Alder reaction (left), the LUMO of the dienophile and the HOMO of the diene interact to form the two new σ bonds. In an inverse electron demand reaction (right), the LUMO of the dienophile and the HOMO of the diene are not close enough in energy to interact in this way, but the *LUMO* of the diene and the *HOMO* of the dienophile *are* sufficiently close: the result is that the reaction proceeds.

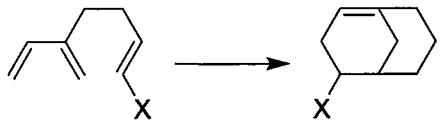
The intramolecular version of the Diels-Alder reaction[3] has a number of distinct advantages over the intermolecular version. As with all intramolecular reactions, the activation entropy is much less negative than in the intermolecular version, resulting in reactions proceeding under considerably milder conditions. Using activated dienes, activated dienophiles or both, intramolecular Diels-Alder reactions have been shown to proceed at and even below room temperature.

There are two types of intramolecular Diels-Alder reactions, known as type I and type II (Figure 3). In a type I reaction the dienophile is attached to the end of the diene, and in a

type II reaction it is attached at one of the internal positions.[4] In this thesis, discussion will focus solely on type I intramolecular Diels-Alder reactions.



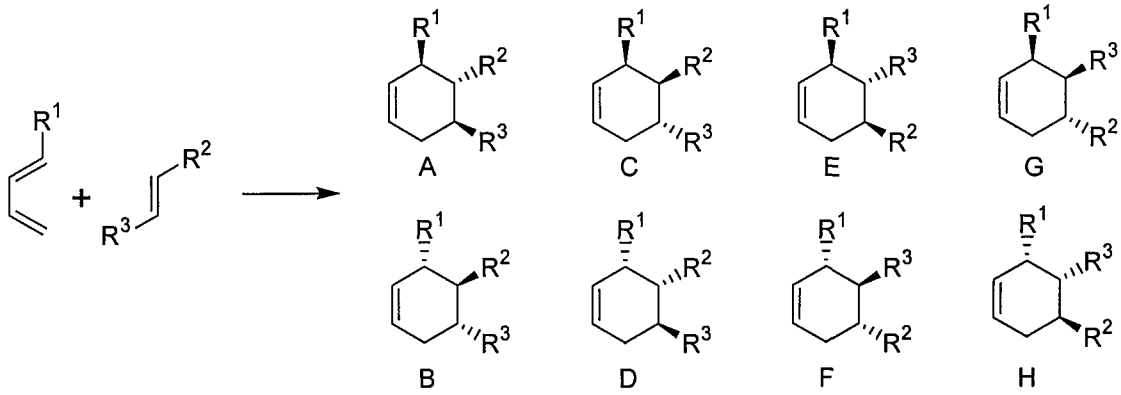
A Type I Intramolecular Diels-Alder Reaction



A Type II Intramolecular Diels-Alder Reaction

Figure 3

One disadvantage of the Diels-Alder reaction is the number of compounds that it can produce: several different types of selectivity in the hypothetical reaction shown in Scheme 1 result in different amounts of compounds A to H. These are regioselectivity (e.g. A vs. E), diastereoselectivity (e.g. A vs. C) and enantioselectivity (e.g. A vs. B).



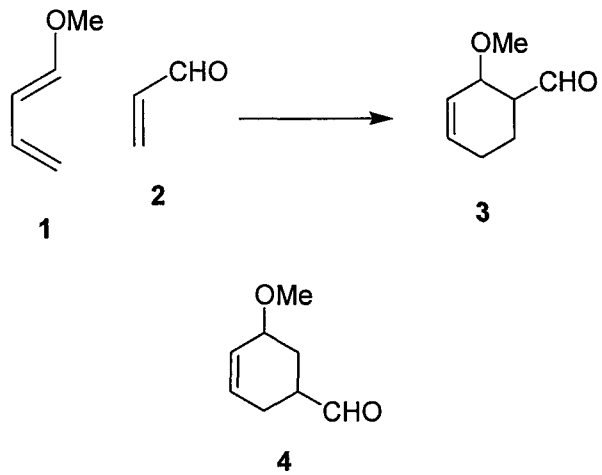
Scheme 1

1.1.1 Regioselectivity in the Diels-Alder Reaction

1.1.1.1 The Intermolecular Reaction

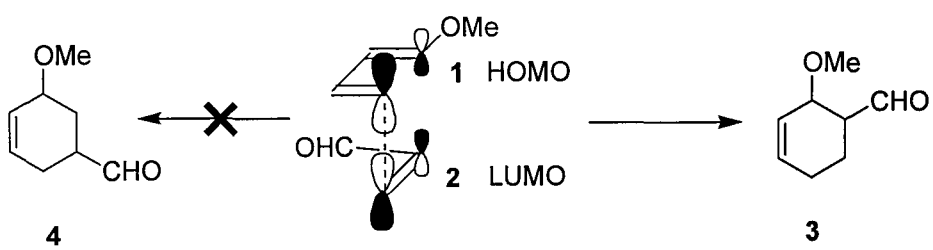
The problem of regioisomerism stems from the fact that the dienophile can attack the diene in one of two orientations, either with R^1 and R^2 adjacent, or with R^1 and R^3 adjacent (to form either **A** or **E**, Scheme 1). The proportions of each regioisomer produced depend upon the substituents present on both reactants. An example is shown in Scheme 2: when

diene **1** is reacted with alkene **2**, the reaction produces solely isomer **3**.[2] None of the meta-substituted product **4** was isolated.



Scheme 2

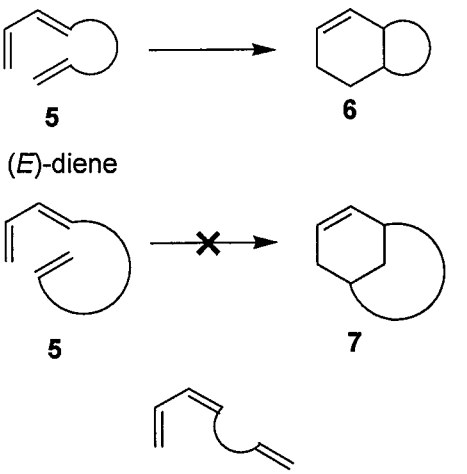
Scheme 1 depicts an explanation of this regioselectivity, using FMO theory. The relevant atomic orbital coefficients have been indicated in Scheme 3: as mentioned earlier, 'normal' Diels-Alder reactions involve the HOMO of the diene and the LUMO of the dienophile, and these are the orbitals depicted. The strongest interaction (the dotted line) is between the orbital on each molecule with the largest orbital coefficient, and thus the reaction proceeds to 'ortho' product **3** as observed.



Scheme 3

1.1.1.2 The Intramolecular Reaction

The intramolecular Diels-Alder reaction does not normally suffer from the regioselectivity issue that affects the intermolecular reaction. The length of the tether that connects the two reacting centres constrains attack of the dienophile (Scheme 4); the reaction of (E)-dienes (**5**) form solely fused products **6**, and not bridged products **7**.[5]



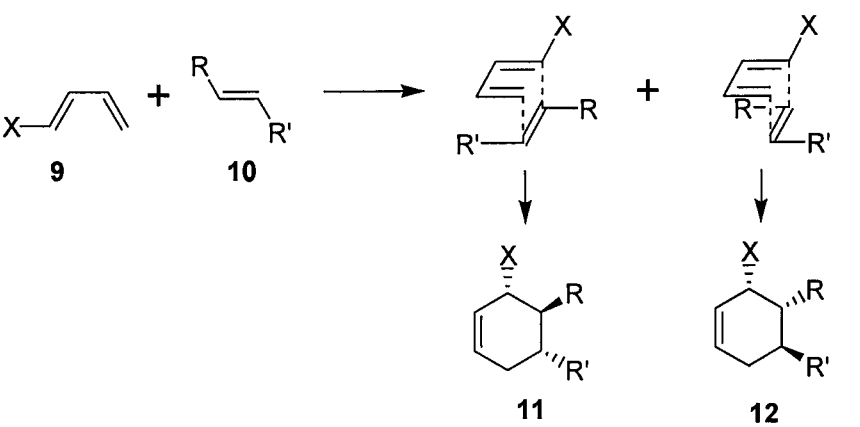
Scheme 4

There are examples in the literature in which the bridged product is formed: if a (Z)-diene such as **8** is used,[6] or if the tether connecting the two reacting centres is very long (greater than ten atoms),[7] the reaction is more likely to form the bridged product. The proportion of reactions that form bridged products is, however, still a tiny minority of those that have been reported.

1.1.2 Diastereoselectivity in the Diels-Alder Reaction

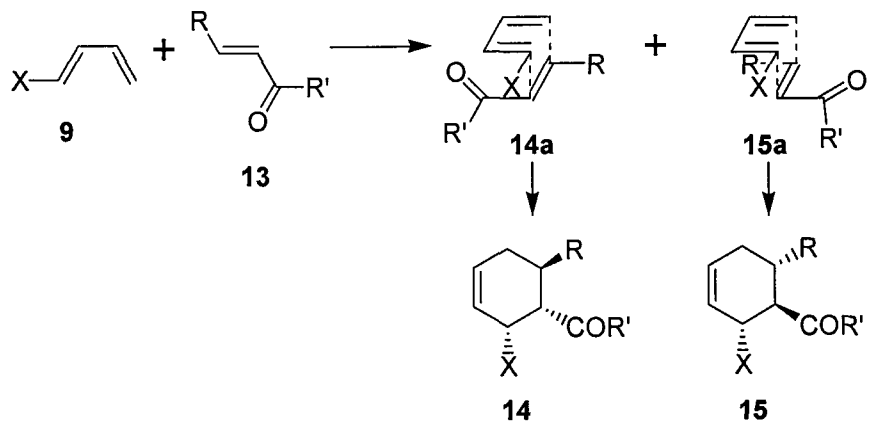
1.1.2.1 The Intermolecular Reaction

Scheme 5 denotes two geometrical isomers that can be formed from an intermolecular Diels-Alder reaction between **9** and **10**: one with X and R *anti* (as in compound **11**), and one with X and R *syn* (compound **12**).



Scheme 5

It is possible to use steric hindrance to induce selectivity in the synthesis of compounds **11** and **12**, but the use of an α,β-unsaturated carbonyl as the dienophile (**13**, Scheme 6) tends to be more effective, and is therefore more commonly used.



Scheme 6

In this situation, compound **14** is formed preferentially over compound **15**. This is known as the Alder endo effect, and it can again be explained by referral to FMO theory (Figure 4).[2]

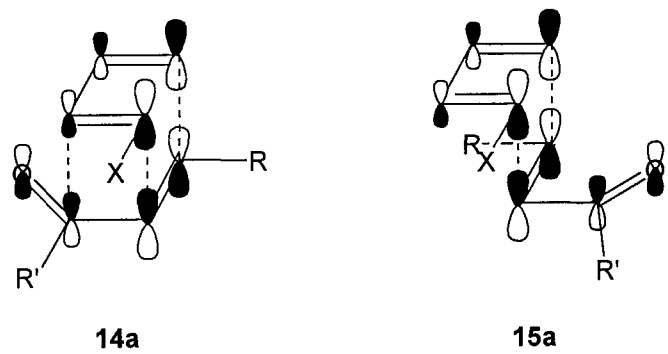
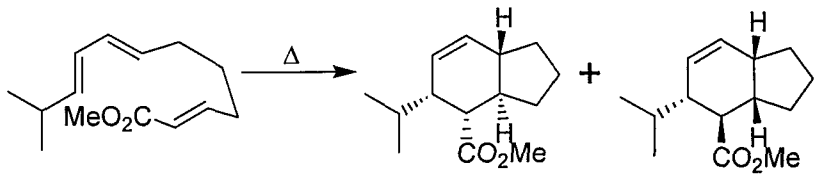


Figure 4

There is an additional favourable orbital overlap in transition state **14a** between the π-orbital in the diene and the π-orbital of the carbonyl. This results in a stabilization of endo transition state **14a**, and thus the reaction preferentially forms transition state **14a**, which in turn forms compound **14**. This type of effect is known as a *secondary orbital effect*, as it does not involve any of the reacting centres directly.

1.1.2.2 The Intramolecular Reaction

This diastereoselectivity is also present in the intramolecular reaction, and the Alder endo rule can be implemented in the same way. This is demonstrated by the example in Scheme 7, in which reaction of **16** forms **17** preferentially over **18**.[8]

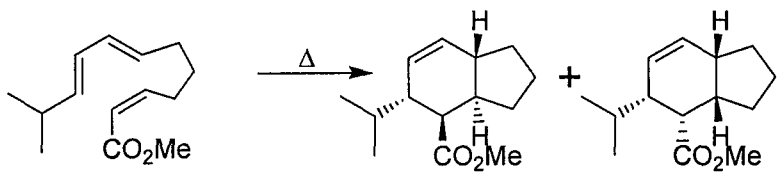


16 **17** **18**

72:28

Scheme 7

Though this reaction does outwardly follow the Alder endo rule, the selectivity is surprisingly low. In fact, there are many reactions that completely disobey the endo rule: one example is the isomer of ester **16** with the dienophile in the Z-form as demonstrated in Scheme 8.



19 **20** **21**

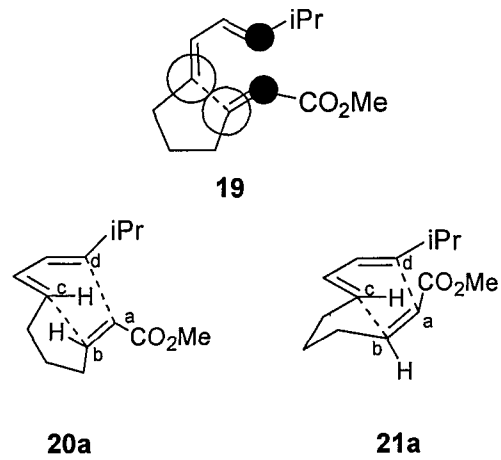
67:33

Scheme 8

According to the endo rule, ester **19** ought to give cis-hydrindene **21**, but the predominant form is trans-hydrindene **20**. It is thought that this and other reactions do not follow the endo rule due to asynchronous bond formation[3c]: though the Diels-Alder reaction forms both bonds in a concerted fashion, they are often formed at significantly different rates. In an intramolecular Diels-Alder reaction, with a tether connecting the two reacting centres that is less than four atoms long, it has been calculated that synchronous bond formation is unlikely, due to the restrictive nature of the tether.[9]

Referring once again to FMO theory, the most advanced bond formation in a concerted reaction such as this will be between the termini of the diene and dienophile that have the

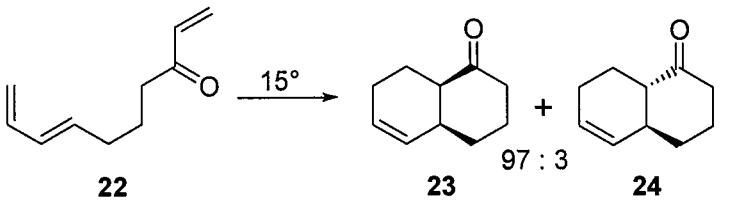
highest orbital coefficients. In ester **19** (Scheme 9, with orbital coefficients shown in plan view), the coefficient at C_b is higher than at C_a, and the coefficient at C_c is higher than at C_d. Therefore, the bond formation between C_b and C_c (indicated with a dotted line) is considerably more advanced than between C_a and C_d.



Scheme 9

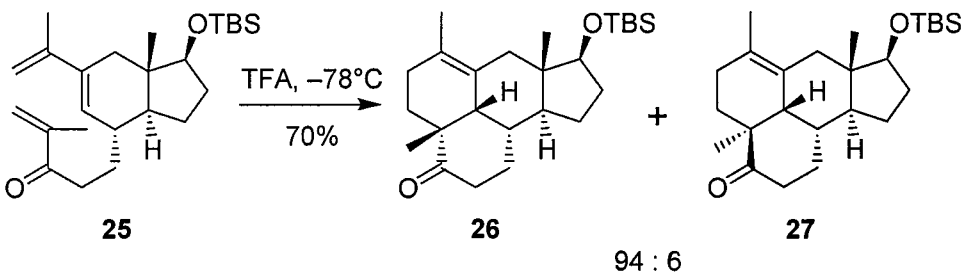
Transition state **21a** shows that to form cis-hydrindene **21** (following the endo rule), the two carbon chains on C_b and C_c in the cyclopentane ring would have to be eclipsed, which is not the case in **20a**. The energy of the staggered configuration of transition state **20a** is likely to be considerably lower than that of the eclipsed transition state **21a**, and thus in transition state **20a** the more advanced bond forms more easily, resulting in compound **20** being preferentially formed.

In general, the endo rule has proved unreliable as a way of predicting the outcome of intramolecular Diels-Alder reactions, particularly those with a three-atom tether. Many ways of improving selectivity for one particular isomer have been investigated.
One example of such a method is the use of internal carbonyls (i.e., carbonyls that form part of the tether): ketone **22** was found to produce cis isomer **23** and trans isomer **24** in 97:3 ratio (Scheme 10).[5]



Scheme 10

The use of a Lewis-acid catalyst (which is discussed in more detail later) can dramatically affect the diastereoselectivity of a Diels-Alder reaction. This can be useful in both inter- and intramolecular forms of the reaction, and tends to be employed regularly in the intramolecular form. An example is shown in Scheme 11: **25** reacts in the presence of TFA to give **26** and **27** in 94:6 ratio.[10] The equivalent ratio when the reaction is carried out without catalyst at 70°C is 60:40.



Scheme 11

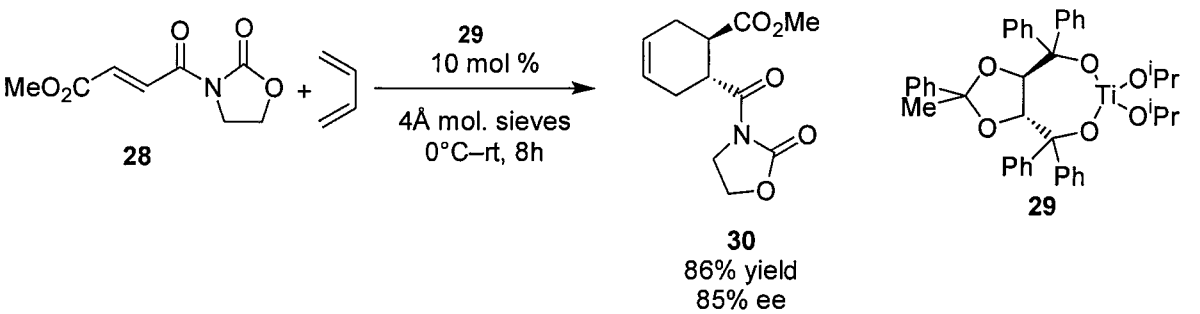
1.1.3 Enantioselectivity in the Diels-Alder Reaction

There remains one selectivity issue in the reaction to be addressed, that of enantio-selectivity: the dienophile can approach the diene from either face, resulting in the two enantiomeric forms of the desired product.

In order to impose enantioselectivity in a reaction between achiral compounds, a chiral reagent system must be used. The literature has demonstrated two methods for introducing chirality into the Diels-Alder reaction: one is to use the chirality of a molecule other than the substrates (i.e. a *chiral catalyst*), and the other is to utilize the remote chirality of one of the reactants, often by way of a *chiral auxiliary.*

1.1.3.1 The Intermolecular Reaction

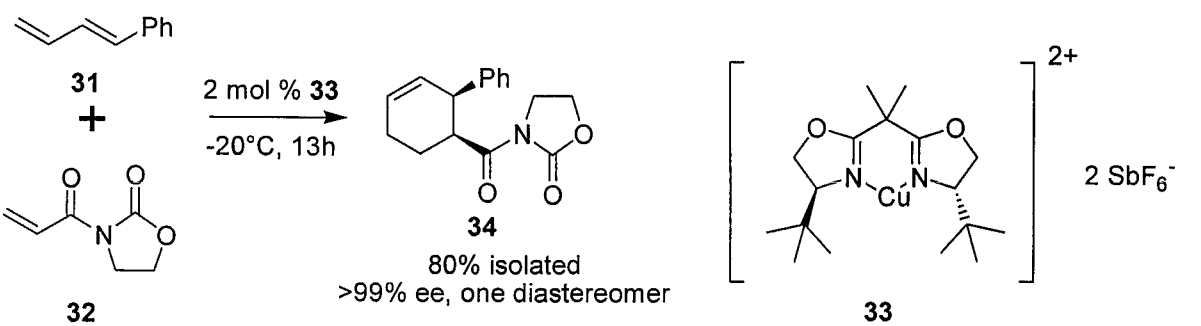
An example of a particularly effective chiral catalyst for the Diels-Alder reaction can be drawn from the TADDOL series of catalysts. The first diol used to prepare a TADDOL group catalyst was synthesized in 1982,[11] and over the subsequent twenty years, this compound and its many analogues have been used to catalyse two major reaction types: nucleophilic additions and Lewis acid catalysed transformations.[12] In 1988, Narasaka and co-workers showed that the TADDOL series of catalysts could introduce enantioselectivity into the Diels-Alder reaction, as illustrated in Scheme 12.[13]



Scheme 12

In this reaction, the TADDOL catalyst **29** was introduced to the reaction between **28** and butadiene, giving **30** in 86% yield with an enantiomeric excess of 85%.

Another example of a chiral catalyst for the Diels-Alder reaction has been reported recently by Evans and co-workers.[14] Their first reported synthesis of copper (II) complex **33** was in 1993, and lately investigations have been undertaken into its use as a catalyst in the Diels-Alder reactions (Scheme 13).



Scheme 13

It was discovered that the presence of 2 mol % of **33** in the reaction of diene **31** with imide **32** at –20°C for 13 hours gave 80% of compound **34** in very high enantiomeric purity (>99% ee) .

Figure 5 is a three-dimensional representation of dienophile **32** chelated to catalyst **33**, and it demonstrates the reason that **33** works so well as a catalyst. The tetrahedral form of the copper results in one of the two tertiary butyl groups being placed directly above (on the Si face of) the dienophile (on the left of the image, with the oxazolidinone behind it), resulting in almost exclusive attack of the diene via the Re face.

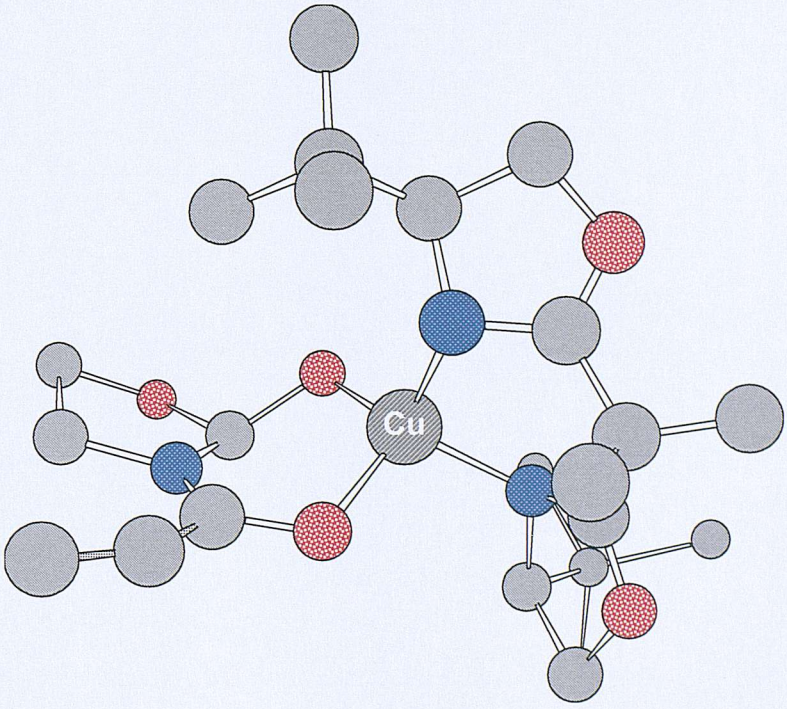
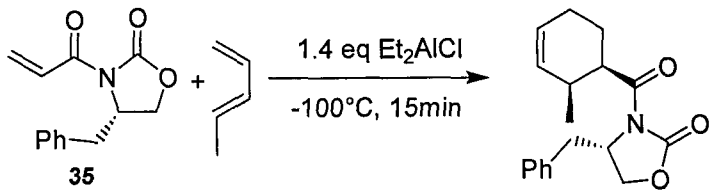


Figure 5

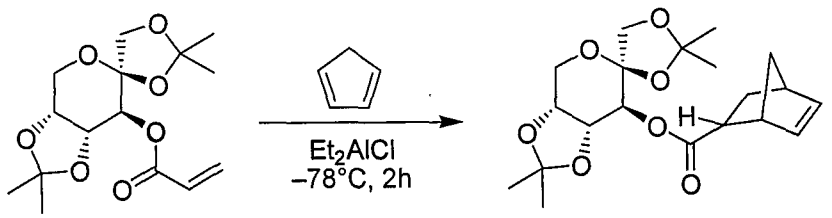
The alternative method for selectively producing a single enantiomer from the Diels-Alder reaction is to use chiral reactants: with knowledge of the Diels-Alder transition state, a reaction can be altered to form preferentially a single enantiomer. Chiral auxiliaries[15] are the most common way to execute this selectivity, and a frequently used example is Evans' chiral auxiliary. Evans' auxiliary was first proposed for use in chiral enolate-based bond construction reactions,[16] but its use was reported in a Diels-Alder reaction in 1984.[17] The example shown in Scheme 14 is a typical example, in which reaction of **35** with 1,3-

pentadiene went in 84% yield, with excellent selectivity (>99% de).[18] Note that for this selectivity a very short reaction time was necessary.



Scheme 14

Another literature example of a chiral auxiliary is shown in Scheme 15: compound **37** was reacted with cyclopentadiene to give **38**.[19] The yield and selectivity in this reaction are not as impressive, but the auxiliary used is easily accessible from fructose, thus making it relatively inexpensive.



Scheme 15

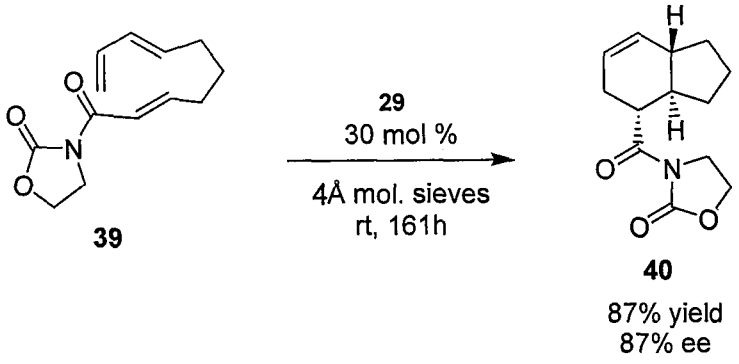
It is worth remembering at this point that when a chiral auxiliary is introduced, a Lewis-acid catalyst must still be used.

1.1.3.2 The Intramolecular Reaction

The methods that have been used to induce enantioselectivity in the intermolecular version of the reaction have also been used in the intramolecular form, but less extensively. One extra restriction exists in the intramolecular reaction: if substituents are present on the

tether that connects the two reacting centres, the substrate becomes chiral.* Thus, the reaction becomes diastereoselective rather than enantioselective, and the reaction is likely to be directed substantially by this stereocentre: this must be taken into account when planning reactions.

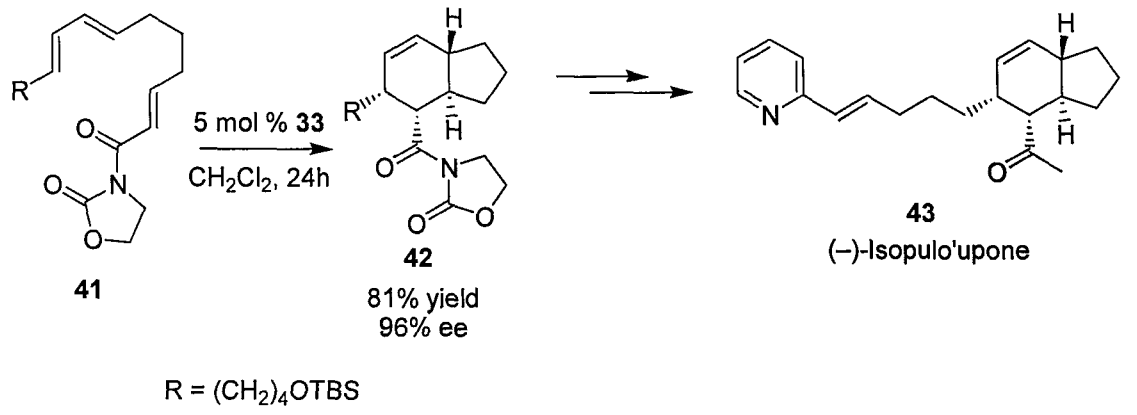
Narasaka and co-workers investigated the use of the previously described TADDOL series of catalysts in the intramolecular Diels-Alder reaction of such substrates as **39** (Scheme 16).[20]



Scheme 16

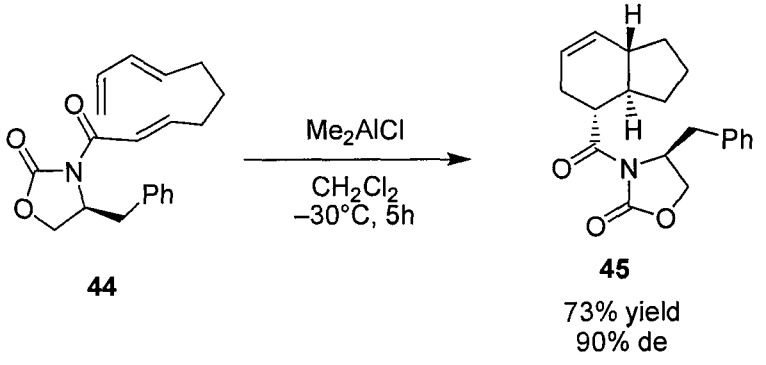
They discovered that using 30 mol % of catalyst **29** they could get a yield of 87% and an optical purity of 87%. For other substrates, they found that only 10 mol % of titanium catalyst **29** was required to give even higher optical purity (up to 91%).
Evans and co-workers used copper catalyst **33** (*supra*) to gain equally impressive results.[21] They employed it in their synthesis of (–)-isopulo'upone (**43**, Scheme 17) from intramolecular Diels-Alder substrate **41**, and found that using 5 mol % of catalyst **33** (Scheme 13, *supra*), they achieved **42** in 81% yield and 96% ee in 24 hours at room temperature.

* There are substituents that do not result in a chiral compound: for example, the use of an acetal or a ketone.



Scheme 17

As an alternative to chiral catalysts, chiral auxiliaries can be used in intramolecular reactions. The first reported example of an Evans' type auxiliary being used in an intramolecular Diels-Alder reaction was in 1984, and this is depicted in Scheme 18.[22]

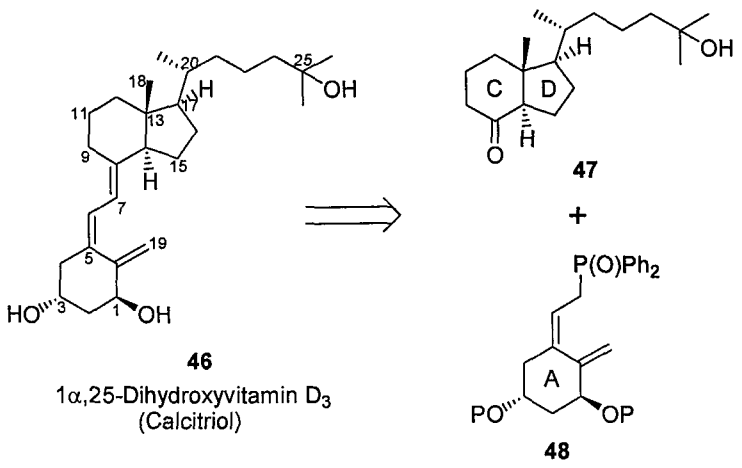


Scheme 18

Compound **44** was found to give **45** in 73% yield. This was the first reaction of its kind, and the selectivity is very good; the reaction gave an optical purity of 90%.

1.2 The Synthesis of the Steroid CD-Ring Fragment via an Intramolecular Diels-Alder Approach

The preparation of seco-B steroids (such as Calcitriol, **46**, illustrated in Scheme 19) generally involves preparation of the CD-ring (**47**) and A-ring[23] (**48**) fragments separately, followed by connection of the two.[24] The CD-ring fragment has a hydrindane ring system as its basic form, and this makes it an ideal candidate for preparation via an intramolecular Diels-Alder reaction.



Scheme 19

1.2.1 An Introduction to the Synthesis of Hydrindane Systems via an Intramolecular Diels-Alder Reaction

Hydrindane (**49** and **50**) is the trivial name given to bicyclo[4.3.0]nonane, and compounds that contain the same basic ring system.[25] A hydrindene is the name given to any hydrindane that contains a double bond, but in this thesis it will refer to a hydrindene with the double bond in the 4,5 position (**51** and **52**).

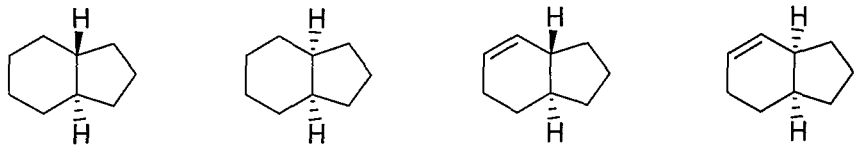
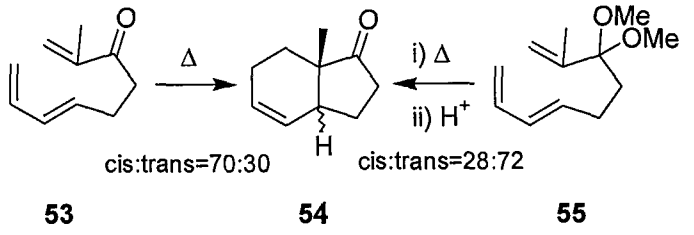


Figure 6

The intramolecular Diels-Alder reaction lends itself particularly well to the preparation of hydrindene systems, and indirectly therefore the preparation of hydrindane systems.

One of the first problems to be overcome when tackling a hydrindene synthesis is ensuring that the correct isomer is formed: the trans form (**51**) or the cis form (**52**). As intramolecular Diels-Alder reactions tend to occur towards the end of syntheses, it is very important to be able to predict the stereochemical outcome. The cis-hydrindene is the more

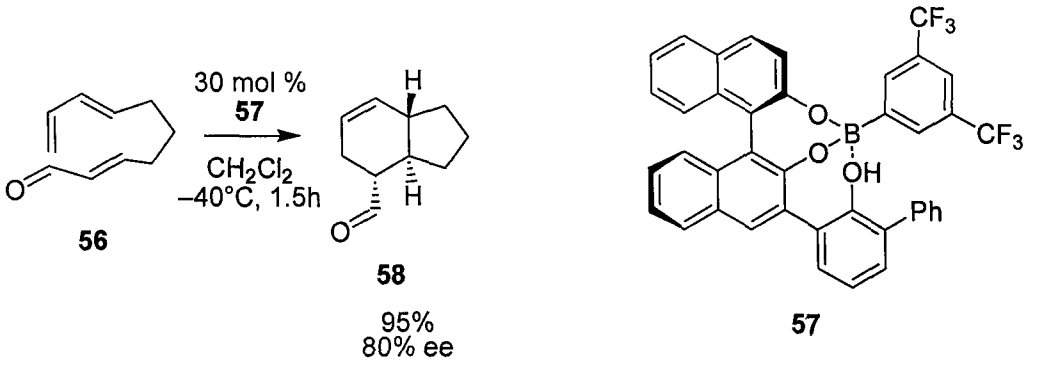
thermodynamically stable, but as stated earlier the Diels-Alder reaction generally favours kinetic products. A great deal of research has gone into understanding the factors that affect the kinetic cis / trans selectivity, but there are a huge number of factors involved. An example of the unpredictability of the reaction is shown in Scheme 20. Triene **53** was found to produce predominantly the cis isomer of hydrindane **54**, whilst compound **55,** the acetal derivative of **53**, afforded mainly the trans product.[25]



Scheme 20

As stated earlier however, there are methods by which this stereochemical outcome can be influenced. The factor that governs which isomer is produced is the orientation of attack of the dienophile, and the determination of this orientation was discussed earlier in section 1.1.2 above. As a brief summary, the Alder endo rule will generally allow the orientation of attack to be determined, but asynchronous bond formation amongst other factors can result in an unexpected outcome. It is also worthy of note, at this point, that in order to form any cis hydrindene from the Diels-Alder reaction, the reaction must proceed via the less favourable eclipsed transition state (**20a**, Scheme 9, *supra*).

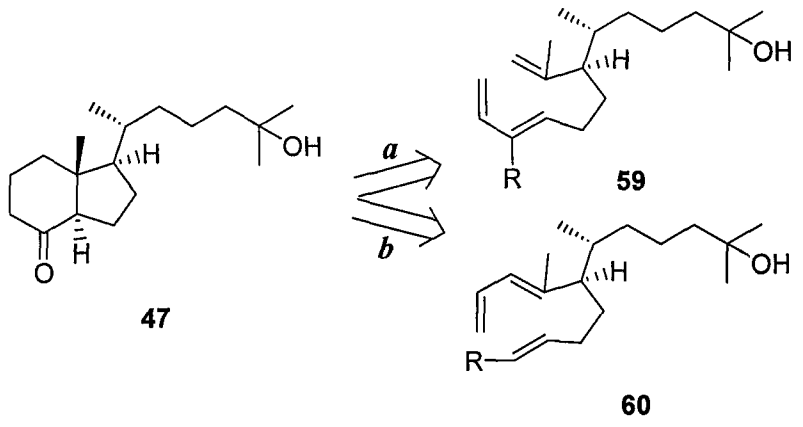
There are numerous examples of enantioselective intramolecular Diels-Alder reactions to produce hydrindene systems, some of which have already been discussed. The example shown in Scheme 21 was the first time that Brønsted acid-assisted chiral Lewis acid catalysts were used to catalyse an intramolecular Diels-Alder reaction:[26] aldehyde **56** was found to give **58** in 95% yield and 80% ee in the presence of 30 mol % of **57**. This is another example of a particular catalyst, known to affect different reaction types, being introduced to the intramolecular Diels-Alder reaction with impressive results.



Scheme 21

1.2.2 Examples of the Synthesis of Steroid CD-Ring Fragments via an Intramolecular Diels-Alder Reaction

Since the intramolecular Diels-Alder reaction is regularly used to prepare hydrindene systems, it has frequently been used in the preparation of steroids: for example, several syntheses of vitamin D related compounds have been reported using an intramolecular Diels-Alder methodology to form the CD-ring fragment (**47**, Scheme 22).[27]

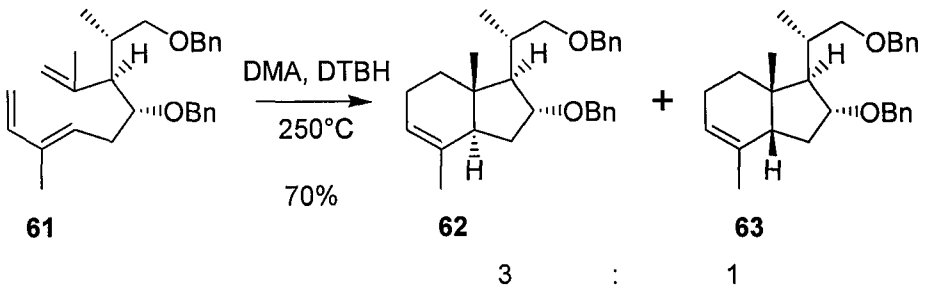


Scheme 22

There are two intramolecular Diels-Alder disconnections that can be used in the preparation of steroids: these are labelled ***a*** and ***b*** in Scheme 22.

The majority of previously reported syntheses have used disconnection ***a***: the example shown in Scheme 23 was reported in 1996 by Taber and co-workers.[28] In this example, the stereochemistry on the side-chain in **61** is fully installed prior to reaction, and the reaction

(which uses dimethylaniline and 2,5-di-*tert*-butylhydroquinone) forms the desired trans-hydrindene **62** in a 3:1 ratio with cis-hydrindene **63**.

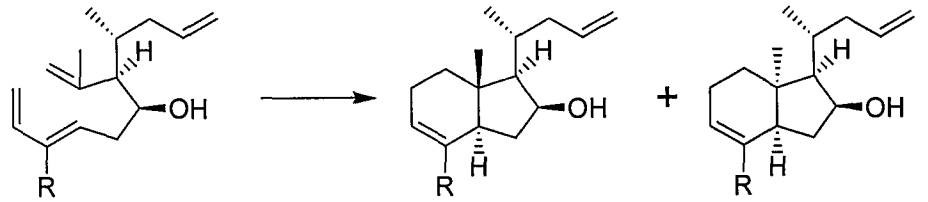


61 **62** **63**

3 : 1

Scheme 23

The example shown in Scheme 24 also uses disconnection ***a***, and demonstrates interesting selectivity issues.[29] With the methyl group installed on the diene, as in **64a**, the reaction proceeds in favour of the trans hydrindene (**65a**) in a 3:1 ratio. When there is no methyl group present on the diene, as in substrate **64b**, the reaction forms a 1:1 mixture of diastereomers **65b** and **66b**. The inference is that a substituent at this position of the diene results in preferential formation of the trans form.



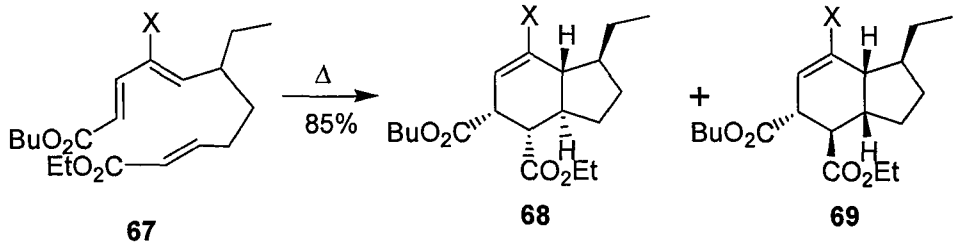
64 **65** **66**

a: R = CH_3 3 : 1

b: R = H 1 : 1

Scheme 24

Though most syntheses have used disconnection ***a***, there are several examples that use disconnection ***b***. One example of a synthesis that uses disconnection ***b*** is shown in Scheme 25.[30] This example again demonstrates the dramatic effect that simple substituents can have on the intramolecular Diels-Alder reaction. With no substituent at the 2-position of the diene in compound **67**, the reaction produces a substantial proportion of cis-hydrindene **69a** alongside the trans-hydrindene **68a**; when a TMS group is added, the trans-hydrindene **68b** is exclusively formed.

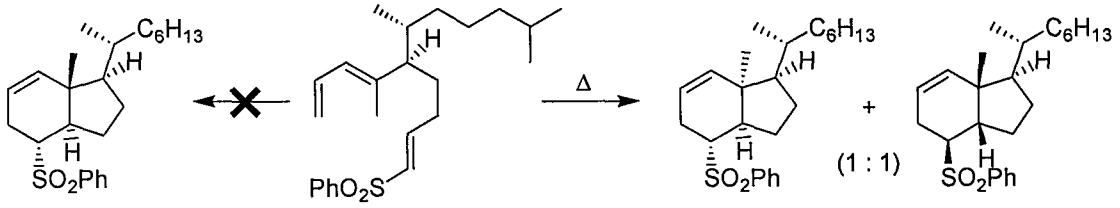


67 68 69

a: X = H	80	:	20
b: X = TMS	100	:	0

Scheme 25

Scheme 26 shows a reaction reported by Craig et al. that also followed disconnection ***b***:[31] using the Alder endo rule, compound **70**was expected to produce trans-hydrindene **71**, but the cis hydrindenes **72** and **73** were formed instead.



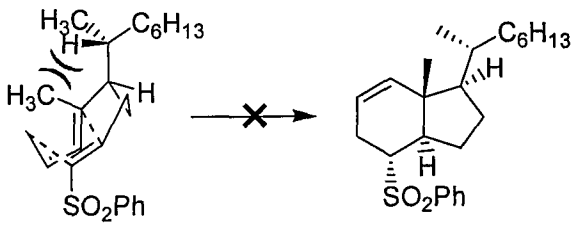
71 70 72 73

Scheme 26

The most likely reason for this departure from the expected behaviour is the sulfone. Sulfones are large groups and in order for the trans hydrindene to have been formed, the sulfone would have to be positioned underneath and close to the diene. The sulfone in compound **70** is also attached to a bulky phenyl group: the combination of the sulfone and the phenyl ring result in a large steric effect. This effect forces the reaction to proceed via the exo transition state, and consequently the formation of cis hydrindenes **72** and **73** is much more likely than trans hydrindene **71**. A carbonyl, as well as being planar and considerably smaller, would demonstrate the favourable orbital overlap with the diene that was discussed previously: it is unlikely that any such effect is present with a sulfone.

The transition state required to give the desired product **71**, transition state **71a**, can be seen in Scheme 27; in addition to the sulfone effect described above, it is thought that there

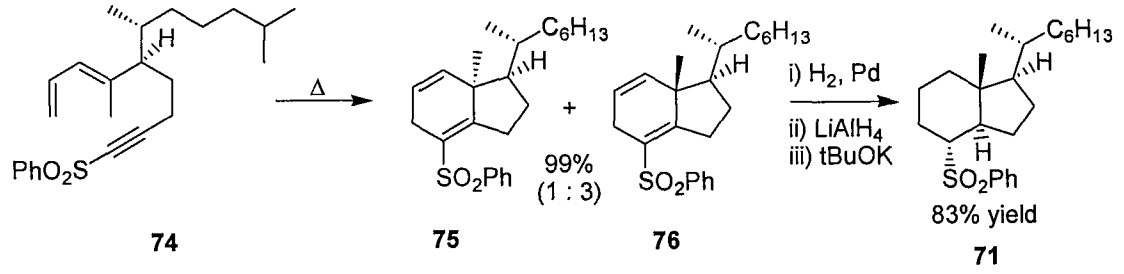
is a steric interaction between the methyl group attached to the diene and the sp^3 centre at the equivalent of steroid C20.



71a **71**

Scheme 27

Craig and co-workers followed up this reaction by preparing an intramolecular Diels-Alder substrate with an alkyne as the dienophile (**74**, Scheme 28). The reaction gave a mixture of cycloadducts **75** and **76** in almost quantitative yield, and upon subjection of diene **76** to reduction conditions, a good yield of the desired trans hydrindane **71** was produced.



74 **75** **76** **71**

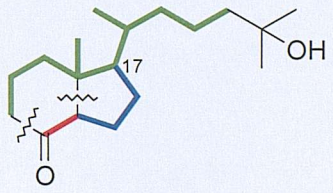
Scheme 28

The major difference between reaction of compound **74** and reaction of compound **70** is that the alkyne dienophile in **74** is linear, and thus no exo / endo attack is possible.

1.3 Aim of the Project: A Novel Intramolecular Diels-Alder Approach towards the Steroid CD-Ring

The aim of this project was to investigate the synthesis of steroid CD-ring fragments via an intramolecular Diels-Alder desymmetrization reaction. A desymmetrization reaction reacts only one of two analogous functionalities in a substrate, and is often used to remove the symmetry present at the end of two-directional syntheses.

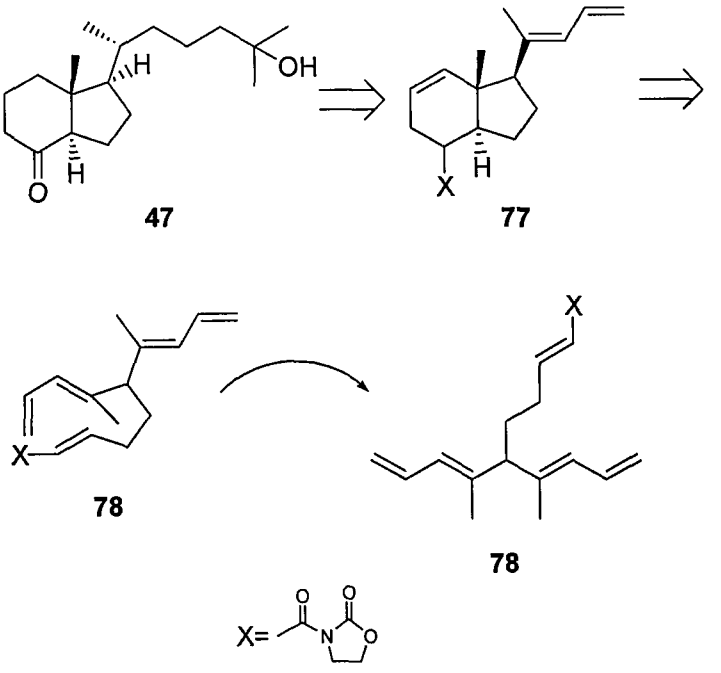
It is not immediately obvious how a steroid CD-ring can be the product of a desymmetrization reaction, but this can be explained with reference to Figure 7 below. Grundmann's ketone (**47**, a frequently used CD-ring synthon[32]) is used as an example, and in order to simplify the diagram, the stereochemistry has not been denoted. The green area clearly indicates two carbon-chains that are symmetrical around C17, and thus the desymmetrization begins to emerge. The section that contains the carbonyl will become the dienophile (marked in red), and the two-carbon tether (marked in blue) will link this to C17.



Grundmann's ketone
47

Figure 7

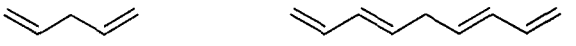
Grundmann's ketone was the target molecule of the proposed synthesis, and the retrosynthetic analysis is depicted in Scheme 29. The intention was to make a 1,3,6,8-tetraene system (as in compound **78**), in order to desymmetrize it by means of an intramolecular Diels-Alder reaction to give hydrindene **77**. Several steps would then take this compound through to Grundmann's ketone (**47**).



Scheme 29

1.3.1 Introduction to Skipped Tetraene Systems

The term "skipped diene" is frequently used to refer to 1,4-diene systems, and in this thesis the term "skipped tetraene" shall also be used to refer to 1,3,6,8-tetraene systems (Figure 8).



skipped diene "skipped tetraene"

Figure 8

The skipped tetraene system (such as that present in **78**) is unstable, due to its unconjugated nature. There have been a number of reports in the past of skipped tetraene systems being prepared, all of them using some sort of stabilising factor. Some examples have included:

- Arranging of the diene moieties around a central ketone (**79**, Figure 9)
- Inclusion of two phenyl groups, one at the terminus of each diene chain (**80**)

79 **80**

Figure 9

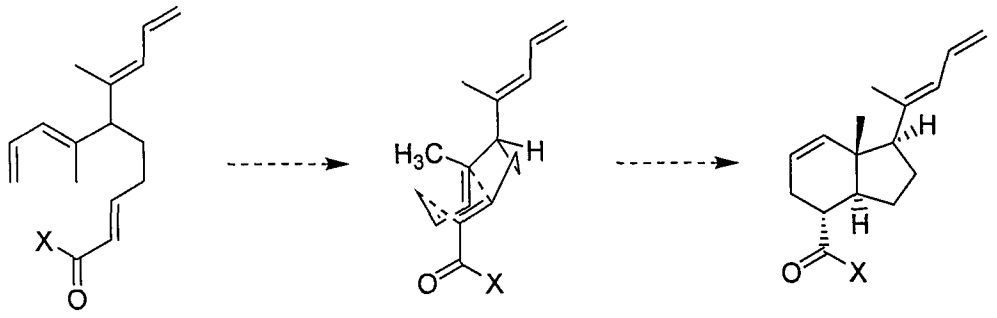
Several reports have used a central ketone in order to improve the stability of these systems: recent examples include both deliberate preparation of the system from 1,4-dialkynes using iridium hydride,[33] and accidental formation of the systems after double nucleophilic attack on dimethyl carbonate.[34]

Investigations into the use of terminal phenyl groups have been continuing for some time: in 1961, a report came out describing a study into these systems with a secondary alcohol at the central position.[35] It was noted that, even with the phenyl groups in place, the systems are unstable to both heat and oxygen. More recent studies have also prepared these systems, again with a central alcohol functionality, but have merely used it as a stepping stone to the fully conjugated 1,3,5,7-tetraene system.[36]

1.4 The Proposed Desymmetrization Reaction

1.4.1 Endo / Exo Selectivity

It is clear at this point that there is a similarity between this investigation (**81–83**, Scheme 30) and the work carried out by Craig et al. (Scheme 26, *supra*). It would appear at first glance that the same steric problems around C17 will be confronted when reacting compound **81** as were encountered when compound **70** was reacted. However, important differences between the two sets of circumstances should dramatically affect the course of the reaction.



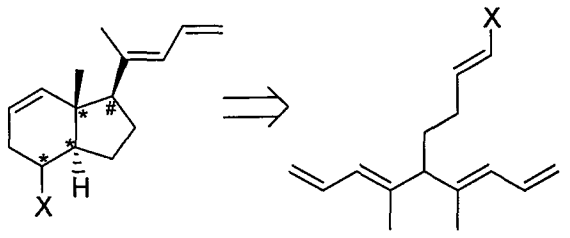
81 **82** **83**

Scheme 30

The most important difference is that compound **81** has a carbonyl group adjacent to the dienophile. Compound **70** from Craig's work contained a tetrahedral sulfone group in this position, which created substantial steric strain when positioned close to the diene.

Another factor in the failure of the key step in Craig's work was the steric hindrance between the side-chain and the substituted diene (**71a**, section 1.2.2, *supra*). In the desymmetrization reaction proposed here, the side chain installed in compound **81** has an sp^2 centre in position C20. This will produce substantially less steric hindrance than the sp^3 centre present in substrate **70**.

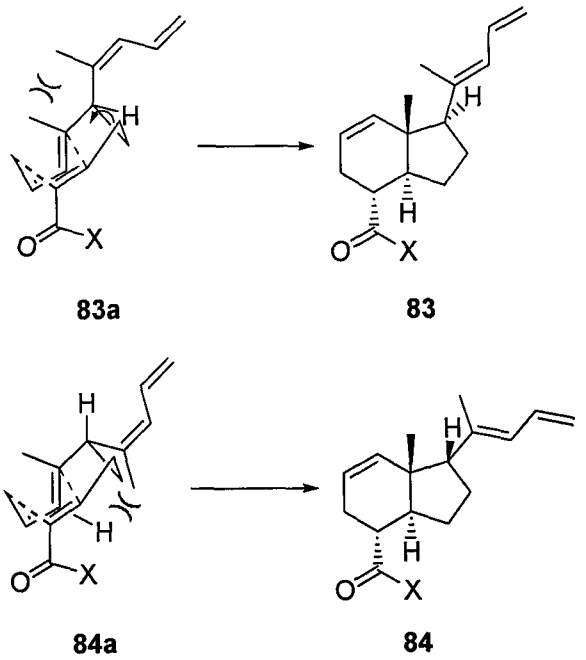
1.4.2 Selectivity at Carbon-17



77 **78**

Scheme 31

An additional selectivity issue is present in our investigation than was present in the investigation carried out by Craig et al. The intramolecular Diels-Alder reaction only directly accounts for three of the four stereocentres that are formed in the desymmetrization reaction (marked * in **77**, Scheme 31): the stereochemistry at the fourth stereocentre, C17 (marked #), depends upon which of the two diene chains reacts with the dienophile. Transition states **83a** and **84a** (Scheme 32) would give compounds **83** and **84**, respectively.



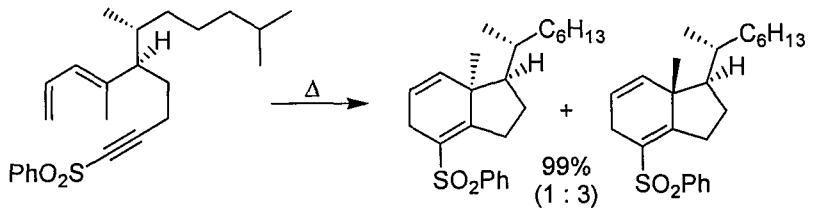
83a **83**

84a **84**

Scheme 32

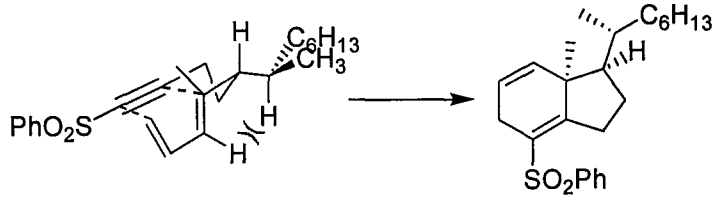
In order to produce the desired compound **83**, transition state **83a** must be formed. In this transition state there is A1,2 strain between the methyl group that is on the reacting diene, and the unreacting diene (depicted). Transition state **84a**, which would produce the undesired isomer **84**, contains A1,3 strain between the diene chain which is not reacting and the hydrogen on the diene chain which is reacting. The product that is formed will depend upon which is the greater out of the A1,3 strain or the A1,2 strain.

There are several literature precedents that suggest that the A1,3 strain would be greater, thus predicting a preference towards the desired product. One example is shown below: as described previously, the work carried out by Craig et al. also involved the use of an alkyne dienophile (**74**, Scheme 33). In this situation, the two different products are formed by the dienophile approaching the diene from opposite faces (transition states **75a** and **76a**, Scheme 34).

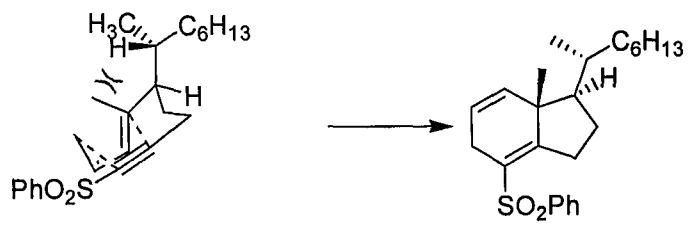


74 **75** **76**

Scheme 33



75a **75**

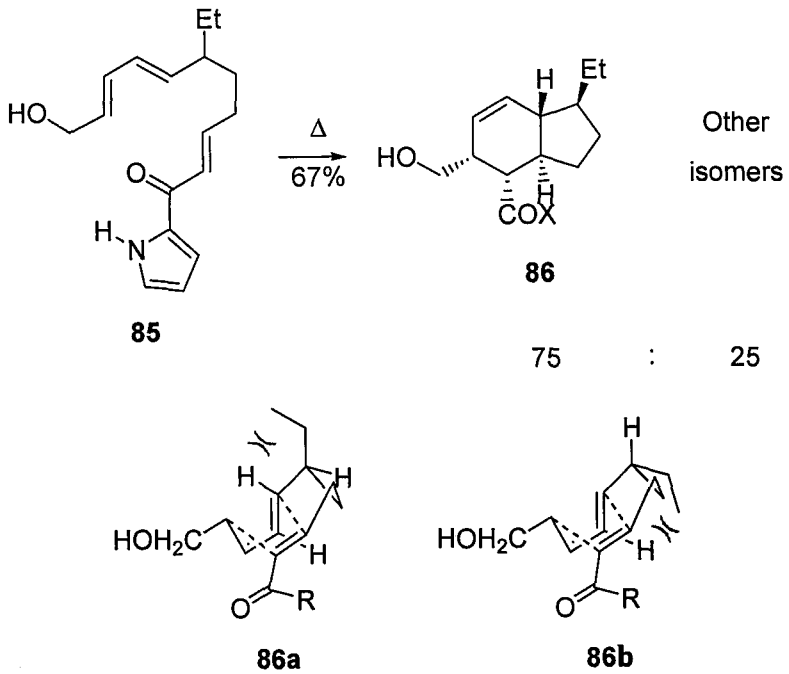


76a **76**

Scheme 34

From the ratios of the products, the preferred transition state is **76a**. This supports our theory that the A1,3 strain (as present in **75a**) will be greater than the A1,2 strain (as present in **76a**).

This is also supported by an example in the literature from Roush and Myers (Scheme 35), which reacts **85** to give predominantly **86**.[37] This particular example is racemic, but the isomer mixture produced indicates that the A1,3 strain indicated in transition state **86b** is significant enough (compared to the A1,2 strain indicated in **86a**) for the reaction to proceed via transition state **86a**.



Scheme 35

1.5 Structure of the Results

The results of this thesis are separated into chapters depending on the proposed method for preparation of the skipped tetraene system.

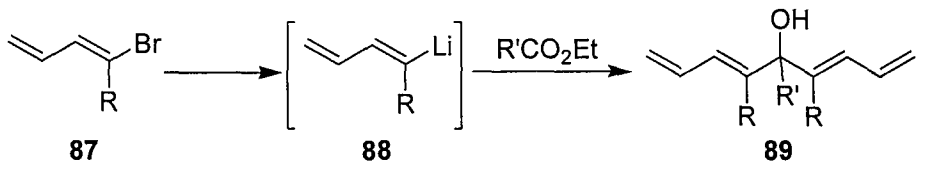
- Chapter two discusses the reaction of butadienyllithium reagents directly with carbonyls
- Chapter three investigates the preparation of skipped (*i.e.* 1,4-) dialkyne systems
- Chapter four examines the use of Wittig methods

Chapter Two

Synthesis of "Skipped Tetraene" Systems via Organolithium Reactions

Chapter 2: Synthesis of "Skipped Tetraene" Systems via Organolithium Reactions

One of the methods that was envisaged to prepare the 1,3,6,8-tetraene system proceeded via an organolithium reaction (Scheme 36).



87 88 89

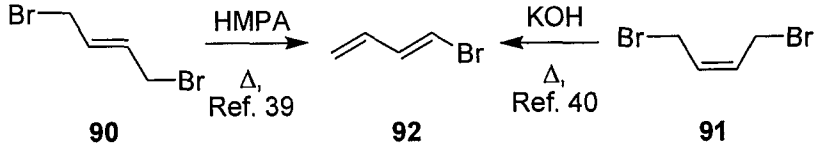
Scheme 36

The proposed reaction would involve a bromine–lithium exchange on a bromodiene (**87**) to form the dienyl anion species **88** followed by reaction with an ester to give the skipped tetraene **89**.

2.1 Preparation of E-1-Bromo-1,3-butadiene

It was decided that work should commence with the unsubstituted diene system (i.e., with R=H in Scheme 36). This decision was taken in order to facilitate rapid attainment of skipped tetraene compounds.

Two key methods for the preparation of the *E*-isomer of 1-bromobutadiene have appeared in the literature. One of these methods uses hexamethylphosphoric triamide to eliminate HBr from *E*-1,4-dibromobutene,[38] and the other uses potassium hydroxide to eliminate HBr from the *Z*-isomer (Scheme 37).[39]

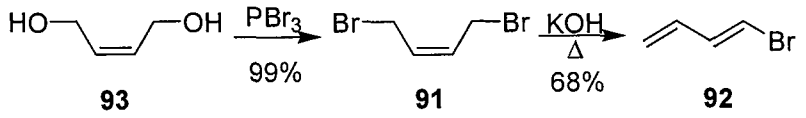


90 92 91

Scheme 37

The approach that used the *E*-isomer of the dibromide was tried first, as the *E*-isomer is the only one of the two that is commercially available.* The paper that was followed was ambiguous as to whether hexamethylphosphor**ic** triamide or hexamethylphosphor**ous** triamide should be used, so reaction of the dibromide with each was attempted at 220°C. In our hands, neither reaction produced any of the desired compound, and thus the potassium hydroxide elimination was attempted.

Use of the *E*-isomer of the dibromide in this reaction would give the undesired *Z*-isomer of the bromobutadiene, and so the *Z*-isomer of the dibromide must be used (Scheme 38).



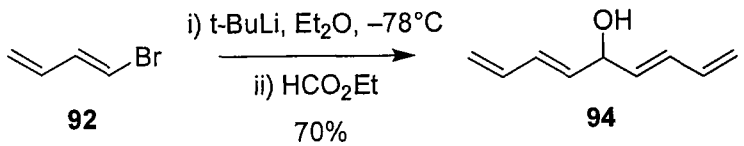
Scheme 38

This was prepared from *Z*-butene-1,4-diol using phosphorus tribromide. The reaction went easily in 99% yield to give dibromide **91** (in a 20:1 *Z*:*E* ratio by ^{1}H NMR), which was noted to be a strong lachrymator. The subsequent elimination was effected using potassium hydroxide as the base, and hexadecane as the solvent. The reaction was heated under reduced pressure, and the unstable bromobutadiene **92** was distilled off *in situ* to give a 68% yield. It was found that the bromobutadiene would remain >95% pure for several weeks if kept dry under nitrogen at –18°C.

2.2 Preparation and Reactions of Secondary Alcohols

2.2.1 Preparation of Secondary Alcohol 94

The first reaction that was undertaken with the bromobutadiene was bromine–lithium exchange using *tert*-butyllithium,[40] followed by the addition of ethyl formate (Scheme 39).



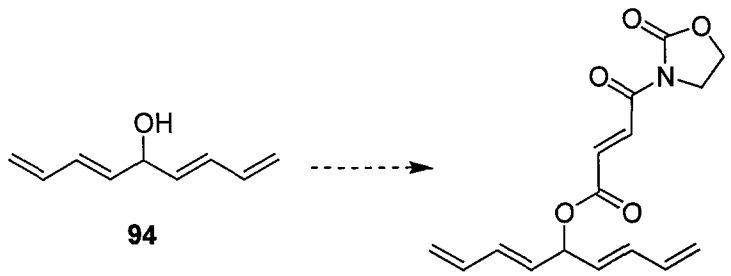
Scheme 39

* trans-1,4-Dibromo-2-butene, 99%, available from Sigma-Aldrich: catalogue number D3,920-7, CAS number [821-06-7]

A solution of ethyl formate in diethyl ether was added to the freshly prepared butadienyllithium, and alcohol **94** was obtained in 70% yield.
Alcohol **94** was also discovered to be unstable: even stored dry at –18°C under nitrogen it decomposed to a gelatinous solid within a week. This was thought to be the result of polymerization of the double bond systems, and so attempts to freeze the compound in solution were tested. It was found that the lifetime could be extended by up to two weeks by freezing the compound as a 1M benzene solution.

2.2.2 Esterification Reactions of Alcohol 94

From **94**, the Diels-Alder precursor **95** would be easily accessible, and it was decided to investigate the diastereoselectivity of the desymmetrization reaction on this model compound.



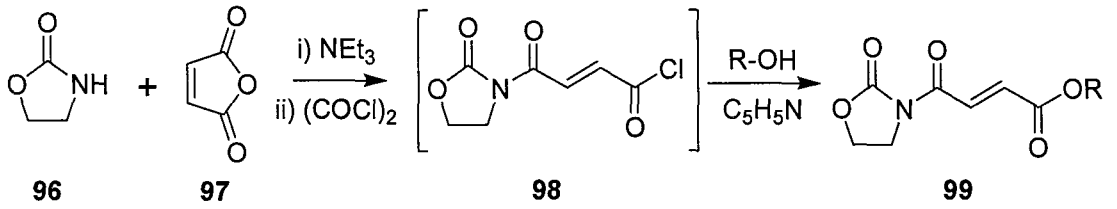
94 **95**

Scheme 40

A wide variety of different esterification methods were investigated in an attempt to prepare compound **95** from alcohol **94**.

2.2.2.1 One-Pot Imide Formation and Esterification

The first approach tested was a one-pot method starting from oxazolidinone **96** and maleic anhydride (**97**) as depicted in Scheme 41.[41]



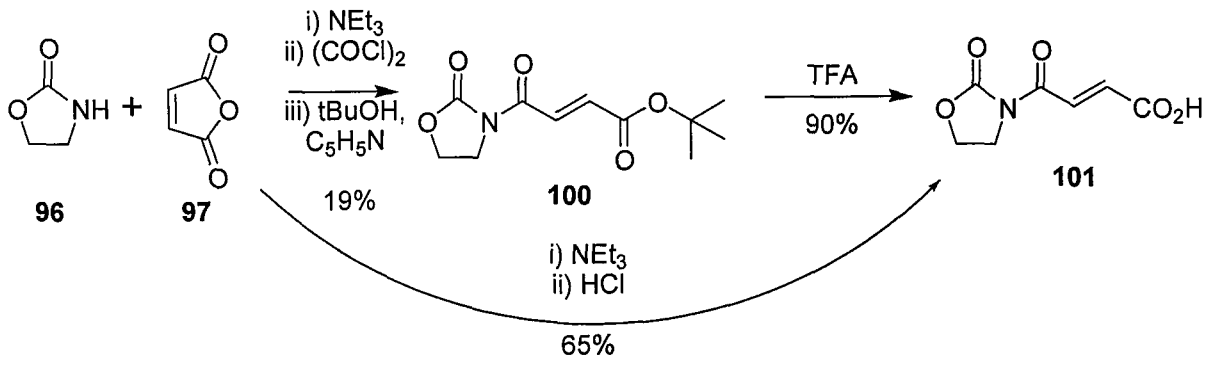
Scheme 41

Acid chloride **98** was prepared by addition of oxalyl chloride to a mixture of oxazolidinone **96**, maleic anhydride and triethylamine. According to a published procedure,[41] the desired alcohol could then be added in pyridine, to give ester **99**. This method has been shown to work in our hands for a range of simple alcohols.* However, upon introduction of **94** in pyridine, none of the desired product was formed.

As a proposed modification to the reported reaction, the organolithium reaction mixture containing alcohol **94** (see Scheme 39) was added before being worked up. In this form, the alcohol was already present as the anion. This reaction produced only the ethyl ester, however, presumably due to the presence of the ethoxy anion after reaction of ethyl formate.

2.2.2.2 Simple Esterification

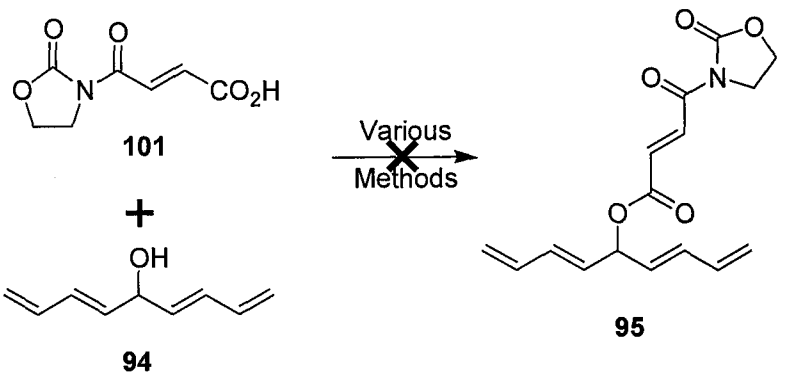
A simple esterification from carboxylic acid **101** was then attempted. The preparation of **101** is shown in Scheme 42.



Scheme 42

* Alcohols tested include ethanol, 1,6-heptadien-4-ol and 2-methyl-2-propanol: see Appendix I for details

Acid **101** was initially prepared by TFA deprotection of the *t*-butyl ester **100**, which was in turn prepared from *t*-butanol using the one pot method described in Scheme 41. The preparation of the ester went in low yield though, and it was discovered that the overall yield of acid **101** could be significantly improved by direct formation of the acid. This was achieved by addition of hydrochloric acid at an early stage of the imide formation reaction, removal of the solvent, and recrystallization from water.

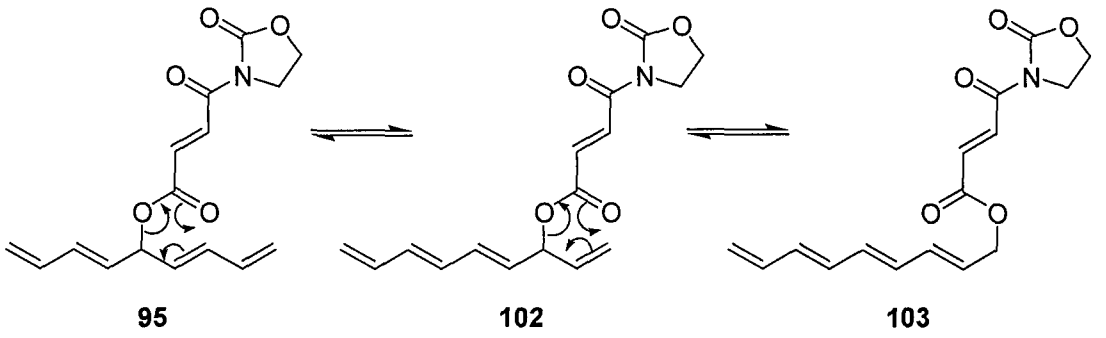


Scheme 43

In order to perform the esterification (Scheme 43), several different procedures were utilized: these included one using DCC and dimethylaminopyridine,[42] one using DCC and pyridine,[43] and another using *p*-toluenesulfonyl chloride[44]. None of these reactions formed a significant amount of ester **95**. TLC of the reaction of alcohol **94** with acid **101** using *p*-toluenesulfonyl chloride showed a number of compounds, but when purified all were seen to be very unstable: an indecipherable mixture of compounds was present by the time the fractions from the column had been evacuated and ^{1}H NMRs taken.

2.2.2.3 Analysis of Esterification Results

All attempts to esterify alcohol **94** have proved fruitless. A number of reasons for this have been put forward, but the most likely is double-bond isomerization (Scheme 44).



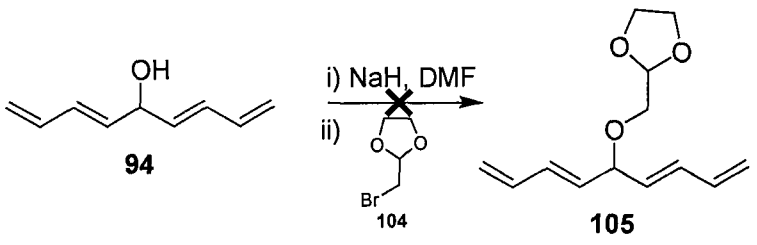
95 **102** **103**

Scheme 44

When the desired ester **95** is formed, it can undergo a sigmatropic rearrangement to **102**, followed by another to **103**. This results in a three-compound mixture being formed, of which both of the individual equilibria lie on the right-hand side, due to the increased stability of conjugated double bonds over "skipped" alkene systems. In addition, all of these compounds contain conjugated alkene systems and isolated electrophilic alkenes, and can thus react both inter- and intramolecularly. It is therefore unlikely that any of the desired ester **95** will remain isolated for any significant length of time. A similar phenomenon has been reported recently in the literature.[45]

2.2.3 Ether Formation Reactions of Alcohol 94

Attempts were also made to use alcohol **94** to prepare an ether, such as ether **105** as shown in Scheme 45.



94 **104** **105**

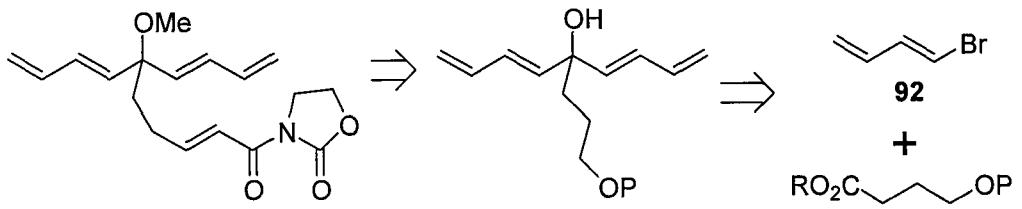
Scheme 45

Sodium hydride was added to a solution of **94** in N,N′-dimethylformamide (c. 1M), and the solution went dark brown. This was unexpected, as the reaction that was used to prepare alcohol **94** involved formation of the oxy-anion, and this produced a pale yellow solution. Both TLC and attempted further reaction with bromide **104** indicated that the desired deprotonation had failed, and a large number of spots were present by TLC. The

deprotonation was re-attempted at various temperatures (between –78°C and 20°C) and using a different base, but the observations did not change.

2.3 Preparation and Reactions of Tertiary Alcohols

In addition to preparation of secondary alcohol **94**, the production of tertiary alcohols was pursued by the use of esters other than ethyl formate. The intention behind this was the production of intramolecular Diels-Alder substrates such as **106**. Scheme 46 demonstrates the retrosynthetic analysis for compound **106**, and the ester required for the organolithium reaction.

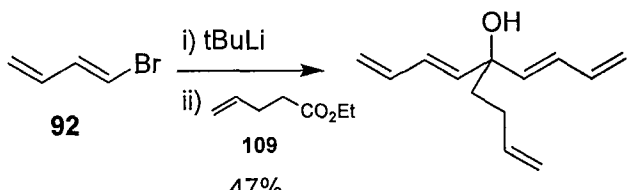


106 **107** **108**

Scheme 46

2.3.1 Preparation of Test Compound 110

Before efforts were begun to synthesize desired ester **108**, the reaction was tested using commercially available ethyl pent-4-enoate (**109**, Scheme 47).



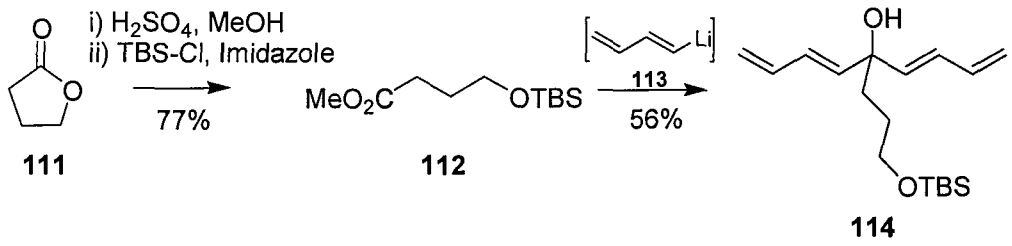
92 **109** 47% **110**

Scheme 47

The reaction was found to give desired compound **110** in 47% yield, and thus the methodology was transferred to reaction with ester **108**.

2.3.2 Preparation of Tertiary Alcohol 114

The ester required for the organolithium reaction, **112**, was produced by opening γ-butyrolactone (**111**) using methanol and sulfuric acid, followed by protection using t-butyldimethylsilyl chloride and imidazole (Scheme 48).[46]

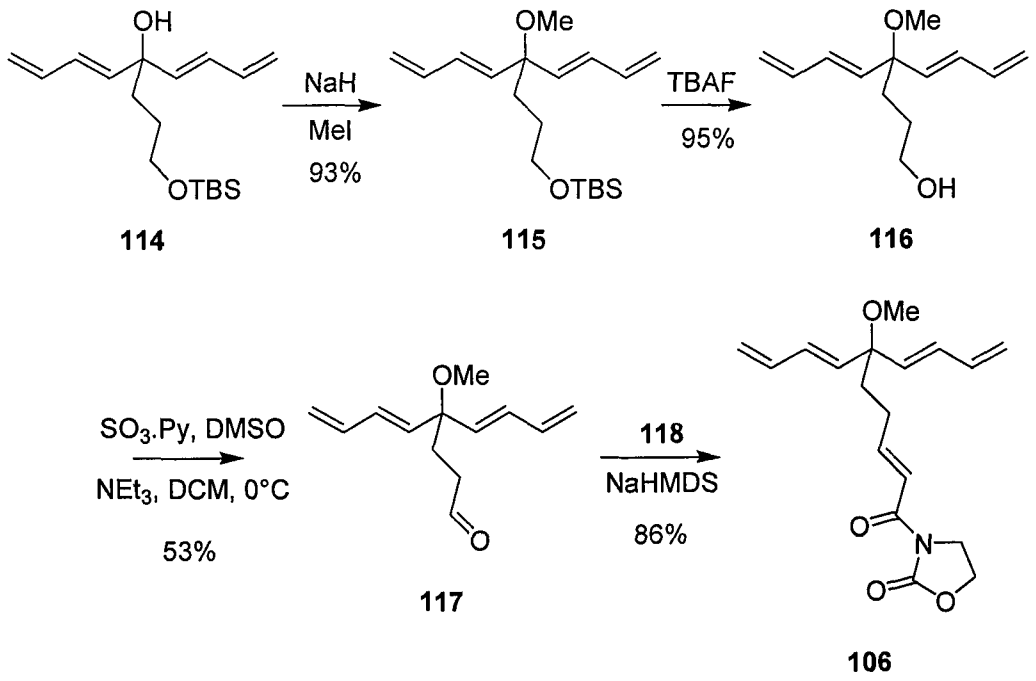


Scheme 48

The path was then clear to react the ester with butadienyllithium **113**. The reaction gave the desired tertiary alcohol **114** in moderate yield (56%).

2.3.3 Subsequent Reactions of Tertiary Alcohol 114

Tertiary alcohol **114** was then stirred with sodium hydride, methyl iodide added and the mixture stirred overnight to give methyl ether **115** in 93% yield (Scheme 49).

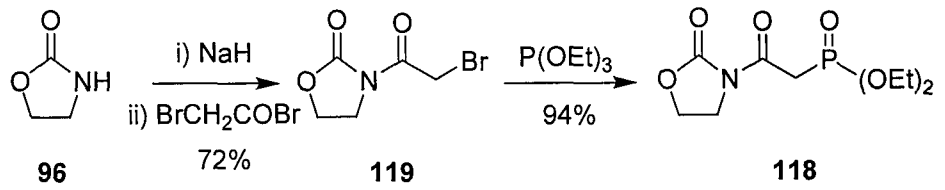


Scheme 49

Methyl ether **115** was then stirred with tetrabutylammonium fluoride for 4½ hours at room temperature in THF to give primary alcohol **116** in 95% yield.

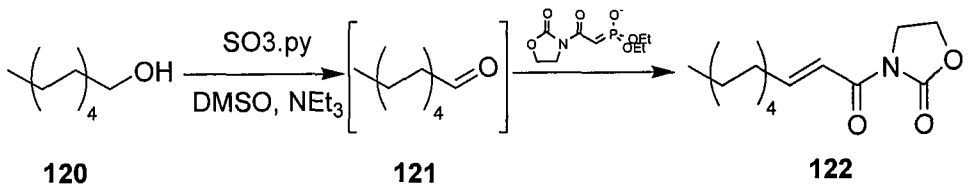
Oxidation of this primary alcohol to aldehyde **117** was accomplished in 53% yield using Parikh-Doering conditions at 0°C. This aldehyde was shown to be unstable, and was used directly in the subsequent step.

The phosphonate required to react with aldehyde **117** was prepared via the two-step strategy shown in Scheme 50. *N*-Bromoacetyloxazolidinone (**119**) was prepared from oxazolidinone **96** and bromoacetylbromide,[47] and this was then stirred in triethylphosphite at 80–100°C to give phosphonate **118** in very good yield (94%).[48]



Scheme 50

Before aldehyde **117** was reacted with phosphonate **118**, it was deemed prudent to carry out a test reaction on alcohol **120** (Scheme 51).



Scheme 51

1-Decanol (**120**) was oxidized under Parikh-Doering conditions to give aldehyde **121**. This was added crude to a stirred solution of phosphonate **118** and NaHMDS to give desired compound **122** in 39% over two steps. This yield was fairly low, and this was thought to be due to use of crude aldehyde in the reaction with the phosphonate. It was therefore decided to attempt purification of aldehyde **117** before reaction with the phosphonate.

Aldehyde **117** was found to easily withstand purification by column chromatography. Phosphonate **118** was then stirred with sodium hexamethyldisilazide at 0°C, and pure aldehyde **117** added to give compound **106** in 86% yield.

2.3.4 Analysis of Intramolecular Diels-Alder Substrate 106

Compound **106** was subjected to thermal intramolecular Diels-Alder conditions (reflux in toluene for 48 hrs), the solvent removed *in vacuo* and purified by column chromatography and HPLC. ^{1}H and ^{13}C NMR analysis of the purified product indicated a mixture of four diastereomers, and was too complicated to assign fully. However, Figure 10 and Figure 11 show the parts of the ^{1}H and ^{13}C spectra (respectively) that relate to the methyl ether moiety. The ^{1}H spectrum indicates four diastereomers, and the ^{13}C spectrum shows three (the fourth is probably obscured, due to the low signal-to-noise ratio).

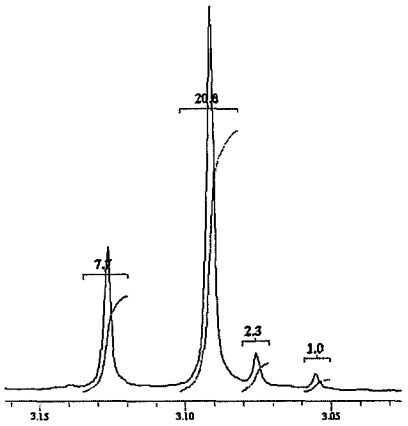


Figure 10

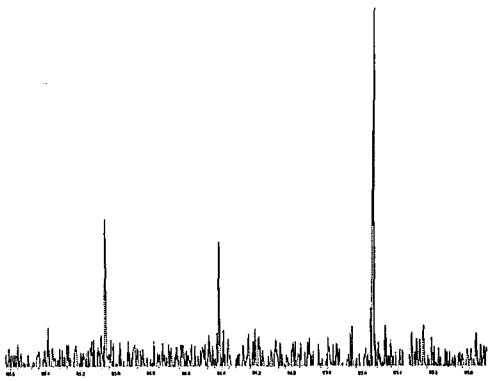


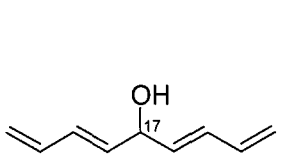
Figure 11

As can be seen from the spectra, one of the diastereomers is significantly more predominant than the others: from the ^{1}H spectrum, the relative percentages are 24:66:7:3.

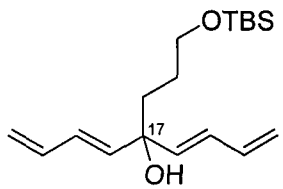
We were unable to separate the diastereomers by HPLC, and therefore it could not be determined which of the diastereoisomers was the most abundant. Though this knowledge would have been interesting, it would not necessarily have indicated which isomer would be preferentially formed from a secondary centre such as that present in vitamin D_3 precursor **78** (section 1.4.2, *supra*). The previously discussed C-17 selectivity depends on the relative strengths of the A1,2 strain and the A1,3 strain. The presence of the methyl ether will result in both of these effects being present for the methoxy group as well as for the diene.

2.4 Discussion of Organolithium Routes

The organolithium methods shown have been revealed as quick and simple methods to form 1,3,6,8-tetraene systems.



94



114

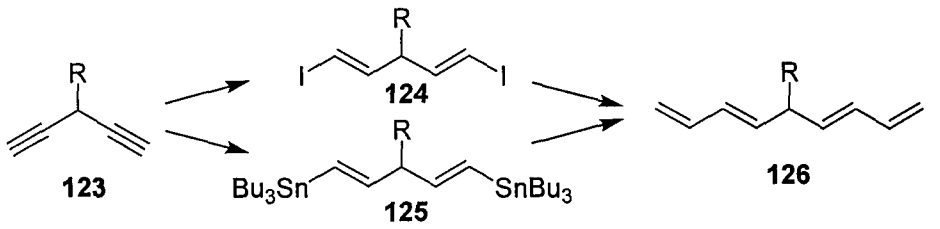
The secondary alcohol **94** is very unstable, and prone to unwanted side-reactions such as polymerization. The tertiary alcohol **114** is a more stable way of retaining the tetraene system (the compound remains >95% pure when kept at –18° for two weeks), but it cannot be used to form our desired intramolecular Diels-Alder substrates, which contain a hydrogen at the C17 position. Attempts were not made to remove the alcohol moiety installed at the C17 position of compound **114**: the tetraene system was judged to be so unstable that any attempted elimination or substitution at this point would result in its immediate scrambling. Separation of such mixtures of alkene isomers would be very challenging, if not impossible.

Chapter Three

Synthesis of "Skipped Tetraene" Systems via 1,4- Dialkyne

Chapter 3: Synthesis of "Skipped Tetraene" Systems via 1,4- Dialkyne

Synthesis of the desired skipped tetraene system was then considered starting from a 1,4-dialkyne, as illustrated in Scheme 52.

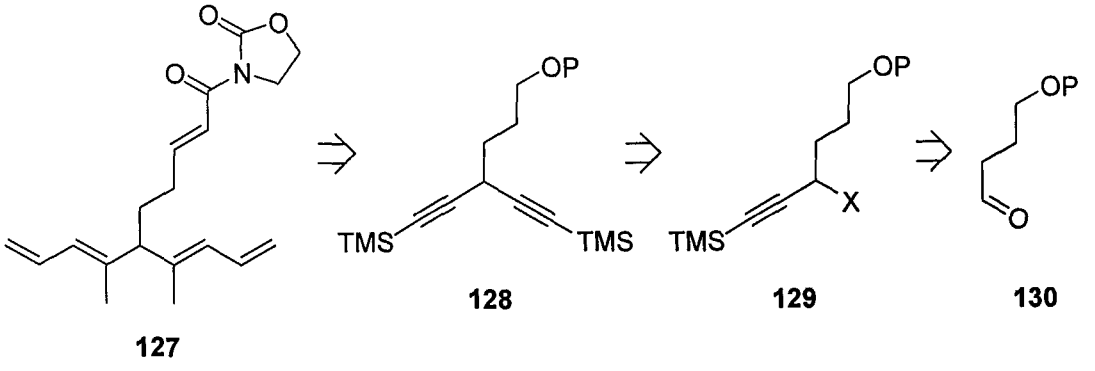


Scheme 52

The proposed route would entail conversion of the terminal alkynes present in **123** into either vinyl iodides[49,50] (**124**) or vinyl stannanes[51,52] (**125**), and from these a Stille coupling[53] using the appropriate vinyl reagent would give the desired 1,3,6,8-tetraene system (**126**). There are also procedures described in the literature that introduce methyl groups in the 4- and 6- positions of the tetraene.[54,55]

3.1 Nucleophilic Displacement Route

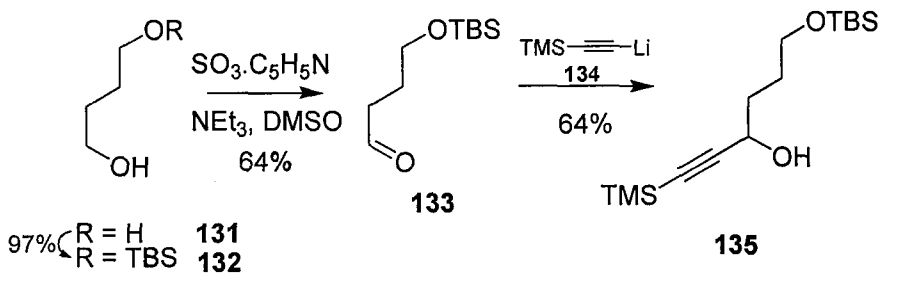
The first route that was undertaken to reach the 1,4-dialkyne system used S_N2 displacement to install the second alkyne moiety (Scheme 53).



Scheme 53

3.1.1 Preparation of Secondary Alcohol

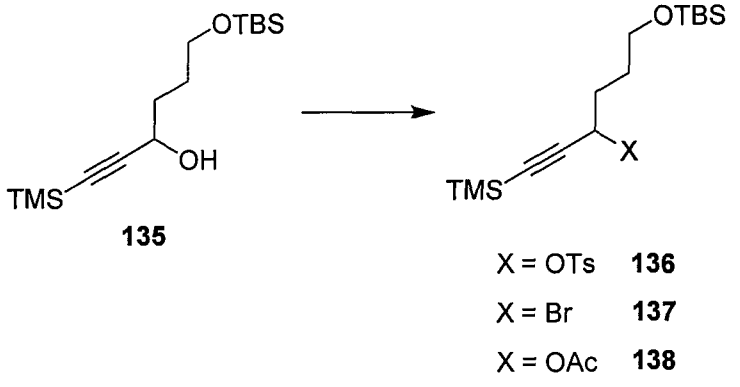
Butane-1,4-diol (**131**) was protected using TBS chloride to give mono silyl ether **132** in 97% yield,[56] and oxidized using Parikh-Doering conditions to give aldehyde **133**[57] in 64% yield (Scheme 54). This was reacted with lithium-TMS-acetylide to give alcohol **135** in 64% yield.



Scheme 54

3.1.2 Preparation of Leaving Groups and Substitution Reactions

In order to perform the S_N2 reaction, it was necessary to install a leaving group in place of the secondary alcohol (Scheme 55 and Table 1). The following leaving groups were tested: the *p*-toluenesulfonate (**136**), the bromide (**137**), and the acetate (**138**).



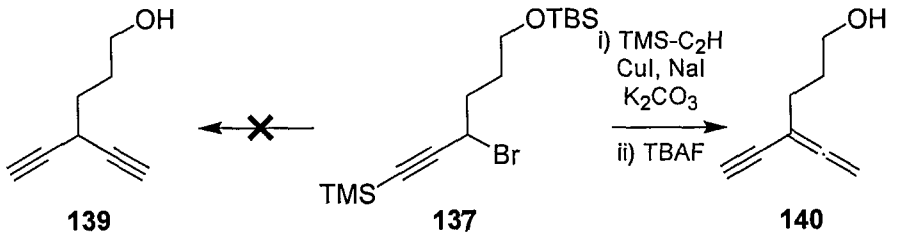
Scheme 55

Product Number	Conditions	Yield
136	TsCl, C_5H_5N	43%
137	CBr_4, PPh_3, C_5H_5N	62%
138	Ac_2O, DMAP, NEt_3	88%

Table 1

Alcohol **135** was reacted with tosyl chloride in pyridine to form tosylate **136** in 43% yield (Scheme 55). Substitution of the tosylate using lithium-TMS-acetylide[58] did not generate any of the desired product. Further attempts were made to displace the tosylate using the sodium-TMS-acetylide, but these also did not produce the desired product.

The bromide (**137**, Scheme 55) was prepared using carbon tetrabromide and triphenylphosphine, and many different methods were used to effect displacement of the bromide with an alkynyl unit.[59–67] None of these methods produced desired dialkyne **139**. Reaction using trimethylsilyl acetylene, copper iodide, sodium iodide, potassium carbonate and dimethylformamide[64] (Scheme 56) produced an inseparable mixture of apolar spots by TLC (R_f= 0.55–0.65, neat hexane).



Scheme 56

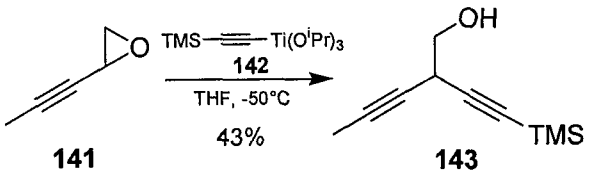
It was decided to subject this mixture to silyl ether removal conditions, in an effort to create more polar compounds, which could be more easily separated by chromatography. The mixture was stirred with TBAF in THF, and TLC revealed a spot that was much lower (R_f= 0.33, 30% acetone in hexane) than the starting material. The compound associated with this polar spot was isolated from the mixture in 28% yield, and spectral analysis indicated it to be allene **140**. Re-examination of the apolar mixture that was produced from the displacement reaction by infrared spectroscopy showed that an allene was present before the silyl ether removal conditions were introduced. Some of the other methods that were attempted for displacement of the bromide were also found to produce this allene in lower yields.

A number of literature references had been found for the displacement of an acetate,[68,69] so the acetate was prepared (**138,** Scheme 55, *supra*) and the methods investigated. None of the methods attempted were found to produce either desired dialkyne **139** or the previously observed allene **140**.

At this stage it was reasoned that the strongly basic conditions necessary in the substitution reaction were resulting in the observed isomerization, and other routes to the 1,4-dialkyne system were investigated.

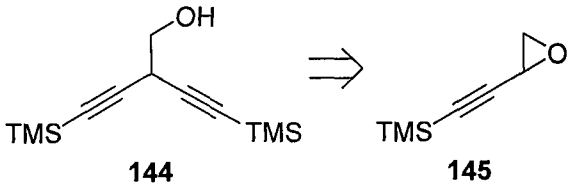
3.2 Epoxide Opening Route

Another route that was investigated was the attack of an acetylide at the activated position of a propargylic epoxide.



Scheme 57

An example of such a reaction from the literature is shown in Scheme 57.[70] The retrosynthetic analysis proposed for our use is shown in Scheme 58.

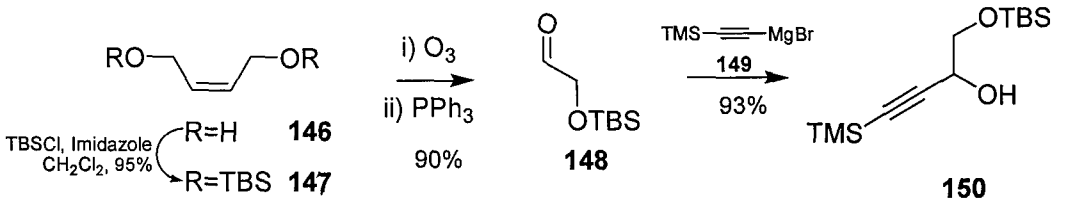


Scheme 58

From alcohol **144**, several steps were envisioned to convert the primary alcohol into the desired dienophile chain. The dialkyne could then be converted into the tetraene system using the methods described at the start of this chapter.

3.2.1 Preparation of Epoxide 145

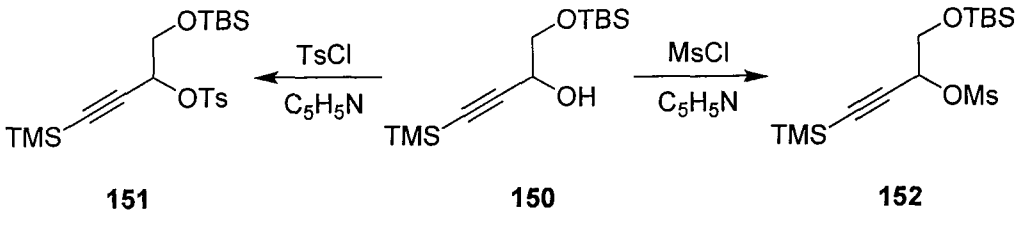
Scheme 59 shows the approach used to prepare epoxide **145**. 2-Buten-1,4-diol (**146**) was diprotected using TBSCl, and the resulting alkene **147** was ozonized using triphenylphosphine as reductant to give two equivalents of aldehyde **148** in good yield (90%).



Scheme 59

Attempts were made to react aldehyde **148** with the acetylide produced from reaction of trimethylsilylacetylene with *n*-butyllithium, but this did not give the desired product. Reaction of the aldehyde with the Grignard reagent produced from trimethylsilylacetylene and ethylmagnesium bromide, however, gave a very good yield of secondary alcohol **150** (93%). This alcohol was shown to be greater than 97% pure by NMR before chromatography.

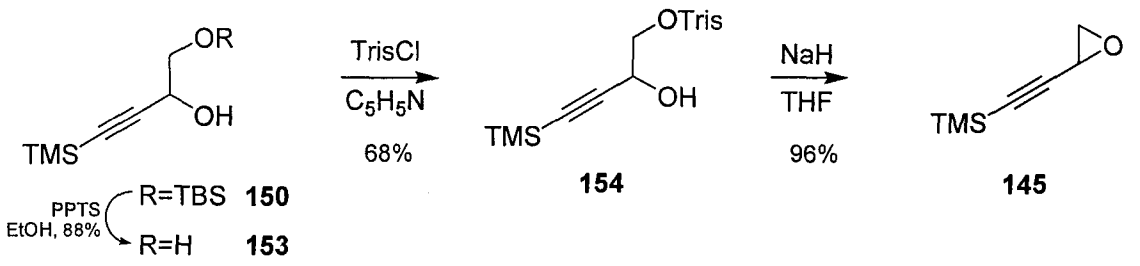
Several methods were attempted for preparation of epoxide **145**, including elimination from the tosylate and mesylate (Scheme 60, prepared using the appropriate sulfonyl chloride and pyridine), reaction of the diol with triphenylphosphine and diisobutylazodicarboxylate (DIAD),[71] and reaction with butyllithium and tosyl chloride.[72]



151 **150** **152**

Scheme 60

The most effective method proved to be deprotection of the primary alcohol by heating in ethanol with pyridinium *p*-toluenesulfonate[73] to give diol **153** in 88% yield (Scheme 61), followed by reaction with triisopropylbenzenesulfonyl chloride (TrisCl) in pyridine to give the sulfonated product **154**.

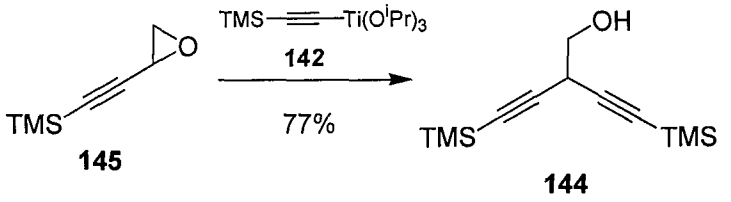


Scheme 61

Deprotonation of the secondary alcohol using sodium hydride then resulted in an intramolecular nucleophilic substitution, giving epoxide **145** in very good yield (96%).

3.2.2 Ring Opening of Epoxide 145 and Further Reactions

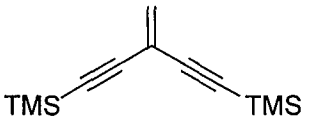
The ring opening reaction was then attempted. Titanium acetylide **142** was prepared from trimethylsilylacetylene, *n*-butyllithium, and titanium (IV) chloride triisopropoxide[74] in ether at –50°C, and epoxide **145** then added in ether (Scheme 62).



Scheme 62

The reaction was found to give desired alcohol **144** in 77% yield, considerably higher than that suggested by the literature.

Various reactions were attempted to follow-up this success. The first was an oxidation to the aldehyde, using Parikh-Doering conditions: this reaction gave one compound by TLC, but when investigated this was found not to be the desired aldehyde. NMR and infrared analysis suggested that the structure was that of compound **155** (Figure 12), an elimination product arising from one of the later stages of the Parikh-Doering reaction.

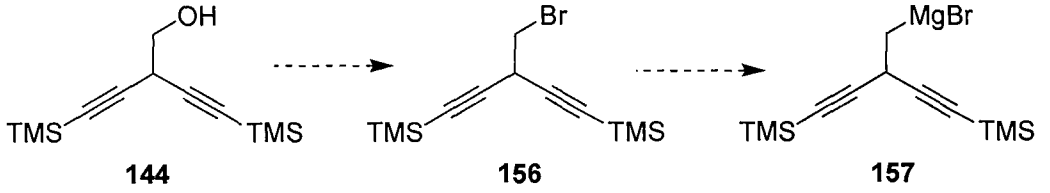


155

Figure 12

The driving force of this elimination appears to have been the conversion of the unconjugated system in **144** into the conjugated one in **155**, proving once again that the conjugated system is considerably lower in energy.

In retrospect, it was considered that even if the aldehyde could be prepared, it would probably exist solely in the enol form. Another method was therefore investigated: conversion of the primary alcohol into bromide **156**, with the intention of converting this into Grignard reagent **157** (Scheme 63).

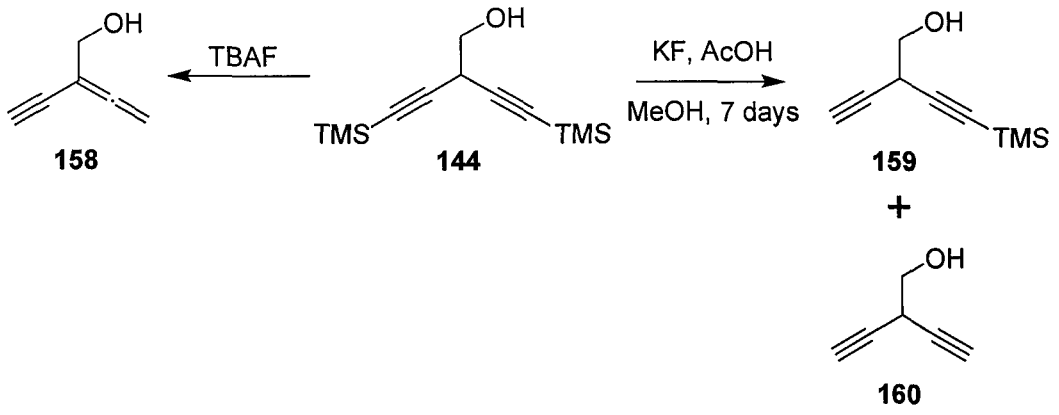


144 **156** **157**

Scheme 63

Conversion of the primary alcohol into the bromide was not successful, however, the evidence suggesting that compound **155** was again produced.

As the dialkyne seemed extremely base sensitive, efforts were made to convert the dialkyne into the tetraene, in order to assess the sensitivity of the tetraene to base. The first step was the deprotection of the two alkynes: stirring compound **144** with four equivalents of 1M TBAF in THF at room temperature did produce a reaction, but ^{1}H and ^{13}C NMR of the resultant mixture demonstrated considerable amounts of allene **158** (Scheme 64).



Scheme 64

This was thought to be due to the basicity of the fluoride, and several other methods for the removal of silyl protecting groups from acetylenes were attempted. Firstly, milder TBAF conditions were tested: two equivalents (one per acetylene) of 0.1M TBAF were added very slowly at – 78°C, but the allene was still predominantly formed. The use of potassium fluoride and 18-crown-6 in THF and water[75] gave similar results, but then a method that performed a similar deprotection using potassium fluoride and acetic acid in methanol[76] was found. This was particularly interesting, as all other procedures that had been found were under basic conditions. The reaction was tested, and after a week stirring at room temperature the reaction had produced a small amount (<10%) of a compound that ^{1}H NMR suggested to be the desired primary alcohol **160**, along with some of the mono-silyl intermediate **159**.

3.3 Discussion of Dialkyne Routes

Attempted nucleophilic substitution on the carbon next to an alkyne followed by silyl-ether removal conditions gave none of the dialkyne, only the undesired allene. Using an epoxide opening method, the preparation of a 1,4-dialkyne system has been accomplished. The system has proved difficult to handle: it is remarkably base sensitive, and literature examples of the removal of an alkynyl silyl protecting-group under acidic conditions are rare. The sole example discovered seemed to have the desired effect, but only after an extensive period of time and unfortunately time-constraints meant that the reaction could not be fully investigated.

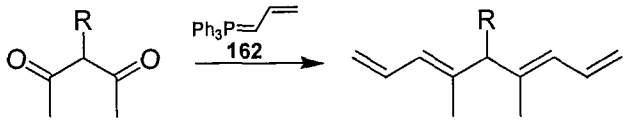
Chapter Four

Synthesis of "Skipped Tetraene" Systems via Wittig Reactions

Chapter 4: Synthesis of "Skipped Tetraene" Systems via Wittig Reactions

4.1 The Standard Wittig Reaction

When tackled with the problem of creating an alkene system, the Wittig reaction springs instantly to mind. The Wittig reaction is not the best suited for preparation of skipped tetraene systems (such as that present in compound **163**, Scheme 65) however, as this would involve reaction of a 1,3-diketone (such as **161**).



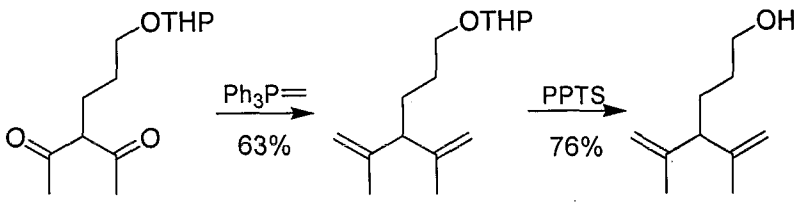
161 **163**

Scheme 65

The complication that this introduces is that the hydrogen between the two carbonyls (i.e. the one at our C17 position) is particularly acidic, resulting in sensitivity to base. Despite this possible obstacle, the route was considered too important to discount without exploration, and investigations were therefore carried out.

4.1.1 Conversion of Diketone into Skipped Diene

Diketone **164** (Scheme 66) was prepared from 2,4-pentanedione and 2-(3-bromopropoxy)tetrahydro-2H-pyran according to the literature procedure.[77] For the initial trial reaction, it was decided to react **164** with methylene triphenylphosphine.



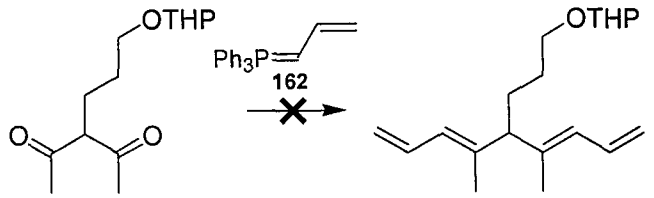
164 **165** **166**

Scheme 66

Reaction with the ylide formed from methyltriphenylphosphonium bromide and potassium *t*-butoxide[78] went well, giving skipped diene **165** in 63% yield. There was substantial signal overlap in the ^{1}H NMR of **165**, and deprotection of the primary alcohol with PPTS produced diene **166**, which gave a much simpler spectrum.

4.1.2 Conversion of Diketone into Skipped Tetraene

In order to prepare the tetraene system, diketone **164** was reacted with ylide **162** (Scheme 67), which was prepared from allyltriphenylphosphonium bromide.



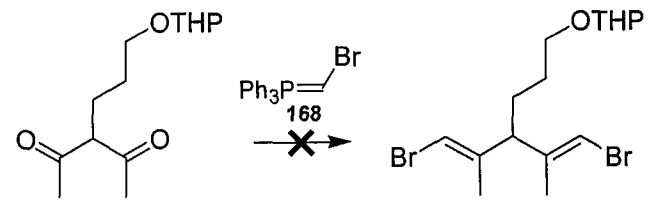
164 **167**

Scheme 67

The reaction did not go as expected, and none of the desired compound **167** was formed. The reaction was repeated under several different sets of conditions, but without any success.

4.1.3 Conversion of Diketone into Di(Vinyl Bromide)

Reaction of diketone **164** was also attempted with the ylide formed from bromomethyl-triphenylphosphonium bromide (**168**, Scheme 68).



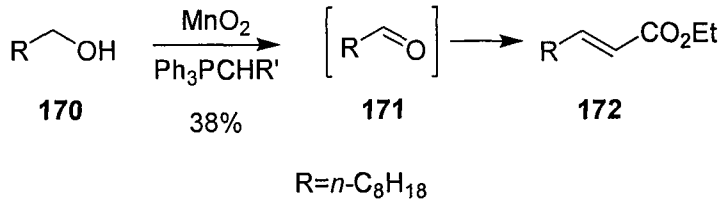
164 **169**

Scheme 68

It was intended that **169** could be converted to the tributyl stannyl derivative, and from this a Pd(0) catalysed Stille reaction could be carried out with vinyl iodide. However, this reaction also failed despite a selection of conditions being tested.

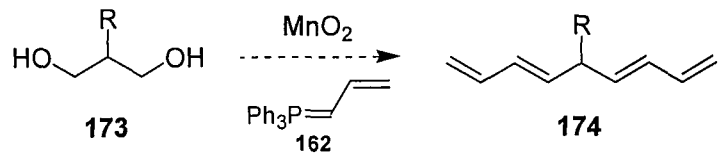
4.2 Combined Oxidation and Wittig Reactions

As stated in section 4.1, the 1,3-dicarbonyl system was identified as having a potential drawback in the form of an acidic hydrogen between the two carbonyls. Therefore, in parallel with the standard Wittig, a combined oxidation and Wittig reaction was investigated.



Scheme 69

Scheme 69 shows an example that has appeared in the literature, in which primary alcohol **170** is converted into α,β-unsaturated ester **172**.[79,80] It was decided to investigate this protocol on a 1,3-diol, in order to lead to a skipped tetraene. The use of a 1,3-diol rather than a 1,3-dicarbonyl as the starting material would eliminate the effect of the acidity of the central hydrogen of a 1,3-dicarbonyl starting material on the reaction (Scheme 70).

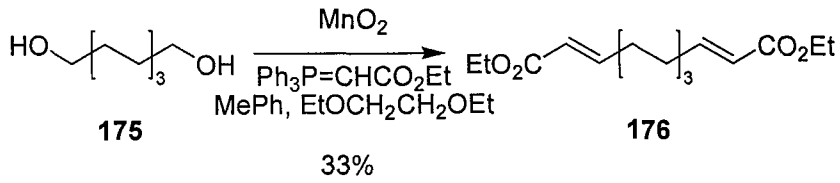


Scheme 70

The literature precedent was carried out on simple alkyl alcohols, and investigations into the suitability of the method for our use were carried out.

4.2.1 Reaction of Diols with Stabilized Ylides

The first study involved the reaction of a long chain diol (octane-1,8-diol, **175**) with one of the stabilized ylides that was utilized in the literature (Scheme 71).



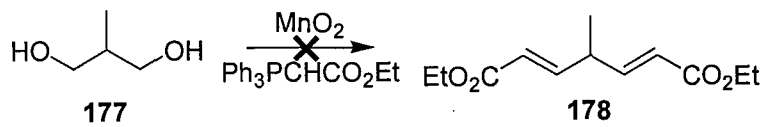
175 **176**

33%

Scheme 71

The literature precedent reaction was carried out in toluene, but it was discovered that diol **175** did not dissolve readily in toluene. Since a high-temperature reflux was necessary for the reaction to proceed, a high-boiling co-solvent was sought. It was found that ethylene glycol diethyl ether* could be used in this way, and the reaction went in modest yield (33%).

From this point, the next logical step was to reduce the chain length of the diol. This would provide us with a synthon for the 1,3-dialdehyde, and introduce the possibility of creating the skipped tetraene system. The reaction of 1,3-diol **177** was therefore investigated (Scheme 72).



177 **178**

Scheme 72

Various different conditions were examined for this reaction, but none of them gave desired product **178**. It is not known exactly why this reaction did not succeed: one possibility is steric hindrance, i.e. the attack of the second ester was hindered by the size of the first. Another possibility is that the 1,3-hydroxyaldehyde polymerized, thus preventing the Wittig reaction from taking place.

* Ethylene glycol diethyl ether, ≥99.0%, is available as a Fluka chemical from Aldrich chemical company: product no 31602, CAS no [629-14-1]

4.3 Discussion of Wittig Routes

Attempts to create the skipped tetraene system using Wittig reactions were unsuccessful. A wide variety of methods was tested, and it was inferred that there were inherent problems with the use of Wittig reagents.

The standard Wittig reaction showed promise by forming the skipped 1,4-diene, but when the skipped 1,3,6,8-tetraene was attempted, there was no reaction. This problem could be due either to the acidity of the central hydrogen, or possibly to steric issues relating to the size of the diene. Another possibility is that the reaction may proceed as desired, but the conditions present in the reaction result in scrambling of the alkene system.

The one-pot oxidation followed by Wittig reaction also gave initially promising results using the long-chain diol and a stabilized ylide, but when a short chain diol was tested, the reaction did not yield the desired product.

4.4 Overall Conclusions

The preparation of skipped tetraene systems was always anticipated to be challenging, due to the sensitivity of the unconjugated system. Attempts to prepare skipped tetraene containing products via Wittig transformations met with no success, probably due to a combination of the basic conditions required and the instability of the product. Though skipped tetraenes were prepared efficiently using organolithium reactions, they proved exceptionally difficult to handle, and further manipulation attempts proved fruitless.

The preparation of another unconjugated system, the 1,4-dialkyne as a precursor for the skipped tetraene system, was also successful, but this system proved extremely base sensitive. Even the relatively mild basic conditions of tetrabutylammonium fluoride in THF resulted in allene formation. Only one further manipulation that was attempted did not appear to scramble the system: the deprotection of the silyl protected terminal alkynes in acidic conditions appeared to proceed as desired, but the reaction time was impractically long and was not further investigated because of lack of time.

Chapter Five

Experimental Details

Chapter 5: Experimental Details

5.1 General Procedures and Instrumentation

Thin Layer Chromatography

Thin layer chromatography was performed on Machery–Nagel Sil G–25 UV_{254} glass backed TLC sheets, and the compounds visualized by UV fluorescence or through potassium permanganate oxidation.

Column Chromatography

Column chromatography was performed on Davisil Silica 60A, particle size 35–70 micron.

Melting Points

All melting points were uncorrected, and were determined in open capillary tubes using Gallenkamp Electrothermal Melting Point Apparatus.

Infrared Spectra

Infrared spectra were recorded using a Nicolet Impact 400 IR spectrometer. Samples were run either neat (oils), as solutions in CH_2Cl_2 or as neat powders (using a Spectratech Thunderdome Accessory) in the range 4000–600cm^{-1}.

Nuclear Magnetic Resonance Spectra

Nuclear magnetic resonance spectra were performed on the following instruments:

- 300 MHz ^1H and 75 MHz ^{13}C spectra: Bruker AC300 and Bruker AM300 spectrometers.
- 400 MHz ^1H and 100 MHz ^{13}C spectra: Bruker DPX400 spectrometer.

All experiments were carried out at 300K. The operating frequencies are given in brackets. Chemical shifts are quoted as δ-values relative to tetramethylsilane and calibrated to residual $CHCl_3$ or acetone. The resonances are described as follows: s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet.

Mass Spectrometry

Low-resolution mass spectrometry experiments were performed on a Thermoquest 2000 mass spectrometer using a gas chromatograph injector.
High-resolution mass spectrometry experiments were performed on a Bruker Apex III FT-ICR-MS with 4.7 T magnet.

Elemental Combustion Analyses

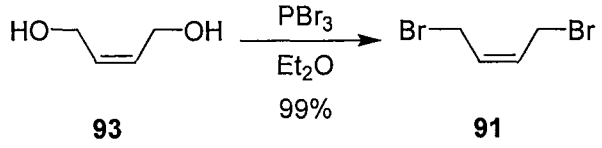
Combustion analyses were performed at MEDAC Ltd, Egham, Surrey.

Solvent Purification

Dry tetrahydrofuran and diethyl ether were distilled from sodium / benzophenone.
Dry dichloromethane and triethylamine were distilled from calcium hydride.
Dry toluene was distilled from sodium.
Dry pyridine was double distilled from calcium hydride and stored in a Schlenk flask.
Dry DMSO was distilled from calcium hydride under reduced pressure and stored over molecular sieves.
Dry ethanol and methanol were distilled from magnesium turnings.

5.2 Preparation of Compounds Involved in the Organolithium Investigations

(Z)-1,4-dibromo-2-butene (91)[39]



Phosphorous tribromide (180.5g, 0.667mol, 0.667eq) was added dropwise to a suspension of diol **93** (88.1g, 1mol, 1eq) in diethyl ether (200mL) at 0°C over one hour. This was then stirred at room temperature for 2 hours, before being added to ice water (200mL). After separation, the organic layer was dried with sodium sulfate, and the ether evaporated *in vacuo* (without heating) to give 210.9g of dibromide **91** as a pale grey oil (99%, Z:E ratio ~ 20:1 by NMR).

IR (film) 3036, 2973 (C–H), 1452 (C–H), 773 (C–Br).

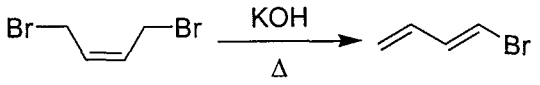
^{1}H NMR (300MHz, $CDCl_3$) δ 5.90 (2H, m, CH), 4.03 (2H, d, J = 8, CH_2), 4.03 (2H, d, J = 4, CH_2).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 129.82 (CH), 24.63 (CH_2).

EIMS *m/z* (%) 214 (34%, $M(^{79}Br^{81}Br)^+$), 133 (100%, $(M–Br)^+$), 135 (100%, $(M–Br)^+$).

Characterization was consistent with the literature.[81]

(E)-1-bromobuta-1,3-diene (92)[39]



91 68% **92**

Dibromide **91** (43g, 0.2mol, 1eq) was stirred mechanically with freshly powdered potassium hydroxide (250g, 4.5mol, 22eq) in hexadecane (100mL) at 35 mmHg. The receiver was then cooled to –78°C, and the reaction heated until a yellow liquid distilled across (approximately 110°C). The contents of the receiver flask were then shaken with concentrated hydrochloric acid (3×10mL). The organic layer was then filtered through magnesium sulfate under nitrogen to give 18.15g of product **92** as a yellow oil (68%).

IR (film) 3087, 3004, 2962 (C–H), 1628, 1581 (C=C–C=C).

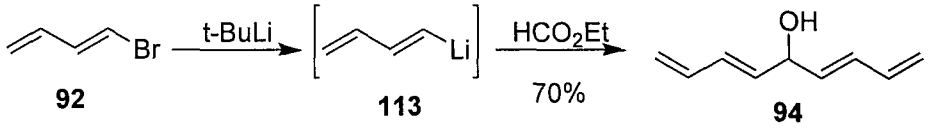
^{1}H NMR (300MHz, d_6-Acetone) δ 6.80 (1H, dddd, J = 10,14,1,1, HC=CBr), 6.59 (1H, dd, J = 14,1, HCBr), 6.37 (1H, ddd, J = 17,10,10, HC=CH_2), 5.32 (1H, ddd, J = 17,1,1, HHC), 5.16 (1H, ddd, J = 10,1,1, HHC).

^{13}C NMR + DEPT (75MHz, d_6-Acetone) δ 138.98 (CHCH_2), 130.92 (CHCHBr), 118.86 (CH_2), 110.40 (CHBr).

EIMS *m/z* (%) 134 (33%, M^+), 132 (33%, M^+), 53 (100%, $(M–Br)^+$).

Characterization was consistent with the literature.[39]

(3E,6E)-Nona-1,3,6,8-tetraen-5-ol (94)



92 113 70% 94

Tertiary butyllithium (8.8mL, 13.2mmol, 1.5M in pentane) was added to a solution of bromobutadiene (**92**, 1.6g, 12mmol) in diethyl ether (35mL) at –78°C. This was stirred for 90 minutes at –78°C, then ethyl formate (444mg, 6mmol) was added in ether (3mL). The reaction was then stirred for 1 hour at –78°C, then at 0°C for 3 hours, and worked up with water (20mL). This mixture was then extracted with ether (3×30mL), washed with brine (20mL), dried over magnesium sulfate, filtered and evaporated. The crude product was then purified by column chromatography (20% ethyl acetate in hexane) followed by HPLC (15% ethyl acetate in hexane) to give 571mg product as a pale yellow oil (**94**, 70%).

$\mathbf{R_f}$ 0.30 (7% ethyl acetate in hexane).

IR (oil) 3336 (O–H), 3086, 3008, 2978 (C–H), 1603 (alkene).

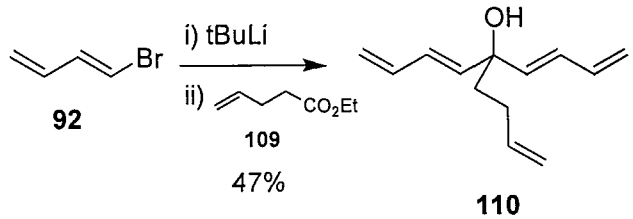
^{1}H NMR (300MHz, $CDCl_3$) δ 6.35 (2H, ddd, J = 10, 10, 17, $\underline{H}C{=}CH_2$), 6.25 (2H, dd, J = 10, 15, $\underline{H}C{=}CHCOH$), 5.74 (2H, dd, J = 7, 15, $\underline{H}CCOH$), 5.23 (2H, dd, J = 17, 2, $\underline{H}HC$), 5.12 (2H, dd, J = 10, 2, $\underline{H}HC$), 4.70 (1H, t, J = 7, $\underline{H}COH$).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 136.34 ($\underline{C}HCH_2$), 134.37 ($\underline{C}HCHOH$), 131.68 ($\underline{C}H{=}CHCH_2$), 118.28 (CH_2), 72.86 (CHOH).

EIMS *m/z* (%) 136 (4%, M^+), 117 (100%), 91 (76%).

This compound could not be attained in sufficient purity to acquire HRMS.

(3E,6E)-5-but-3-enylnona-1,3,6,8-tetraen-5-ol (110)



92 109 47% 110

1-Bromo-1,3-butadiene (**92**, 532mg, 4 mmol, 2 eq) was dissolved in diethyl ether (20mL) and cooled to –78°C. *t*-Butyllithium (1.5M in pentane, 4.2 mmol, 2.1 eq) was added producing a yellow colour, and the reaction stirred at –78°C for 30 minutes. Ethyl pent-4-enoate (**109**, 256mg, 2 mmol, 1 eq) was added slowly giving a colourless solution, and the reaction stirred at –78°C for 1 hour and 0°C for 3 hours. After this time sodium hydrogencarbonate solution (5%, 10mL) was added, extracted with ether (3×10mL), and the organic extracts dried over magnesium sulfate and evaporated. This was then purified by column chromatography (10% ethyl acetate in hexane), giving alcohol **110** as a colourless oil (177 mg, 47%).

$\mathbf{R}_f$ 0.30 (10% ethyl acetate in hexane).

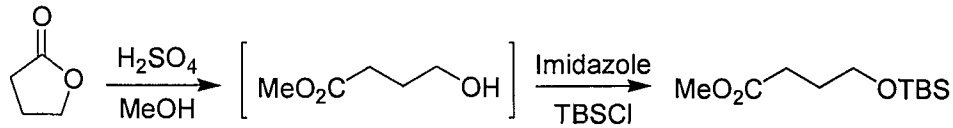
IR (film): 3432 (OH), 3077 (C=C–H), 2969, 2936 (C–H), 1687 (C=C), 1635, 1597 (C=C–C=C).

^{1}H NMR (300MHz, $CDCl_3$) δ 6.35 (2H, ddd, J = 16, 10, 10, CH_2=C**H**–CH=CH–), 6.27 (2H, dd, J = 15, 10, CH_2=CH–C**H**=CH–), 5.83 (1H, tdd, J = 6, 10, 17, –CH_2–C**H**=CH_2), 5.77 (2H, d, J = 15, CH_2=CH–CH=C**H**–), 5.23 (2H, dd, J = 16, 2, C**H**$_2$=CH–CH=CH– [cis to chain]), 5.10 (2H, dd, J = 10, 2, C**H**$_2$=CH–CH=CH–), 5.03 (1H, dd, J = 17, 2, –CH_2–CH=C**H**$_2$), 4.96 (1H, dd, J = 10, 2, –CH_2–CH=C**H**$_2$), 2.12 (2H, m, HO–C–C**H**$_2$), 1.72 (2H, m, C**H**$_2$–CH=CH_2).

^{13}C NMR (75MHz, $CDCl_3$): 138.8 (CH_2=CH–CH=**C**H–), 138.3 (CH_2–**C**H=CH_2), 136.5 (CH_2=**C**H–CH=CH–), 129.4 (CH_2=CH–**C**H=CH–), 117.7 (**C**H2=CH–CH=CH–), 114.8 (CH_2–CH=**C**H_2), 75.2 (HO–**C**), 40.5 (HO–C–**C**H_2), 28.2 (**C**H_2–CH=CH_2).

EIMS *m/z* (%) 190 (13%, M^+), 189 (20%, $(M–H)^+$), 173 (33%, $(M–OH)^+$), 135 (75%, $(M–C_3H_5)^+$), 55 (100%, $C_3H_5^+$).

Methyl-4-(t-butyldimethylsilyloxy)butanoate (112)[46]



111 77% **112**

γ-Butyrolactone (**111**, 5.0g, 58 mmol, 1 eq) was stirred in methanol (40mL), then concentrated sulfuric acid (5 drops, cat) was added, and the mixture refluxed overnight. Imidazole (0.2g, 2.9mmol) was added, and the mixture stirred for 10 minutes at room temperature, at which time the methanol was removed *in vacuo*. The residue was dissolved in anhydrous dimethylformamide (30mL), and *t*-butyldimethylsilyl chloride (13.14g, 87mmol, 1.5 eq) and imidazole (9.9g, 145mmol, 2.5 eq) added. This was stirred for 6 hours at room temperature water (50mL) added, and extracted with ether (3×50mL) The combined organic extracts were washed with saturated ammonium chloride solution (3×50mL) and brine (50mL) before being dried over $MgSO_4$ and evaporated. This crude product (14.00 g) was purified by column chromatography (5% ethyl acetate in hexane) to give pure ester **112** as a colourless oil (10.39 g, 77%).

R_f 0.32 (5% ethyl acetate in hexane).

IR (film) 2955, 2930, 2886, 2858 (C–H), 1743 (C=O), 1256 (C–Si).

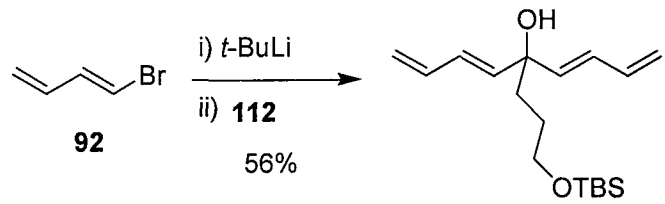
^{1}H NMR (400MHz, $CDCl_3$) δ 3.65 (3H, s, CO_2Me), 3.60 (2H, t, J = 6, CH_2OSi), 2.35 (2H, t, J = 8, $C\underline{H}_2CO_2Me$), 1.80 (2H, tt, J = 6, 8, $C\underline{H}_2CH_2OSi$), 0.85 (9H, s, $SiC(CH_3)$), 0.00 (6H, s, $SiCH_3$).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 174.20 ($\underline{C}O_2Me$), 62.10 (CH_2OSi), 51.50 ($\underline{Me}O_2C$), 30.60 ($\underline{C}H_2CO_2Me$), 28.00 ($\underline{C}H_2CH_2OSi$), 26.00 ($\underline{C}H_3CSi$), 19.40 ($CH_3\underline{C}Si$), –4.90 (CH_3Si).

CIMS *m/z* (%) 233 (92%, $(M+H)^+$), 175 (100%, $(M-C_4H_9)^+$).

Characterization was consistent with the literature.[46]

(3E,6E)-5-(3-t-butyldimethylsilyloxypropyl)-nona-1,3,6,8-tetraen-5-ol (114)



92 **114**

1-Bromobutadiene (**92**, 1.06g, 8 mmol, 2 eq) was dissolved in ether (40mL) and cooled to –78°C. *t*-Butyllithium (1.5M in pentane, 5.6mL, 8.4 mmol, 2.1 eq) was added producing a yellow colour, and the reaction was stirred at –78°C for 30 minutes. Ester **112** (0.93g, 4 mmol, 1 eq) was added slowly, and the reaction stirred at –78°C for 1¾ hour and 0°C for 1½ hours. After this time sodium hydrogencarbonate solution (5%, 20mL) was added, extracted with ether (3×20mL), and the organic extracts dried over magnesium sulfate and evaporated. This was then purified by column chromatography (8% ethyl acetate in hexane), to give pure alcohol **114** as a colourless oil (691 mg, 56%). 9% of ester **112** was recovered.

$\mathbf{R}_f$ 0.24 (8% ethyl acetate in hexane).

IR (film) 3416 (OH), 2955, 2935, 2853 (C–H), 1598 (C=C).

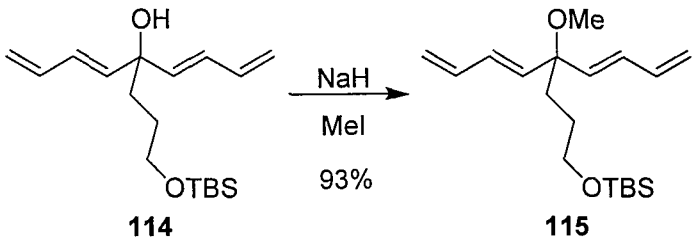
^{1}H NMR (400MHz, $CDCl_3$) δ 6.40 (2H, ddd, J = 16, 11, 10, $\underline{H}C{=}CH_2$), 6.20 (2H, dd, J = 15, 11, $\underline{H}C{=}C{-}COH$), 5.65 (2H, d, J = 15, $\underline{H}C{-}COH$), 5.10 (2H, dd, J = 16, 2, $\underline{H}HC{=}C$), 5.00 (2H, dd, J = 10, 2, $\underline{H}HC{=}C$), 3.60 (2H, t, J = 6, $\underline{H}_2COSi$), 3.35 (1H, s, OH), 1.70 (2H, t, J = 7, CH_2), 1.50 (2H, tt, J = 6, 7, CH_2), 0.80 (9H, s, $\underline{H}_3C{-}C{-}Si$), 0.00 (6H, s, $\underline{H}_3C{-}Si$).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 139.20 ($\underline{C}HCOH$), 137.00 ($\underline{C}H{=}CH_2$), 129.40 ($\underline{C}H{=}C{-}COH$), 117.40 ($\underline{C}H_2{=}C$), 74.80 ($\underline{C}(OCH_3)$), 64.20 (CH_2OSi), 39.30 ($\underline{C}H_2COH$), 27.30 ($\underline{C}H_2CH_2{-}OSi$), 26.40 ($\underline{C}H_3CSi$), 18.50 ($\underline{C}(CH_3)_3Si$), –5.00 ($CH_3Si$).

CIMS *m/z* (%) 293 (30%, $(M{-}CH_3)^+$), 251 (5%, $(M{-}C_4H_9)^+$), 161 (100%).

HRMS (EIMS) for $C_{18}H_{32}O_2Si_1$ (M^+) calcd 308.21716, found 308.21706.

(3E,6E)-5-(3-t-butyldimethylsilyloxypropyl)-5-methoxynona-1,3,6,8-tetraene (115)



114 **115**

Sodium hydride (60% dispersion in mineral oil, 97mg, 2.39mmol, 1.5 eq) was suspended in THF (10mL), alcohol **114** (0.49g, 1.59 mmol, 1 eq) added in THF (4mL), and the mixture stirred at room temperature for 10 minutes. Methyl iodide (0.47g, 3.3mmol, 2.1 eq) was then added, and the mixture stirred at room temperature overnight. Effervescence was noted when saturated ammonium chloride solution (5mL) was added, and the mixture was extracted with ether (3×10mL). The combined organic phases were dried over magnesium sulfate and evaporated, giving 558mg crude product. This was purified by column chromatography (3% ethyl acetate in hexane) to give methyl ether **115** as a colourless oil (475 mg, 93%).

$\mathbf{R}_f$ 0.25 (2% ethyl acetate in hexane).

IR (film) 2950, 2921, 2888, 2850 (C–H), 1601 (C=C).

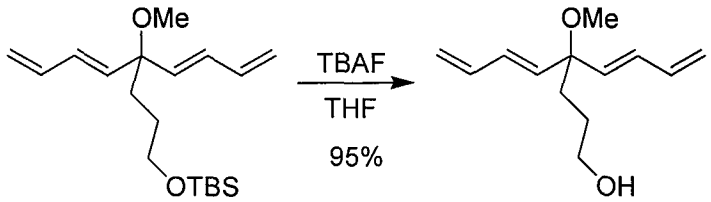
^{1}H NMR (400MHz, $CDCl_3$) δ 6.40 (2H, ddd, J = 17, 11, 10, $\underline{H}C{=}CH_2$), 6.20 (2H, dd, J = 11, 16, $\underline{H}C{=}C{-}C(OCH_3)$), 5.60 (2H, d, J = 16, $\underline{H}C{-}C(OCH_3)$), 5.20 (2H, dd, J = 17, 2, $\underline{H}HC{=}C$), 5.10 (2H, dd, J = 10, 2, $\underline{H}HC{=}C$), 3.60 (2H, t, J = 6, $\underline{H}_2COSi$), 3.20 (3H, s, $\underline{H}_3C{-}O$), 1.70 (2H, m, alkyl), 1.50 (2H, m, alkyl), 0.90 (9H, s, $\underline{H}_3C{-}C{-}Si$), 0.00 (6H, s, $\underline{H}_3C{-}Si$).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 136.80 ($\underline{C}HC(OCH_3)$), 136.50 ($\underline{C}H{=}CH_2$), 131.60 ($\underline{C}H{=}C{-}C(OCH_3)$), 117.40 ($\underline{C}H_2{=}C$), 79.40 ($\underline{C}(OCH_3)$), 63.40 ($CH_2OSi$), 50.70 ($CH_3{-}O$), 33.60 ($\underline{C}H_2C(OCH_3)$), 26.90 ($\underline{C}H_2CH_2{-}OSi$), 26.10 ($\underline{C}H_3CSi$), 18.50 ($\underline{C}(CH_3)_3Si$), –5.20 ($CH_3Si$).

EIMS *m/z* (%) 322 (8%, M^+), 269 (5%, $(M{-}C_4H_5)^+$), 265 (11%, $(M{-}C_4H_9)^+$), 159 (100%), 149 (96%, $(M{-}C_9H_{21}OSi)^+$).

HRMS (EIMS) for $C_{19}H_{34}O_2Si_1$ (M^+) calcd 322.2327, found 322.2331.

(5E)-4[(1E)-buta-1,3-dienyl]-4-methoxyocta-5,7-dienol (116)



115 **116**

Silyl ether **115** (1.16g, 3.6mmol, 1 eq) and TBAF (1M in THF, 7.2mL, 7.2 mmol, 2.0 eq) were stirred in THF (20mL) at room temperature for 4½ hours. After this time the reaction mixture was filtered through silica and evaporated. The crude product was purified by column chromatography (20% acetone in hexane) to give pure alcohol **116** as a colourless oil (710mg, 95%).

$\mathbf{R}_f$ 0.30 (20% acetone in hexane).

IR (film) 3357 (O–H), 2952, 2873 (C–H), 1602 (C=C), 1005 (C–O).

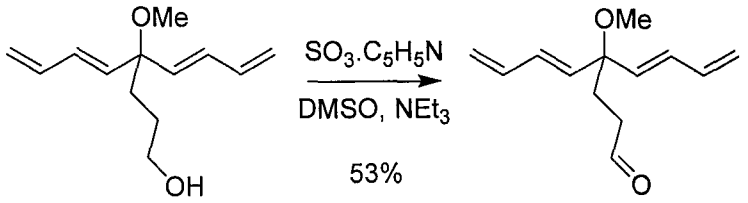
^{1}H NMR (300MHz, $CDCl_3$) δ 6.40 (2H, ddd, J = 17, 11, 10, $\underline{H}C{=}CH_2$), 6.20 (2H, dd, J = 11, 16, $\underline{H}C{=}C{-}C(OCH_3)$), 5.60 (2H, d, J = 16, $\underline{H}C{-}C(OCH_3)$), 5.20 (2H, dd, J = 17, 2, HHC=C), 5.10 (2H, dd, J = 10, 2, HHC=C), 3.60 (2H, t, J = 6, $\underline{H_2}C{-}OH$), 3.20 (3H, s, $H_3C{-}O$), 2.30 (1H, broad s, OH), 1.70 (2H, m, alkyl), 1.60 (2H, m, alkyl).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 136.70 ($\underline{C}HC(OCH_3)$), 135.90 ($\underline{C}H{=}CH_2$), 131.90 ($\underline{C}H{=}C{-}C(OCH_3)$), 117.70 ($\underline{CH_2}{=}C$), 79.60 ($\underline{C}(OCH_3)$), 63.10 ($CH_2OH$), 51.00 ($CH_3{-}O$), 34.70 ($\underline{C}H_2C(OCH_3)$), 26.80 ($\underline{C}H_2CH_2OH$).

EIMS *m/z* (%) 177 (10%, $(M{-}OCH_3)^+$), 135 (79%), 87 (100%).

HRMS (EIMS) for $C_{12}H_{17}O_1$ ($(M{-}OCH_3)^+$) calcd 177.12794, found 177.12731.

(5E)-4[(1E)-buta-1,3-dienyl]-4-methoxyocta-5,7-dienal (117)



116 **117**

Alcohol **116** (0.21g, 1mmol, 1eq) was dissolved in CH_2Cl_2 (12mL), and cooled to 0°C. Sulfur trioxide / pyridine complex (0.80g, 5mmol, 5eq), DMSO (0.39g, 5mmol, 5eq), and triethylamine (0.51g, 5mmol, 5eq) were dissolved in CH_2Cl_2 (20mL), and cooled to 0°C. This was added dropwise to the alcohol solution, and stirred at 0°C for 1¾ hours. The reaction mixture was then poured into a 50:50 ether / ammonium chloride (aq, ½ saturated, 10mL) mixture, and extracted with ether (3×15mL). The organic phase was washed with brine (10mL), dried over magnesium sulfate, and evaporated to give 240mg crude product. This was purified by column chromatography (8% ethyl acetate in hexane) to give 110mg of pure aldehyde **117** as a pale yellow oil (53%).

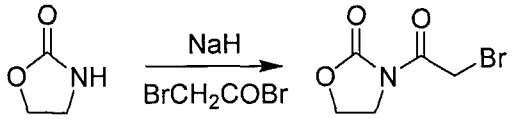
$\mathbf{R_f}$ 0.28 (8% ethyl acetate in hexane).

^{1}H NMR (400MHz, $CDCl_3$) δ 9.77 (1H, t, J = 1, CHO), 6.36 (2H, dddd, J = 17, 10, 10, 1, $\underline{H}C{=}CH_2$), 6.23 (2H, dd, J = 15,10, $\underline{H}C{=}C{-}C(OCH_3)$), 5.60 (2H, dd, J = 15, 1, $\underline{H}C{-}C(OCH_3)$), 5.25 (2H, dd, J = 17, 2, HHC=C), 5.13 (2H, dd, J = 10, 2, HHC=C), 3.13 (3H, s, OCH_3), 2.48 (2H, dt, J = 1, 8, $\underline{H_2}CCHO$), 2.02 (2H, t, J = 8, $\underline{H_2}CCOCH_3$).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 202.10 (CHO), 136.30 ($\underline{C}HC(OCH_3)$), 135.10 ($\underline{C}H{=}CH_2$), 132.20 ($\underline{C}H{=}C{-}C(OCH_3)$), 117.90 ($\underline{C}H_2{=}C$), 78.80 ($\underline{C}(OCH_3)$), 50.80 ($CH_3{-}O$), 38.40 ($\underline{C}H_2C(OCH_3)$), 29.70 ($\underline{C}H_2CHO$).

CIMS *m/z* (%) 224 (73%, $(M+NH_4)^+$), 207 (86%, $(M+H)^+$), 154 (100%).

3-(Bromoacetyl)-2-oxazolidinone (119)[47]



96 72% **119**

Sodium hydride (60% dispersion in mineral oil, 2.2g, 55 mmol, 1.15 eq) was suspended in THF (70mL). 2-Oxazolidinone (**96**, 4.18g, 48 mmol, 1 eq) was added and the mixture refluxed for 1 hour, and then cooled to 0°C. Bromoacetylbromide (10.1g, 50 mmol, 1.04 eq) was then added in THF (10mL), and the reaction stirred at room temperature overnight. Saturated ammonium chloride solution (50mL) was added, and extracted with ethyl acetate (2×100mL). The combined organic extracts were dried over magnesium sulfate and evaporated, and the residue purified by column chromatography (diethyl ether) to give pure bromide **119** (7.117 g, 72%).

$\mathbf{R_f}$ 0.40 (diethyl ether).

IR (film) 3066, 2968, 2925 (C–H), 1782, 1701 (C=O).

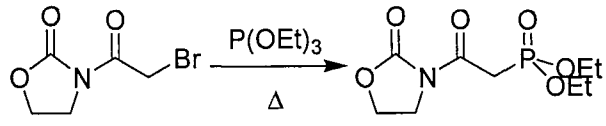
^{1}H NMR (300MHz, $CDCl_3$) δ 4.50 (2H, s, CH_2Br), 4.45 (2H, t, J = 8, CH_2N), 4.15 (2H, t, J = 8, CH_2O).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 166.20 (O–C=O), 153.30 (C=O–CH_2Br), 62.80 (CH_2O), 42.90 (CH_2N), 28.00 (CH_2Br).

CIMS *m/z* (%) 225 (10%, $(M+NH_4)^+$), 223 (10%, $(M+NH_4)^+$), 88 (100%, $(C_3H_6NO_2)^+$), 130 (60%).

Characterization was consistent with the literature.[47]

Diethyl 2-oxo-2-(2-oxo-1,3-oxazolidin-3-yl)ethylphosphonate (118)[48]



119 94% **118**

Bromide **119** (3.7g, 18 mmol, 1eq) was stirred with triethyl phosphite (9.3g, 56 mmol, 3.1 eq) at 80–100° for 2 hours. The reaction mixture was purified by column chromatography (50% acetone in hexane to neat acetone) to give pure phosphonate **118** as a pale yellow oil (4.49g, 94%).

$\mathbf{R}_f$ 0.18 (ethyl acetate).

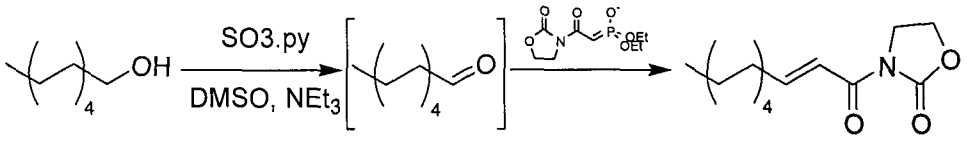
IR (film) 2986, 2931 (C–H), 1778, 1697 (C=O), 1260 (P=O), 1024 (P–O).

^{1}H NMR (300MHz, $CDCl_3$) δ 4.40 (2H, t, J = 8, CH_2N), 4.10 (4H, dq, J = 7, 7, $OC\underline{H}_2CH_3$), 4.00 (2H, t, J = 8, CH_2O), 3.70 (2H, d, J = 22, CH_2P), 1.30 (6H, t, J = 7, $OCH_2C\underline{H}_3$).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 165.40 (J_P=6Hz, C(O)–C), 153.80 (C(O)–O), 63.10 (CH_2O), 62.60 (J_P=77Hz, $O\underline{C}H_2CH_3$), 43.10 (CH_2N), 34.20 (J_P=132Hz, $\underline{C}H_2P$), 16.80 ($OCH_2\underline{C}H_3$).

EIMS *m/z* (%) 265 (5%, M^+), 220 (9%, $(M–OC_2H_5)^+$), 179 (49%, $(M–C_3H_4NO_2)^+$), 87 (100%, $(C_3H_5NO_2)^+$).

3-[(2E)-dodec-2-enoyl]1,3-oxazolidin-2-one (122)



120 **121** **122**

1-Decanol (**120**, 158mg, 1mmol, 1eq) was stirred in CH_2Cl_2 (6mL) at 0°C, and sulfur trioxide / pyridine complex (795mg, 5mmol, 5eq), DMSO (2mL, 5mmol, 5eq), triethylamine (370µl, 5mmol, 5eq) added. The reaction was stirred at 0°C for 10 minutes, then ½ hour at room temperature. Ice water (8mL) was added, the mixture diluted with ethyl acetate (10mL), and washed with $KHSO_4$ (aq, 1M, 2×10mL) and brine (10mL). This was dried over $MgSO_4$ and evaporated to give the crude aldehyde **121**.

Meanwhile, phosphonate **118** (1mmol, 1eq) was stirred in THF (5mL) at 0°C, and sodium hexamethyldisilazide (1M in THF, 1mL, 1mmol, 1eq) added slowly. This mixture was stirred at 0°C for 10 minutes, then room temperature for one hour, before the crude aldehyde was added in THF (2mL). This was stirred for 2 hours at room temperature, before being poured into pH7 phosphate buffer (10mL). This mixture was washed with ethyl acetate (2×15mL), water (2×15mL), $NaHCO_3$ (aq, saturated, 20mL) and brine (20mL), before being dried and evaporated to give 293mg crude product. This was purified by column chromatography (20% acetone in hexane) to give 103mg of product **122** (39%).

$\mathbf{R}_f$ 0.29 (20% acetone in hexane).

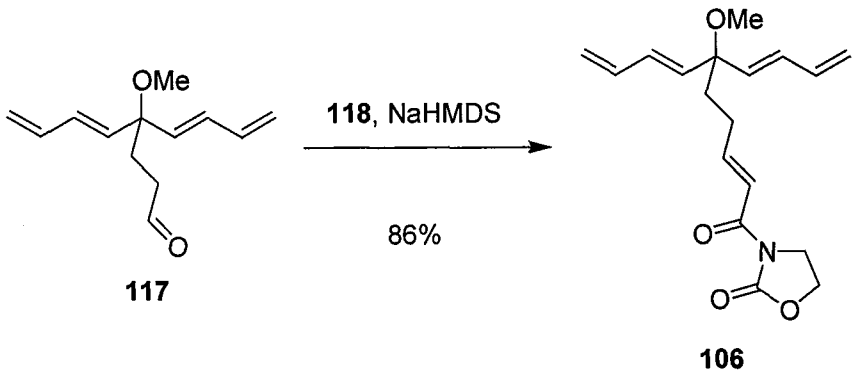
^{1}H NMR (400MHz, $CDCl_3$) δ 7.19 (1H, dd, J = 1, 15, CH=C**H**–C=O), 7.12 (1H, ddt, J = 1, 15, 7, C**H**=CH–C=O), 4.34 (2H, t, J = 8, N–CH_2–C**H**$_2$–O), 3.99 (2H, t, J = 8, N–C**H**$_2$–CH_2–O), 2.20 (2H, dt, J = 7, 7, C**H**$_2$–CH=CH), 1.5–1.1 (14H, m, alkyl chain), 0.81 (3H, t, J = 7, CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ 165.2 (N–**C**(O)–O), 153.4 (CH–**C**(O)–N), 151.6 (**C**H–C(O)–N), 119.8 (CH_2–**C**H=CH), 61.9 (N–CH_2–**C**H$_2$–O), 42.6 (N–**C**H$_2$–CH_2–O), 32.6 (**C**H$_2$–CH=CH), 31.7, 29.4, 29.3, 29.1, 29.1, 28.0, 22.5 (alkyl chain), 14.0 (CH_3).

CIMS *m/z* (%) 285 (20%, $(M+NH_4)^+$), 268 (100%, $(M+H)^+$), 88 (22%, $(C_3H_6NO_2)^+$).

HRMS (ES+) for $C_{15}H_{25}N_1O_3$ (M^+) calcd 267.18344, found 267.18265.

3-{(2E,7E)-6-[(1E)-buta-1,3-dienyl]-6-methoxydeca-2,7,9-trienoyl}-1,3-oxazolidin-2-one (106)



117 **106**

Phosphonate **118** (0.21g, 0.8mmol, 1.5eq) was stirred in THF (5mL) at 0°C, and sodium hexamethyldisilazide (1M in THF, 0.64mL, 0.64 mmol, 1.2eq) added slowly. This was stirred for ten minutes at 0°C and one hour at room temperature, at which time aldehyde **117** (0.11g, 0.53mmol, 1eq) was added in THF (2mL). This was stirred for 1½ hours at room temperature, then added to 10mL of pH7 phosphate buffer. The resulting mixture was diluted with ethyl acetate (10mL), separated, and then washed with $KHSO_4$ (aq, 1M, 10mL), water (10mL), $NaHCO_3$ (aq, saturated, 10mL) and brine (10mL). The organic phase was dried over $MgSO_4$ and evaporated, and the resulting oil purified by column chromatography (22% acetone in hexane) to give 145mg pure substrate **106** as a colourless oil (86%).

$\mathbf{R_f}$ 0.22 (22% acetone in hexane).

IR (film) 3087, 2937, 2826 (C–H), 1778, 1713 (Imide), 1682 (C=O), 1634 (C=C), 1602 (C=C), 1386.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.26 (1H, d, J = 15, C=HCC(O)), 7.15 (1H, dt, J = 15, 7, C=HCCH$_2$), 6.37 (2H, dddd, J = 17, 10, 10, 1, HC=CH$_2$), 6.23 (2H, dd, J = 16, 10, HC=C–C(OCH$_3$)), 5.62 (2H, dd, J = 16, 1, HC–C(OCH$_3$)), 5.25 (2H, dd, J = 17, 1, HHC=C), 5.12 (2H, dd, J = 10, 1, HHC=C), 4.42 (2H, t, J = 8, CH$_2$N), 4.06 (2H, t, J = 8, CH$_2$O), 3.16 (3H, s, OCH$_3$), 2.30 (2H, m, H$_2$CC=C), 1.84 (2H, m, H$_2$CCOCH$_3$).

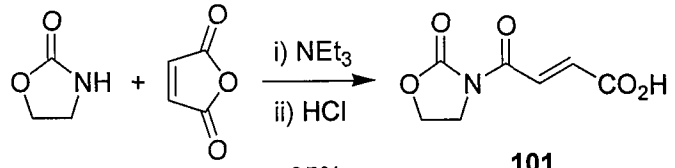
^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 165.20 (C(O)–C), 153.50 (C(O)–O), 151.40 (C=CCH$_2$), 136.40 (CHC(OCH$_3$)), 135.40 (CH=CH$_2$), 132.00 (CH=C–C(OCH$_3$)), 119.90

(C=CC(O)), 117.70 ($\underline{C}H_2$=C), 79.10 ($\underline{C}(OCH_3)$), 62.00 (CH_2O), 50.80 (CH_3–O), 42.70 (CH_2N), 35.80 ($\underline{C}H_2C(OCH_3)$), 26.80 ($\underline{C}H_2C$=C).

EIMS *m/z* (%) 317 (5%, M^+), 285 (10%, $(M–H_2O)^+$), 198 (100%), 91 (89%).

HRMS (ES+) for $C_{18}H_{23}N_1O_4Na_1$ ($(M+Na)^+$) calcd 340.1519, found 340.1517.

(*E*)-4-Oxo-4-(2-oxo-oxazolidin-3-yl)-but-2-enoic acid (101)



96 **97** **101**

2-Oxazolidinone (**96**, 870mg, 10mmol, 1eq) and maleic anhydride (**97**, 980mg, 10mmol, 1eq) were stirred in CH_2Cl_2 (20mL), and triethylamine (1.5mL, 10mmol, 1eq) added slowly. The resulting purple mixture was stirred overnight, and then water (0.36mL, 2eq) added. This was stirred for a further 20 minutes, at which point HCl (1M, 10mL) was added. The solvent was then removed at reduced pressure, and the resulting solid washed with acetone (200mL). The acetone was removed to give 2.3g crude product, which was recrystallized from water to give compound **101** as off-white needles (1.2g, 65%).

Mp 184–186°C.

IR (neat powder) 3499 (OH), 2976 (C–H), 1765 (C=O), 1682 (C=O), 1636 (C=O).

^{1}H NMR (300MHz, d_6-Acetone) δ 8.18 (1H, d, J = 16, $\underline{H}$C=C–CO_2H), 6.81 (1H, d, J = 16, C=$\underline{H}$C–CO_2H), 4.54 (2H, t, J = 8, CH_2N), 4.12 (2H, t, J = 8, CH_2O).

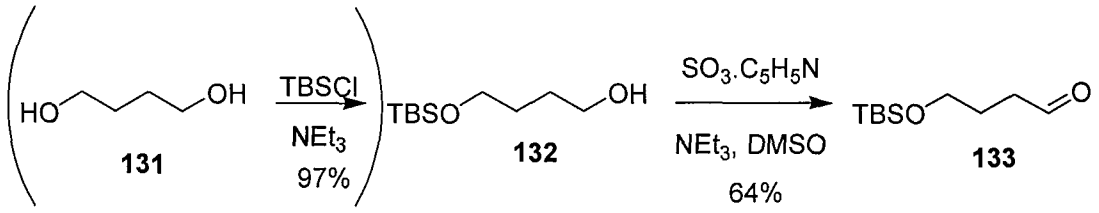
^{13}C NMR + DEPT (75MHz, d_6-Acetone) δ 166.00 (COOH), 164.06 ($\underline{C}$(O)–C), 154.30 (N–C(O)–O), 133.70 (C=$\underline{C}$–COOH), 133.43 ($\underline{C}$=C–COOH), 63.44 (CH_2O), 43.28 (CH_2N).

ES– MS *m/z* (%) 184 (28%, $(M–H)^-$), 175 (100%).

Anal. Calcd for $C_7H_7N_1O_5$: C, 45.41; H, 3.81; N, 7.57. Found: C, 45.59; H, 3.83; N, 7.53.

5.3 Preparation of Compounds Involved in the Dialkyne Investigations

4-(t-butyldimethylsilyloxy)butan-1-al (133)



4-(t-butyldimethylsilyloxy)butan-1-ol (**132**, which was readily prepared in 97% yield from butan-1,4-diol (**131**, 10g, 1.1eq) by stirring with TBSCl (15g, 1eq) and NEt_3 (13mL, 2.2eq) in CH_2Cl_2 (200mL) at 0°C for 5 hours[57]) (204mg, 1mmol) was stirred in CH_2Cl_2 (5mL) at 0°C, and a solution of $SO_3.C_5H_5N$ (478mg, 3eq), DMSO (1.1mL, 15 eq) and NEt_3 (0.42mL, 3eq) in CH_2Cl_2 (5mL) added dropwise. This solution was stirred at 0°C for 2 hours, at which point TLC indicated that no starting material remained. The mixture was poured onto 50:50 ether:NH_4Cl (aq, ½ sat) (10mL), and extracted with ether (3×15mL). The organic phase was dried over magnesium sulfate and evaporated, and the residue purified by column chromatography (5–10% ether in pentane) to give **133** as a pale yellow oil (130mg, 64%).

R_f 0.47 (20% ether in pentane).

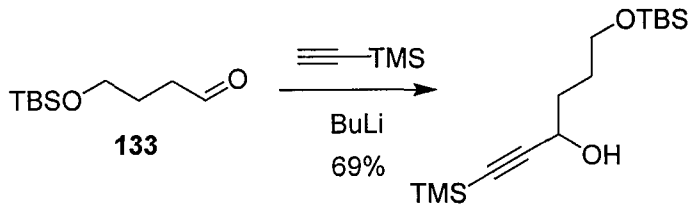
IR (film) 2955, 2930, 2887, 2858 (C–H), 2715 (CHO), 1728 (C=O), 1256 (C–Si).

^{1}H NMR (300MHz, $CDCl_3$) δ 9.79 (1H, t, J = 2, CHO), 3.65 (2H, t, J = 6, $SiOCH_2$), 2.51 (2H, dt, J = 2, 7, $C\underline{H}_2CHO$), 1.86 (2H, tt, J = 6, 7, $C\underline{H}_2CH_2CHO$), 0.91 (9H, s, $SiCCH_3$), 0.09 (6H, s, $SiCH_3$).

CIMS *m/z* (%) 203 (5%, $(M+H)^+$), 145 (28%, $(M-C_4H_9)^+$), 57 (100%, $(C_4H_9)^+$).

Characterization was consistent with the literature.[57]

1-trimethylsilyl-6-t-butyldimethylsilyloxyhex-1-yn-3-ol (135)



135

TMS-acetylene (7.3mL, 52mmol, 1.05eq) was dissolved in THF (70mL) at 0°C, and *n*-butyllithium (2.4M in hexanes, 23mL, 55.2mmol, 1.1eq) was added via cannula. The mixture was stirred at 0°C for 30 minutes, at which point it was added to a solution of aldehyde **133** (10.0g, 49.5mmol, 1eq) at –78°C via cannula. The mixture was then stirred at –78°C for 45 minutes and then at room temperature for a further three hours, at which point TLC indicated that no starting material remained. NH_4Cl (aq) (200mL, ½ saturated) was added, and the aqueous layer extracted with CH_2Cl_2 (3×20mL). The organic phase was then dried with brine (20mL) and $MgSO_4$ and evaporated. This was purified by column chromatography to give 10.22g pure product **135** as a colourless oil (69%).

$\mathbf{R}_f$ 0.31 (8% ethyl acetate in hexane).

IR (film) 3388 (O–H), 2956, 2858 (C–H), 2171 (C≡C), 1250, 840 (Si–C).

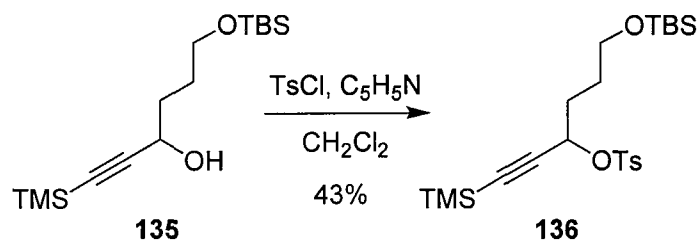
^{1}H NMR (300MHz, $CDCl_3$) δ 4.41 (1H, m, C<u>H</u>OH), 3.67 (2H, m, CH_2OSi), 3.39 (1H, broad s, OH), 1.9–1.6 (4H, m, alkyl), 0.90 (9H, s, $SiCCH_3$), 0.15 (9H, s, $C{\equiv}CSiCH_3$), 0.07 (6H, s, $OSiCH_3$).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 106.94 (SiC≡<u>C</u>), 89.00 (Si<u>C</u>≡C), 63.32 (COH), 62.51 (COSi), 35.38 (<u>C</u>H_2COH), 28.57 (<u>C</u>H_2COSi), 26.01 (<u>C</u>H_3CSiO), 18.39 (CH_3<u>C</u>SiO), 0.37 (<u>C</u>H_3SiC≡C), –5.14 (CH_3SiO).

CIMS *m/z* (%) 301 (14%, $(M+H)^+$), 283 (19%, $(M–H_2O+H)^+$), 203 (100%, (M+H–(TMS–C≡C))$^+$), 145 (58%), 71 (57%).

HRMS (CIMS) for $C_{15}H_{33}O_2Si_2$ ($(M+H)^+$) calcd 301.20191, found 301.20197.

3-trimethylsilyl-1-(3-t-butyldimethylsilyloxypropyl)prop-2-ynyl p-toluene-sulfonate (136)



135 **136**

Pyridine (10mL) was added to alcohol **135** (600mg, 2mmol, 1eq) in CH_2Cl_2 (4mL), and the mixture cooled to 0°C. Tosyl chloride (847mg, 4.4mmol, 2.2eq) in CH_2Cl_2 (4mL) was added, and the reaction stirred for 2 hrs at 0°C, and overnight at room temperature. At this stage TLC indicated that no starting material was left, and ice water (20mL) was added. After extraction with ethyl acetate (3×10mL), the organic phase was dried over magnesium sulfate and evaporated, and the crude product purified by column chromatography and HPLC (5% ethyl acetate in hexane) to give 392mg of **136** (43%) as a colourless oil.

$\mathbf{R_f}$ 0.40 (10% ether in hexane).

IR (film) 2957, 2929, 2897, 2857 (C–H), 2179 (C≡C), 1599, 1496 (C=C (Ar)), 1370, 1178 (SO_2–O), 1251, 844 (Si–C).

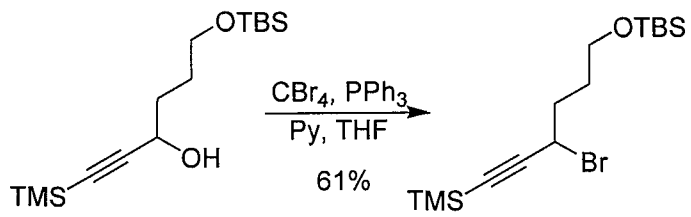
^{1}H NMR (300MHz, $CDCl_3$) δ 7.82 (2H, d, J = 8, ArH), 7.32 (2H, d, J = 8, ArH), 5.12 (1H, t, J = 7, HCOTs), 3.62 (2H, t, J = 6, H_2COSi), 2.44 (3H, s, H_3CAr), 1.90 (2H, m, H_2CCOSi), 1.65 (2H, m, H_2CCOTs), 0.88 (9H, s, H_3CCSi), 0.04 (6H, s, H_3CSiO), 0.02 (9H, s, H_3CSiC).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 144.50 (Ar), 134.19 (Ar), 129.55 (Ar), 128.11 (Ar), 99.81 (C≡CSi), 93.44 (SiC≡C), 72.13 (CHOTs), 62.13 (CH_2OSi), 32.61 (CH_2COSi), 27.88 (CH_2COTs), 25.88 (CH_3CSi), 21.61 (CH_3Ar), 18.23 (CH_3CSi), –0.58 (CH_3SiC), –5.39 (CH_3SiO).

CIMS *m/z* (%) 283 (29%, $(M–TsO)^+$), 225 (69%, $(M–TsOH–{}^tBu)^+$), 73 (100%, $(TMS)^+$).

This compound could not be attained in sufficient purity to acquire HRMS.

1-trimethylsilyl-3-bromo-6-t-butyldimethylsilyloxyhex-1-yne (137)



135 **137**

Alcohol **135** (1.2g, 4mmol, 1eq) and triphenylphosphine (2.52g, 9.6mmol, 2.4eq) were stirred in THF (40mL), and pyridine (0.47g, 6mmol, 1.5eq) added by syringe. Resublimed carbon tetrabromide (1.52g, 4.6mmol, 1.15eq) was added, and after two hours stirring at room temperature, TLC indicated that no starting material remained. The reaction mixture was evaporated, hexane (20mL) added, and filtered. The liquid organic phase was washed with HCl (1M, 30mL), Na_2SO_4 solution (saturated, 2×30mL), and brine (30mL), before being dried over magnesium sulfate and evaporated. The resulting colourless oil was purified by column chromatography (0–1% ethyl acetate in hexane) to give 1.1g c4:1 bromide **137**:PPh_3 (61%). A sample of this was stirred with methyl iodide (4eq) overnight in ether, and worked up with water. After ether extraction, NMR indicated that no PPh_3 remained.

$\mathbf{R}_f$ 0.57 (1% ethyl acetate in hexane).

IR (film) 2956, 2929, 2897, 2858 (C–H), 2172 (C≡C), 1252 (C–Si), 843 (C–Si).

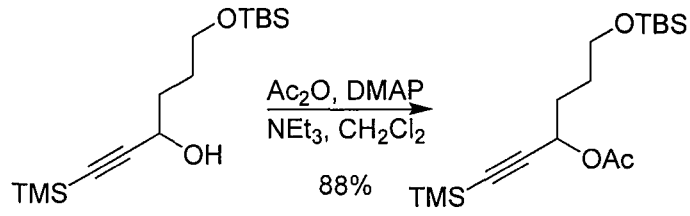
^{1}H NMR (400MHz, $CDCl_3$) δ 4.58 (1H, t, J = 7, HCBr), 3.67 (2H, t, J = 6, H_2COSi), 2.08 (2H, m, H_2CCOSi), 1.75 (2H, m, H_2CCBr), 0.91 (9H, s, H_3CCSi), 0.18 (9H, s, H_3CSiC), 0.06 (6H, s, H_3CSiO).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 103.84 (SiC≡<u>C</u>), 92.01 (Si<u>C</u>≡C), 62.15 (CH_2OSi), 37.16 (CHBr), 36.50 ($\underline{C}H_2CH_2OSi$), 30.46 ($\underline{C}H_2CHBr$), 25.92 ($\underline{C}H_3CSi$), 18.29 ($CH_3\underline{C}Si$), –0.28 ($\underline{C}H_3SiC$), –5.32 (CH_3SiO).

CIMS *m/z* (%) 365 (5%, $(M+H)^+$), 363 (5%, $(M+H)^+$), 285 (35%), 147 (75%), 73 (100%, $(TMS)^+$).

HRMS (EIMS) for $C_{15}H_{30}O_1Si_2{}^{79}Br_1$ ($(M–H)^+$) calcd 361.10186, found 361.10078.

3-trimethylsilyl-1-(3-t-butyldimethylsilyloxypropyl)prop-2-ynyl acetate (138)



135 **138**

Alcohol **135** (608mg, 2mmol, 1eq) was stirred in CH_2Cl_2 (20mL), and NEt_3 (0.20g, 2mmol, 1eq) and DMAP (10mg, 0.08mmol, 4mol%) added. The mixture was cooled to 0°C, and acetic anhydride (0.184mL, 2mmol, 1eq) added slowly. The mixture was allowed to warm to room temperature, and stirred overnight. $NaHCO_3$ (aq, saturated, 5mL) was then added and the mixture extracted with CH_2Cl_2 (2×20mL). The organic phase was dried over magnesium sulfate, evaporated and the crude product purified by column chromatography (5% ethyl acetate in hexane) to give pure acetate **138** (590mg, 88%) as a colourless oil.

$\mathbf{R}_f$ 0.28 (5% ethyl acetate in hexane).

IR (film) 2957, 2930, 2897, 2858 (C–H), 2180 (C≡C), 1748 (C=O), 1251, 1231, 842, 776 (Si–C).

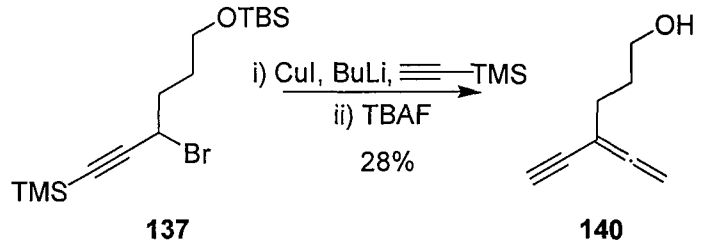
^{1}H NMR (400MHz, $CDCl_3$) δ 5.25 (1H, t, J = 7, HCBr), 3.48 (2H, t, J = 6, H_2COSi), 1.91 (3H, s, H_3COO), 1.64 (2H, m, H_2CCBr), 1.49 (2H, m, H_2CCOSi), 0.73 (9H, s, H_3CCSi), 0.00 (9H, s, H_3CSiC), –0.12 (6H, s, H_3CSiO).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 103.84 (SiC≡C), 92.01 (SiC≡C), 62.15 (CH_2OSi), 37.16 (CHBr), 36.50 (CH_2CH_2OSi), 30.46 (CH_2CHBr), 25.92 (CH_3CSi), 18.29 (CH_3CSi), –0.28 (CH_3SiC), –5.32 (CH_3SiO).

CIMS *m/z* (%) 343 (6%, $(M+H)^+$), 283 (100%, $(M–OAc)^+$), 73 (52%, $(TMS)^+$).

HRMS (EIMS) for $C_{13}H_{25}O_3Si_2$ ($(M–^tBu)^+$) calcd 285.13459, found 285.13423.

4-ethynylhexa-4,5-dien-1-ol (140)



137 **140**

Copper (I) iodide (235mg, 1.24mmol, 1.24eq) was suspended in THF (2mL), trimethylsilylacetylene (179mL, 1.26mmol, 1.26eq) added, and the mixture cooled to –78°C. Butyllithium (2.5M in hexanes, 0.573mL, 1.4mmol, 1.4eq) was added, and the mixture stirred at –78°C for 15 minutes. Bromide **137** (363mg, 1mmol, 1eq) was added in THF (4mL), and the reaction warmed slowly to 35°C and stirred for 60 hours. Despite TLC not indicating completion, $NaHCO_3$(aq) (saturated, 3mL) was added and extracted with ether (3×5mL), and the organic layer dried over magnesium sulfate and evaporated. Column chromatography (5% ethyl acetate in hexane) gave 330mg of a crude mixture (infra-red spectroscopy of this mixture suggested that isomerization to the allene had already taken place). The mixture was stirred in THF (20mL), and TBAF (1M in THF, 2mL, 2mmol) added. After 1½ hours stirring at room temperature, TLC indicated that no starting material remained. The mixture was filtered through silica gel, washed with ether (50mL) and evaporated. The crude mixture was purified by column chromatography to give 30mg of allene **140** (28%) as a pale yellow oil.

$\mathbf{R}_f$ 0.31 (30% acetone in hexane).

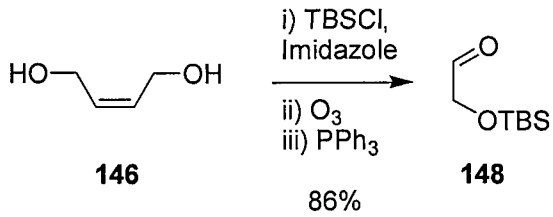
IR (film) 3276 (OH), 2941, 2870 (C–H), 1933 (C=C=C).

^{1}H NMR (400MHz, $CDCl_3$) δ 4.96 (2H, 2×dd, J = 3, 2, H_2C=C=C), 3.68 (2H, t, J = 6, H_2COH), 2.98 (1H, dd, J = 1, HC≡C), 2.20 (2H, m, H_2CCOH), 1.78 (2H, m, H_2CC=C), 1.50 (1H, s, OH).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 213.91 (C=<u>C</u>=CH_2), 87.97 (<u>C</u>=C=CH_2), 79.53 (<u>C</u>≡CC), 78.92 (C≡<u>C</u>C), 77.46 (C=C=<u>C</u>H_2), 61.75 (COH), 30.47 (CH_2C=C), 29.23 (CCOH).

CIMS *m/z* (%) 138 (26%, $(M+NH_4)^+$), 123 (7%, $(M+H)^+$), 99 (87%), 87 (100%).

(tert-Butyl-dimethyl-silanyloxy)-acetaldehyde (148)



146 **148**

86%

But-2-en-1,4-diol (**146**, 5.3g, 60mmol, 1eq) was suspended in CH_2Cl_2 (200mL), and cooled to 0°C. Imidazole (19.6g, 264mmol, 4.4eq) was added, followed by TBSCl (21.7g, 144mmol, 3.6eq), and the reaction stirred at 0°C until TLC (50% acetone in hexane) indicated no starting material (four hours). The reaction was then poured over saturated sodium hydrogencarbonate solution (50mL), and extracted with CH_2Cl_2 (2×50mL). The organic phase was dried and evaporated to give 22.6g of a pale yellow oil. This oil was then dissolved in CH_2Cl_2 (40mL in 50mL flask), and cooled to –78°C. Ozone was then bubbled through until a blue colour was observed (4h), and triphenylphosphine (63g, 240mmol, 6eq) added in five portions. The mixture was then warmed to room temperature and stirred overnight. The CH_2Cl_2 was removed carefully *in vacuo*, and two equivalents of aldehyde **148** (18.00g, 86%, 2 steps) was distilled off under reduced pressure (65°C, 12mmHg).

IR (film) 2955, 2930, 2886, 2858 (C–H), 1735 (C=O), 1257 (C–Si).

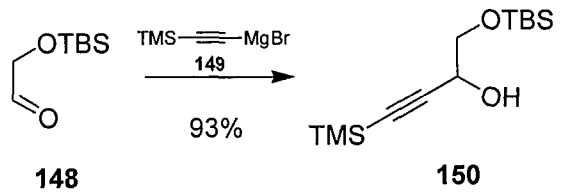
^{1}H NMR (300MHz, $CDCl_3$) δ 9.60 (1H, d, J = 1, CHO), 4.05 (2H, t, J = 1, CH_2), 0.84 (9H, s, H_3CCSi), –0.01 (6H, s, H_3CSi).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 202.40 (CHO), 69.76 (CH_2), 25.90 ($\underline{C}H_3CSi$), 18.48 ($CH_3\underline{C}Si$), –3.45 (CH_3Si).

CIMS *m/z* (%) 174 (14%, $(M+NH_4–H_2O)^+$), 117 (100%, $(M–C_4H_9)^+$).

Characterization was consistent with the literature.[82]

1-(tert-Butyl-dimethyl-silanyloxy)-4-trimethylsilanyl-but-3-yn-2-ol (150)



148 **150**

Trimethylsilylacetylene (5.64mL, 40mmol, 5.2eq) was dissolved in THF (50mL) and the mixture cooled to –78°C. Ethylmagnesium bromide (3M in diethyl ether, 13.3mL, 40mmol, 5.2eq) was added slowly and the mixture stirred at –78°C for 30 minutes, and then for 90 minutes at room temperature. After this time the mixture was cooled to 0°C, and aldehyde **148** (1.34g, 7.7mmol, 1eq) in THF (15mL) added. The mixture was then stirred for 3 hours at 0°C at which point an aqueous solution of ammonium chloride (saturated, 2mL) was added carefully. Water (5mL) was then added, the mixture separated, and the aqueous phase extracted with ether (3×20mL). The organic phase was washed with saturated brine (10mL), dried over magnesium sulfate and the solvent evaporated. The resulting mixture (which NMR indicated to be >95% pure) was purified by column chromatography (10% ethyl acetate in hexane) to give compound **150** as a colourless oil (5.06g, 93%).

$\mathbf{R}_f$ 0.31 (5% ethyl acetate in hexane).

IR (film) 3418 (O–H), 2957, 2929, 2898, 2857 (C–H), 2175 (C≡C), 1251 (Si–C).

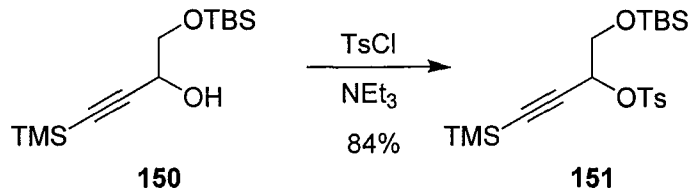
^{1}H NMR (300MHz, $CDCl_3$) δ 4.39 (1H, m, HC–OH), 3.76 (1H, dd, J = 10, 4, HHC–OSi), 3.65 (1H, dd, J = 10, 7, HHC–OSi), 2.60 (1H, d, J = 5, OH), 0.92 (9H, s, H_3CCSiO), 0.17 (9H, s, H_3CSi–C≡C), 0.11 (3H, s, H_3CSiO), 0.10 (3H, s, H_3CSiO).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 103.56 (C≡C–Si), 90.11 (C≡C–Si), 66.88 (C–OH), 63.54 (C–OSi), 25.84 (CH_3CSiO), 18.33 (CH_3CSiO), –0.20 (CSi–C≡C), –5.27 (H_3CSiO), –5.40 (H_3CSiO).

CIMS *m/z* (%) 273 (16%, $(M+H)^+$), 255 (100%, $(M–H_2O+H)^+$), 215 (27%, $(M–C_4H_9)^+$), 199 (20%, $(M–SiC_3H_9)^+$).

HRMS (EIMS) for $C_{12}H_{25}O_2Si_2$ ($(M–CH_3)^+$) calcd 257.13931, found 257.13883.

1-(tert-Butyl-dimethyl-silanyloxymethyl)-3-trimethylsilanyl-prop-2-ynyl p-toluene-sulfonate (151)



150 **151**

To alcohol **150** (272mg, 1mmol, 1eq) in CH_2Cl_2 (5mL) was added triethylamine (126mg, 1.25mmol, 1.25eq) and *p*-toluenesulfonyl chloride (228mg, 1.2mmol, 1.2eq), and the mixture stirred at room temperature overnight. At this stage, TLC in CH_2Cl_2 indicated no starting material. Ether (10mL) was added, and the mixture washed with aqueous sodium bicarbonate (saturated, 2×10mL) and saturated brine (10mL). The mixture was dried over magnesium sulfate and evaporated, and purified by column chromatography (10% ethyl acetate in hexane) to give tosylate **151** pure as a colourless oil (357mg, 84%).

$\mathbf{R_f}$ 0.29 (5% ethyl acetate in hexane).

IR (film) 2957, 2858 (C–H), 2184 (C≡C), 1252 (Si–C), 1372, 1178 (SO_2–O).

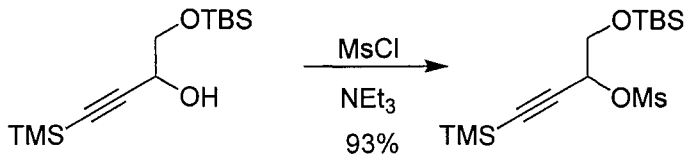
^{1}H NMR (300MHz, $CDCl_3$) δ 7.83 (2H, d, J = 8, ArH), 7.32 (2H, d, J = 8, ArH), 5.08 (1H, dd, J = 7, 5, HC–OS), 3.83 (1H, dd, J = 11, 7, HHC–OSi), 3.79 (1H, dd, J = 11, 5, HHC–OSi), 2.44 (3H, s, $ArCH_3$), 0.88 (9H, s, H_3CCSiO), 0.08 (3H, s, H_3CSiO), 0.07 (3H, s, H_3CSiO), 0.04 (9H, s, H_3CSi–C≡C).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 144.50 (ArC), 134.32 (ArC), 129.55 (ArCH), 128.15 (ArCH), 97.82 (C≡C–Si), 94.26 (C≡C–Si), 72.42 (C–OS), 65.17 (C–OSi), 25.73 (CH_3CSiO), 21.60 (Ar–CH_3), 18.25 (CH_3CSiO), –0.59 (CSi–C≡C), –5.32 (H_3CSiO), –5.45 (H_3CSiO).

CIMS *m/z* (%) 255 (100%, $(M–TsO)^+$), 171 (54%, $(TsO)^+$).

HRMS (EIMS) for $C_{16}H_{25}O_4S_1Si_2$ ($(M–^tBu)^+$) calcd 369.10121, found 369.10278.

1-(tert-Butyl-dimethyl-silanyloxymethyl)-3-trimethylsilanyl-prop-2-ynyl methanesulfonate (152)



150 **152**

To alcohol **150** (1.36g, 5mmol, 1eq) in CH_2Cl_2 (20mL) was added triethylamine (555mg, 5.5mmol, 1.1eq) and the mixture cooled to 0°C. Methanesulfonyl chloride (0.425mL, 5.5mmol, 1.1eq) was added and the mixture stirred at room temperature for 2 hours. TLC in CH_2Cl_2 showed no starting material, and water (5mL) was added and the mixture extracted with CH_2Cl_2 (2×30mL). The organic phase was washed with HCl (0.1M, 20mL) and brine (2×20mL). The mixture was dried over magnesium sulfate and evaporated, and purified by column chromatography (10% ethyl acetate in hexane) to give mesylate **152** pure as a colourless oil (1.628g, 93%).

R_f 0.30 (5% ethyl acetate in hexane).

IR (film) 2957, 2930, 2898, 2858 (C–H), 2183 (C≡C), 1368, 1180 (SO_2–O), 1253 (Si–C).

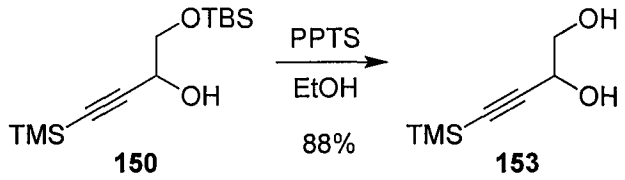
^{1}H NMR (300MHz, $CDCl_3$) δ 5.15 (1H, t, J = 6, HC–OS), 3.86 (2H, d, J = 6, H_2C–OSi), 3.12 (3H, s, H_3C–S), 0.91 (9H, s, H_3CCSiO), 0.19 (9H, s, H_3CSi–C≡C), 0.10 (6H, s, H_3CSiO).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 98.01 (C≡C–Si), 95.20 (C≡C–Si), 72.95 (C–OS), 65.17 (C–OSi), 39.12 (S–CH_3), 25.74 (CH_3CSiO), 18.27 (CH_3CSiO), –0.50 (CSi–C≡C), –5.31 (H_3CSiO), –5.42 (H_3CSiO).

CIMS *m/z* (%) 293 (5%, $(M–C_4H_9)^+$), 255 (100%, $(M–MsOH+H)^+$), 197 (14%, $(M–MsOH–C_4H_9)^+$), 73 (24%, $(TMS)^+$), 57 (35%, $(C_4H_9)^+$).

HRMS (EIMS) for $C_{13}H_{27}O_4Si_2S_1$ ($(M–Me)^+$) calcd 335.11686, found 335.11652.

4-Trimethylsilanyl-but-3-yne-1,2-diol (153)



To alcohol **150** (1.36g, 5mmol, 1eq) in ethanol (20mL) was added PPTS (380mg, 1.5mmol, 35mol%). The reaction was stirred at 65° for 24 hrs, and the solvent then removed *in vacuo*. Ethyl acetate (30mL) and brine (20mL) were then added, and the mixture separated. The organic phase was washed with water (2×10mL), dried over magnesium sulfate, and the solvent evaporated. This crude product was purified by column chromatography (10–50% ethyl acetate in hexane) to give product **153** as a white solid (690mg, 88%).

$\mathbf{R_f}$ 0.27 (50% ethyl acetate in hexane).

Mp 52–54°C.

IR (solution, CH_2Cl_2) 3366 (O–H), 3054, 2960, 2903 (C–H), 2174 (C≡C), 1252 (Si–C).

^{1}H NMR (300MHz, $CDCl_3$) δ 4.45 (1H, dd, J = 7, 4, HCOH), 3.73 (1H, dd, J = 12, 4, HHCOH), 3.65 (1H, dd, J = 12, 7, HHCOH), 3.40 (1H, s, OH), 3.00 (1H, s, OH), 0.17 (9H, s, H_3CSi).

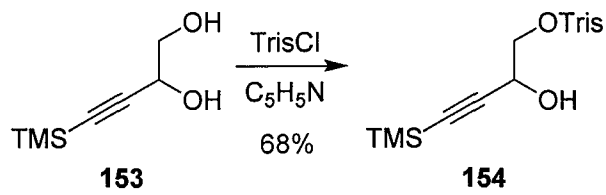
^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 103.02 (C≡C–Si), 91.18 (C≡C–Si), 66.36 (CH–OH), 63.59 (CH_2–OH), –0.23 (CSi–C≡C).

EIMS *m/z* (%) 128 (63%), 125 (61%, $(M–H_2O–Me)^+$), 99 (100%).

HRMS (EIMS) for $C_6H_9O_1Si_1$ ($(M–H_2O–Me)^+$) calcd 125.04227, found 125.04200.

Anal. Calcd for $C_7H_{14}O_2Si_1$: C, 53.12; H, 8.92. Found: C, 53.29; H, 9.02.

2-Hydroxy-4-trimethylsilanylbut-3-ynyl-2,4,6-triisopropylbenzenesulfonate (154)



153 **154**

To a solution of diol **153** (3.95g, 25mmol, 1eq) in pyridine (50mL) was added triisopropyl-benzenesulfonyl chloride (11.4g, 38mmol, 1.5eq). This was stirred overnight at room temperature, and the pyridine then removed *in vacuo*. The residue was then filtered through a plug of silica, washed with CH_2Cl_2, and then purified by column chromatography (10% ethyl acetate in hexane) to give 7.2g (68%) of sulfonate **154** as a colourless oil.

$\mathbf{R}_f$ 0.56 (20% ethyl acetate in hexane).

IR (film) 3510 (O–H), 2059, 2930, 2859 (C–H), 2176 (C≡C), 1600, 1564, 1463 (C=C (Ar)), 1348, 1179 (SO_2–O).

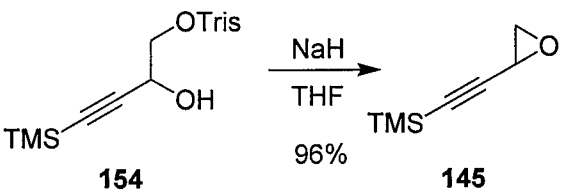
^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (2H, s, ArH), 4.68 (1H, ddd, J = 4, 6, 8, HCOH), 4.22 (1H, dd, J = 11, 4, HHC–OS), 4.14 (2H, septet, J = 7, HCAr (2–)), 4.09 (1H, dd, J = 11, 8, HHC–OS), 2.92 (1H, septet, J = 7, HCAr (4–)), 2.37 (1H, broad m, OH), 1.28 (12H, d, J = 7, H_3C–C–Ar (2–)), 1.27 (6H, d, J = 7, H_3C–C–Ar (4–)), 0.16 (9H, s, H_3CSi).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 154.16 (ArC), 151.06 (ArC), 129.33 (ArC), 124.02 (ArCH), 100.90 (Si–C≡C), 92.56 (Si–C≡C), 71.53 (CH_2–OS), 61.57 (CH–OH), 34.42 (CH–Ar), 29.84 (CH–Ar), 24.90 (CH_3–C–Ar), 23.67 (CH_3–C–Ar), –0.21 (CH_3Si).

EIMS *m/z* (%) 409 (39%, $(M–Me)^+$), 391 (42%), 267 (100%).

HRMS (EIMS) for $C_{22}H_{36}O_4Si_1S_1$ (M^+) calcd 424.21036, found 424.21123.

Trimethyl(oxiranylethynyl)silane (145)



154 **145**

To a solution of alcohol **154** (1.5g, 3.5mmol, 1eq) in THF (20mL) was added sodium hydride (849mg, 21mmol, 6eq), and the reaction stirred vigorously overnight. The sodium hydride was then filtered off through $MgSO_4$, washed with CH_2Cl_2, and the filtrate concentrated and purified by column chromatography (5% CH_2Cl_2 in pentane) to give 475mg (96%) of epoxide **145** as a colourless oil. This epoxide was later distilled using Kugelrohr apparatus between 40 and 60°C at 20mmHg (b.p. 44–48°C, 20mmHg).

R_f 0.28 (2% dichloromethane in pentane).

IR (film) 3061 (C–H (epoxide)), 2961, 2901 (C–H), 2179 (C≡C), 1251 (epoxide), 845.4 (broad) (C–Si & epoxide).

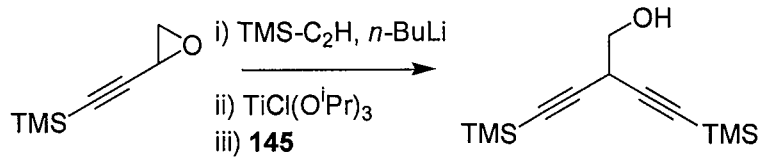
^{1}H NMR (400MHz, $CDCl_3$) δ 3.35 (1H, t, J = 4, HC–O), 2.90 (2H, d, J = 4, H_2C–O), 0.18 (9H, s, H_3CSi).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 101.88 (Si–C≡C), 89.33 (Si–C≡C), 48.94 (CH_2), 39.92 (CH), –0.30 (CH_3Si).

CIMS *m/z* (%) 158 (6%, $(M+NH_4)^+$), 141 (18%, $(M+H)^+$), 126 (74%, $(M-CH_3+H)^+$), 74 (54%, $(C_3H_{10}Si)^+$).

HRMS (EIMS) for $C_7H_{12}O_1Si_1$ (M^+) calcd 140.06462, found 140.06574.

4-Trimethylsilanyl-2-trimethylsilanylethynylbut-3-yn-1-ol (144)



145 77% **144**

To a solution of TMS-acetylene (0.565mL, 4mmol, 4eq) in diethyl ether (5mL) at 0°C was added *n*-butyllithium (2.5M in hexanes, 1.6mL, 4mmol, 4eq), and the reaction warmed to room temperature for ten minutes. This was then cooled to –50°C, and a solution of $TiCl(O^iPr)_3$ in THF (1.66M, 2.4mL, 4mmol, 4eq) was added. After five minutes stirring, epoxide **145** (140mg, 1mmol, 1eq) was added in diethyl ether (1mL) and the reaction warmed quickly to room temperature. After stirring overnight, hydrochloric acid (2M, 3mL) was added, and the mixture separated. The organic phase was washed with water (5mL) and brine (5mL), dried over magnesium sulfate, concentrated and purified by column chromatography (10% ethyl acetate in hexane) to give 183mg (77%) of dialkyne **144** as a brown oil.

R_f 0.33 (10% acetone in hexane).

IR (film) 3364 (O–H), 2960, 2899 (C–H), 2179 (C≡C), 1251, 843 (Si–C).

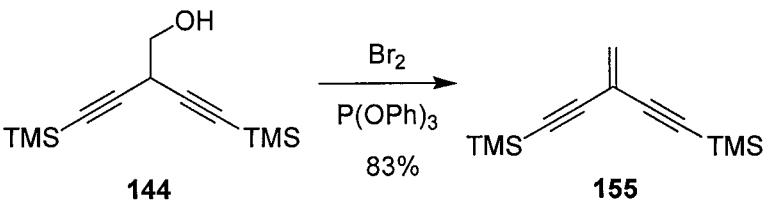
^{1}H NMR (400MHz, $CDCl_3$) δ 3.70 (1H, dd, J = 6, 6, HC–C≡C), 3.62 (1H, d, J = 6, HHC–OH), 3.60 (1H, d, J = 6, HHC–OH), 2.22 (1H, bs, OH), 0.17 (18H, s, H_3CSi).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 100.68 (Si–C≡C), 87.77 (Si–C≡C), 65.32 (CH_2–OH), 29.58 (CH–CH_2–OH), 0.02 (CH_3–Si).

EIMS *m/z* (%) 238 (5%, M^+), 220 (35%, $(M–H_2O)^+$), 165 (27%, $(M–C_3H_9Si)^+$), 73 (89%, $(C_3H_9Si)^+$).

HRMS (EIMS) for $C_{11}H_{19}O_1Si_2$ ($(M–Me)^+$) calcd 223.09745, found 223.09798.

1-trimethylsilyl-3-methylene-5-trimethylsilylpenta-1,4-diyne (155)



144 **155**

Triphenly phosphite (265μL, 1.01mmol, 1.2eq) was stirred in diethyl ether (5mL), bromine (47μL, 0.92mmol, 1.1eq) added, and the mixture cooled to 0°C. Alcohol **144** (200mg, 0.84mmol, 1eq) and pyridine (68μL) in diethyl ether (2mL) were added slowly, and the mixture stirred at room temperature for four hours. Water (10mL) was then added, and the mixture extracted with diethyl ether (2×5mL). The organic phase was washed with brine (5mL), dried over magnesium sulfate, and the solvent removed *in vacuo*. The crude mixture was purified by column chromatography (2% ethyl acetate in hexane) to give 155mg (83%) of compound **155**.

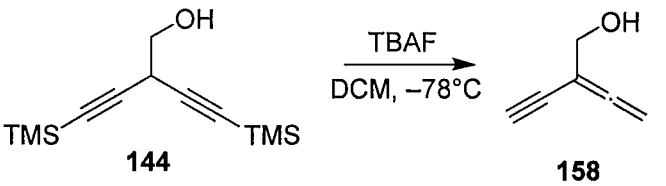
R_f 0.31 (2% ethyl acetate in hexane).

IR (film) 2961, 2899, (C–H), 2182 (C≡C), 1251, 843 (Si–C).

^{1}H NMR (400MHz, $CDCl_3$) δ 5.60 (2H, s, H_2C=C), -0.05 (9H, s, H_3C).

EIMS *m/z* (%) 220 (25%, M^+), 205 (100%, $(M–CH_3)^+$), 73 (58%, $(C_3H_9Si)^+$).

2-ethynylbut-2,3-dien-1-ol (158)



Scheme 73

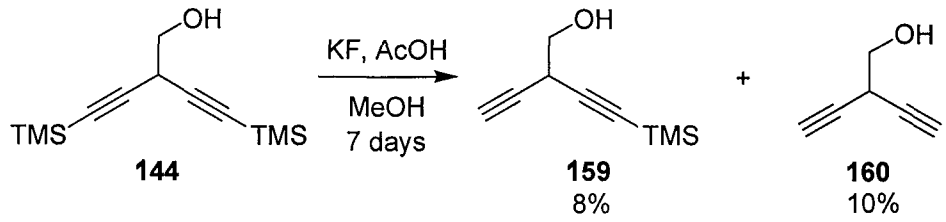
Alcohol **144** (101mg, 0.42mmol, 1eq) was stirred in THF (5ml) at –78°C. TBAF (1M in THF, 4.23mL, 0.84mmol, 2eq) was added very slowly, and the reaction stirred for ten minutes. After this time the reaction mixture was filtered through silica, washed with diethyl ether, and the solvent evaporated. The crude product was purified by column chromatography (10-20% ethyl acetatein hexane) to give pure alcohol **158** as a colourless oil (35mg, 88%).

$\mathbf{R}_f$ 0.29 (20% ethyl acetate in hexane).

^{1}H NMR (400MHz, $CDCl_3$) δ 5.11 (1H, dd, J = 2, 3, H_2C=C=C), 5.10(1H, dd, J = 2, 3, H_2C=C=C), 4.05 (2H, m, CH_2O), 2.95 (1H, dd, J = 2, 2, HC≡C), 2.00 (1H, bs, OH).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 212.74 (C=C=CH_2), 89.85 (C=C=CH_2), 80.80 (HC≡C), 79.46 (HC≡C), 77.12 (C=C=CH_2), 62.97 (COH).

2-(trimethylsilanylethynyl)but-3-yn-1-ol *and* 2-ethynylbut-3-yn-1-ol (159 and 160)



144 **159** 8% **160** 10%

Alcohol **144** (181mg, 0.8mmol, 1eq) was dissolved in methanol (5mL), and acetic acid (0.27mL, 4.6mmol, 6eq) added. Potassium fluoride (0.17g, 3.0mmol, 4eq) was added in one portion, and the reaction stirred at room temperature for 7 days. After this time, TLC (20% acetone in hexane) indicated that three major compounds were present: the starting material (R_f = 0.43) and two lower spots (R_f = 0.25 and 0.13). The mixture was filtered through silica and purified by column chromatography (10–50% acetone in hexane). The two compounds were indicated by NMR to be the mono-desilylated product **159** (10mg, 8%) and the bi-desilylated product **160** (7mg, 10%).

2-(trimethylsilanylethynyl)but-3-yn-1-ol (159)

R_f 0.25 (20% acetone in hexane).

^{1}H NMR (400MHz, $CDCl_3$) δ 3.75 (2H, 2×d, *J* = 7, 7, C<u>H</u>$_2$OH), 3.60 (1H, ddd, *J* = 3, 7, 7, C<u>H</u>CH$_2$OH), 2.25 (1H, d, *J* = 3, HC≡C), 0.18 (9H, s, H_3CSi).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 100.16 (<u>C</u>≡C–Si), 88.12 (C≡<u>C</u>–Si), 79.47 (<u>C</u>≡CH), 71.07 (C≡<u>C</u>H), 65.31 (CH_2OH), 28.45 (<u>C</u>HCH$_2$OH), –0.01 ($SiCH_3$).

2-ethynylbut-3-yn-1-ol (160)

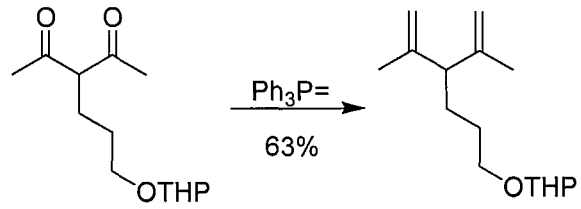
R_f 0.13 (20% acetone in hexane).

^{1}H NMR (400MHz, $CDCl_3$) δ 3.80 (2H, d, *J* = 7, C<u>H</u>$_2$OH), 3.59 (1H, tt, *J* = 3, 7, C<u>H</u>CH$_2$OH), 2.27 (2H, d, *J* = 3, HC≡C).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 79.07 (<u>C</u>≡CH), 71.34 (C≡<u>C</u>H), 65.20 (CH_2OH), 27.27 (<u>C</u>HCH$_2$OH).

5.4 Preparation of Compounds Involved in the Wittig investigations

2-[(4-isopropenyl-5-methyl-5-hexenyl)oxy]tetrahydro-2H-pyran (165)



164 **165**

Methyltriphenylphosphonium bromide (1.52g, 4.26 mmol, 3 eq) was stirred in toluene (20mL). Potassium t-butoxide (0.48g, 4.26 mmol, 3 eq) was added, giving the yellow coloured ylide, and the reaction refluxed for one hour. Diketone **164** (0.34g, 1.42 mmol, 1 eq) was then added at room temperature, and the mixture then refluxed for 3½ hours. After this time, saturated ammonium chloride solution (10mL) was added, extracted with ether (2×10mL) and washed with brine (10mL). The organic extracts were then dried over magnesium sulfate and evaporated. The residue was purified by column chromatography (4% ethyl acetate in hexane) to give diene **165** as a colourless oil (214 mg, 63%).

$\mathbf{R}_f$ 0.30 (4% ethyl acetate in hexane).

IR (film) 3068 (C=C–H), 2941, 2870 (C–H), 1639 (C=C).

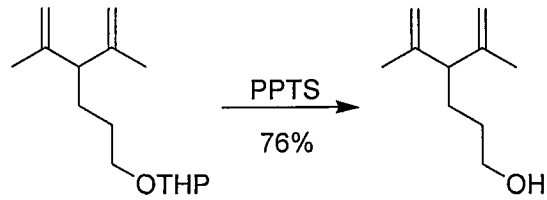
^{1}H NMR (300MHz, $CDCl_3$) δ 4.82 (2H, s, alkene CH), 4.77 (2H, s, alkene CH), 4.58 (1H, t, J = 3, O–CH–O), 3.80 (2H, m, CH_2–O), 3.40 (2H, m, CH_2–O), 2.60 (1H, t, J = 7, C=C–C<u>H</u>–C=C), 1.4–1.8 (16H, m, alkyl).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 146.30 (<u>C</u>=CH_2), 111.40 (<u>C</u>H_2=C), 98.90 (O–C–O), 67.70 (CH_2–O–), 62.40 (CH_2–O–), 54.10 (C=C–<u>C</u>H–C=C), 30.90 (THP), 20.30 (<u>C</u>H_3–C=C), 28.00 (), 26.80 (), 25.60 (), 19.80 (alkyl).

CIMS *m/z* (%) 239 (17%, $(M+H)^+$), 85 (100%, $(THP)^+$).

HRMS (CIMS) for $C_{15}H_{26}O_2$ (M^+) calcd 238.19328, found 238.19318.

4-isopropenyl-5-methyl-5-hexen-1-ol (166)



165 **166**

THP ether **165** (42mg, 0.18 mmol, 1 eq) was dissolved in ethanol (2mL), and pyridinium *p*-toluenesulfonate (5 mg, 0.020mmol, 11mol%) added. The reaction was then heated to 55°C (oil bath temperature) for 3 hours, and the solvent then removed *in vacuo*. The residue was then purified by column chromatography (20% acetone in hexane) to give pure alcohol **166** as a colourless oil (22 mg, 76%).

$\mathbf{R}_f$ 0.30 (20% acetone in hexane).

IR (film) 3333 (OH), 3077 (C=C–H), 2936, 2869 (C–H), 1635 (C=C).

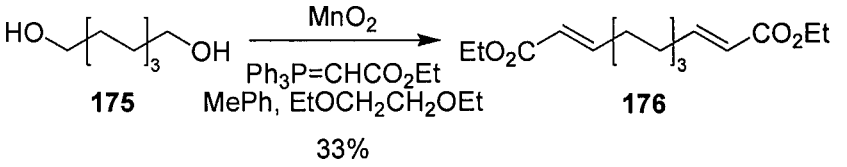
^{1}H NMR (300MHz, $CDCl_3$) δ 4.80 (2H, dq, J = 1, 2, HC=C), 4.70 (2H, m, HC=C), 3.60 (2H, t, J = 6, $\underline{H}_2COH$), 2.50 (1H, t, J = 7, C=C–CH–C=C), 1.3–1.6 (10H, m, alkyl).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 146.20 ($\underline{C}$=CH_2), 111.40 ($\underline{C}H_2$=C), 63.20 (CH_2OH), 54.10 (C=C–$\underline{C}$H–C=C), 31.10 ($\underline{C}H_2CH_2OH$), 26.40 ($\underline{C}H_2CH_2CH_2OH$), 20.30 ($\underline{C}H_3C$=C).

CIMS *m/z* (%) 155 (66%, $(M+H)^+$), 137 (84%, $(M–OH)^+$), 95 (100%, $(M–C_3H_7O)^+$).

HRMS (ElMS) for $C_{10}H_{18}O_1$ (M^+) calcd 154.13576, found 154.13615.

(2E,10E)-Dodeca-2,10-dienedioic acid diethyl ester (176)



175 **176**

Activated manganese (IV) oxide (0.6g) was added to a solution of octane-1,8-diol (**175**, 146 mg) and the Wittig reagent (1.40g) in toluene (50mL) and ethylene glycol diethyl ether (10mL). The reaction was brought to reflux, and a portion of manganese (IV) oxide (0.6g each) was added after ½ hour and then again after 1 hour. This was then refluxed overnight, before being filtered through celite. The crude product was purified by column chromatography (10% ethyl acetate in hexane) to give 94mg of the desired diester (**176**, 33%).

$\mathbf{R}_f$ 0.30 (10% ethyl acetate in hexane).

^{1}H NMR (300MHz, $CDCl_3$) δ 6.90 (1H, dt, J = 16, 7, $\underline{H}CCH_2$), 5.74 (1H, d, J = 16, $\underline{H}CC(O)$), 4.12 (2H, q, J = 7, $\underline{H_2}CCH_3$), 2.13 (2H, dt, J = 7, 7, $\underline{H_2}CC{=}C$), 1.25 (7H, m, alkyl hydrogens).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 166.88 (C=O), 149.35 ($\underline{C}{=}C{-}CO_2Et$), 121.48 ($\underline{C}{-}CO_2Et$), 60.28 ($\underline{C}H_2CH_3$), 32.24 ($\underline{C}H_2C{=}C$), 29.01 (alkyl), 28.01 (alkyl), 14.41 ($\underline{C}H_3CH_2$).

CIMS *m/z* (%) 283 (100%, $(M+H)^+$).

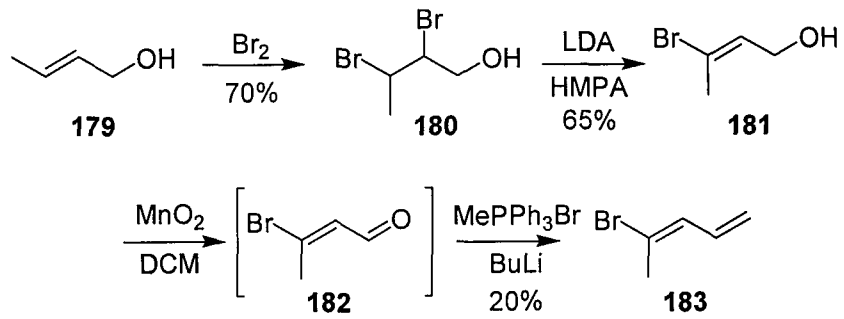
Appendix I: Additional Reactions

In the course of the research, a number of reactions were carried out that have not been included in the main body of the thesis. This was either because the compounds produced were not fully characterized, because they were compounds that have been previously reported in the literature, or because the encompassing reaction schemes were not deemed to fit into the main discussion of the results. Some of these reactions are discussed below.

I.1 Reactions Related to Chapter 2: The Organolithium Route

I.1.1 Attempted Preparation of 4-Bromopenta-1,3-diene

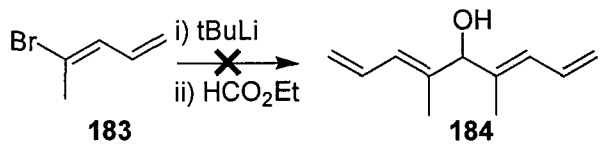
As an alternative to 1-bromobuta-1,3-diene (**92**), a route to 4-bromopenta-1,3-diene (**183**) was envisaged. It was judged that the substitution of this substrate into the organolithium reaction shown in Scheme 36 (*supra*) could prepare dimethyl analogues of compounds **94** and **114**.



Scheme 74

Crotyl alcohol (**179**) was reacted with bromine to give dibromoalcohol **180**. This was then reacted with LDA in the presence of HMPA to give alkene **181**. Oxidation of this using manganese dioxide gave the desired aldehyde **182**, which was then used without further purification. Methyltriphenylphosphonium bromide was reacted with butyllithium, and the aldehyde was added to give diene **183** in 20% yield over two steps.

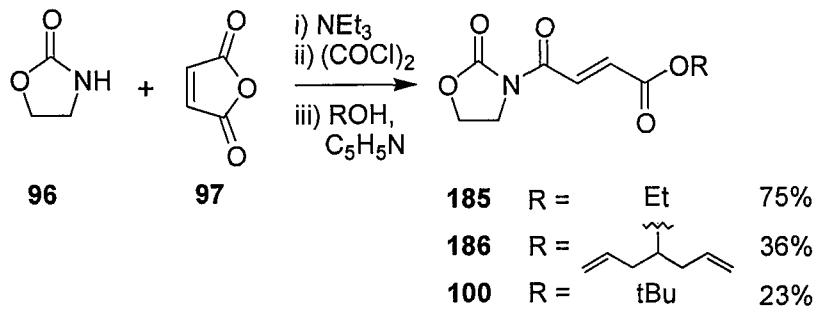
Reaction of bromide **183** with ethyl formate using *tert*-butyllithium was attempted (as illustrated in Scheme 75), but the reaction gave none of desired secondary alcohol **184**.



Scheme 75

I.1.2 Test One-Pot Acylation and Esterification Reactions

Feringa's method for one-pot imide formation followed by esterification was tested using three different alcohols.

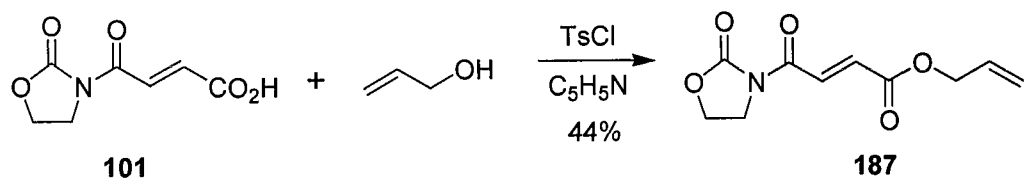


Scheme 76

Reaction of the acid chloride intermediate with ethyl alcohol was found to proceed in good yield (75%), but the yield dropped off dramatically when secondary or tertiary alcohols were used (36% & 23% respectively).

I.1.3 Test of Esterification Reaction using Toluenesulfonyi Chloride

The esterification of carboxylic acid **101** was tested by reaction with allyl alcohol using toluenesulfonyl chloride and pyridine, as depicted in Scheme 77.

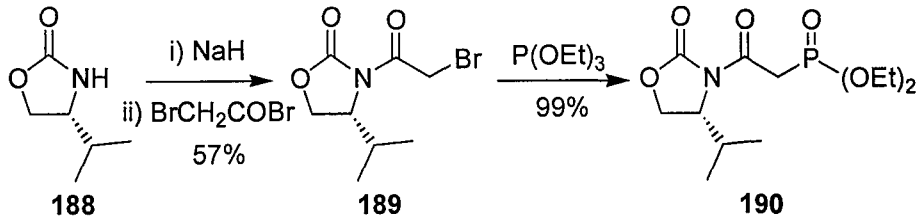


Scheme 77

This reaction was found to give ester **187** in moderate yield.

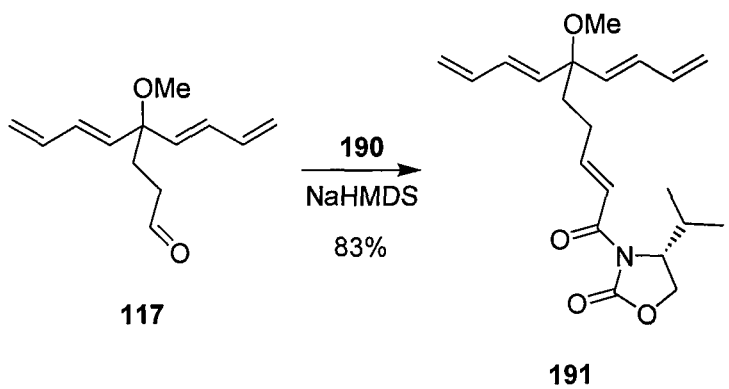
I.1.4 Preparation of a Chiral Diels-Alder Substrate

The use of chiral auxiliaries in the intramolecular Diels-Alder reaction was discussed in chapter one. The preparation of a chiral phosphonate was undertaken using a chiral oxazolidinone as starting material (Scheme 78).



Scheme 78

Oxazolidinone **188** was reacted with sodium hydride and bromoacetylbromide[47] to give bromide **189** in 57% yield. This was then heated with triethylphosphite to give the desired chiral phosphonate **190** in excellent yield (99%).



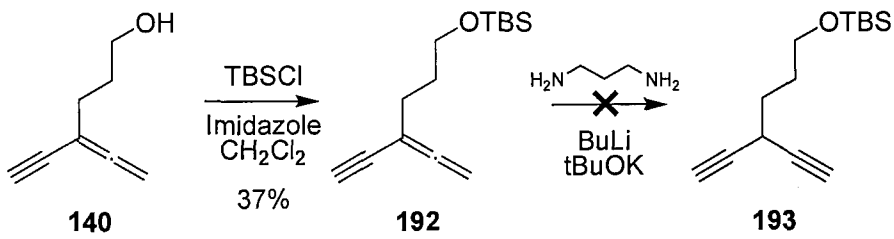
Scheme 79

Aldehyde **117** was then reacted with **190** using NaHMDS as base, which provided compound **191** in 83% yield. **191** was not reacted further, as it was discovered that the achiral form (compound **106**, *supra*) decomposed upon subjection to Lewis acid catalysis conditions.

I.2 Reactions Related to Chapter 3: The Dialkyne Route

I.2.1 Preparation of TBS protected allene

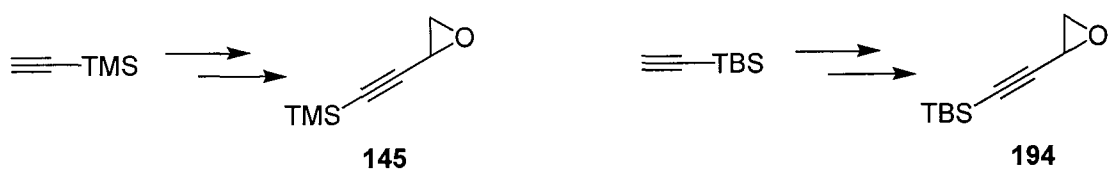
Once allene **140** had been isolated, an isomerization reaction was considered to convert the allene back to the alkyne. The first stage of this was to protect the primary alcohol, and this was accomplished using TBSCl and imidazole in CH_2Cl_2, giving silyl ether **192** in 37% yield. Isomerization reactions, using potassium 3-aminopropylamine, gave none of the desired dialkyne and returned only a small amount of starting material.



Scheme 80

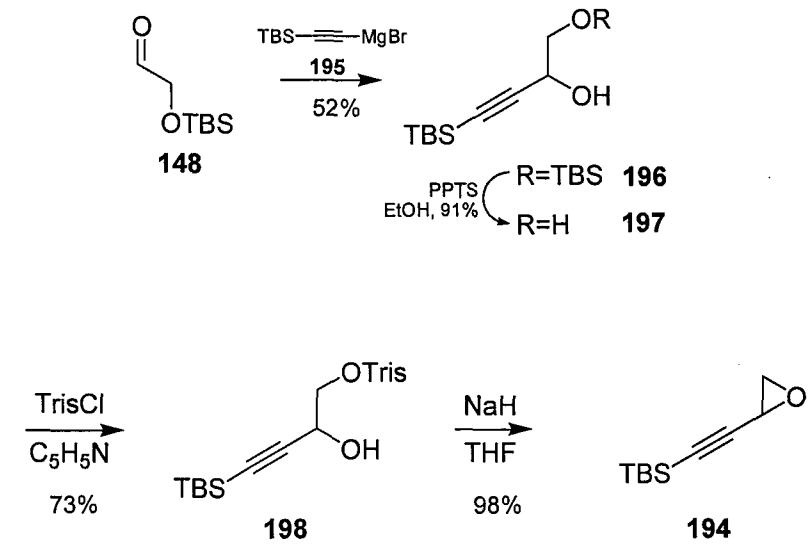
I.2.2 Preparation of Epoxide 145 Equivalent Using TBS-Acetylene

In order to assist in the determination of the structure of compound **155** (3.2.2, *supra*), the equivalent of epoxide **145** was prepared using TBS-acetylene as the initial starting material, rather than TMS-acetylene (Scheme 81).



Scheme 81

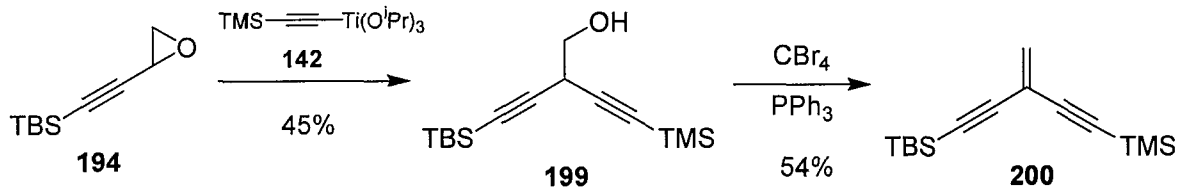
Epoxide **194** was prepared from TBS-acetylene in the same way as epoxide **145** was from TMS-acetylene: the acetylene was reacted with ethylmagnesium bromide to give Grignard reagent **195**, which was then reacted with aldehyde **148** to give secondary alcohol **196** in moderate yield (52%, Scheme 82).



Scheme 82

Alcohol **196** was then deprotected using PPTS in ethanol to give 91% of diol **197**, which was then sulfonated using triisopropylbenzenesulfonyl chloride to give **198** in 73% yield. This sulfonate was found to provide desired epoxide **194** in excellent yield (98%) upon stirring with sodium hydride in THF.

Reaction of **194** with titanium acetylide **142** (which was prepared as described in section 3.2.2) was found to give asymmetric primary alcohol **199** in 45% yield (Scheme 83).



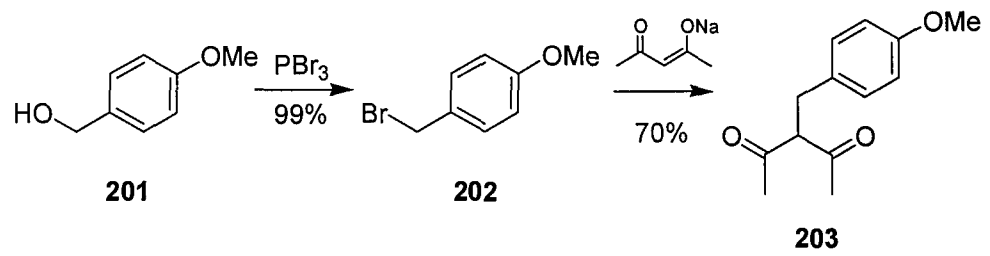
Scheme 83

Reaction of compound **199** under bromination conditions formed conjugated system **200** in 54% yield.

I.3 Reactions Related to Chapter 4: The Wittig Route

I.3.1 Preparation of Alternative Diketone

Before diketone **164** (Scheme 66, *supra*) was prepared, test compound **203** was synthesized. This was prepared in two steps from *p*-methoxybenzyl alcohol (**201**, Scheme 84).



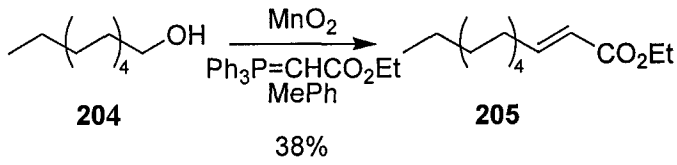
201 **202** **203**

Scheme 84

Primary alcohol **201** was reacted with phosphorus tribromide to give benzyl bromide **202** in excellent yield. The anion of 1,3-pentanedione was prepared by stirring it with sodium ethoxide, and bromide **202** added to provide diketone **203** in 70% yield.

I.3.2 Initial Experiments with One-Pot Oxidation-Wittig Reactions

Prior to the experiment with long-chain diols (section 4.2.1, *supra*), a simple long chain alcohol was tested (Scheme 85).



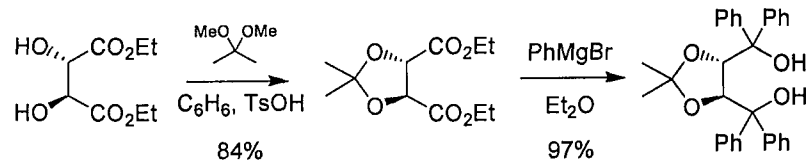
204 **205**

Scheme 85

Undecanol (**204**) was refluxed with the Wittig reagent, and manganese dioxide added to give desired α,β-unsaturated ester **205** in 38% yield.

I.4 Preparation of Diols for Use as TADDOL Catalysts

In order to synthesize TADDOL series catalysts, the C_2 symmetric diol **208** was prepared (Scheme 86).



206 **207** **208**

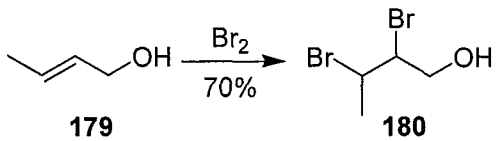
Scheme 86

(–)-Diethyl tartrate (**206**) was reacted with dimethoxypropane in benzene with *p*-toluenesulfonic acid to give diester **207** in 84% yield. **207** was reacted with phenylmagnesium bromide in ether to give diol **208** in very good yield (97%).

Appendix II: Procedures and Characterization of Compounds from Appendix I

II.1 Compounds from Section I.1

2,3-dibromobutan-1-ol (180)



179 **180**

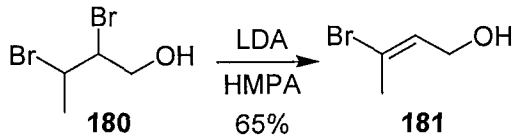
Crotyl alcohol (**179**, 28.8g, 0.4 moles, 1eq) was stirred in carbon tetrachloride (200mL) at –78°C. Bromine (64g, 0.4 moles, 1eq) was added in carbon tetrachloride (200mL) over 45 minutes. The reaction was stirred for ten minutes, the solvent removed *in vacuo*, and the residue vacuum distilled (106°C, 9–10mmHg) to give 65.0g pure **180** as a crystalline solid.

Bp 106°C (9–10mmHg)

^{1}H NMR (400MHz, $CDCl_3$) δ 4.30 (1H, m, C**H**CH_3), 4.20 (1H, m, C**H**BrCH_2OH), 4.00 (2H, d, J = 4, HHCOH), 2.40 (1H, bs, OH), 1.80 (3H, d, J = 7, CH_3).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 66.157 (COH), 62.311 (**C**BrCH_2OH), 47.833 (**C**BrCH_3), 25.551 (CH_3).

_E_-3-bromobut-2-ene-1-ol (181)



180 65% **181**

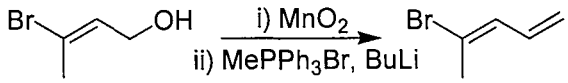
Diisopropylamine (16.8mL, 0.119 moles, 2.3eq) was stirred in THF (180mL) at –78°C, and *n*-butyllithium (40.0mL, 0.119 moles, 2.3eq) added over five minutes. The mixture was stirred at –78°C for 20 minutes, before being warmed to 0°C and stirred for five minutes. Dibromide **180** was then added in THF (60mL) via cannula, and the reaction stirred at –78°C for five hours. Water (20mL) was then added, and the reaction warmed to room temperature. The organic phase was extracted with ether (3×50mL), dried over magnesium sulfate, and the solvent removed *in vacuo*. The crude product was purified by column chromatography (20% acetone in hexane) to give 5.11g of **181** (65%).

$\mathbf{R}_f$ 0.32 (20% acetone in hexane).

^{1}H NMR (300MHz, $CDCl_3$) δ 6.04 (1H, tq, J = 7, 1, CH=C), 4.06 (2H, d, J = 7, C**H**$_2$OH), 2.70 (1H, bs, OH), 2.28 (3H, m, CH_3).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 130.985 (**C**H=C), 124.069 (**C**=CH), 59.716 (CH_2OH), 23.698 (CH_3).

_E_-4-bromopenta-1,3-diene (183)



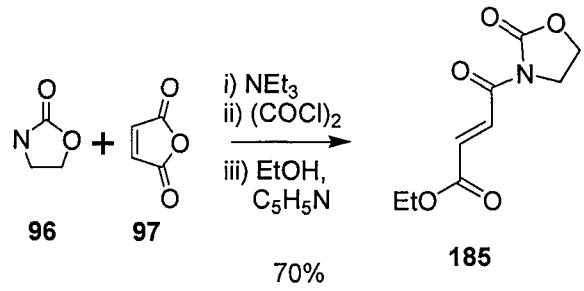
181 20% **183**

Alcohol **181** (5.01g) was stirred in CH_2Cl_2 (100mL), and MnO_2 (30g) added in one portion. The reaction was stirred at room temperature for 60 hours, at which point it was filtered through celite, and the solvent evaporated carefully at room pressure. Meanwhile, a mixture of methyltriphenylphosphonium bromide (14.6g, 1.2eq), and butyllithium (2.5M in hexanes, 15.6mL, 1.1eq) in ether (175mL) was brought to reflux for 1½ hours. This was then cooled to 0°C, and the crude aldehyde in ether (25mL) added slowly. This was stirred for 1 hour at 0°C, and then brought to reflux for two hours, at which point the starting material was not apparent by TLC. Na_2SO_4 (6.8g in 100mL water) was added carefully, the mixture separated, and the organic phase washed with water. $MgSO_4$ was added, and both ether and product distilled off at room pressure (98°C). The product was redistilled using a Kugelrohr (95–100°C) to give 1.0g of pure **183** as a yellow liquid (20%, 2 steps).

^{1}H NMR (300MHz, $CDCl_3$) δ 6.40 (1H, ddd, J = 10,1,1, HC=CBr), 6.27 (1H, ddd, J = 17,10,10, HC=CH_2), 5.16 (1H, ddd, J = 17,1,1, HHC), 5.06 (1H, ddd, J = 10,1,1, HHC), 2.26 (3H, s, CH_3).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 133.15 (CHCH$_2$), 131.83 (CHCBr), 118.17 (CH_2), 123.76 (CBr), 31.61 (CH_3).

Ethyl-4-oxo-4-(2-oxo-oxazolidin-3-yl)-but-2-enoate (185)



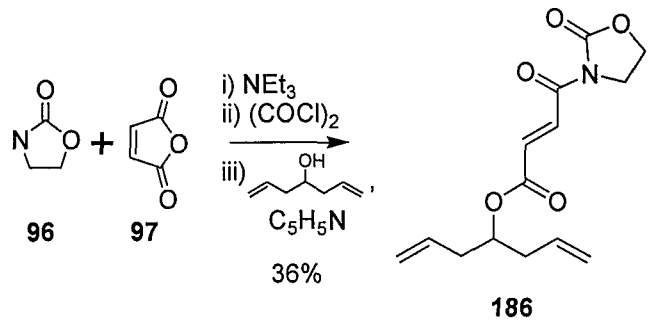
Maleic anhydride (**97**, 5.11g, 44mmol), 2-oxazolidinone (**96**, 3.83g, 44mmol) and triethylamine (4.86g, 48mmol) were stirred overnight in CH_2Cl_2 (20mL). The reaction was cooled to 0°C, and DMF (50µl) and oxalyl chloride (5.59g, 44mmol) were added. This was warmed to room temperature, and ethanol (4.8mL) added in pyridine (20mL). This was stirred for one and a half hours, and the resulting reaction mixture filtered through silica. This crude product was purified by column chromatography (36–50% ethyl acetate in hexane), giving 6.57g of pure product **185** as a crystalline solid (70%).

$\mathbf{R_f}$ 0.28 (40% ethyl acetate in hexane).

^{1}H NMR (300MHz, $CDCl_3$) δ 8.10 (1H, d, J = 15, CH–C(O)–N), 6.84 (1H, d, J = 15, CH–C(O)–O), 4.91 (2H, t, J = 8, N–C**H**$_2$–CH$_2$–O), 4.20 (2H, q, J = 7, C**H**$_2$–CH$_3$), 4.06 (2H, t, J = 8, N–CH$_2$–C**H**$_2$–O), 1.73 (3H, t, J = 7, CH$_3$).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 164.962 (CH–**C**(O)–O), 163.950 (CH–**C**(O)–N), 153.267 (N–**C**(O)–O), 134.446 (**C**H–C(O)–O), 131.919 (**C**H–C(O)–N), 62.547 (N–CH$_2$–**C**H$_2$–O), 61.542 (N–**C**H$_2$–CH$_2$–O), 42.739 (**C**H$_2$–CH$_3$), 14.248 (CH$_3$).

1-Allylbut-3-enyl-4-oxo-4-(2-oxo-oxazolidin-3-yl)-but-2-enoate (186)



Maleic anhydride (**97**, 0.98g, 10mmol, 1eq), 2-oxazolidinone (**96**, 0.87g, 10mmol, 1eq) and triethylamine (1.11g, 11mmol, 1.1eq) were stirred overnight in dichloromethane (20mL). The reaction was cooled to 0°C, and ten drops of DMF and oxalyl chloride (1.27g, 10mmol, 1eq) were added. This was stirred for three and a half hours, and hepta-1,6-dien-4-ol (2.24g, 20mmol, 2eq) added in pyridine (5mL). This was stirred for one and a half hours, and the resulting reaction mixture filtered through silica. This crude product was purified by column chromatography using 40–45% ethyl acetate in hexane as eluent, giving 0.999g of pure product **186** as a viscous orange oil (36%).

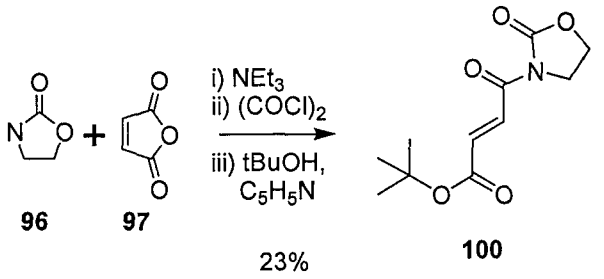
$\mathbf{R}_f$ 0.55 (10% ethyl acetate in hexane).

IR (film) 3078 (C=C–H), 2979, 2916 (C–H), 1790, 1721, 1682 (C=O), 1642.7 (C=C).

^{1}H NMR (300MHz, $CDCl_3$) δ 8.13 (1H, d, J = 16, CH=C**H**–CO–N), 6.91 (1H, d, J = 16, O–CO–C**H**=CH), 5.74 (2H, ddt, J = 17, 10, 7, C**H**=CH_2), 5.08 (5H, m, C**H**–O–C(O) & C=C$\mathbf{H}_2$), 4.47 (2H, d, J = 8, N–CH_2–C$\mathbf{H}_2$–O), 4.09 (2H, d, J = 8 Hz, N–C$\mathbf{H}_2$–CH_2–O), 2.37 (4H, m, C$\mathbf{H}_2$–CH=CH_2).

^{13}C NMR (75MHz, $CDCl_3$) δ 164.456 (O–**C**O–C), 163.955 (C–**C**O–N), 153.243 (N–**C**O–O), 134.554 (**C**H=CH_2), 133.226 (C=**C**–CO–N), 131.956 (O–CO–**C**=C), 118.448 (**C**H_2=C), 73.795 (**C**H–O–C(O)), 62.531 (N–CH_2–**C**H_2–O), 42.737 (C$\mathbf{H}_2$–CH=CH_2), 38.023 (N–**C**H_2–CH_2–O).

t-Butyl-4-oxo-4-(2-oxo-oxazolidin-3-yl)-but-2-enoate (100)



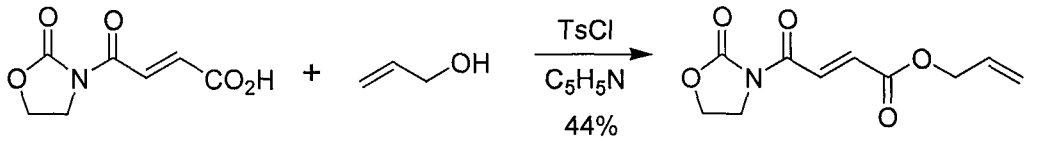
Maleic anhydride (**97**, 0.11 moles, 1eq) and oxazolidinone (**96**, 0.11 moles, 1eq) were stirred in CH_2Cl_2 (200mL). Triethylamine (0.12 moles, 1.1eq) was added, and a yellow colour was observed. The mixture was stirred overnight, and then cooled to 0°C. DMF (10 drops) was added, and oxalyl chloride (0.11 moles, 1eq) added slowly. The mixture was then stirred for 3½ hours at room temperature. After this time, 2-methylpropanol (0.22 moles, 2eq) was added in pyridine (50mL), and stirred for a further 2 hours. This was filtered through a plug of silica twice, and finally purified by column chromatography (20% acetone in hexane) to give 6.19g of **100** (23%).

$\mathbf{R_f}$ 0.30 (20% acetone in hexane).

^{1}**H NMR** (300MHz, $CDCl_3$) δ 7.96 (1H, d, J = 16, CH=C**H**–CO–N), 6.78 (1H, d, J = 16, CH=C**H**–CO–O), 4.40 (2H, t, J = 8, N–C**H**$_2$–CH$_2$–O), 4.05 (2H, t, J = 8, N–CH$_2$–C**H**$_2$–O), 1.46 (9H, s, CH_3).

^{13}**C NMR** (75MHz, $CDCl_3$) δ 164.095 (CH–C(O)–O), 136.52 (CH–C(O)–N), 131.38 (N–C(O)–O), 82.30 (C–CH_3), 62.80 (N–CH$_2$–**C**H$_2$–O), 42.99 (N–**C**H$_2$–CH$_2$–O), 28.32 (CH_3).

4-Oxo-4-(2-oxo-oxazolidin-3-yl)-but-2-enoic acid allyl ester (187)



101 **187**

Acid **101** (555mg, 3mmol) was dissolved in pyridine (10mL), and *p*-toluenesulfonyl chloride (1.15g, 6mmol) added in one portion. Having been stirred for 10 minutes, the mixture was cooled to 0°C and allyl alcohol (174mg, 3mmol) added dropwise. This mixture was stirred at 0°C for an hour, and subsequently overnight at room temperature. The mixture was then poured over HCl (1M, 10mL), and extracted with ethyl acetate (3×50mL). The organic phase was washed with brine (10mL), dried over $MgSO_4$ and evaporated. The crude product was then purified by column chromatography (40% ethyl acetate in hexane – 40% acetone in hexane) to give pure product **187** as white crystals (300mg, 44%).

Mp (hexane) 50–52°

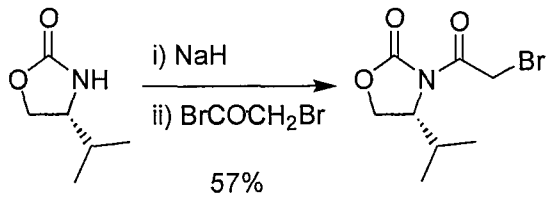
$\mathbf{R}_f$ 0.29 (40% ethyl acetate in hexane).

^{1}H NMR (400MHz, $CDCl_3$) δ 8.19 (1H, d, J=16, CH=C**H**–CO–N), 6.98 (1H, d, J=16, CH=C**H**–CO–O), 5.97 (1H, ddd, J=17, 10, 6, C**H**=CH_2), 5.37 (1H, ddd, J=17, 3, 1, C**H**H=CH), 5.29 (1H, ddd, J=11, 3, 1, C**H**H=CH), 4.72 (2H, ddd, J=6, 1, 1, $\mathbf{CH_2}$–CH=CH_2), 4.49 (2H, t, J=8, N–$\mathbf{CH_2}$–CH_2–O), 4.12 (t, J=8, 2H, N–CH_2–$\mathbf{CH_2}$–O).

^{13}C NMR (100MHz, $CDCl_3$) δ 164.42 (C–**C**O–N), 163.75 (O–**C**O–C), 153.02 (N–**C**O–O), 134.00 (**C**H=CH_2), 132.10 (C=**C**–CO–N), 131.49 (O–CO–**C**=C), 118.81 ($\mathbf{CH_2}$=C), 65.90 (h $\mathbf{CH_2}$–CH=CH), 62.33 (N–CH_2–$\mathbf{CH_2}$–O), 42.57 (N–$\mathbf{CH_2}$–CH_2–O).

IR (film) 3092.9, 3025.0, 2989.5, 2926.9 (C–H), 1766.5, 1721.0, 1678.4 (C=O).

[4R]-3-(Bromoacetyl)-4-isopropyl-2-oxazolidinone (189)



188 **189**

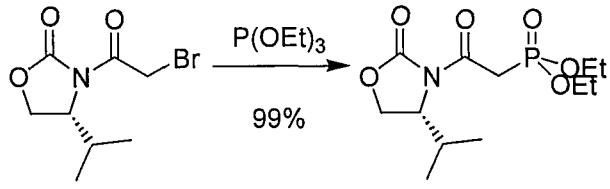
Sodium hydride (60% dispersion in mineral oil, 8.05mmol, 1.15eq) was suspended in THF (10mL). [4R]-4-isopropyl-2-oxazolidinone (**188**, 7mmol, 1eq) was added and the mixture refluxed for 1 hour, and then cooled to 0°C. Bromoacetylbromide (7.3mmol, 1.04eq) was then added in THF (3mL), and the reaction stirred at room temperature overnight. Saturated ammonium chloride solution (20mL) was added, and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and evaporated, and the residue purified by column chromatography (neat hexane – 22% acetone in hexane) to give pure bromide **189** (1.143g, 57%).

$\mathbf{R}_f$ 0.40 (diethyl ether)

^{1}H NMR (300MHz, $CDCl_3$) δ 4.52 (2H, 2×d, J = 12, CH_2Br), 4.46 (1H, ddd, J = 3, 3, 8, CH–N), 4.35 (1H, dd, J=8, 9, C**H**H–O), 4.27 (1H, dd, J=3, 9, C**H**H–O), 2.42 (1H, d sept, J=4, 7, C**H**–CH_3), 0.92 (6H, 2×d, J=7, CH_3).

^{13}C NMR (75MHz, $CDCl_3$) δ 174.3 (O–C(O)–N), 166.0 (C(O)–CH_2Br), 63.8 (CH_2–O), 58.7 (CH–N), 28.1 (CH_2–Br), 17.8 (CH–CH_3), 14.6 (CH_3).

Diethyl-2-oxo-2-([4R]-4-isopropyl-2-oxo-oxazolidin-3-yl)ethylphosphonate (190)



189 **190**

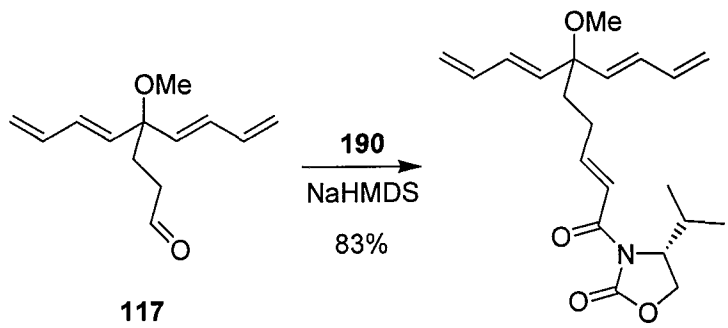
Bromide **189** (18 mmol, 1eq) was stirred with triethyl phosphite (56 mmol, 3.1eq) at 100° for 3 hours. The reaction mixture was purified by column chromatography (40–50% acetone in hexane) to give pure phosphonate **190** (4.49g, 99%).

$\mathbf{R}_f$ 0.31 (50% acetone in hexane)

^{1}H NMR (400MHz, $CDCl_3$) δ 4.46 (1H, ddd, *J*=3, 3, 8, CH–N), 4.20 (6H, m, C**H**H–O & O**C**$\mathbf{H}_2$$CH_3$), 3.78 (2H, 2×dd, *J*=14, 22, C**H**H–P), 2.38 (1H, d sept, *J*=4, 7, C**H**–CH_3), 1.33 (6H, dt, *J*=2, 7, ($OCH_2C\mathbf{H}_3$)), 0.92 (6H, 2×d, *J*=7, CH_3).

^{13}C NMR (100MHz, $CDCl_3$) δ 164.9 (J_P=26, N–**C**(O)–CH_2), 153.9 (O–C(O)–N), 63.3 (O–CH_2), 62.7 (J_P=35, P(O**C**H_2CH_3)$_2$), 58.8 (CH–N), 28.5 (**C**H–CH_3), 34.2 (J_P=131, CH_2–P), 16.8 (O–CH_2–**C**H_3), 17.9 (CH_3), 14.6 (CH_3).

(4R)-3-{(2E,7E)-6-[(1E)-buta-1,3-dienyl]-6-methoxydeca-2,7,9-trienoyl}-4-isopropyl-1,3-oxazolidin-2-one (191)



117 **191**

Phosphonate **190** (0.52mmol, 1.5eq) was stirred in THF (3mL) at 0°C, and sodium hexamethyldisilazide (1M in THF, 0.41 mmol, 1.2eq) added slowly. This was stirred for ten minutes at 0°C, and one hour at room temperature, at which time aldehyde **117** (0.35mmol, 1eq) was added (filtered through Na_2SO_4) in THF (5mL). This was stirred for 3 hours at room temperature, then added to pH7 phosphate buffer (10mL). The resulting mixture was diluted with ethyl acetate (20mL), and washed with $KHSO_4$ (aq, 1M, 10mL), water (10mL) and brine (10mL). The organic phase was dried over $MgSO_4$, and evaporated, and the resulting oil purified by column chromatography (20% acetone in hexane) to give 103mg pure substrate **191** (83%).

$\mathbf{R}_f$ 0.28 (20% acetone in hexane)

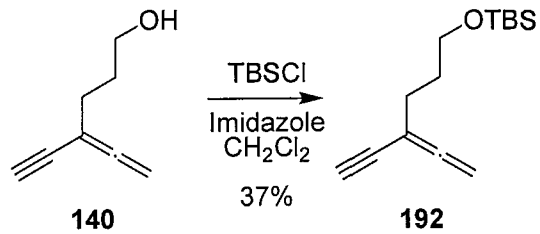
^{1}H NMR (400MHz, $CDCl_3$): 7.27 (1H, d, J = 15, CH–C(O)), 7.15 (1H, dt, J = 15, 7, C**H**=CH–C(O)), 6.37 (2H, ddd, J = 17, 10, 10, C**H**=CH_2), 6.23 (2H, dd, J=16, 11, C**H**–CH–CH_2), 5.62 (2H, d, J=16, CH_2=C**H**–CHOMe), 5.24 (2H, dd, J=17, 1, C**H**H=CH), 5.12 (2H, dd, J=10, 1, C**H**H=CH), 4.49 (1H, ddd, J=8, 4, 4, CH–N), 4.28 (1H, dd, J=8, 9, C**H**H–O), 4.21 (1H, dd, J=4, 9, CHH–O), 3.16 (3H, s, OMe), 2.41 (1H, dtt, J=4, 7, 7, C**H**–CH_3), 2.29, (2H, m, C**H**$_2$–CH=CH), 1.85 (2H, m, C**H**$_2$–CHOMe), 0.91 (6H, 2×d, J=7, CH_3).

^{13}C NMR (100MHz, $CDCl_3$): 165.5 (N–**C**(O)–CH), 154.5 (O–C(O)–N), 151.6 (**C**H=CH–C(O)), 136.8 (CH_2=**C**H–CHOMe), 135.9 (**C**H=CH_2), 132.4 (**C**H–CH=CH_2), 120.8 (**C**H–C(O)), 118.1 (**C**H_2=CH), 79.5 (**C**HOMe), 63.8 (CH_2–O), 58.9 (CH–N), 51.2 (OMe), 36.2 (**C**H_2–CH=CH), 28.9 (**C**H–CH_3), 27.2 (**C**H_2–CHOMe), 18.4 (CH_3), 15.1 (CH_3).

EIMS *m/z* (%) 359 (8%, M^+), 327 (12%, $(M–H_2O)^+$), 198 (100%).

II.2 Compounds from Section I.2

6-t-butyldimethylsilyloxy-3-ethynylhexa-1,2-diene (192)



140 **192**

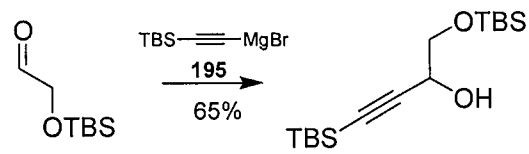
Allene **140** (41mg, 0.34mmol, 1eq) was stirred in CH_2Cl_2 (2mL), and imidazole (139mg, 2.04mmol, 6eq) and TBSCl (103mg, 0.68mmol, 2eq) added. The reaction was stirred for four hours, after which time sodium bicarbonate (aq, 1mL) was added. The aqueous phase was extracted with CH_2Cl_2 (2×5mL), and the combined organic phases dried over magnesium sulfate and the solvent removed *in vacuo*. The residue was purified by column chromatography (5% ethyl acetate in hexane) to give 30mg pure **192** (37%) as a colourless oil.

$\mathbf{R_f}$ 0.39 (20% acetone in hexane)

^{1}H NMR (400MHz, $CDCl_3$): 4.90 (2H, bs, HHC=C=C), 3.62 (2H, m, CH_2–O), 2.20 (2H, m, CH_2–C=C), 1.84 (1H, s, H–C≡C), 1.75 (2H, m, $C\underline{H}_2$–CH_2–O), 0.80 (9H, s, CH_3–C), –0.04 (6H, s, CH_3–Si).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 214.18 (C=$\underline{C}$=CH_2), 88.47 ($\underline{C}$=C=CH_2), 79.42 (H$\underline{C}$≡C), 78.92 (HC≡$\underline{C}$), 77.46 (C=C=$\underline{C}H_2$), 61.41 (CH_2–O), 30.80 ($\underline{C}H_2$C=C), 29.45 ($\underline{C}H_2$–CH_2–O), 26.05 ($\underline{C}H_3$C), 18.43 ($\underline{C}CH_3$), –4.60 (CH_3Si).

1-(tert-Butyl-dimethyl-silanyloxymethyl)-3-(tert-Butyl-dimethyl-silanyl)-prop-2-ynol (196)



148 **196**

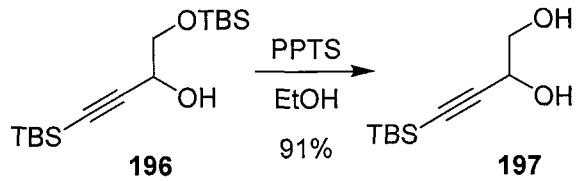
tert-Butyldimethylsilylacetylene (5.00g, 36mmol, 2eq) was dissolved in THF (50mL) and the mixture cooled to –78°C. Ethylmagnesium bromide (3M in diethyl ether, 11.9mL, 36mmol, 2eq) was added slowly and the mixture stirred at –78°C for 40 minutes. After this time the mixture was warmed to 0°C, and aldehyde **148** (3.10g, 17.8mmol, 1eq) in THF (15mL) added. The mixture was then stirred for 3 hours at 0°C at which point an aqueous solution of ammonium chloride (saturated, 2mL) was added carefully. Water (5mL) was then added, the mixture separated, and the aqueous phase extracted with ether (3×20mL). The organic phase was washed with saturated brine (10mL), dried over magnesium sulfate and the solvent evaporated. The resulting mixture was purified by column chromatography (10% ethyl acetate in hexane) to give compound **196** as a colourless oil (3.64g, 65%).

$\mathbf{R}_f$ 0.33 (5% ethyl acetate in hexane).

^{1}H NMR (300MHz, $CDCl_3$) δ 4.39 (1H, m, HC–OH), 3.76 (1H, dd, J = 10, 4, HHC–OSi), 3.65 (1H, dd, J = 10, 7, HHC–OSi), 2.61 (1H, d, J = 5, OH), 0.92 (18H, 2×s, H_3C–C–Si–O & H_3C–C–Si–C), 0.11 (12H, bs, H_3C–Si–O & H_3C–Si–C).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 104.38 (C≡C–Si), 88.38 (C≡C–Si), 67.03 (C–OH), 63.64 (C–OSi), 26.16 (CH_3CSiO), 25.96 (CH_3CSiC), 18.45 (CH_3CSiO), 16.54 (CH_3CSiC), –4.56 (H_3CSiC), –5.40 (H_3CSiO).

4-tert-Butyldimethylsilanyl-but-3-yne-1,2-diol (197)



196 **197**

To alcohol **196** (2.94g, 9.34mmol, 1eq) in ethanol (20mL) was added PPTS (2.35g, 9.34mmol, 1eq). The reaction was stirred at 60° for 16 hours, and the solvent then removed *in vacuo*. Ethyl acetate (30mL) and brine (20mL) were then added, and the mixture separated. The organic phase was washed with water (2×10mL), dried over magnesium sulfate, and the solvent evaporated. This crude product was purified by column chromatography (40% ethyl acetate in hexane) to give product **197** as a white solid (1.70g, 91%).

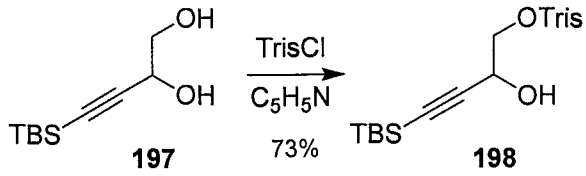
$\mathbf{R}_f$ 0.25 (40% ethyl acetate in hexane).

IR (solution, CH_2Cl_2) 3366 (O–H), 3054, 2960, 2903 (C–H), 2174 (C≡C), 1252 (Si–C).

^{1}H NMR (300MHz, $CDCl_3$) δ 4.46 (1H, dd, J = 7, 4, HCOH), 3.72 (2H, m, HHCOH), 2.50 (1H, bs, OH), 2.24 (1H, bs, OH), 0.92 (9H, s, H_3C–C–Si), 0.11 (6H, s, H_3C–Si).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 103.75 (C≡C–Si), 89.85 (C≡C–Si), 66.70 (CH–OH), 63.84 (CH_2–OH), 26.11 (CH_3–C–Si), 16.49 (CH_3–C–Si) –4.63 (CH_3Si–C≡C).

2-Hydroxy-4-tert-butyldimethylsilanylbut-3-ynyl-2,4,6-triisopropylbenzenesulfonate (198)



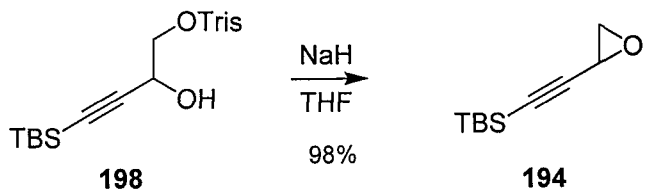
To a solution of diol **197** (810mg, 4.04mmol, 1eq) in pyridine (20mL) was added triisopropylbenzenesulfonyl chloride (1.80g, 6.06mmol, 1.5eq). This was stirred overnight at room temperature, and the pyridine removed *in vacuo*. The residue was then filtered through a plug of silica, washed with CH_2Cl_2, and purified by column chromatography (10% ethyl acetate in hexane) to give 1.39g (73%) of sulfonate **198** as a colourless oil.

$\mathbf{R}_f$ 0.28 (10% ethyl acetate in hexane).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (2H, s, ArH), 4.67 (1H, ddd, J = 4, 6, 8, HCOH), 4.21 (1H, dd, J = 11, 4, HHC–OS), 4.13 (2H, septet, J = 7, HCAr (2–)), 4.09 (1H, dd, J = 11, 8, HHC–OS), 2.91 (1H, septet, J = 7, HCAr (4–)), 2.16 (1H, s, OH), 1.26 (12H, d, J = 7, H_3C–C–Ar (2–)), 1.25 (6H, d, J = 7, H_3C–C–Ar (4–)), 0.89 (9H, s, H_3C–C–Si), 0.07 (6H, s, H_3C–Si).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 154.16 (ArC), 151.06 (ArC), 129.33 (ArC), 124.02 (ArCH), 101.62 (Si–C≡C), 90.87 (Si–C≡C), 71.53 (CH_2–OS), 61.57 (CH–OH), 34.42 (CH–Ar), 29.84 (CH–Ar), 26.055 (CH_3–C–Si), 24.90 (CH_3–C–Ar), 23.67 (CH_3–C–Ar), 16.45 (CH_3–C–Si), –4.75 (CH_3Si).

tert-Butyldimethyl(oxiranylethynyl)silane (194)



198 **194**

To a solution of alcohol **198** (270mg, 0.58mmol, 1eq) in THF (10mL) was added sodium hydride (120mg, 3.48mmol, 6eq), and the reaction stirred vigorously overnight. The sodium hydride was then filtered off through $MgSO_4$, washed with CH_2Cl_2, and the filtrate concentrated and purified by column chromatography (2% CH_2Cl_2 in pentane) to give 103mg (98%) of epoxide **194** as a colourless oil.

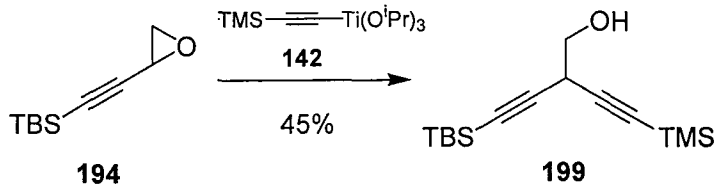
R_f 0.27 (2% dichloromethane in pentane).

^{1}H NMR (400MHz, $CDCl_3$) δ 3.37 (1H, dd, J = 4, 5, HC–O), 2.90 (2H, m, HHC–O), 0.93 (9H, s, H_3C–C–Si), 0.11 (6H, s, H_3C–Si).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 102.65 (Si–C≡C), 87.66 (Si–C≡C), 49.06 (CH_2), 40.00 (CH), 26.09 (CH_3–C), 16.54 (Si–C–CH_3), –4.71 (CH_3Si).

CIMS *m/z* (%) 200 (8%, $(M+NH_4)^+$), 183 (13%, $(M+H)^+$), 126 (100%, $(M-C_3H_9+H)^+$), 109 (95%).

4-Trimethylsilanyl-2-trimethylsilanylethynylbut-3-yn-1-ol (199)



To a solution of TMS-acetylene (1.42mL, 10mmol, 4eq) in THF (10mL) at 0°C was added *n*-butyllithium (2.5M in hexanes, 4.0mL, 10mmol, 4eq), and the reaction warmed to room temperature for ten minutes. The solvent was removed *in vacuo*, and the mixture cooled to –50°C. The residue was dissolved in THF (15mL), and a solution of $TiCl(O^iPr)_3$ in THF (1.61M, 6.2mL, 10mmol, 4eq) was added. After five minutes stirring, epoxide **194** (438mg, 2.4mmol, 1eq) was added in THF (8mL) and the reaction warmed slowly to room temperature. After stirring overnight, hydrochloric acid (1M, 10mL) was added, the mixture separated, and the aqueous phase extracted with ether (2×20mL). The organic phase was washed with water (5mL) and brine (5mL), dried over magnesium sulfate, concentrated and purified by column chromatography (8% acetone in hexane) and HPLC (8% acetone in hexane) to give 300mg (45%) of dialkyne **199** as a brown oil.

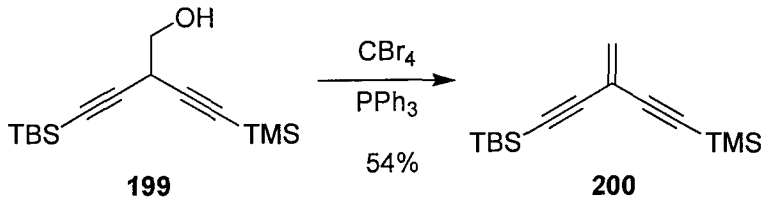
$\mathbf{R}_f$ 0.27 (8% acetone in hexane).

^{1}H NMR (400MHz, $CDCl_3$) δ 3.70 (1H, m, HC–C≡C), 3.62 (2H, m, HHC–OH), 2.05 (1H, t, J = 7, OH), 0.95 (9H, s, H_3C–C–Si), 0.17 (9H, s, $(H_3C)_3Si$), 0.11 (6H, s, $(H_3C)_2Si$).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 101.32 (TBS–C≡C), 100.73 (TMS–C≡C), 87.78 (TMS–C≡C), 86.15 (TBS–C≡C), 65.35 (CH_2–OH), 29.64 (CH–CH_2–OH), 26.15 (CH_3–C–Si), 16.73 (Si–C–CH_3), 0.00 ($(CH_3)_3$–Si), –4.59 ($(CH_3)_2$–Si).

CIMS *m/z* (%) 298 (10%, $(M+NH_4)^+$), 281 (5%, $(M+H)^+$), 74 (100%, $(C_3H_{10}Si)^+$).

1-tert-Butyldimethylsilyl-3-methylene-5-trimethylsilylpenta-1,4-diyne (200)



199 **200**

Alcohol **199** (200mg, 0.71mmol, 1eq) and triphenylphosphine (447mg, 1.70mmol, 2.4eq) were stirred in THF (5mL) at room temperature. Pyridine (66μL) and carbon tetrabromide (272mg, 0.82mmol, 1.15eq) were added, and the reaction stirred at room temperature for two hours. The reaction mixture was then concentrated, and hexane added. This mixture was washed with HCl (1M, 10mL), Na_2SO_4 (aq, 10mL) and brine (10mL), dried over magnesium sulfate, and the solvent removed *in vacuo*. The crude mixture was purified by column chromatography (10% ethyl acetate in hexane) to give 100mg (54%) of compound **200**.

$\mathbf{R_f}$ 0.32 (10% ethyl acetate in hexane).

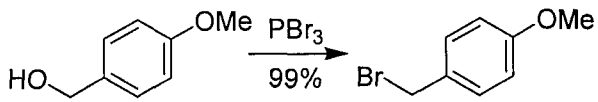
IR (film) 2956, 2930, 2898, 2858 (C–H), 2250, 2154 (C≡C), 1471 (C=C), 1269, 1251, 909, 843 (Si–C).

^{1}H NMR (400MHz, $CDCl_3$) δ 5.60 (2H, s, H_2C=C), 0.86 (9H, s, H_3C–C–Si), 0.17 (9H, s, $(H_3C)_3Si$), 0.11 (6H, s, $(H_3C)_2Si$).

^{13}C NMR + DEPT (100MHz, $CDCl_3$) δ 132.20 ($\underline{C}H_2$=C), 113.25 ($\underline{C}$=CH_2), 102.66 (TBS–C≡$\underline{C}$), 102.00 (TMS–C≡$\underline{C}$), 94.01 (TMS–$\underline{C}$≡C), 92.57 (TBS–$\underline{C}$≡C), 26.14 (CH_3–C–Si), 16.86 (Si–$\underline{C}$–CH_3), –0.20 ($(CH_3)_3$–Si), –4.75 ($(CH_3)_2$–Si).

II.3 Compounds from Section I.3

4-Methoxybenzyl bromide (202)



201 **202**

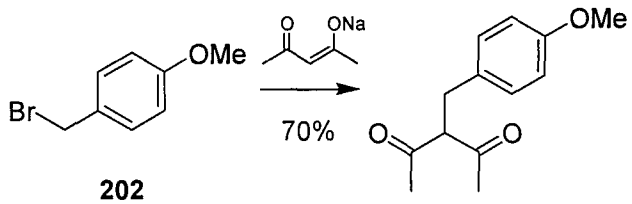
4-Methoxybenzyl alcohol (**201**, 13.8g, 0.1mol, 1eq) was suspended in ether (25mL) and cooled to –5°C. Phosphorous tribromide (9.02g, 33mmol, 0.33eq) was added dropwise, and the reaction stirred at room temperature for two hours. Ice water (50mL) was added, and the mixture shaken vigorously. The organic layer was extracted with ether (3×50mL), dried over magnesium sulfate and the solvent removed *in vacuo*, giving 19.95g of pure product **202** (99%).

$\mathbf{R}_f$ 0.22 (30% acetone in hexane).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.34 (2H, d, J = 10, ArH), 6.89 (2H, d, J = 10, ArH), 4.53 (2H, s, CH_2Br), 3.82 (3H, s, CH_3O).

^{13}C NMR + DEPT (75MHz, $CDCl_3$) δ 159.83 (ArC), 130.64 (ArCH), 130.12 (ArC), 114.38 (ArCH), 55.50 (CH_3O), 34.21 (CH_2Br).

3-(4-Methoxybenzyl)-pentane-2,4-dione (203)



202 **203**

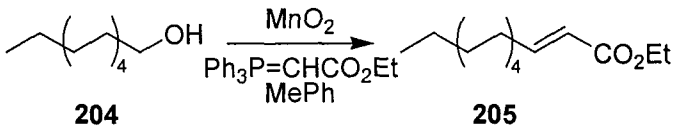
2,4-Pentanedione (0.95g, 9.5mmol, 1eq) was dissolved in diethyl ether (15mL), and sodium ethoxide (21% in EtOH, 3.44g, 10mmol, 1.05eq) added. The reaction was stirred for 2 hours at room temperature, and bromide **202** (2.01g, 10mmol, 1.05eq) then added dropwise. This was then stirred for ½ hour at room temperature, and refluxed overnight. HCl (2M, 15mL) was then added, and the mixture extracted with diethyl ether (20mL). This was dried over magnesium sulfate, evaporated, and purified by column chromatography (20% acetone in hexane) to give 1.41g of compound **203** (70%). A sample was purified by HPLC (20% acetone in hexane), and a separate sample recrystallized from ethanol.

$\mathbf{R_f}$ 0.30 (20% acetone in hexane).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.06 (2H, d, $J = 9$, ArH), 6.86 (2H, d, $J = 9$, ArH), 3.79 (3H, s, H_3C–O), 3.58 (2H, s, Ar–$C\underline{H}_2$–CH), 2.08 (6H, s, H_3C–C(O)).

EIMS *m/z* (%) 220 (8%, M^+), 177 (73%, $(M–COCH_3)^+$), 43 (100%, $(COCH_3)^+$).

Tridec-2-enoic acid ethyl ester (205)



204 **205**

38%

Activated manganese dioxide (0.3g, 3.4mmol, 3.4eq) was added to a solution of undecanol (**204**, 172mg, 1mmol, 1eq) and the Wittig reagent (418mg, 1.2mmol, 1.2eq) in toluene (30mL). The reaction was brought to reflux, and portions of MnO_2 (0.3g, 3.4mmol, 3.4eq each) were added after ½ hour and 1 hour. This was then refluxed overnight, before being filtered through celite. The crude product was purified by column chromatography (1–10% ethyl acetate in hexane) to give 91mg of desired ester **205** (38%).

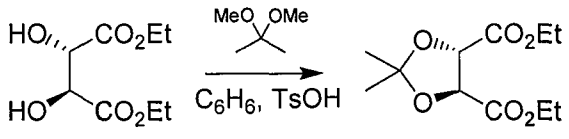
$\mathbf{R_f}$ 0.30 (1% ethyl acetate in hexane).

^{1}H NMR (300MHz, $CDCl_3$) δ 6.96 (1H, dt, J = 7, 16, C<u>H</u>=CH–CO_2Et), 5.80 (1H, d, J = 16, CH=C<u>H</u>–CO_2Et), 4.19 (2H, q, J = 7, O–C<u>H_2</u>–CH_3), 2.19 (2H, dt, J = 7, 6, C<u>H_2</u>–CH=CH), 1.30 (19H, m, alkyl H), 0.87 (3H, t, J = 7, C<u>H_3</u>–CH_2–CH_2).

CIMS *m/z* (%) 258 (10%, $(M+NH_4)^+$), 241 (15%, $(M+H)^+$).

II.4 Compounds from Section I.4

Diethyl-(4S, 5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (207)



84%

206 **207**

A solution of (–)-diethyl tartrate (**206**, 5.0g, 24mmol, 1eq), 2,2-dimethoxypropane (3.0g, 29mmol, 1.2eq) and *p*-toluenesulfonic acid (20mg) in benzene (12mL) was heated, and the benzene-methanol azeotrope distilled off (58°C). When the internal temperature started to rise, the mixture was washed with K_2CO_3 solution (10%), and the aqueous layer extracted with ether. The organic phases were dried over potassium carbonate overnight, and then with sodium sulfate. Evaporation of solvent followed by vacuum distillation gave 5.00g of pure **207** (84%).

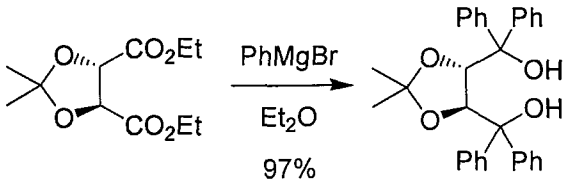
$\mathbf{R_f}$ 0.50 (33% ethyl acetate in hexane).

^{1}H NMR (300MHz, $CDCl_3$) δ 4.71 (2H, s, CH–O), 4.21 (4H, q, $J = 7$, OCH_2), 1.42 (6H, s, $(H_3C)_2C$), 1.23 (6H, t, $J = 7$, $C\underline{H}_3CH_2$).

^{13}C NMR (75MHz, $CDCl_3$) δ 169.791 (C=O), 113.871 ($\underline{C}(CH_3)_2$), 77.283 (CH–O–), 62.016 (CH_2–O), 26.481 ($(\underline{C}H_3)_2C$), 14.222 ($\underline{C}H_3CH_2$).

CIMS *m/z* (%) 264 (32%, $(M+NH_4)^+$), 247 (100%, $(M+H)^+$), 231 (13%, $(M-CH_3)^+$).

((4S, 5S)-5-(hydroxy(diphenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl(diphenyl)methanol (208)



207 **208**

A solution of diester **207** (1.23g, 5mmol, 1eq) in diethyl ether (10mL) was added dropwise to a solution of phenylmagnesium bromide (7.3g, 40mmol, 8eq) in ether (13mL). This mixture was refluxed for two hours, then stirred at room temperature for a further 15 hours. The reaction was worked up with saturated NH_4Cl solution (10mL) at 0°C, and the organic phase removed and evaporated. This was added to pentane (10mL), and triturated. The solid was recrystallized from CCl_4 giving 2.27g of crystalline product (**208**, 97%).

$\mathbf{R_f}$ 0.50 (33% ethyl acetate in hexane).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.5–7.1 (20H, m, ArH), 4.51 (2H, s, CH–O), 3.98 (2H, bs, –OH), 0.98 (6H, s, H_3C).

^{13}C NMR (75MHz, $CDCl_3$) δ 146.06, 128.76, 128.29, 127.78 (ArCH), 109.70 ($\underline{C}(CH_3)_2$), 81.08 ($\underline{C}H$–O), 78.31 ($\underline{C}$–OH), 27.30 (($\underline{C}H_3)_2$–C).

References

[1] *For a review of the Diels-Alder reaction, see* Oppolzer, W. in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 5.

[2] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, 1976, 120–140.

[3] *For a review of intramolecular Diels-Alder reactions, see* (a) Craig, D. in *Houben-Weyl: Methoden der Organischen Chemie*; eds. Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E.; Thieme: Stuttgart, **1995**, vol. E21c, 2872–2904; (b) Roush, W. R. in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 5; (c) Ciganek, E. *Org. React.* **1984**, *32*, 1–374.

[4] *For a review of Type II intramolecular Diels-Alder reactions, see* Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 820–849.

[5] Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta.* **1981**, *64*, 2002–2021.

[6] Ramamurthy, V.; Liu, R. S. H. *J. Org. Chem.* **1974**, *39*, 3435–3436.

[7] Corey, E. J.; Petrzilka, M. *Tetrahedron Lett.* **1975**, *16*, 2537–2540.

[8] Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269–2283.

[9] White, J.D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273–2280.

[10] (a) Stork, G.; Clark, G.; Shiner, C. S. *J. Am. Chem. Soc.* **1981**, *103*, 4948; (b) Stork, G.; Saccomano, N. A. Tetrahedron Lett. **1987**, *28*, 2087.

[11] Seebach, D.; Beck, A. K.; Schiess, M.; Widler, L.; Wonnacott, A. *Pure Appl. Chem.* **1983**, *55*, 1807–1822.

[12] *For a review of TADDOLs and their analogues, see* Seebach, D.; Beck, A. K.; Heckel, A. Angew. *Chem. Int. Ed.* **2001**, *40*, 92–138.

[13] Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345.

[14] Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594.

[15] *For a review of the use of auxiliaries in Diels-Alder reactions, see* Rück-Braun, K.; Kunz, H. *Chiral Auxiliaries in Cycloadditions*, Wiley, London, 1999, 30–71.

[16] Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23–32.

[17] Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261–4263.

[18] Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.

[19] Enholm, E. J.; Jiang, S. *J. Org. Chem.* **2000**, *65*, 4756–4758.

[20] Iwasawa, N.; Sugimori, J.; Kawase, Y.; Narasaka, K. *Chem. Lett.* **1989**, 1947–1950.

[21] Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786–787.

[22] Evans, D. A.; Chapman, K. T.; Bisaha, J. *Tetrahedron Lett.* **1984**, *25*, 4071–4074.

[23] Knölker, H.-J.; Ecker, A.; Struwe, P.; Steinmeyer, A.; Müller, G.; Neef, G. *Tetrahedron* **1997**, *53* (1), 91–108.

[24] Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098–3108.

[25] *For a review of trans-Hydrindane construction reactions, see* Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071–12150.

[26] Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920–6930.

[27] *For a review of Vitamin D synthesis, see* Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877–1952.

[28] Taber, D. F.; Song, Y. *J. Org Chem.* **1996**, *61*, 7508–7512.

[29] Wilson, S. R.; Haque, M. S. *Tetrahedron Lett.* **1984**, *25*, 3147–3150.

[30] Boeckman, R. K., Jr.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421–3423.

[31] Clasby, M. C.; Craig, D.; Jaxa-Chamiec, A. A.; Lai, J. Y. Q.; Marsh, A.; Slawin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1996**, *52* (1), 4769–4802.

[32] *Examples of preparations of Grundmann's ketone: (a)* Curci, R.; Detomaso, A.; Prencipe, T.; Carpenter, G. B. *J. Am. Chem. Soc.* **1994**, *116*, 8112–8115; *(b)* Lythgoe, B.; Roberts, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. I* **1977**, 2608–2612.

[33] Guo, C.; Lu, X. *Tetrahedron Lett.* **1991**, *32 (51)*, 7549–7552.

[34] Prandi, C.; Venturello, P. *J. Org. Chem.* **1994**, *59*, 5458–5462.

[35] Vogel, E.; Roos, O.; Disch, L.-H. *Angew. Chim.* **1961**, *10*, 342.

[36] Thiele, G.; Streitwieser, A. *J. Am. Chem. Soc.* **1994**, *116*, 446–454.

[37] Roush, W. R.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509–1511.

[38] Kraus, G. A.; Landgrebe, K. *Synth. Comm.* **1984**, 885.

[39] Keegstra, M. A.; Verkruijsse, H. D.; Andringa, H.; Brandsma, L. *Synth. Comm.* **1991**, 721–726.

[40] Ramondenc, F.; Ple, G. *Tetrahedron* **1993**, *49*, 10855–10876.

[41] Knol, J.; Feringa, B. L. *Synth. Lett.* **1995**, 1025–1026.

[42] Wipf, P.; Methot, J.-L. *Org. Lett.* **1999**, *1 (8)*, 1253–1255.

[43] Batchelor, M. J.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. I* **1989**, 985–995.

[44] Brewster, J. H.; Ciotti, C. J. *J. Am. Chem. Soc.* **1955**, *23*, 6214–6215.

[45] Clarke, P. A.; Davie, R. L.; Peace, S. *Tetrahedron Lett.* **2002**, *43*, 2753–2756.

[46] Solladié, G.; Almario, A. *Tetrahedron: Asymmetry* **1995**, *6*, 559–576.

[47] Narasaka, K.; Hayashi, Y.; Shimada, S.; Yamada, J. *Isr. J. Chem.* **1991**, *31*, 261–271.

[48] Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237–12254.

[49] Chong, J. M.; Heuft, M. A. *Tetrahedron* **1999**, *55*, 14243–14250.

[50] Yu, Q.; Wu, Y.; Ding, H.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1183–1188.

[51] Hayes, M. P.; Hatala, P. J.; Sherer, B. A.; Tong, X.; Zanatta, N.; Borer, P. N.; Kallmerten, J. *Tetrahedron* **2001**, *57*, 1515–1524.

[52] Yamano, Y.; Sato, Y.; Watanabe, Y.; Namikawa, K.; Miki, W.; Ito, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1862–1869.

[53] *For a review of the Stille reaction, see* Farina, V.; Krishnamurthy, V. *Org. React.* **1997**, *50*.

[54] Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639–6647.

[55] Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221–2224.

[56] Cramer, C. J.; Harmata, M.; Rashatasakhon, P. *J. Org. Chem.* **2001**, *66*, 5641–5644.

[57] Tori, M.; Toyoda, N.; Sono, M. *J. Org. Chem.* **1998**, *63*, 306–313.

[58] Leigh, W. J.; Postigo, J. A.; Zheng, K. C. *Can. J. Chem.* **1996**, *74*, 951–964.

[59] Gueugnot, S.; Alami, M.; Linstrumelle, G.; Mambu, L.; Petit, Y.; Larchevêque, M. *Tetrahedron* **1996**, *52*, 6635–6646.

[60] Gronquist, M. R.; Meinwald, J. *J. Org. Chem.* **2001**, *66*, 1075–1081.

[61] Brudermüller, M.; Musso, H. *Angew. Chem. Int. Ed. Engl.* **1988**, *2*, 298–299.

[62] Taniguchi, H.; Mathai, M.; Miller, S. I. *Org. Synth.* **1966**, *50*, 97–102.

[63] Ashe, A. J. III, Chan, W.-T. *J. Org. Chem.* **1979**, *44*, 1409–1413.

[64] Durand, S.; Parrain, J.-L.; Santelli, M. *Synthesis* **1998**, 1015–1018.

[65] Ashe, A. J. III, Chan, W.-T. *Tetrahedron Lett.* **1975**, *32*, 2749–2752.

[66] Nicolaou, K. C.; Petasis, N. A.; Li, W.S.; Ladduwahetty, T.; Randall, J. L.; Webber, S. E.; Hernandez, P. E. *J. Org. Chem.* **1983**, *48*, 5400–5403.

[67] Ivanov, I. V.; Groza, N. V.; Romanov, S. G.; Kühn, H.; Myagkova, G. I. *Synthesis* **2000**, 691–694.

[68] Ameer, N.; Drewes, S. E.; Drewes, M. W.; Roos, G. H. P.; Watson, M. C. *J. Chem. Soc., Perkin Trans. I* **1988**, 1425–1430.

[69] Hiyama, T.; Inoue, M. *Synthesis* **1986**, 689–691.

[70] Krause, N.; Seebach, D. *Chem. Ber.* **1988**, *121*, 1315–1320.

[71] Sanière, M.; Charvet, I.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron* **1995**, *51*, 1653–1662.

[72] Tsuboi, K.; Ichikawa, Y.; Naganawa, A.; Isobe, M.; Ubukata, M.; Isono, K. *Tetrahedron* **1997**, *53*, 5083–5102.

[73] Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19–22.

[74] Prepared by mixing titanium (IV) chloride and titanium (IV) isopropoxide in a 1:3 ratio: Dijkgraaf, C.; Rousseau, J. P. G. *Spectrochim. Acta* **1968**, *24A*, 1213–1217.

[75] Ernst, A.; Gobbi, L.; Vasella, A. *Tetrahedron Lett.* **1996**, *37*, 7959–7962.

[76] Taylor, E. C.; Zhou, P.; Tice, C. M. *Tetrahedron Lett.* **1997**, *38*, 4343–4346.

[77] Mori, M.; Washioka, Y.; Urayama, T.; Yoshiura, K.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1983**, *48*, 4058–4067.

[78] Tanaka, M; Imai, M; Fujio, M.; Sakamoto, E.; Takahashi, M.; Eto-Kato, Y.; Wu, X.-M.; Funakoshi, K.; Sakai, K.; Suemune, H. *J. Org. Chem.* **2000**, *65*, 5806–5816.

[79] Wei, X.; Taylor, R. J. K. *J. Org. Chem.* **2000**, *65*, 616–620.

[80] Blackburn, L.; Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1999**, 1337–1338.

[81] Feigenbaum, A.; Lehn, J.-M. *Bull. Soc. Chim. Fr.* **1973**, 198–202.

[82] Aszodi, J.; Bonnet, A.; Teutsch, G. *Tetrahedron* **1990**, *46*, 1579–1586.